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The origin of delayed polymorphism in molecular crystals under mechanochemical conditions

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Abstract

We show that mechanochemically driven polymorphic transformations can require extremely long induction periods, which can be tuned from hours to days by changing ball milling energy. The robust design and interpretation of ball milling experiments must account for this unexpected kinetics that arises from energetic phenomena unique to the solid state. Detailed thermal analysis, combined with DFT simulations, indicates that these marked induction periods are associated with processes of mechanical activation. Correspondingly, we show that the pre-activation of reagents can also lead to marked changes in the length of induction periods. Our findings demonstrate a new dimension for exerting control over polymorphic transformations in organic crystals. We expect mechanical activation to have a much broader implication across organic solid-state mechanochemistry.

The mechanochemical processing of molecules and molecular materials has risen to the forefront of chemical research, promising a revolution in sustainable chemistry and industry. Reactions between solids seem to defy many traditional rules of chemistry. In many cases, this makes it difficult to both rationalise and predict the outcome of any given mechanochemical reaction. Designing robust mechanochemical processes therefore remains a significant challenge, with urgent need to better understand what parameters influence these solvent-free reactions.¹⁻³

With the development of techniques for time-resolved in situ (TRIS) monitoring of mechanochemical reactions,^{4,5} there is mounting evidence that typical mechanochemical reactions proceed in three ‘kinetic stages’: (*i*) an induction period, (*ii*) the reaction phase, and (*iii*) the final steady-state reaction plateau.^{1,4} To control a mechanochemical reaction we need therefore to understand the origins of each stage. The elementary mechanisms of stage (*ii*) are chemical and will depend on the chemistry in question. In contrast, both stages (*i*) and (*iii*) are physical in nature and arise from the unique physico-chemical behaviour of the solid state. In stage (*i*), the periodic dynamic mechanical stresses imposed by ball milling drive the solid away from its thermodynamic equilibrium state (*i.e.* the state obtained from slow crystallisation) and into a metastable (activated) state.⁶⁻⁸ For inorganic compounds, activation in stage (*i*) is known to occur by increasing surface area or through the formation of defects in the solid.^{9,10} Similarly the composition – both chemically and crystallographically – achieved at stage (*iii*) results from an interplay between the continued mechanical stressing and the reverse thermal relaxation processes. Any changes to the mechanochemical conditions (*e.g.* change in mechanical energy, bulk temperature, presence of additives) can change this balance and influence the product that is ultimately obtained from the reaction.¹¹ Importantly, these kinetic stages are not isolated, and the physical processes associated with stages (*i*) and (*iii*) are interdependent with the chemical processes in stage (*ii*). For example energy barriers for chemical reactions can be significantly suppressed

by mechanical activation in stage (i)⁹ or the activation can open entirely new reaction paths.

The physical phenomena accounting for stages (i) and (iii) have been widely studied for inorganic materials, and many factors are known to influence their behaviour. Correspondingly, a significant degree of control over inorganic mechanochemical reactions has been possible. However, very little is known about whether these rules are transferable to organic solids, and if so, how they can be used to control the outcome of organic mechanochemical transformations. As mechanical treatment can have markedly different effects on inorganic as compared to organic materials,¹² there is a pressing need to investigate the origins of the kinetic behaviour of mechanochemical transformations related specifically to organic solids.

The energies associated with both mechanical activation and different mechanochemical steady states are usually quite small. To probe these phenomena in organic crystals, solid-state transformations with small energetic barriers are needed. Crystal polymorphism (i.e. the ability of a molecule to crystallize in different packing arrangements) has proven to be an excellent probe for such investigations.^{13–16} Polymorphic crystalline forms typically differ only slightly in energy (*ca.* $< 5 \text{ kJ.mol}^{-1}$),¹⁷ and their interconversions occur with only small changes in environmental conditions.^{18,19} Therefore, even small changes in temperature, pressure, or the energy of impact during grinding can cause a polymorph transformation. Controlled synthesis of polymorphs remains a challenge today.

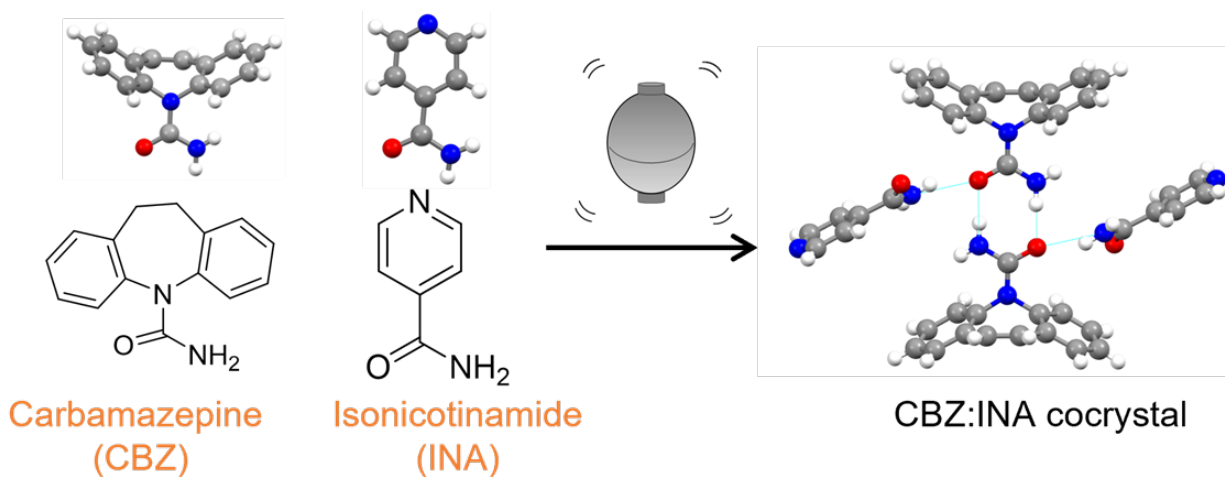


Figure 1: Formation of carbamazepine (CBZ) and isonicotinamide (INA) cocrystal.

In light of efforts to control the mechanical activation and polymorphism of inorganic solids^{20,21} our research aims to establish whether similar physical phenomena can be observed in organic solids. We use as a model system the 1:1 cocrystal of carbamazepine (CBZ) and isonicotinamide (INA), Figure 1. Importantly, INA and CBZ do not react to form the cocrystal upon aging (see ESI S3.6), suggesting any cocrystal formation is driven by the ball mill. Moreover, this system is ideal for investigating how the impact energy affects the mechanochemical steady state, as its two polymorphic modifications are known to be accessible at room temperature and close in energy: a monoclinic form²² (**Form II**) and a triclinic form²³ (**Form I**). While both polymorphs can be obtained from solution, only **Form II** has so far been produced by ball milling.²² Early reports indicate that mechanochemically synthesised **Form II** converts to **Form I** upon aging,²³ suggesting that the latter is thermodynamically stable under ambient conditions. However, in our studies, **Form II** prepared by ball milling remained stable during storage for over one year (see ESI S3), casting doubt on its relative phase stability.

Consistent with literature,²² our Differential Scanning Calorimetry (DSC) measurements showed that **Form I** melts at a lower temperature than **Form II**, with neither phase showing signs of thermally induced polymorphic transition (see ESI S7). This indicates that **Form II** is more stable than **Form I**, though slow cooling of the melt of either polymorph led to crystallization of **Form I**. Similarly, slurry experiments conducted in a range of solvents led to the formation of **Form I** (see ESI S3). Together, these results indicate that **Form I** is thermodynamically stable under ambient conditions, with the system appearing to show enantiotropic thermal behaviour, wherein polymorph stability is inverted with temperature.

We further investigated polymorph stability using Density Functional Theory (DFT) simulations, ESI S3.3. At the 0 K limit (with zero-point energy corrections), our PBE-TS simulations agree with literature that **Form I** is the most stable bulk form (by 1.92 kJ.mol⁻¹). However, **Form II** becomes thermodynamically favoured (by 4.59 kJ.mol⁻¹) when simulations were done using the 373 K experimental unit cell geometry to account for

thermal expansion. This indicates that **Form I** should convert to **Form II** upon heating. However, no such transition was observed by DSC, even after annealing **Form I** for 12 h at 423 K, ESI S7.21. We suggest that the apparent monotropic behaviour observed by DSC results from a marked kinetic barrier to transition,²⁴ hindering the experimental realization of the phase transformation.

We have previously shown that similar kinetic barriers can be overcome by neat (solvent-free) ball milling,²⁴ and again explored this approach here. From the classical equation for kinetic energy ($E_{kin} = 1/2mv^2$), we can vary the milling energy by changing the mass of the milling ball (m), or its velocity (v) via the milling frequency. The associated kinetic energies for each milling ball and frequency are given in ESI S1 under the highly simplified assumption that the milling balls adopt purely linear trajectories. Although this trajectory is not strictly adhered to in jars with hemispherical ends, it serves as a semi-quantitative guide to compare milling experiments. We note that altering the velocity has the secondary effect of changing the interval between the impacts, and hence the time for relaxation of the mechanical stress.^{2,25} This secondary effect cannot be entirely ruled out in the present work, but requires model studies to isolate energy and frequency *e.g.* by using a drop hammer device.^{26,27}

Our ball milling experiments were done at three milling frequencies (50 Hz, 35 Hz, and 20 Hz) using one stainless steel milling ball with varying size (15 mm, 10 mm, and 8 mm; mass 13.66 ± 0.02 g, 4.04 ± 0.02 g, and 2.07 ± 0.01 g, respectively). The combinations of frequency and ball mass provide nominal impact energies ranging from $6.84 \text{ mJ} \cdot \text{impact}^{-1}$ to $0.17 \text{ mJ} \cdot \text{impact}^{-1}$, ESI S1. Under each of the applied conditions, ball milling an equimolar mixture of INA and CBZ (Figure 1, orange circles) led first to the formation of cocrystal **Form I** (Figure 2, green squares). Within relatively short milling times, a powder of pure **Form I** was typically obtained. Depending on the milling conditions, this product remained the apparent mechanochemical product for over 24 h of continuous ball milling. This strongly suggested that the reaction had reached its final steady state.²⁸

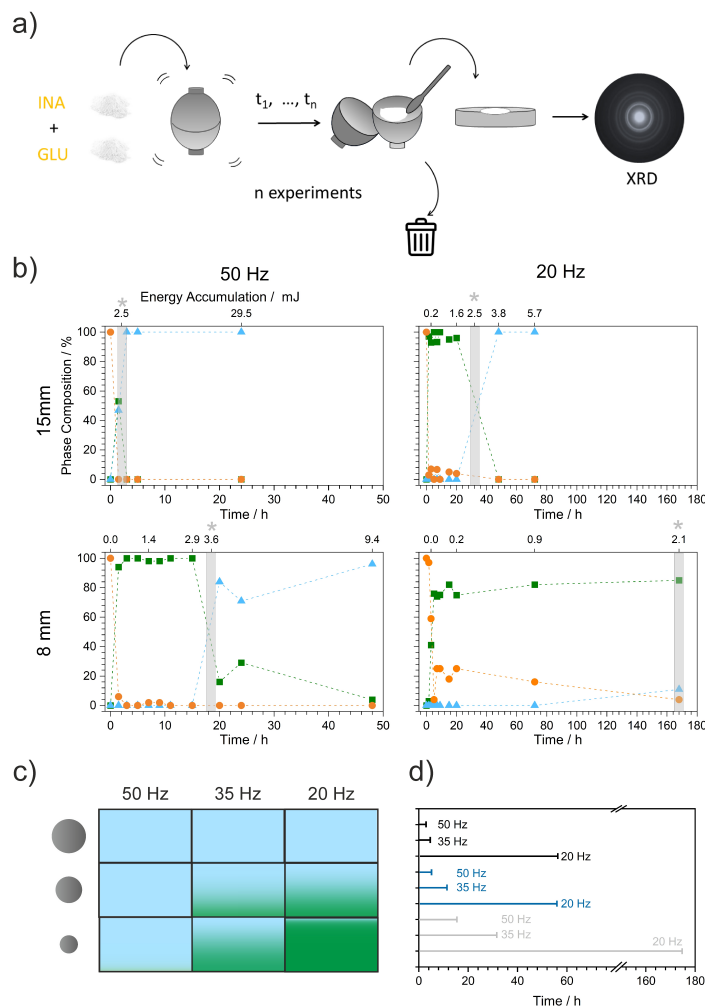


Figure 2: Reaction profile for mechanochemical cocrystallisation and polymorphism of INA + CBZ. a) Schematic of the experimental procedure used in this study, with each experiment performed using a freshly prepared mixture of the starting materials. This avoids potential changes to composition during sampling, or disturbing the powder between measurements.²⁹ b) Phase composition obtained after milling a fresh mixture of INA + CBZ for the indicated time at 50 Hz (left) and 20 Hz (right) with different ball diameters, 15 mm (top) and 8 mm (bottom). Data show the total reactant composition (sum of INA and CBZ) (orange circles), Form I (green squares) and Form II (blue triangles). Approximate accumulated impact energy is shown above the graphs. The first observation of Form II is indicated with a grey star above the graph. c) Phase composition of Form I (green) and Form II (blue) obtained at the final apparent mechanochemical reaction plateau (see (b)); d) The approximate time when reflections of Form II were first detected at each milling condition.

Remarkably, we found that by continuing to ball mill, this apparent steady state product began to convert into **Form II** (Figure 2b, blue triangles). To the best of our knowledge this is to date the longest induction period found for an organic mechanochemical transformation

and poses an important question as to when (and if) one can unambiguously assign a ‘steady state’ for a mechanochemical reaction. Moreover, we note that for this system, the degree of conversion, and hence the composition at the final plateau, depended on the magnitude of milling energy, Figure 2c. No chemical decomposition was observed, even when the system was milled for extended time at high energy conditions, ESI S9.

The lifetime of the apparent steady state of **Form I** correlated strongly with the approximate amount of energy that accumulated during ball milling; the **Form I** to **Form II** transformation occurred consistently after accumulating *ca.* 2-3 kJ of energy. We note that this accumulated energy is consistent with the polymorph energy difference calculated by DFT. For the highest energy ball milling experiments (50 Hz, 15 mm ball; *ca.* 6.84 mJ.impact⁻¹), the conversion of **Form I** to **Form II** occurred within *ca.* 1.5 h. As the nominal impact energy decreased, the lifetime of **Form I** increased from < 5 h (50 Hz, 10 mm; *ca.* 2.03 mJ.impact⁻¹) to nearly seven days (20 Hz, 8 mm; *ca.* 0.17 mJ.impact⁻¹). These results suggest that the onset time of polymorphic transformation is dictated by the total accumulated impact energy. This total accumulated impact energy can be reached either through short grinding at high energy inputs, or over long milling times with low energy inputs. In the case of low energy milling (20 Hz, 8 mm; *ca.* 0.17 mJ.impact⁻¹), a complete consumption of the starting reagents was never observed, despite the powder remaining free flowing without obvious signs of caking or tableting within the jar. While we cannot rule out rheological origins, it does appear that the phase composition of the steady state differs, depending on the ball milling conditions, as has been reported previously for inorganic mechanochemical reactions.³⁰

The milling induced polymorphic transformation from **Form I** to **Form II** poses a fundamental question regarding the mechanism that underpins mechanically driven solid state transformations in organic solids. What physical processes drive the system to overcome the energy barrier associated with the transformation and give rise to such significant induction periods? The internal energy of a mechanochemical system can be increased in at least two

ways: (1) by increasing the average temperature of the system, or (2) by introducing defects via particle size reduction (increase surface energy) or by causing structural defects within the crystals themselves, Figure 3a. Both processes lead to an overall increase of the system energy, thereby decreasing the effective activation energy for the polymorph conversion.

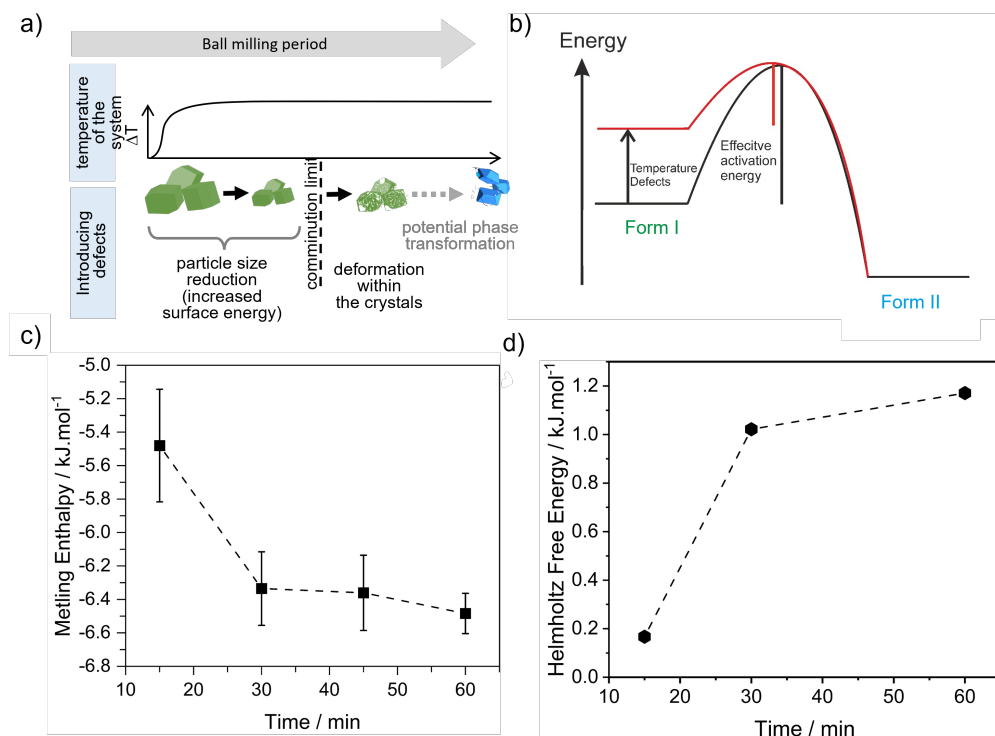


Figure 3: Solid state transformations under mechanochemical conditions. (a) During ball milling, the global temperature of the system initially increases before reaching a plateau. Simultaneously, milling causes the formation of defects in the crystals. Defects initially form through crystal comminution with an increase in crystal surface energy. At some comminution limit, further breakage is not possible, and excess energy is stored in the crystal as a structural defect. (b) schematic representation of energy diagram for polymorphic transformation by activation. (c) Effect of ball milling at 50 Hz with 15 mm ball on the melting enthalpy. (d) Effect of ball milling at 50 Hz with 15 mm ball on free energy (see ESI S7 for details)

To see if heating was responsible for the slow onset of the observed mechanochemical polymorphic transition, the global temperature of the milling jar was measured for a representative set of milling conditions, ESI S6. In all cases, the temperature first increased with milling time, but quickly plateaued. Importantly, the average temperature never exceeded 325 K for our highest intensity milling experiments, see Figure S6.1. This upper bound tem-

perature is well below the temperature needed to cause thermally induced transformations (*e.g.* polymorphism or melting; *ca.* 433 K) in either phase, as indicated by DSC (see ESI S7.19 and S7.20). In all cases, this plateau was achieved within 3 h of milling, well before the observed onset of the phase transition. It therefore seems unlikely that temperature is itself the cause of the delayed polymorphic transformation.

We instead sought an explanation for the delayed polymorphic transformation through phenomena of material activation, Figure 3b. The first stage of material activation is achieved by reducing the crystallite size and hence increasing the influence of excess surface energy on the structural stability, Figure 3a.^{18,31} Consistent with previous reports on mechanochemical polymorphism,¹⁸ both **Form I** and **Form II** were found to have characteristic crystallite sizes (Scherrer size), thus indicating that comminution may be an origin for the onset of polymorphism. However, while the crystallite size of **Form I** clearly decreased (from > 100 nm to *ca.* 60 nm) in the early stages of ball milling, it did not typically continue to decrease up to the phase transition (see ESI S5), though particle agglomeration was observed. Instead, the **Form I** crystallite size was generally found to remain constant over many hours of continuous ball milling before polymorphic transformation to **Form II** was observed (crystallite size < 60 nm). Moreover, Scanning Electron Microscopy (SEM) images suggested that no significant morphological changes in **Form I** particles occurred with prolonged ball milling (ESI S8), although particle agglomeration certainly occurs with continued milling. Though we cannot discount it entirely, activation purely via excess surface energy seems unlikely to account for the extensive induction period observed for the polymorphism of the CBZ:INA cocrystal system, notably as neither morphology nor crystallite size change with prolonged milling.

Once a minimum crystallite size – or comminution limit – has been achieved (which depends on milling energy), excess mechanical energy can instead accumulate as structural defects within the crystal structure itself, Figure 3a.²⁰ These defects can be measured *e.g.* by a shift of the melting temperature³² or increase in lattice melting / sublimation enthalpy.

Although the melting temperature of **Form I** did not change to a measurable degree with ball milling (beyond the shifts expected for nanocrystallites), ESI S7, the modulus of the melting enthalpy ($|\Delta H|$) increased systematically with milling time (ESI S7), as shown for ball milled **Form I** (milled at 50 Hz, 15 mm), Figure 3c and ESI S7. Through temperature modulated DSC we were also able to assess how ball milling affects the vibrational entropy of **Form I** via the specific heat capacity of the material, ESI S7. It was therefore possible to approximate the Helmholtz free energies of mechanical activation for ball milled **Form I**, Figure 3d. It was encouraging to find that ball milling for even short periods of time (*ca.* 60 min) led to a measurable increase in the Helmholtz free energy of **Form I**, on the order of energies (here *ca.* 0.5 kJ.mol⁻¹) which separates polymorphic forms. We can therefore suggest that the prolonged induction period observed in the polymorphic transformation of **Form I** to **Form II** was – at least in part – due to the rate and degree of mechanical activation (defect formation).

By increasing the internal energy of **Form I** – likely by both surface activation and accumulation of defects – the effective energy barrier to transition to **Form II** decreases, Figure 3cd. Within this model, the rate and degree of activation can be accelerated by increasing the energy of ball milling, consistent with our experimental findings, Figure 2. Though we have only explored material activation in a single system, we do expect that this phenomenon will be a more general feature that underpins the induction periods that are consistently observed in solid state mechanochemical transformations.⁴

Within the framework that a mechanochemical induction period originates from the need to activate the powder reagents, we might also expect that this kinetic stage could be hastened by 'pre' activating the reagents. To this end, we performed a final set of experiments wherein the individual cofomers (INA and CBZ) were first milled individually (following protocol in Figure 2 c,d; 50 Hz, 10 mm ball, 1 h), and subsequently mixed for the mechanochemical cocrystallisation. Remarkably, not only did this pre-activation step lead to faster formation of the initial Form I cocrystal, but it also caused a significant reduction in

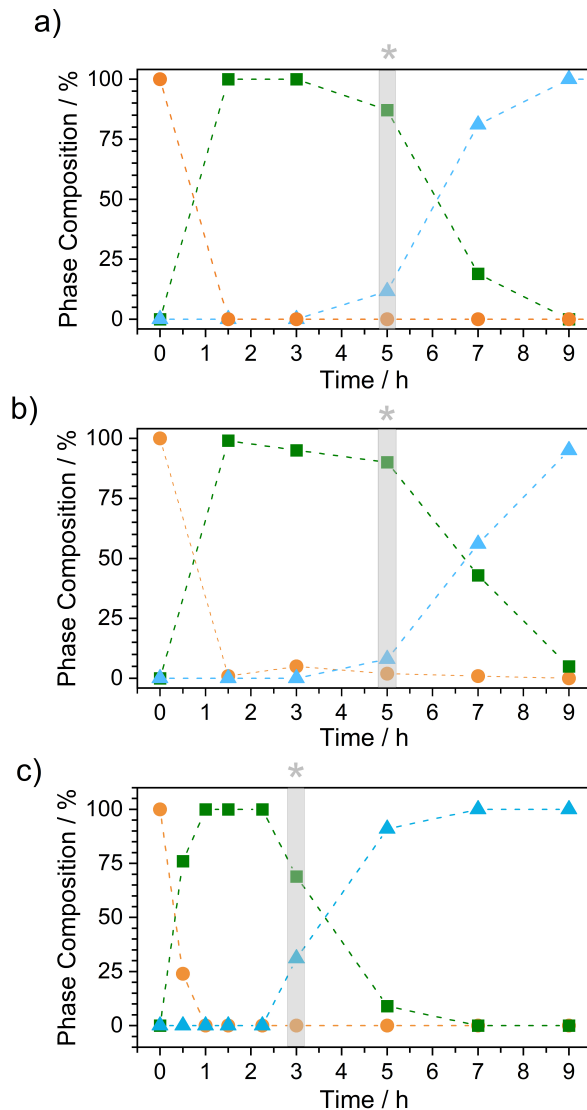


Figure 4: Effect of mechanical pre-treatment on the kinetics of polymorphic transformation under ball milling conditions. (a) No pre-treatment, reproduced from Fig. 3. (b) Effect of pre-mixing powders. (c) Effect of pre-activating powders by milling components individually at 50 Hz with one 10 mm ball for 1 hour. Data show the total reactant composition (sum of INA and CBZ) (orange circles), Form I (green squares) and Form II (blue triangles).

the length of the induction period needed to convert Form I to Form II. Specifically, whereas the induction period without pre-activation was *ca* 5 h, it dropped to *ca* 3 h with pre-activation, Figure 4c. In fact, some repeat experiments even indicated the formation of Form II within only 90 min milling of the pre-activated material (see ESI S4), a result that was never observed when milling non-activated reagents. We propose that pre-activation greatly reduces the difference in the relative energetic barriers needed to form Forms I and II, for example by increasing the mobility of molecules and easing their rearrangement. Importantly, these marked kinetic effects does not result from the improved mixing associated with smaller particles in the pre-activated reaction, Figure 4b and ESI S10. Though it is not entirely clear how pre-activation changes the induction period of the subsequent cocrystal polymorphic transformation, pre-activation certainly has a profound effect on mechanochemical kinetics, and its detailed study will be the subject of follow up investigation.

In summary, we report (overview in ESI S11) the mechanically driven polymorphic transformation of a 1:1 cocrystal of carbamazepine and isonicotinamide. To the best of our knowledge, this transformation has the longest (by orders of magnitude) induction period for any organic mechanochemical transformation, which appears to result from a need to mechanically activate the material prior to transformation. The rate and degree of activation – and hence the rate of polymorphic transformation – can be tuned from hours to days, simply by changing the energy of ball milling, but always appears to require the same total accumulated energy. Moreover, the induction period can be significantly reduced by pre-activating the individual reagents. This provides an important, and often overlooked, control parameter for designing mechanochemical processes in organic systems. Though we have identified this phenomenon in a single system, nearly all organic mechanochemical reaction profiles exhibit clear induction periods. We therefore expect material activation to be an important and general feature that underpins the kinetics of mechanochemical transformations. With further studies into these phenomena in organic materials, we envision control over material activation to become an important strategy for the selective design of mechanochemical

technologies.

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