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Perspective

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# Real-Time and In Situ Monitoring of Mechanochemical Reactions: A New Playground for All Chemists

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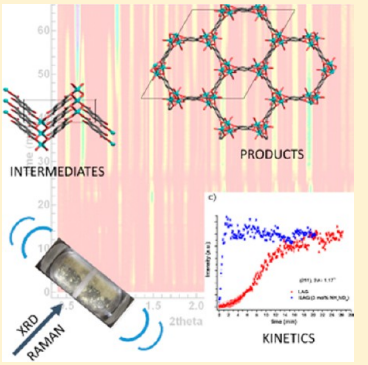
**ABSTRACT:** We provide a brief overview of the first techniques for direct, real-time observation of mechanochemical reactions by milling. Whereas mechanisms and kinetics of solid-state reactions induced by temperature or pressure have been extensively investigated, transformations of materials under continuous impact in a milling assembly remain largely unexplored and based on ex situ studies. The recent introduction and development of techniques for in situ monitoring of milling reactions by synchrotron X-ray powder diffraction and Raman spectroscopy has enabled the first direct insight into milling mechanochemistry, opening a new area for studies of chemical reactivity. So far, these techniques have revealed rapid, multistep reaction mechanisms and metastable intermediates that are impossible or difficult to observe or isolate in solution and have highlighted shortcomings of ex situ mechanistic studies. These pioneering advances also highlight the low level of mechanistic understanding and future challenges in developing a clear mechanistic picture of physicochemical transformations by milling.




This Perspective provides a brief overview of the recently introduced and rapidly developing methodologies for direct monitoring of mechanochemical reactions[1] by X-ray diffraction and Raman spectroscopy.[2−5] These in situ monitoring techniques have just begun to provide so far unprecedented insight into physicochemical processes by milling, both at the level of bulk phase transformations as well as structural changes at the molecular level. As the scope of this overview is limited to the applications and instrumentation behind these novel techniques, for a broader overview of contemporary mechanochemistry, we recommend a number of recent review articles and highlights.[1,6−10]

The recent introduction and development of techniques for in situ monitoring of milling reactions by synchrotron X-ray powder diffraction and Raman spectroscopy has enabled the first direct insight into milling mechanochemistry, opening a new area for studies of chemical reactivity.

Mechanochemical reactions were first defined by Ostwald in the early 20th century as chemical reactions enabled through input of mechanical energy.[11] This original definition addressed transformations by scratching, shearing, grinding, or milling that normally involved bulk solids. In the absence of a better comparison, such bulk mechanochemistry can be considered a subdiscipline of solid-state chemistry. Contemporary mechanochemistry, however, also encompasses other types of operations, for example, mechanical deformation and cleavage of molecular fragments (mechanophores) upon sonic irradiation or cleavage of individual bonds using atomic force microcopy.[12,13] Mechanochemistry of bulk solids is of outstanding technological importance (e.g., in metallurgy and alloying,[14] mineral processing,[15] and, recently, treatment of wood mass and cellulose[16]) and has been a ubiquitous human activity since antiquity.[17] Although the interest of chemists in mechanochemistry has been sporadic over the past 2 centuries,[18,19] the field is now experiencing a revival inspired by its potential in clean and efficient synthesis.[20,21] Over the past 2 decades, a number of unexpected benefits of solvent-free mechanochemical reactivity have emerged, such as excellent reaction selectivity[22,23] and access to chemical transformations,[24] molecules,[25] and materials[26] that are difficult or impossible to achieve using conventional solution techniques. Recent development of mechanochemistry has been greatly aided by the introduction of advanced but mechanistically still poorly understood techniques in which mechanochemical reactivity is enhanced by catalytic amounts of a liquid additive, either alone (liquid-assisted grinding, LAG,[27] also known as kneading[28]) or in combination with catalytic amounts of a salt (ion- and liquid-assisted grinding, ILAG[29]). These methodologies have been discussed in earlier reviews and research articles.[1,27−30]

Recent interest in mechanochemical reactions has also highlighted a surprising lag in mechanistic understanding

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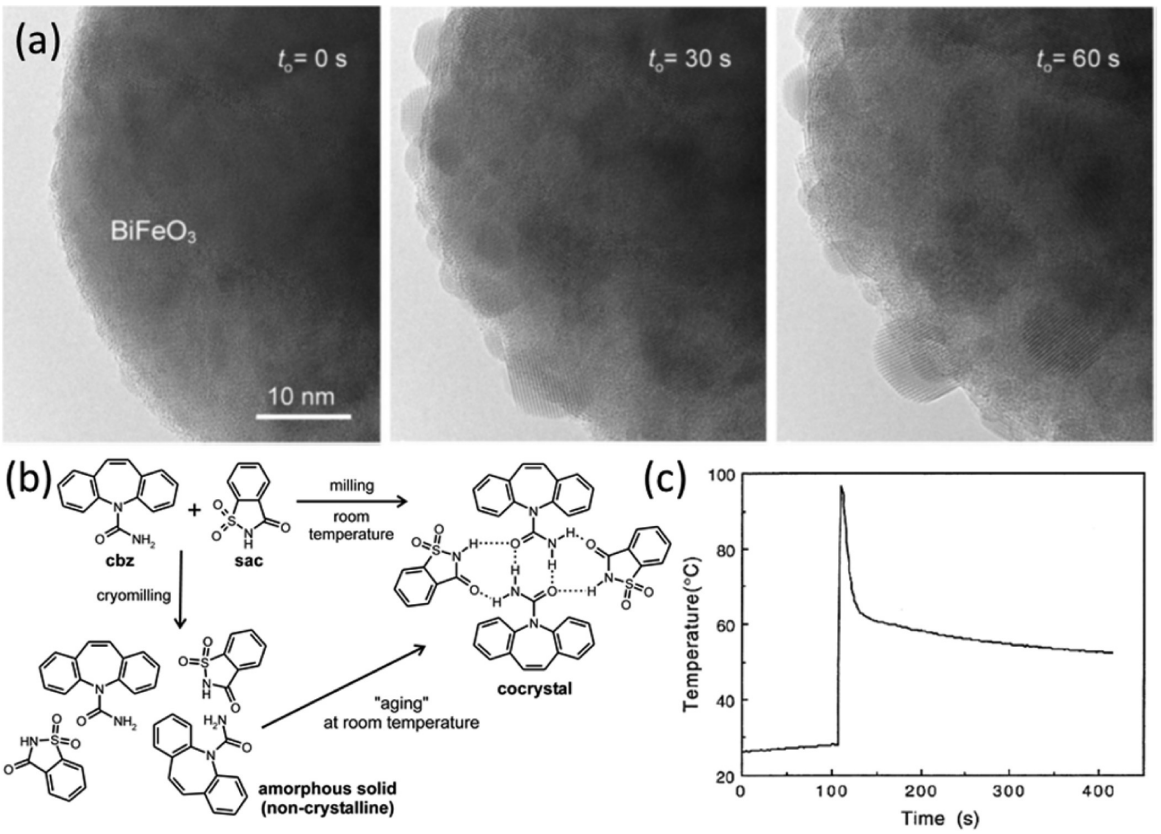


**Figure 1.** (a) Upon exposure to the electron beam during electron microscopy studies, the metastable amorphous phase formed by mechanical activation of $BiFeO_3$ rapidly crystallizes; reproduced with permission from ref 41. (b) The participation of the amorphous phase in mechanochemical milling cocrystallization of saccharin (**sac**) and carbamazepine (**cbz**) was deduced through cryomilling, which enabled the isolation of the amorphous intermediate,[44] and (c) a MSR reaction during milling is recognized as a rapid change in temperature of the reaction vessel, monitored through thermocouples embedded in the jar walls; reproduced with permission from ref 47.

compared to other types of solid-state reactivity, such as heat-, light-, or pressure-induced transformations. This can be related to the, until recently, largely impassable difficulty to directly monitor physical and chemical transformations taking place under violent impact of rapidly moving grinding media, made of steel, ceramic (e.g., zirconia, alumina), or tungsten carbide. As pointed out by Drebuschak and co-workers,[31] "It is a challenge to understand the processes taking place in a powder sample during its grinding in a mill, or compacting, since one can neither measure local temperature, pressure, shear stresses, nor follow the changes in the diffraction patterns or vibrational spectra in situ." As a result, kinetics and mechanisms of reactions by milling have been investigated largely by ex situ (stepwise) approaches, wherein milling is periodically interrupted and the reaction mixture analyzed by suitable solid-state techniques, including powder X-ray diffraction (PXRD),[32] Raman[33] or infrared spectroscopy,[34] surface area measurements,[35] thermal analysis, or solid-state nuclear magnetic resonance (ssNMR) spectroscopy.[36] It is, however, becoming increasingly clear that mechanistic ex situ analysis is limited due to the often not realized possibility that chemical or structural transformations may continue even after mechanical treatment[4,37] or that reactivity of mechanically activated samples may be changed or promoted by the surrounding atmosphere.[38] An example of the latter is the formation of Schiff bases by grinding of aldehydes and amines, which has been known since at least the 1980s[39] but was only recently established to be catalyzed by air moisture.[40] This example also highlights how reactions between solids can contrast conventional chemical intuition; aldimine condensation in solution is reversed by water but catalyzed by moisture in the solid state.

It is generally accepted that mechanochemical reactions involve activation of reactants.[1,6] The nature of such mechanochemical activation is complex and can involve different processes, from creation of highly reactive nanoparticles and intimate mixing of reactants at the atomic or molecular scale to structural defects and amorphization.[6] For hard ionic materials, such as metal oxides, activated phases are kinetically stable and relax only at high temperatures or other types of stress.[41] This permits observation of activated phases at room temperature, for example, the formation of core−shell particles in which the crystalline core of the starting oxide material is surrounded by an activated phase in the form of a nanometer-thick layer of an amorphous or otherwise defective material (Figure 1a).[42] For softer organic and metal−organic materials, such activated forms are less stable and, due to rapid relaxation, are often difficult to detect by ex situ analysis. For example, the appearance of an amorphous phase as the intermediate during mechanochemical cocrystallization of saccharin (**sac**) and carbamazepine (**cbz**) to form the pharmaceutical cocrystal[43] (**cbz**)(**sac**) was demonstrated only indirectly, through the application of cryomilling techniques in which low temperature hindered the otherwise rapid crystallization of the intermediate (Figure 1b).[44] Rapid relaxation of activated intermediates can interfere with the stepwise analysis of a milling reaction, as evidenced by


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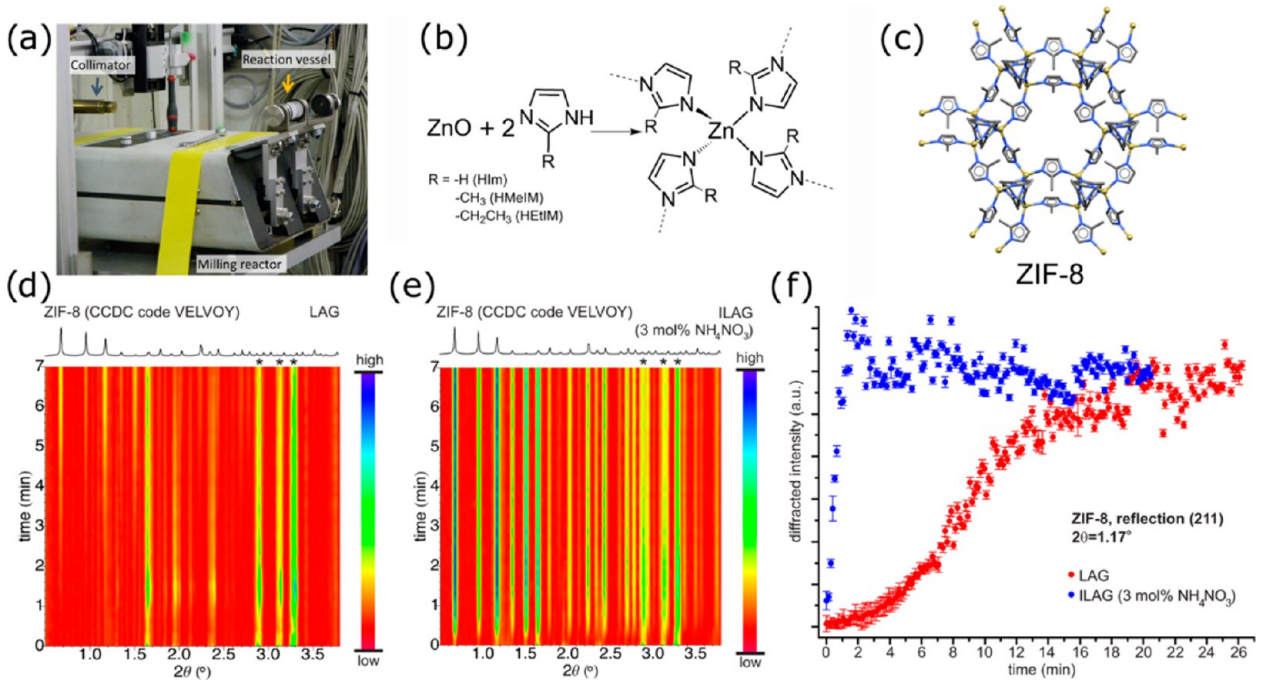


**Figure 2.** (a) Experimental setup for in situ and real-time monitoring of mechanochemical milling reactions by synchrotron X-ray powder diffraction; (b) mechanochemical synthesis of ZIFs; (c) fragment of the ZIF-8 structure. Time-resolved diffractograms for the (d) LAG and (e) ILAG synthesis of ZIF-8 from ZnO and **HMeIm**. (f) Time-dependent variation of the intensity of the (211) reflection of the ZIF-8 product in LAG (red) and ILAG (blue) synthesis.[2,3] Individual images adapted from ref 2 with permission from the author.

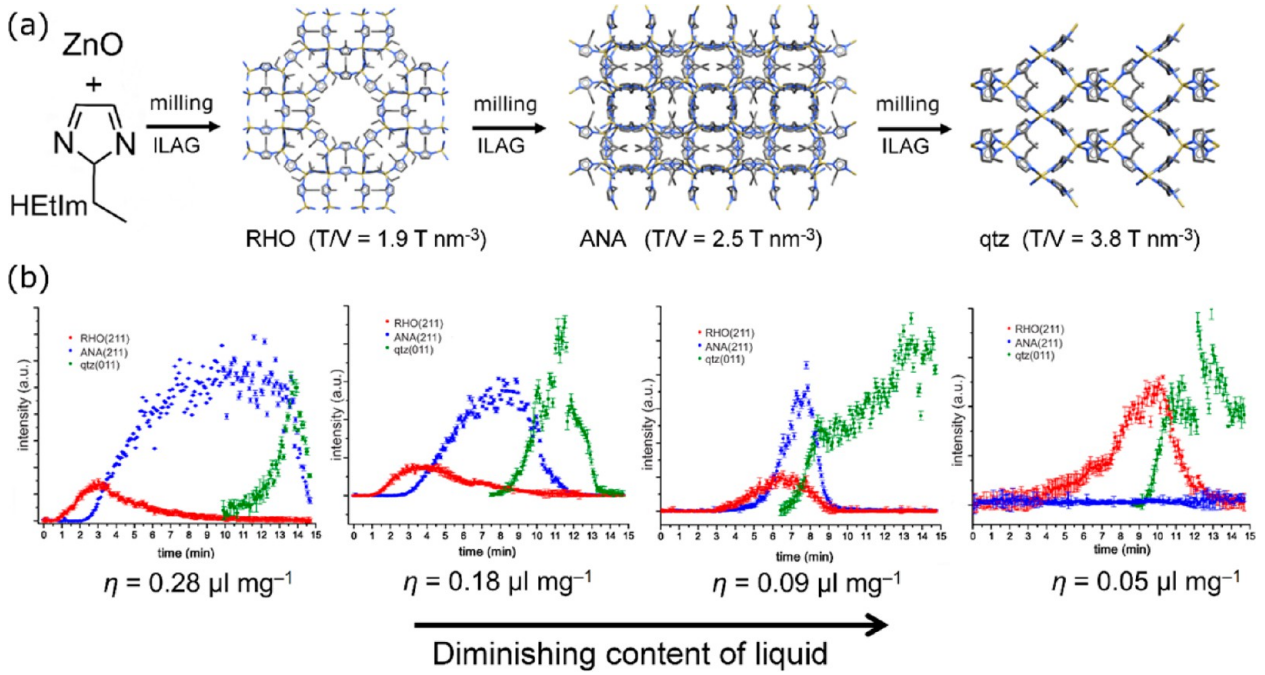


**Figure 3.** Mechanochemical ILAG reaction of ZnO and **HEtIm** to form metal−organic frameworks: (a) the stepwise reaction sequence and (b) the effect of decreasing the amount of liquid phase on the lifetime of reaction intermediates, established by in situ reaction monitoring by synchrotron PXRD.[2] (b) Adapted from ref 2 with permission from the author.

mechanochemical complexation of cadmium chloride with cyanoguanidine, which gives different product compositions if milling is periodically interrupted.[45]

The described examples illustrate that in-depth understanding of mechanochemical reactivity necessitates direct and in situ reaction monitoring. So far, such real-time monitoring has been possible only for a small number of milling transformations, notably those involving gaseous reactants or products or highly exothermic reactions (mechanochemically induced self-sustaining reactions, MSRs), for which reaction monitoring was enabled by observing changes in pressure or temperature within the milling assembly, respectively.[46,47] Although highly informative, such measurements still do not provide any detailed information on the



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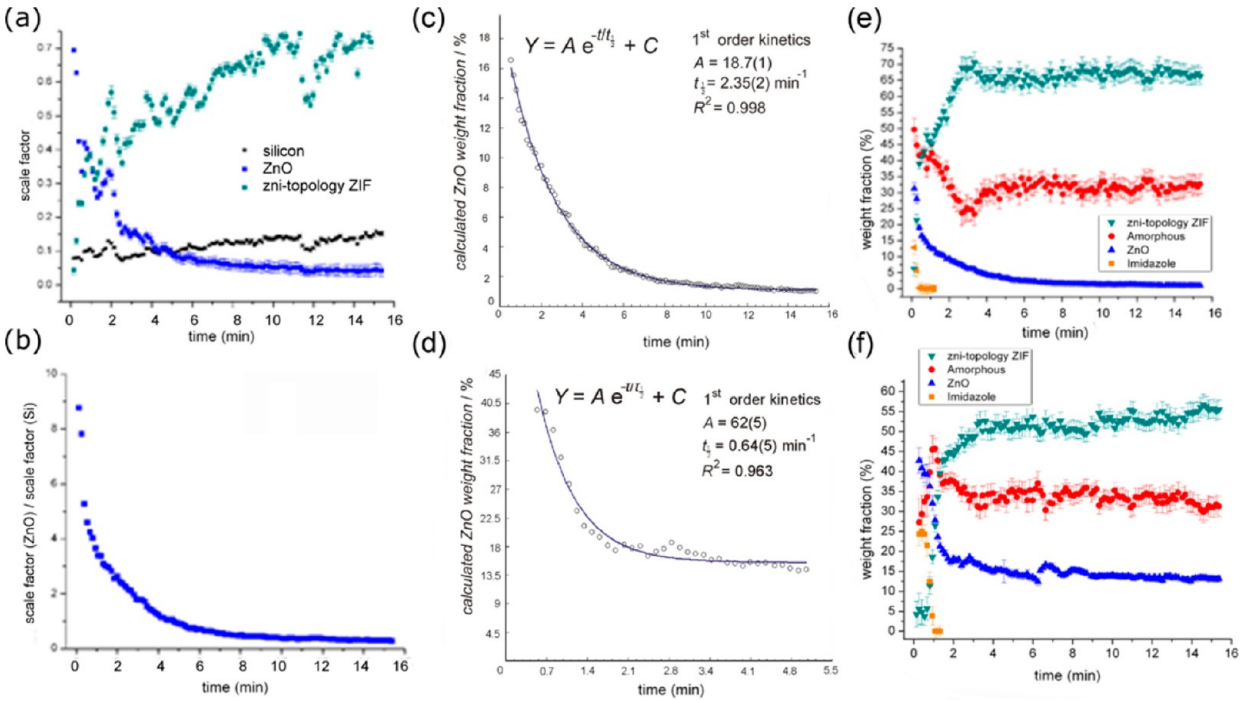


**Figure 4.** (a) Variation in intensity of diffraction signals of ZnO reactant, ZIF product, and the silicon internal diffraction standard during mechanochemical synthesis of **zni**-Zn(**Im**)$_2$, caused by variation of the amount of diffracting sample and (b) variation of the diffraction signal of ZnO, after normalization to the internal diffraction standard. Time-dependent quantitative analysis of the reaction mixture for (c) ILAG and (d) LAG reaction of ZnO and **HIm**, established through Rietveld analysis. The disappearance of ZnO reactant in (e) ILAG and (f) LAG reaction with **HIm** fits to a first-order rate law.[55] Individual images adapted from ref 55 with permission from the author.

nature of activated phase or structural changes taking place at the level of the molecule or bulk material (Figure 1c).

*In Situ and Real-Time Monitoring of Mechanochemical Reactions by Synchrotron PXRD.* In 2013, our group reported the first generally applicable technique for real-time observation of transformations of solid phases during milling by in situ PXRD of synchrotron radiation.[2,3] The technique relies on X-rays of sufficiently high energy ($E \approx 90$ keV, $\lambda \approx 0.1$ Å) to pass through the walls of the oscillating reaction vessel, interact with the milled sample, and be detected after leaving the vessel (Figure 2a). The technique was developed using a Retsch MM200 shaker mill modified to allow mounting a custom-made milling jar (~14 mL volume) in the path of the incident X-ray beam. Milling was achieved by horizontal oscillatory motion of the milling jar perpendicular to the incident beam and the diffracted radiation detected using a two-dimensional detector with an exposition of 4 s per image. With the mill operating at 30 Hz, a single diffraction pattern provided a snapshot of the reaction mixture over 120 oscillations of the milling jar, enabling monitoring with resolution in seconds with a high level of sample homogeneity. Although the technique was applicable to jars made of conventional materials, such as steel or aluminum, poly(methyl)metacrylate (PMMA, also known as Perspex) was found to be the material of choice due to its good mechanical properties, amorphous structure, and low absorption for utilized X-rays. The first application of this in situ monitoring technique was on the formation of zeolitic imidazolate frameworks (ZIFs)[48] by neat milling, LAG, and ILAG of zinc oxide with imidazole (**HIm**), 2-methylimidazole (**HMeIm**), or 2-ethylimidazole (**HEtIm**) (Figure 2b).[2,3]

The reaction involving **HMeIm** is of particular relevance as it yields one of the few commercially available MOFs, the open Zn(**MeIm**)$_2$ framework of sodalite (SOD) topology known as ZIF-8 (Figure 2c).[49] Product formation was monitored through the change in intensity of the characteristic (211) reflection of ZIF-8, which, for both LAG and ILAG approaches, exhibited a sigmoidal pattern characteristic of a nucleation and growth mechanism (Figure 2d–f).[2,50] Product formation by ILAG, which relied on the use of ammonium salts as catalytic protic additives, was considerably faster and gave maximum conversion in 4 min. The analogous LAG reaction led to maximum conversion after 25 min of milling.

A more complex reaction mechanism was observed for the ILAG reaction of ZnO and **HEtIm**, which proceeded in a sequence of steps generating first the low-density Zn(**EtIm**)$_2$ framework with zeolite $\rho$ (RHO) topology that subsequently converts to more dense analcime topology structure (ANA) and, ultimately, to a close-packed framework of quartz (qtz) topology (Figure 3a).[2]

The stability of a zeolitic structure is inversely related to its density, which is often expressed as $T/V$, that is, the ratio of the number of tetrahedral sites ($T$) per unit cell volume ($V$). The $T/V$ ratios for the RHO → ANA → qtz mechanochemical sequence reveal that the transformation is consistent with Ostwald's rule of stages, wherein the thermodynamically stable product is formed in a sequence of metastable phases,[51] representing an analogy to transformations seen in zeolite chemistry.[52] The reaction sequence is also consistent with previously noted formation of low-density or highly solvated materials as early intermediates in the mechanochemical formation of coordination polymers and metal–organic frameworks (MOFs).[53] Monitoring of time-dependent changes in intensities of characteristic X-ray reflections for each crystalline phase revealed how a reaction is affected by different amounts of a liquid additive, expressed as $\eta$, that is, the ratio of liquid volume to the mass of solid reactants (Figure 3b).[54] For


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the transformation of ZnO to qtz-Zn(**EtIm**)$_2$, reaction profiles were strikingly different as decreasing $\eta$ led to increasingly shorter lifetimes of the ANA-Zn(**MeIm**)$_2$ intermediate. At the lowest explored $\eta$ value of 0.05 $\mu$L mg$^{-1}$, the intermediate did not appear, while for the highest explored $\eta$ of 0.28 $\mu$L mg$^{-1}$, it persisted throughout most of the experiment. This first real-time observation of a multistep mechanochemical reaction clearly reveals a direct influence of the liquid and its amount on the reaction mechanism, contrasting the view of the liquid being simply a reaction "lubricant".

*Quantitative In Situ PXRD Monitoring of Mechanochemical Reactions.* X-ray diffraction data collected over the course of a mechanochemical reaction should, in principle, allow quantitative reaction mixture analysis using the Rietveld method. However, besides problems pertinent to mechanosynthesis of porous MOFs, where the contribution of included guest molecules to X-ray scattering is generally not known and is likely to change as the reaction progresses, mechanochemical reactions often comprise a noncrystalline component that scatters X-rays but does not produce a diffraction signal. Quantitative reaction monitoring by PXRD is thus hindered by the inability to directly determine amorphous fraction of the reaction mixture, as well as by variations in the diffracted intensity caused by the nonuniform, time-dependent distribution of the sample in the reaction vessel (Figure 4a,b). Averaging of the diffraction signal over a few seconds, a typical time resolution required to capture fast reactions, was not enough to eliminate random variations in the amount of the sample exposed to the incident X-ray beam. Combined with variation in absorption of X-rays by the steel milling media, this leads to random artifacts in diffracted intensity (Figure 4a,b).[2,3] These effects can be remedied by adding microcrystalline silicon into the reaction mixture as an internal scattering standard.[55] Normalization of the in situ collected diffraction data relative to the silicon diffraction signal revealed fast homogenization of the reaction mixture and enabled its quantitative analysis during milling. Rietveld analysis of LAG and ILAG reactions of ZnO and **HIm** yielding the nonporous Zn(**Im**)$_2$ framework with zinc iodide (**zni**) topology revealed that LAG with ethanol (EtOH) as the grinding liquid is slower than the corresponding ILAG reaction conducted with $NH_4NO_3$ additive (Figure 4c,d).[55] The additive accelerated the depletion of ZnO, as well as **HIm**, the latter being in agreement with a proposed reaction model involving activation

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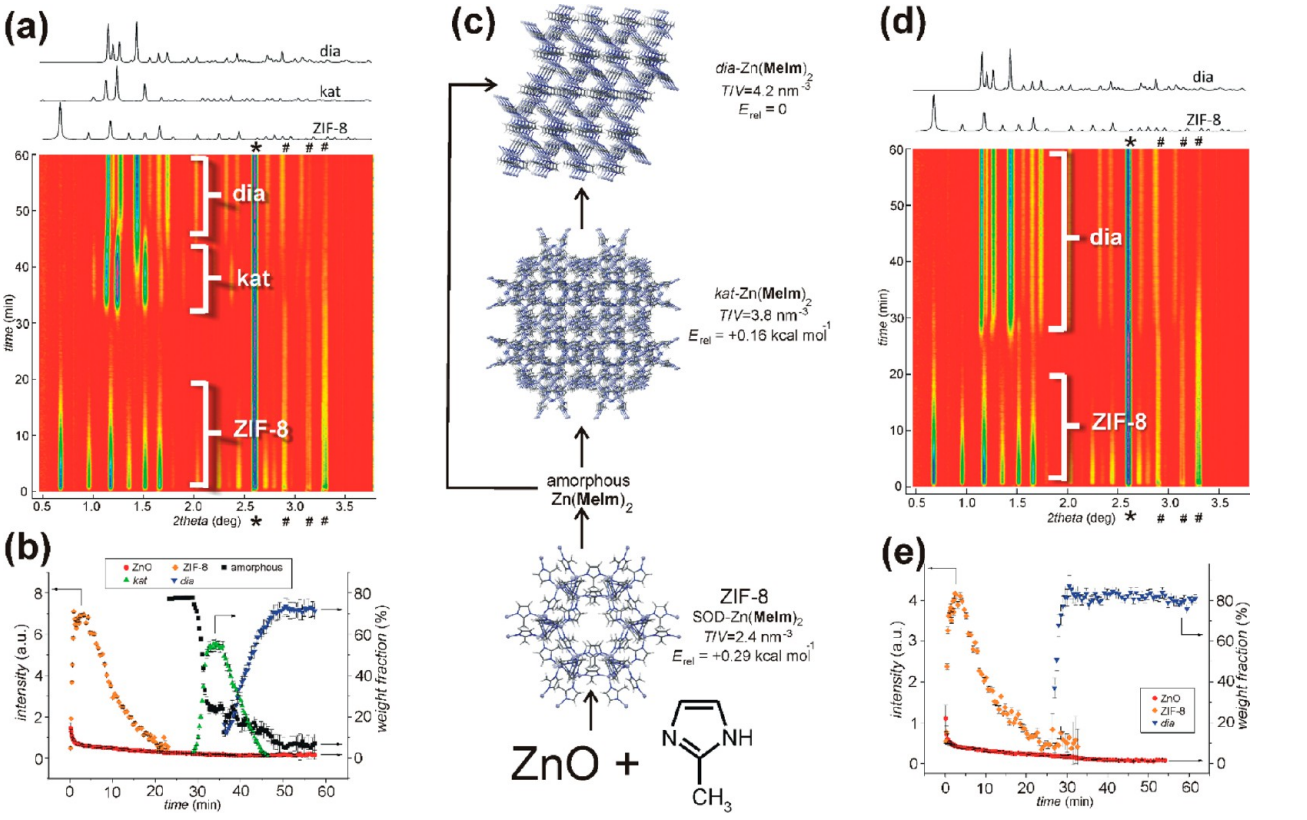


**Figure 5.** Discovery of a metastable MOF through in situ reaction monitoring:[25] (a) time-resolved X-ay diffractogram for the LAG reaction of ZnO and **HMeIm** with aqueous acetic acid as the milling liquid, with * denoting the diffraction signal of a silicon standard and (b) corresponding plot for the evolution of each phase. (c) Representation of the observed transformation. (d) Time-resolved X-ray diffractogram for LAG reaction of ZnO and **HMeIm** in the presence of aqueous acetic acid and (e) a corresponding plot of the evolution of each phase, demonstrating that the reaction can also take place without participation of the **kat**-Zn(**MeIm**)$_2$ intermediate.[25] Individual images adapted from ref 25 with permission from the author.



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of imidazole ligands by protonation.[56] The disappearance of **HIm** reflections in the PXRD pattern of the milled reaction mixture was attributed to several parallel processes, including amorphization and chemical reaction with ZnO. Loss of ZnO, on the other hand, was significantly slower. As amorphization of an ionic binary oxide by milling in a relatively soft PMMA jar is not likely to be significant, the rate of ZnO disappearance was assumed to be largely due to reaction with **HIm** and, therefore, suitable for assessing the kinetics of the chemical reaction underlying ZIF formation. Surprisingly, modeling of the loss of ZnO content revealed excellent fit to the first-order reaction rate law (Figure 4e).[55] The ability to model a mechanochemical reaction using rate laws established for reactions in solution speaks in favor of a pseudofluid model of mechanochemical reactivity, proposed by the James group.[33]

Perhaps the most striking result of quantitative reaction monitoring is the evaluation of amorphous content in the milled reaction mixture.[55] Upon ILAG and LAG synthesis of **zni**-Zn(**Im**)$_2$, the amorphous content rapidly reached a steady state of 30 or 35% by weight, respectively (Figure 4c,d). In contrast, ex situ analysis for the LAG reaction revealed no more than 12 wt % of amorphous phase. The discrepancy between amorphous contents observed by Rietveld assessment based on in situ and ex situ diffraction data was explained by rapid relaxation of the amorphous phase, highlighting how delays incurred during sample preparation and analysis can hinder stepwise mechanistic studies. Observation of high amorphous content during LAG contrasts with ex situ studies in which the liquid additive was found to enable the formation of highly crystalline products.[57] It is, however, supportive of a previously proposed model for mechanochemical interconversion of MOFs mediated by an amorphous phase.[58]

Monitoring of mechanochemical amorphization was key to the recent discovery of a topologically novel MOF.[25] The LAG reaction of ZnO and **HMeIm** in the presence of aqueous acetic acid led to almost instantaneous formation of ZIF-8, which was followed by its complete amorphization, evidenced by a featureless PXRD pattern obtained after ∼20 min of milling. Surprisingly, further milling led to recrystallization of the amorphous matrix into a new polymorph of ZIF-8 with a previously unknown katsenite (**kat**) topology (Figure 5a−c). The **kat** phase is metastable and completely converts to a close-packed diamondoid (**dia**) topology structure upon further milling (Figure 5c).

While the isolated **kat** framework readily converts to the **dia** structure upon heating to 40 °C or exposure to solvents, it can be safely stored at room temperature for months, which enabled characterization by PXRD structure determination, solid-state NMR spectroscopy, and other techniques.[25] The synthesis of the **kat** phase was only partially reproducible as the mechanochemical crystalline → amorphous → crystalline transformation sometimes gave directly the **dia** product, providing tentative evidence for the importance of nucleation effects during milling transformations (Figure 5d,e).

*In Situ PXRD Monitoring of Pharmaceutical Cocrystallization.* Applicability of in situ PXRD reaction monitoring to weakly scattering organic materials was evaluated on the mechanosynthesis of pharmaceutical cocrystals.[59] Monitoring of neat milling of **cbz** and **sac** revealed the gradual disappearance of X-ray reflections for both reactants, directly confirming amorphization asserted by the Rodríguez-Hornedo group through cryomilling experiments (Figure 6a).[44] In contrast, LAG of the two reactants with acetonitrile as the grinding liquid

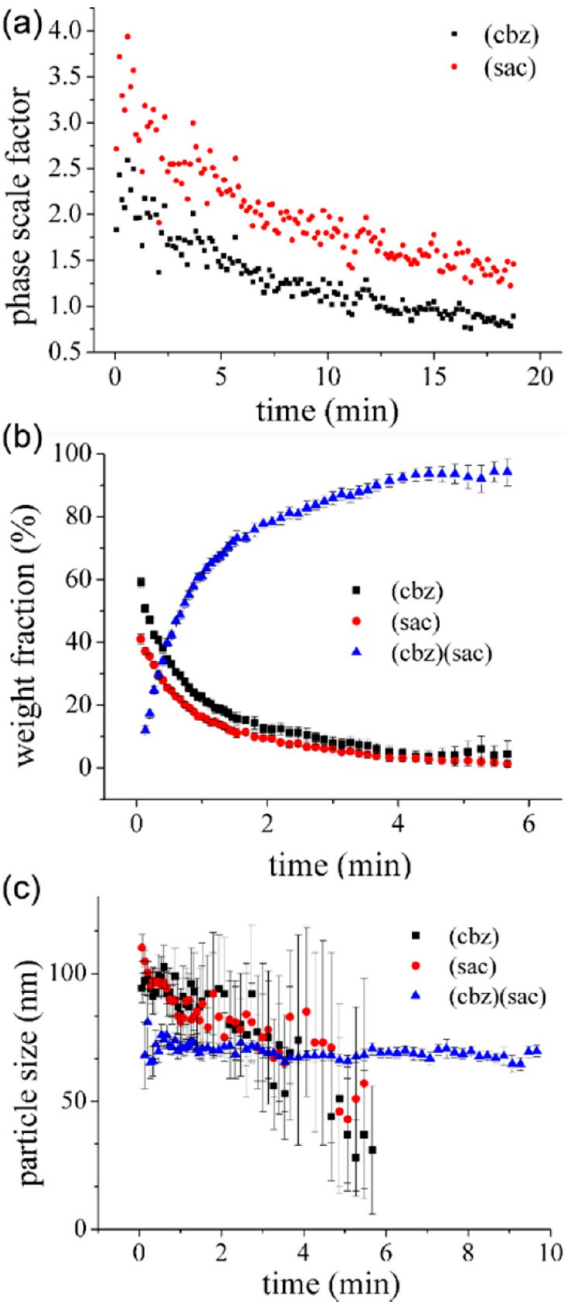


**Figure 6.** Real-time in situ PXRD monitoring of mechanochemical cocrystallization of **cbz** and **sac**: (a) change in phase scale factors of the two components upon neat milling, indicating amorphization; (b) change in reactant and product (**cbz**)(**sac**) weight fraction upon LAG; and (c) evaluation of changes in reactant and product particle sizes during LAG synthesis, evaluated through the Scherrer method.[59] Individual images adapted from ref 59 with permission from the author.

led to quantitative cocrystal formation concomitant with the disappearance of reactants within minutes, demonstrating the speed and simplicity of mechanochemical cocrystallization in comparison to solution techniques (Figure 6b). The application of the Scherrer method also enabled the direct and in situ insight into trends in particle size changes for milled reaction products and reactants (Figure 6c). Partial amorphization of starting materials upon mechanochemical cocrystallization was also recently observed by Fischer and co-workers upon in situ


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PXRD monitoring of neat grinding cocrystallization of oxalic acid and theobromine.[60]

A more complex cocrystallization mechanism was observed for the neat grinding reaction of nicotinamide (**na**) with suberic acid (**sub**) in a respective 2:1 ratio, wherein the formation of the $(\mathbf{na})_2(\mathbf{sub})$ cocrystal took place via the (**na**)(**sub**) intermediate that appears ~1 min into milling and completely converts to the stoichiometrically determined product $(\mathbf{na})_2(\mathbf{sub})$ within ~40 min (Figure 7a,b). These observations

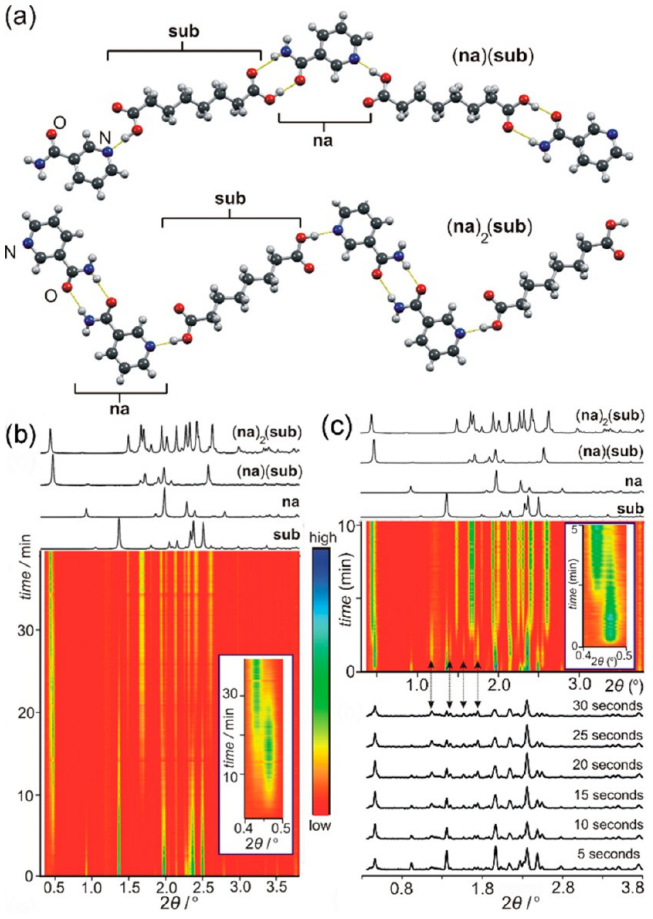


**Figure 7.** Real-time and in situ PXRD monitoring of cocrystallization of nicotinamide (**na**) and suberic acid (**sub**): (a) fragments of structures of the (**na**)(**sub**) and $(\mathbf{na})_2(\mathbf{sub})$ cocrystals; (b) time-resolved diffractogram for mechanochemical stepwise formation of (**na**)(**sub**) by neat milling; and (c) the corresponding LAG reaction, with the diffraction signals of the metastable short-lived intermediate highlighted on individual diffractograms. Images adapted from ref 59 with permission from the author.

are consistent with the initial ex situ study,[61] which noted the stepwise mechanism of the neat grinding reaction, explained by competition of supramolecular hydrogen-bonded synthons of different strengths. However, in situ reaction monitoring also permitted the analysis of the corresponding LAG reaction that was previously established to be too fast for ex situ analysis. Milling of the two reactants in the presence of acetonitrile revealed the unexpected formation of an unknown phase that disappears within the first 3 min of milling and is followed by the formation of (**na**)(**sub**) and, ultimately, $(\mathbf{na})_2(\mathbf{sub})$ (Figure 7c).[59] However, further and more detailed characterization of this new phase was prevented by its instability and disappearance upon aging. Discovery of a new material in a model system already studied by several groups points to the potential of in situ diffraction monitoring in pharmaceutical solid form discovery.

Discovery of a new material in a model system already studied by several groups points to the potential of in situ diffraction monitoring in pharmaceutical solid form discovery.

*Real-Time Monitoring of Mechanochemical Reactions by Raman Spectroscopy.* A major limitation of studying mechanochemical reactions by in situ X-ray diffraction is the need for a synchrotron source. Also, although PXRD analysis is highly informative with respect to transformations of bulk crystalline phases, it provides little or no insight into amorphous materials or the molecular-level transformations that are critical in early stages of mechanochemical reactions. However, information on molecular-level complexation, of particular importance for understanding the role and behavior of liquid additives in LAG and ILAG transformations, might be readily available through different spectroscopic techniques, such as infrared and Raman spectroscopy.[34] With that in mind, we introduced a methodology for in situ and real-time monitoring of mechanochemical reactions using Raman spectroscopy (Figure 8a).[4] Whereas the use of conventional steel- or ceramic-based milling equipment represents an insurmountable obstacle for spectroscopic investigations, introducing optically translucent PMMA milling vessels also provided access to reaction monitoring with inexpensive, readily available laboratory Raman spectroscopy equipment. This technique was recently adapted into a tandem monitoring methodology using PXRD and Raman spectroscopy (Figure 8b).[5]

The first application of this novel spectroscopic monitoring technique addressed the formation of selected model coordination polymers and organic cocrystals. For example, Raman monitoring clearly revealed the mechanochemical complexation of cadmium chloride and cyanoguanidine (**cnge**) to form either the three-dimensional polymer Cd(**cnge**)$Cl_2$ or the two-dimensional one $Cd(\mathbf{cnge})_2Cl_2$ (Figure 8c).[4] The formation of each individual coordination polymer and the disappearance of **cnge** reactant was readily observed through changes in absorption bands located at around 2200 $cm^{-1}$ associated with the **cnge** nitrile functionality (Figure 8d). The disappearance of cadmium chloride reactant and formation of product could also be readily followed via changes in spectral bands at around 200 $cm^{-1}$, associated with changes in the coordination environment of the metal ion (Figure 8d). These spectral regions provided excellent handles to study the effect of reactant stoichiometry, the choice of milling media, and the presence of a grinding liquid on the reaction course. Importantly, in situ monitoring of coordination polymer synthesis provided different results than our earlier[45] ex situ study; whereas stepwise analysis revealed the formation of the three-dimensional Cd(**cnge**)$Cl_2$ structure as the kinetic intermediate in the synthesis of the two-dimensional $Cd(\mathbf{cnge})_2Cl_2$, Raman reaction monitoring revealed the direct formation of $Cd(\mathbf{cnge})_2Cl_2$. This discrepancy highlights the effects of relaxation and sample aging on stepwise reaction analysis.


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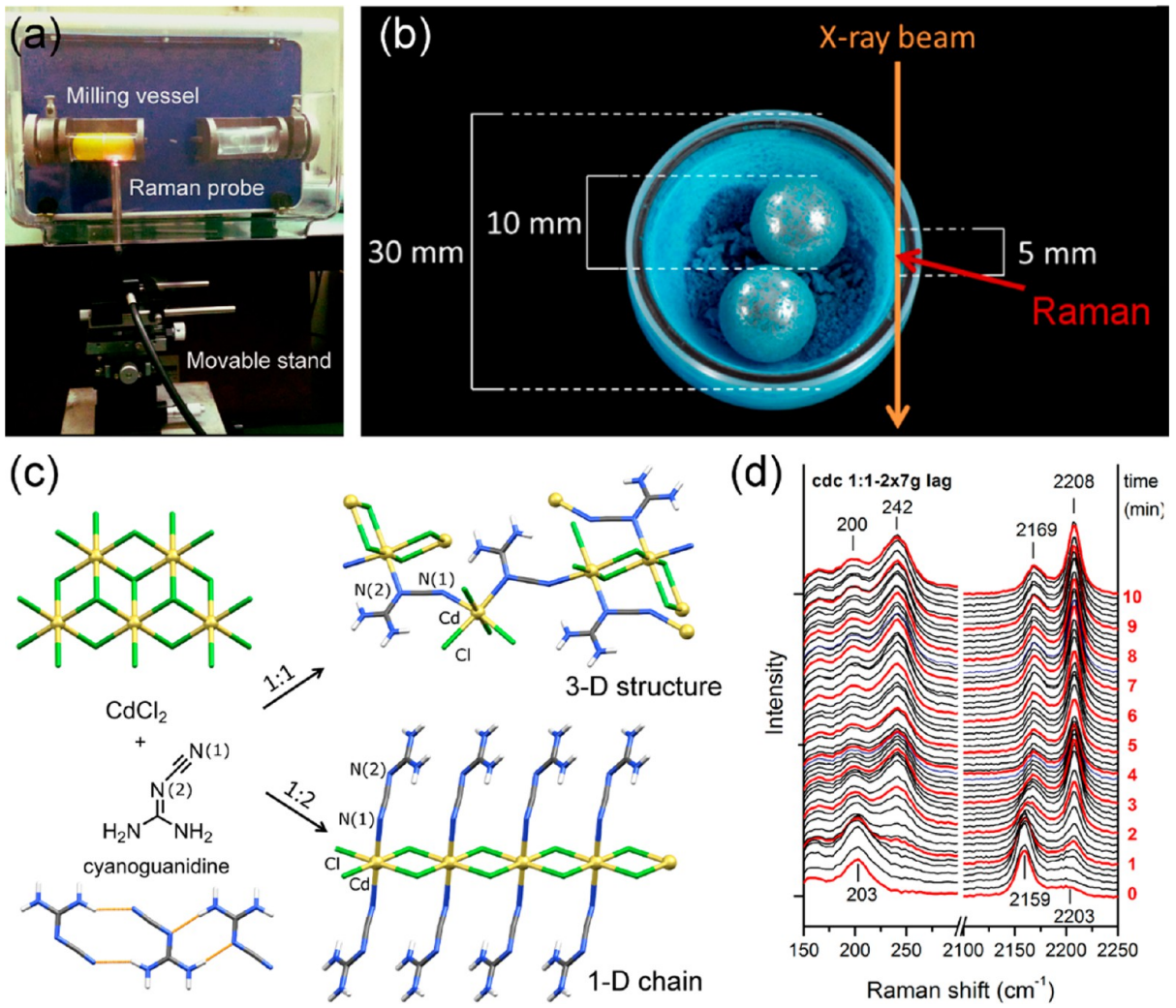


**Figure 8.** Real-time and in situ monitoring of mechanochemical reactions using Raman spectroscopy: (a) the first reported experimental setup;[4] (b) the design for tandem PXRD and Raman measurements;[5] (c) the mechanochemical reactions of $CdCl_2$ with the **cnge** ligand in different stoichiometries; and (d) in situ collected Raman spectra for the mechanochemical LAG reaction of $CdCl_2$ and **cnge** in 1:1 stoichiometric ratio. Product formation is noted by changes in Raman emission bands associated with the metal coordination environment (left) and the ligand nitrile group (right).[4] Individual images adapted from refs 4 and 5 with permission of the author.

Raman spectroscopy is also a convenient method for monitoring of milling organic transformations, which can often involve short-lived amorphous or eutectic liquid intermediates not readily detectable by PXRD.[62,63] For example, Raman spectroscopy enabled monitoring the mechanochemical reaction of an acyl azide with an aniline by changes in resonances of the product amide group and the reactant carbonyl group (Figure 9a).[64] The reaction could also be followed by reduction in the intensity of the Raman resonance of the reactant azide group antisymmetric stretching at 2136 $cm^{-1}$. Monitoring of the same reaction in the presence of different organic liquid additives revealed a clear correlation between LAG reaction time and the basicity of the organic liquid, expressed as Gutmann's donor number[65] (Figure 9b). Importantly, no correlation was observed between the reaction times and solubilities of participating solids in respective liquids or its other properties, such as molecular dipole moment or relative permittivity.[64] Sensitivity of Raman spectra to changes in molecular structure was demonstrated for in situ monitoring of the mechanochemical C−H bond activation involving palladium(II) acetate and the 4-amino-4′-nitroazobenzene (Figure 9c).[66] Raman spectroscopy clearly revealed the formation of a monopalladated intermediate on the way to a bis(cyclopalladated) product. Importantly, the analysis of changes in stretching resonances of the $C_{aromatic}$−$N_{azo}$ and $N_{azo}$═$N_{azo}$ bonds revealed that the intermediate formation was fully regioselective, with the first cyclopalladation step taking place on the 4-dimethylamino portion of the molecule.

Fundamental differences between LAG and reactions in solution were demonstrated through real-time Raman spectroscopy monitoring of thiocarbamoylation of anilines using bis(benzotriazolyl)methanethione (Figure 9d).[67] In solution,[68] these reactions yield thioureas through *N*-thiocarbamoylbenzotriazole intermediates deemed impossible to isolate due to rapid dissociation into isothiocyanates. Unexpectedly, these intermediates were readily observable by in situ Raman monitoring during mechanosynthesis, which was also optimized to quantitatively yield these elusive molecules, enabling their full characterization (Figure 9e) and application as bench-stable alternatives to toxic isothiocyanates.[67] Although readily prepared by LAG, the *N*-thiocarbamoylbenzotriazoles rapidly dissociated upon dissolution, highlighting a difference in


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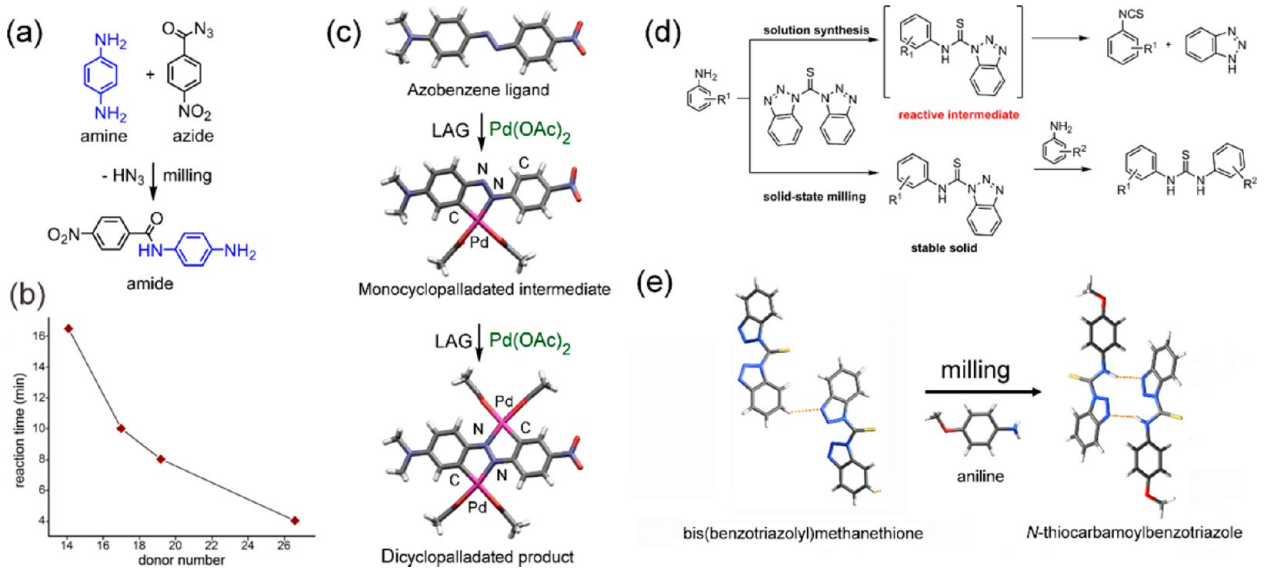


**Figure 9.** Advances in understanding mechanochemical reactivity by using in situ Raman reaction monitoring: (a) mechanochemical transformation of an acyl azide into an amide; (b) the dependence of LAG amide formation on the basicity of catalytic milling liquid; (c) mechanochemical C−H bond activation through a two-step palladation of an azobenzene; (d) thiocarbamoylation of anilines with bis(benzotriazolyl)methanethione in solution was proposed to proceed through not isolable *N*-thiocarbamoylbenzotriazole intermediates that were readily obtained through mechanochemistry; and (e) structurally characterized using X-ray powder diffraction.

reactivity of a liquid when used as a low-$\eta$ additive in LAG, as compared to being used as a bulk solvent.

*Combined In Situ X-ray Diffraction and Raman Spectroscopy Reaction Monitoring.* The most recent innovation in real-time and in situ exploration of mechanochemical reaction mechanisms is a methodology for simultaneous reaction monitoring by synchrotron PXRD and Raman spectroscopy, introduced by the Emmerling group (Figure 8b).[5] This combined technique provides a so far unique level of insight into processes conducted by milling as it allows detection of the transformation of bulk crystalline phases through X-ray diffraction while simultaneously gathering molecular-level information via Raman scattering. This methodology was readily applicable to the syntheses of metal−organic materials, such as ZIF-8 or HKUST-1, as well as of model pharmaceutical cocrystals, as exemplified by the cocrystal of benzoic acid with theophylline. Perhaps the best illustration of the potential of this monitoring technique is the assembly of a metal−organic cobalt(II) phosphonate framework from cobalt(II) acetate and phenylphosphonic acid. As evidenced by in situ PXRD, the reaction proceeds via a layered structure intermediate that appears 1 min into milling and begins to convert into the final phosphonate framework product after a total of ∼3 min of milling.[5] Whereas PXRD did not reveal the presence of residual reactants upon intermediate formation, Raman spectroscopy clearly indicated the presence of unreacted benzenephosphonic acid, most likely included as a guest into the layered structure of the intermediate.

The herein presented overview reveals the development of methodologies for in situ and real-time monitoring of mechanochemical milling reactions as a new and highly dynamic field. Introduced only 2 years ago as a synchrotron X-ray diffraction technique accessible to a small number of research teams, real-time monitoring rapidly expanded to include Raman spectroscopy, as well as the combined Raman/PXRD technique. These new research tools are now being deployed by different research groups to address the long-standing and previously inaccessible fundamental questions of mechanochemical milling reactions, such as the rate of transformations, appearance of elusive intermediate phases and complexation in amorphous or liquid phases. The new insight into mechanochemical reactivity revealed an unexpectedly dynamic environment involving new framework architectures, polymorphs, and molecular species that are not accessible through conventional solution-based techniques. These exciting discoveries, however, represent only the tip of the iceberg of the new (mechano)chemical environment that has been unlocked for studying. A number of fundamental concepts underlying mechanochemical reactivity still remain elusive, such as the balance of input energy and frictional heating,[69,70] the impact of temperature and mechanically generated "hot spots" on reactivity,[71] the nature of mechanochemical activation, or the molecular-level mechanisms of even the chemically simplest transformations, such as amorphization, polymorph transformation, or cocrystallization. Another important area of mechanochemistry that is of high technological importance and is likely to be probed in the future are structural defects and a detailed view of particle mixing and comminution.[72] Addressing these questions will require not only a new set of in situ monitoring tools, complementary to the existing ones, but also the development of modeling[73] and theoretical[74,75] approaches to be closely integrated with arising experimental work. In the context of advancing experimental designs, we are most interested in expanding the PXRD reaction monitoring technique to address the structural evolution of amorphous phases through pair distribution function (PDF)[76] analysis, already used by Cao et al. to elucidate the structure of amorphous material made by neat milling of ZIF-8.[77] We also foresee considerable benefits arising from fluorescence emission spectroscopy, a scattering technique that is operationally similar to Raman spectroscopy but can provide considerably more insight into the behavior and structure of amorphous phases, as demonstrated by ex situ studies[78] of mechanoluminescent systems. In that context, it is worth mentioning the recent


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successful application of fluorescence emission spectroscopy for in situ investigation of solid-state crystallization of amorphous indomethacin[79] and solid-state NMR spectroscopy monitoring of pharmaceutical cocrystallization in premilled mixtures.[80] In the context of modeling mechanochemical reactions, recently made accessible techniques for discrete element modeling[73] of mechanical motion inside of the milling assembly hold great promise for resolving technologically important problems of scaling-up and optimizing the input and distribution of energy in mechanochemical processes.[81,82] It is our firm belief that understanding mechanochemical reactions at a molecular scale is impossible without sophisticated techniques for modeling the structure and dynamics of solids. Significant strides in that respect have recently been made, and DFT approaches were already successfully employed to rationalize the behavior of mechanochemical reversible covalent reactions.[83,84]

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### Notes

The authors declare no competing financial interest.

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