

# Unintended Rate Enhancement in Mechanochemical Kinetics by Using Poly(methyl methacrylate) Jars

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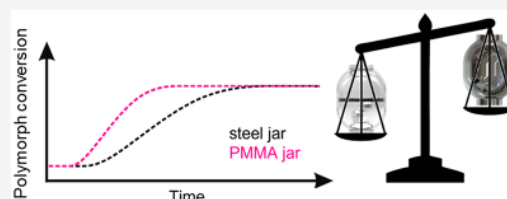


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Supporting Information

**ABSTRACT:** Time-resolved *in situ* (TRIS) X-ray diffraction has changed how mechanochemical transformations are studied but requires the use of X-ray transparent jars often made from poly(methyl methacrylate) (PMMA). However, using PMMA jars can alter the apparent kinetics of mechanochemical polymorphism by an order of magnitude, questioning the interpretability of established TRIS methods. Our results suggest that rate enhancement in PMMA jars may not be dominated by chemical effects of the polymer, but rather a result of different equilibrium temperatures within the jar. These features must be better understood before control over mechanochemical reactions can be achieved.

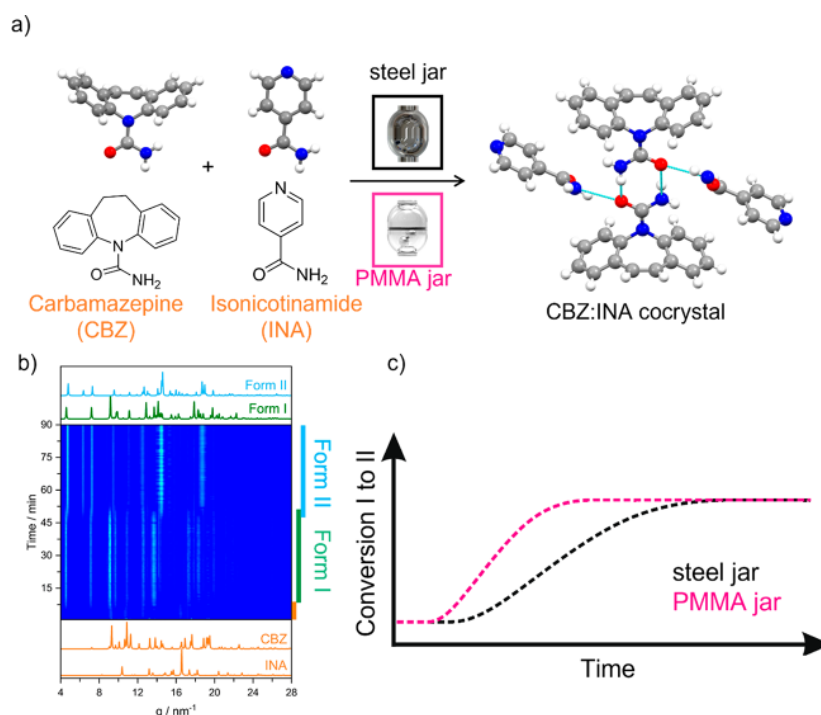


Time-resolved *in situ* (TRIS) monitoring of mechanochemical transformations has changed the way mechanochemistry is being studied.<sup>1</sup> Numerous TRIS methods have been developed based on laboratory instrumentation, such as Raman spectroscopy,<sup>2</sup> solid-state NMR spectroscopy,<sup>3</sup> and thermometry.<sup>4</sup> These laboratory TRIS methods have proved useful to study the evolution and kinetics of mechanochemical reactions, providing information on the reaction conditions and insights into material and molecular structure.<sup>5</sup> However, the most striking details about mechanochemical transformation have come from synchrotron-based TRIS methods, namely, powder X-ray diffraction (PXRD).<sup>6,7</sup> By using TRIS PXRD, it has been possible to follow the evolution of bulk phase composition, including polymorphic transformation (*i.e.*, changes in molecular packing within the crystal structure<sup>8</sup>) and of crystal microstructure during ball milling.<sup>7,9</sup> Studies of physical transformations under ball milling have been explored in significant detail in the inorganic materials literature (albeit *ex situ*) for many years.<sup>10,11</sup> In contrast, similar studies dedicated to organic materials are relatively recent.

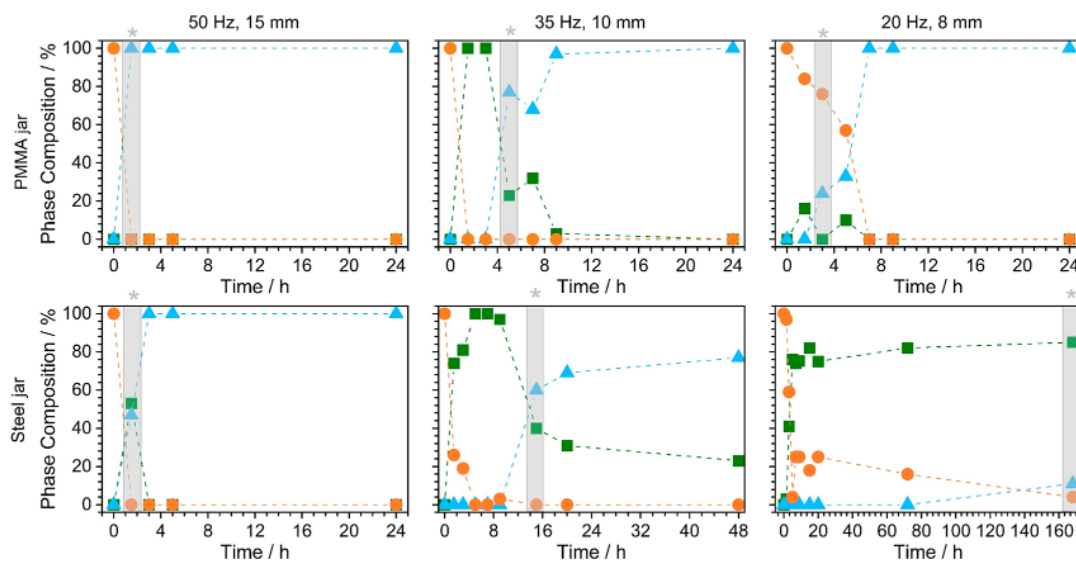
All TRIS techniques have a single common requirement: the probing radiation must be able to penetrate the grinding vessel. When performing TRIS PXRD, it is therefore necessary to use a milling jar that is transparent to X-rays. Typically, this is achieved by manufacturing milling jars from polymer materials, with poly(methyl methacrylate) (PMMA) being the most common.<sup>12</sup> PMMA absorbs only weakly at photon energies above *ca.* 15 keV and has no sharp Bragg reflections, unlike other polymers such as PEEK or polyimide.<sup>13</sup> PMMA jars therefore contribute only a broad, amorphous scattering feature to the data, which is easy to handle in data processing.<sup>8</sup> Such polymer jars will likely play an increasingly important role in the mechanochemical community as they can be manufactured with conventional 3D printers, making them accessible to a wide user base.<sup>9</sup>

It is becoming clear that the selection of jar material can be crucial for the successful control over a mechanochemical transformation. For example, softer polymer milling jars provide insufficient energy for processing hard, inorganic materials, which instead requires the use of steel jars for a successful reaction.<sup>14</sup> Similarly, the stability of polymorphic forms after ball milling depends on the material of the jar.<sup>15</sup> Qualitative evidence indicates that the rate of polymorphic transformation driven by ball milling can vary slightly (by a few minutes) with the use of polymer or steel jars.<sup>16</sup> Recent trends in polymer-assisted grinding (POLAG),<sup>17,18</sup> where the addition of “inert” polymer powder to the reactant mixture influences the reaction, may provide an origin for the different effects of polymer and steel jars. However, this chemical origin has not yet been investigated. The variation in mechanochemical reaction by changing jar materials is particularly problematic when attempting to compare the results of exploratory *ex situ* analysis with TRIS analysis, for example, studies at a synchrotron facility. In this regard, there is an urgent need for quantitative analysis to identify how jar material can influence mechanochemical kinetics. Only in this way can we validate comparisons between increasingly popular TRIS data with laboratory analyses. Moreover, identifying the effect of milling jar material on mechanochemical reaction rates is crucial for comparing results obtained between laboratories, and for developing robust synthesis strategies to translate to industrial applications.

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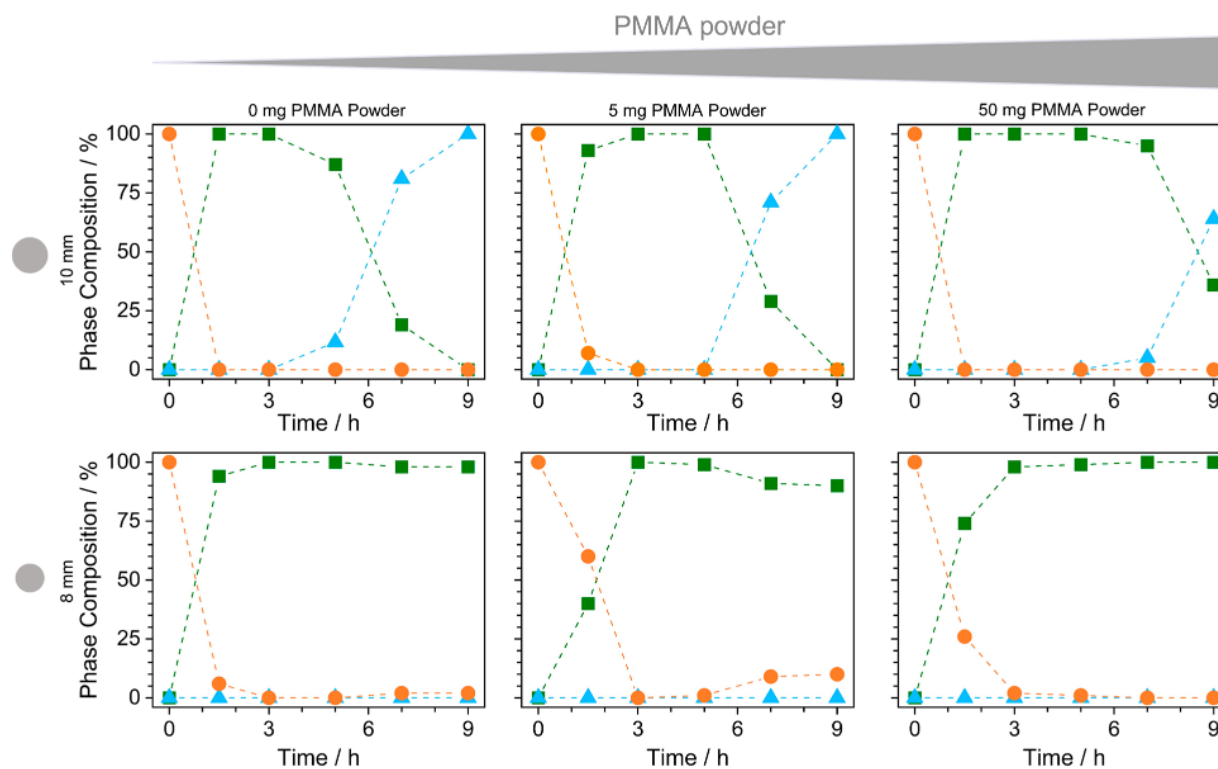
**Figure 1.** Formation of stoichiometric cocrystal of isonicotinamide (INA) and carbamazepine (CBZ) by ball milling. (a) Reaction scheme for the cocrystal formation. (b) TRIS PXRD monitoring of cocrystal formation (50 Hz, 15 mm stainless steel ball), showing the initial formation of **Form I** followed by its conversion to **Form II** on extended milling. (c) Schematic for the conversion rate using different milling jars.



**Figure 2.** Phase composition of the ball milling experiments of INA:CBZ in a PMMA jar (top) and a steel jar (bottom) with different energy impacts (left, 50 Hz and 15 mm ball; middle, 35 Hz and 10 mm ball; right, 20 Hz and 8 mm ball). Data were collected using *ex situ* PXRD analysis. Data are shown as sum of starting materials INA and CBZ (orange circle), **Form I** (green square), and **Form II** (blue triangle). The first observation of **Form II** is marked with a gray star. Additional ball milling conditions are given in the [Supporting Information](#).

With the aim of quantifying the effects of the jar material on the kinetics of mechanochemical polymorphism, we investigate the 1:1 polymorphic cocrystal of isonicotinamide (INA) and carbamazepine (CBZ). We have recently reported that ball milling a stoichiometric mixture of INA and CBZ leads to the formation of a 1:1 cocrystal in two polymorphic forms, [Figure 1a](#).<sup>19</sup> Consistent with our early *ex situ* reports,<sup>19</sup> TRIS PXRD measurements in PMMA jars showed that the cocrystal appears first in **Form I** but transforms to **Form II** when milled for extended periods of time, [Figure 1b](#). Using the

polymorphic transformation of this cocrystal as a model system we provide the first evidence for an order-of-magnitude difference in the kinetics of the transformation when performed in steel and PMMA milling jars, [Figure 1c](#). Such significant differences in mechanochemical kinetics are unprecedented. Kinetic differences of this magnitude raise questions about the interpretability of TRIS PXRD kinetic data and may even be the root of interlaboratory discrepancies stating whether a reaction is even mechanochemically viable.



**Figure 3.** Phase composition of the ball milling experiments of the cocrystal INA:CBZ in a steel jar with addition of different amounts of PMMA powder (left, 0 mg; middle, 5 mg; right, 50 mg) at a frequency of 50 Hz and two different ball sizes (top, 10 mm; bottom, 8 mm). Data were collected using *ex situ* PXRD analysis. Data are shown as the sum of the starting materials INA and CBZ (orange circle), **Form I** (green square), and **Form II** (blue triangle).

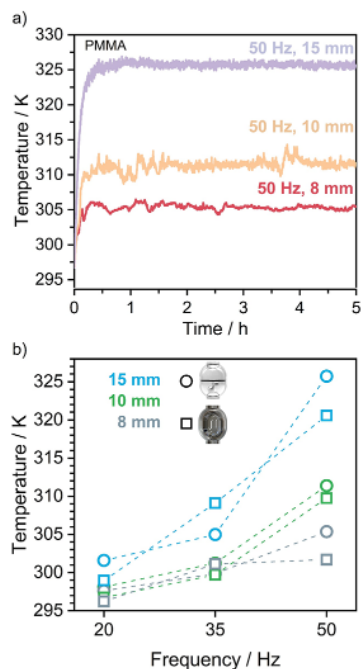
Our initial experiments were done by ball milling a stoichiometric mixture of INA and CBZ with a 10 mm stainless steel ball at 50 Hz in a stainless steel jar.<sup>19</sup> Under these milling conditions, the starting materials reacted within 1.5 h to form a pure phase of the stoichiometric cocrystal as **Form I**. The powder of **Form I** remained stable for up to 3 h of continuous milling before its conversion to **Form II** was detected. By decreasing either the milling frequency or the ball size, the lifetime of **Form I** increased from 3 h (50 Hz, 10 mm ball) to 7 days (20 Hz, 8 mm ball).<sup>19</sup> Hence, there appears to be a strong correlation between the input of mechanical energy and the rate of conversion from **Form I** to **Form II**. We believe the lengthy induction period for the polymorphic transformation to be related to the rate of activation of **Form I** under different ball milling conditions.<sup>19</sup>

In preparation for TRIS PXRD studies, we began to prepare the reactions in typical PMMA jars with the same geometry as the steel jars. Remarkably, we observed by *ex situ* PXRD a significant acceleration of the **Form I** to **Form II** transition, as compared with the reaction in stainless steel jars, **Figure 2**. At our highest impact energy conditions in PMMA jars (50 Hz, 15 mm ball), the transition of **Form I** to **Form II** was observed within 1.5 h of milling (**Figure 2**, blue triangle). This is *ca.* 1.5 h faster than the same transformation in stainless steel jars. Similarly, for lower energy ball milling in the PMMA jars (35 Hz, 10 mm ball), the polymorphic transformation occurred after only 5 h of milling (**Figure 2**, blue triangle), *i.e.*, 11 h faster than in stainless steel jars. The difference in the kinetics of polymorph transformation with different milling jar materials is remarkable, achieving up to a 110 times faster transformation. This effect demonstrates the more significant

influence of the milling jar material on reaction kinetics than previously thought.

There are a variety of material parameters that could be responsible for the strong influence of jar material on the kinetics of the polymorphic transformation. PMMA is known to charge under external stimuli,<sup>20</sup> and one could therefore assume the rate of polymorphic transformation may be affected by local electric fields. Alternatively, it is possible that the hydrophobic surfaces of PMMA favor **Form II**, as compared to stainless steel. By adding PMMA powder into the steel jar we aimed to probe for the chemical origins of PMMA on the observed kinetics, **Figure 3**. Surprisingly, rather than enhancing the kinetics, the addition of PMMA powder decreased the rate of polymorphic interconversion. In fact, the polymorphic transformation became increasingly slower as the amount of PMMA powder in the jar was increased. This effect was observed for both a 10 mm and an 8 mm diameter milling ball, suggesting that the rate reducing effect of the polymer is a general feature of mechanochemical reaction design in this system. We note that this is contrary to recent reports in polymer assisted grinding (POLAG), where the addition of polymer powder led to significant rate enhancement.<sup>21</sup> In our case, the rate-reducing effect is presumably because PMMA powder acts to “cushion” the impact energy. We can therefore suggest that a reduced coefficient of restitution of PMMA (and thus lower impact energy) is not responsible for the observed effect. Similarly, adding a small piece of the PMMA jar to the reaction mixture in a stainless-steel jar also slowed the rate of polymorphic interconversion (see **Supporting Information S2.4**). It does not appear that PMMA exerts its effects on the transformation kinetics through chemical effects.

We instead sought an explanation for the reaction rates by noting that PMMA is thermally insulating, while steel is highly conductive. It is worth noting that the temperature profiles always plateau during milling within approximately 30 min (Figure 4a), meaning heating rates themselves are not



**Figure 4.** Effects of milling parameters on the equilibrium temperature of the milling jar. (a) Temperature evolution of a PMMA milling jar as a function of time at different grinding parameters (50 Hz; purple, 15 mm; orange, 10 mm; red, 8 mm). (b) Comparison of the highest average temperature with different ball sizes (blue, 15 mm; green, 10 mm; gray, 8 mm) as a function of frequency and different jar material (PMMA (shown as a white jar in the picture), circle; steel (shown as a gray jar in the picture), square).

responsible for the different transformation kinetics. Instead, as expected, the maximum temperatures measured at the inner and outer walls of the milling jars were consistently higher in the PMMA jars, albeit by only a few degrees, Figure 4 (temperature measurements for all milling parameters are in Figure S3.1). For example, at the highest energy impact (50 Hz, 15 mm ball) the temperatures of the PMMA and steel jars differed by  $\Delta T = 5$  K. For the lowest energy impacts (20 Hz, 8 mm ball) a non-negligible temperature difference of  $\Delta T = 3$  K was observed.

Such small differences in milling temperature were not initially expected to be able to influence the polymorphic transformation kinetics to such a degree. However, to our surprise, the polymorphic transformation was found to be highly sensitive to small changes in equilibrium temperature, Figure S3.2. When ball milling experiments (50 Hz, 10 mm ball) were done at ambient conditions in a stainless steel milling jar (Figure S3.2 left), a polymorph transformation from Form I to Form II required 5 h of milling. Instead, the same transformation occurred in <1 h (i.e., at least 5 times faster) when ball milled (in a steel jar) at  $T = 313$  K or higher. A similar thermal acceleration of the polymorph transformation was observed with a ball size of 8 mm. While it is unlikely that the significant kinetic enhancement is solely due to variations in milling temperature, our results do suggest that a thermal

origin plays a non-negligible role in changing mechanochemical reactivity, especially given the sensitivity of solid state stability to temperature.<sup>22,23</sup>

Our studies demonstrate that by changing the material of the jar, the rate of a mechanochemical transformation can be drastically altered. This must be considered, especially in preparation for *in situ* investigations, where the change from steel to another material can change the mechanochemical transformation. Our results suggest that the chemical composition of PMMA is not itself responsible for the accelerating effect nor is a simple explanation based on the restitution coefficients of the material. Instead, our findings suggest that the different thermal conductivities of the jars play a significant role (albeit certainly not the only factor) in the acceleration of the polymorph transformation. Our experiments demonstrate just how extremely different jar materials can alter mechanochemical reactions. A better understanding of the influence of this behavior on mechanochemical reactions promises further developments toward greener chemistry.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.cgd.2c01227>.

Experimental details; Rietveld refinements for ex situ kinetic studies; time-resolved *in situ* thermometric investigations; kinetic studies of ball milling experiments. (PDF)

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### Notes

The authors declare no competing financial interest.

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