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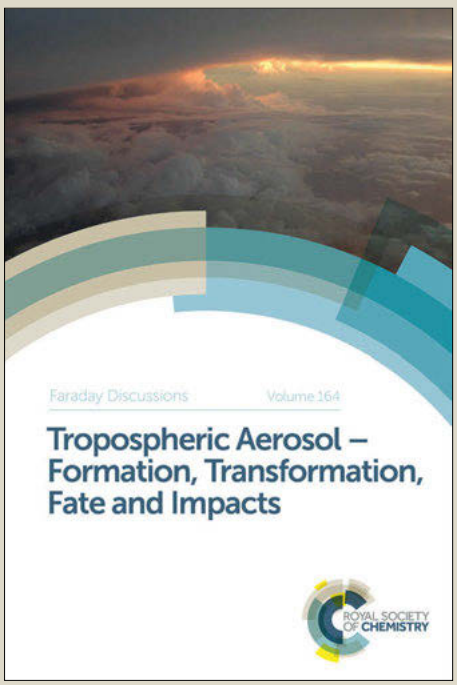

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Advances in Elucidating Mechanochemical Complexities *via* Implementation of a Simple Organic System

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Mechanochemistry is becoming increasingly popular amongst both the academic and industrial communities as an alternative method for inducing physical and chemical reactions. Despite its rapidly expanding application, little is understood of its mechanisms, greatly limiting its capacity. In the present work the application of specialty devices allowed submission of the simple organic system, α-glycine + β-malonic acid, to isolated shearing and impact treatment. In doing so, unique products were observed to result from each of these major mechanical actions; shear inducing formation of the known salt, glycinium semimalonate (GSM), and impact yielding formation of a novel phase. Correlation of these isolated treatments with a more common ball mill indicated two unique regions within the milling jar, each characterised by varying ratios of shear and impact, leading to different products being observed. It is widely accepted that, particularly when considering organic systems, mechanical treatment often acts by inducing increases in local temperature, leading to volatilisation or melting. A combination of DSC and TGA were used to investigate the role of temperature on the system in question. Invariably, heating induced formation of GSM, with evidence supporting a eutectic melt, rather than a gas-phase reaction. Shear heating alone is unable to describe formation of the novel phase obtained through impact treatment. By considering the formation and character of mechanically produced tablets, a model is described that may account for formation of this novel phase. This system and methodology for mechanochemical study offers intriguing opportunities for continued study of this widely used and exciting field.

1 Introduction

Mechanochemistry is often believed to simply be an alternative method to induce thermal reactions, in addition to its milling capabilities. The first evidence in opposition to this simplicity can be found in the works by Carey-Lea[1,2] demonstrating the unique decomposition products on heating and mechanically treating silver halides. Later, a detailed comparative study of the products of thermal and mechanochemical decomposition of a series of inorganic salts demonstrated that the products formed on crystal cleaving depend on the rate of fracture propagation.[3–7] Slow propagation rates resulted in decomposition products coinciding with those of thermal decomposition, while rapid fracture propagation yielding products corresponding to radiolysis.[8,9] Much effort was therefore made through the 20^{th} century in an attempt to understand the mechanisms that underlay mechanochemical reactions, especially in the event that mechanical heating offered little by means of an explanation.[10,11] While substantial progress has been made to understanding mechanochemical mechanisms,[12–14] there remain more questions than answers. With current trends of mechanochemistry suggesting immense potential for such areas as co-crystal screening[15–19], green chemistry,[13,20–23] materials processing and tuning,[24–27] amongst others, and substantial application in industry – in particular the pharmaceutical industry – it is of growing importance to obtain an understanding of the fundamentals of mechanochemistry. As a particularly pressing example, one might consider the effects of mechanical treatment on the polymorphism of pharmaceutical compounds, which may result from explicit treatment or as a consequence of technological processes.[28,29] In the latter, unexpected transformations may occur, having drastic consequences on both the tableting (*e.g.* paracetamol[30]) and biological performance[31] of the compound, *e.g.* by altering dissolution profiles.[32] Of equal importance is the growing field of "dry synthesis" of solid pharmaceuticals, their salts and co-crystals.[33–37]

Efforts in understanding mechanochemical transformations have seen the development of methods for monitoring mechanochemical reactions on co-grinding at intermediate intervals either *ex situ*[4,40–43] and *in situ*[4,44,45], with the latter now possible at very short time intervals without need to stop

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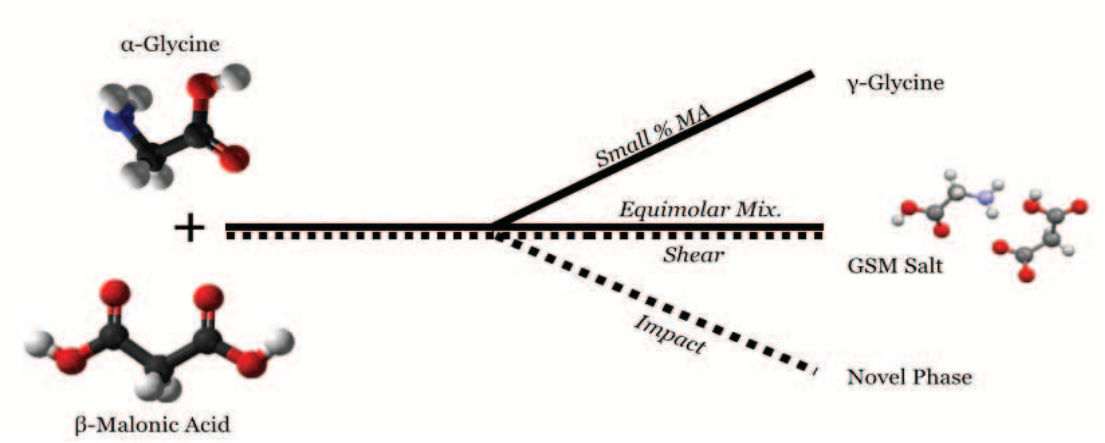

Fig. 1 Schematic outlining the complexities of α-glycine + β-malonic acid mechanochemical reactivity. This encompasses studies by Losev *et al.*[38,39] (solid line) and Michalchuk *et al.*[40] (dashed line).

mechanical treatment[33,46]. Here an accumulative approach to mechanistic mechanochemistry is presented in which the complex problem is initially segregated into somewhat scientifically well-developed components, ultimately combining to yield a more complete understanding of the process. In this approach, a mechanochemical reaction can be thought of as being composed of two parts, (1) an interaction between the mechanoreactor and the system and (2) an interaction between the system components.

The present work aims to address the mechanochemistry of a model system, α-glycine + β-malonic acid, by means of this approach, expanding on previous works that have attempted to separate the major types of mechanical action, impact[41] and shear[42]. In section III.I we present a summary of an earlier paper[40] in which an initial understanding of the workings of a common ball mill were presented. Section III.II then extends to the second component of this methodology, discussing work to elucidate the intra-system interactions. Finally, section III.III presents a model to extend section III.II to otherwise unexplainable trends.

The selected system was originally identified by Losev *et al.* as a system with immense mechanochemical complexity.[38,39] The mechanochemical product of α-glycine + β-malonic acid was found to be tunable under treatment in an SPEX-8000 mill by means of controlling the initial mixture composition. Small quantities of β-malonic acid led to an $\alpha \rightarrow \gamma$-glycine polymorphic transitinon, while mechanical treatment of near-equimolar compositions of the system induced formation of a known salt, glycinium semi-malonate (GSM)[47]. This complexity was further ameliorated when studies[40] demonstrated product selectivity through controlling the type of mechanochemical treatment applied, Figure 1. With current interest in both amino acids and small dicarboxylic acids, this relatively simple, yet mechanochemically complex system offered an intriguing opportunity to study mechanistic mechanochemistry on a system of current scientific and biological interest.

2 Experimental

2.1 Materials

All materials used were commercially available and were used without further purification. The chemicals used were α-glycine (Reactiv, Russia) and β-malonic acid (Fluka, grade $\geq$ 99.0%).

2.2 Experimental protocols

2.2.1 GSM salt growth. Pure GSM salt was obtained by slow evaporation from aqueous solution of equimolar quantities of the reagents. Purity was verified by XRPD and DSC.

2.2.2 Milling. Milling was performed using a Retsch Cryomill ball mill. 0.5 g mixture of equimolar quantities of α-glycine and β-malonic acid were prepared in milling jars (stainless steel: 7 mm internal diameter $\times$ 44.6 mm total internal length). To each jar, two milling balls (stainless steel: 0.691 g, 5.6 mm diameter) were added. Three variations of experimental protocol were then observed. In the first, samples were milled at 24 Hz for the appropriate duration of time. Alternatively, samples were milled at 24 Hz for 20 minutes, followed by a pause of 3 minutes, after which a second bout of 20 minutes milling was endured. This process of pause and mill was repeated a second time for a total milling time of 60 minutes. Finally, the third protocol entailed milling samples at

24 Hz for 20 minutes, followed by manual mixing of the sample (during which any pellet formed was carefully broken) and resubmitting the sample for 20 minutes of milling. This process of mixing and milling was again repeated a second time for a total milling time of 60 minutes. In all cases, samples were immediately characterized by XRPD.

2.2.3 Impact treatment. Impact treatment was applied using a purpose-built device.[41] Treatment was performed at 2.3 Hz with *ca.* 10 mJ per impact. All powders were sieved to control particle size, p: 100 mm $<$ p $<$ 200 mm. 0.125 g samples were prepared as 75 mol% α-glycine/25 mol% β-malonic acid and manually rotated in a glass vial to ensure sufficient mixing prior to impact treatment. Impact treatment was then performed for the desired period of time, after which the sample was immediately tested by XRPD.

2.2.4 Shear treatment. Shear treatment was applied using a purpose-built device.[42] Treatment was performed at 33 rpm under 1 kg loaded mass, or approximately 4 kPa. All powders were sieved to control particle size, p: 100 mm $<$ p $<$ 200 mm. 0.5 g samples were prepared as 75 mol% α-glycine/25 mol% β-malonic acid and manually rotated in a glass vial to ensure sufficient mixing prior to impact treatment.

2.2.5 Vibratory treatment. Vibratory treatment was performed using a NARVA Vibrator DDR-GM9458 (30 W, 50 Hz). 0.5 g samples were treated in the presence of one milling ball (stainless steel: 4.049 g, 10.0 mm diameter) for sufficient time to cause a noticeable change in consistency (powder to sticky) of the entire mixture. This change occurred between 8 and 20 minutes. The samples were then allowed to stand for 1 hour to allow solidification of the sticky sample. Phases were verified by XRPD.

2.2.6 Liquid Assisted Grinding. Liquid assisted grinding (LAG) was performed using a range of solvents. Following addition of 0.5 g sample to the milling vessel, a single drop (20 μL) liquid was added prior to milling: $\eta = 0.04$.[48] Continuous milling (machine as described above) was performed for varying lengths of time. Sample was characterised by XRPD and quantitative phase analysis performed as outlined below.

2.3 Characterisation

2.3.1 X-Ray powder diffraction.
All samples were characterised by XRPD analysis using a Bruker GADDS diffractometer: Cu Kα radiation ($\lambda = 1.5418$ Å, $5.0° \leq 2\theta \leq 46.0°$, with an operating potential of 40 keV and a current of 40 mA. All data were obtained in reflection mode with scanning time of 180 s per frame.

2.3.2 Differential Scanning Calorimetry.
DSC was carried out using a DSC-204 Netzsch machine with standard aluminium crucibles. Samples of approximately 3-4 mg powder were used with particle size, p: 100 μm $<$ p $<$ 200 μm. Heating rate was 6.0 °K/min.

2.3.3 Thermal Gravimetric Analysis.
TGA was carried out using a NETZSCH TG 209 with standard aluminium crucibles. Samples of approximately 14-16 mg powder were used with particle size, p: 100 μm $<$ p $<$ 200 μm. Heating rate was 6.0 °K/min

2.4 Programmes and Literature Crystallographic Data

For all programmes, literature crystallographic data were obtained from the CCDC database: α-Glycine (GLYCIN29), β-Malonic Acid (MALNAC06), GSM (AWIHIY). Void surface was calculated using Crystal Explorer 3.0.[49,50] Quantitiative phase analysis was performed using Powder Cell V2.3[51] and errors were estimated at 5% in accordance with previous works on this system.[39]

3 Results and Discussion

3.1 Complexities of Mechanochemical Processes

Studies of the mechanochemical reactivity of the α-glycine + β-malonic acid system were performed on individual reactant components. Under no conditions were there any observable effects on the consistency of the product mixture, nor did mechanical treatment induce any noticeable effect on the phase of individual reactant components. In contrast, mechanical treatment on mixtures of these components led to formation of a range of sticky product mixtures. Except in the case of shear treatment, in which apparent 100% reaction yields were often obtainable, all reaction mixtures contained residual reactant along with one or both obtainable products, GSM salt and an unidentifiable, novel phase. While GSM has previously been shown to be formed through various crystallisation techniques,[38–40] the novel phase was not obtainable but through mechanical treatment as outlined below.

3.1.1 Isolated Treatment - Impact.
The use of equimolar α-glycine + β-malonic acid mixtures proved impractical due to both product formation resulting from mixing of initial samples and the inability to produce product mixtures containing both products, each in isolation. Instead, 3:1 (*i.e.* 75mol% α-glycine + 25mol% β-malonic acid) mixtures were used, overcoming these issues and allowing observation of an initial induction period. A series of independent experiments indicate that impact treatment of the current system results in formation of both GSM and the novel phase, Figure 2. Interestingly, these two products appear to

occur in succession. GSM first appears following less than 10 minutes of treatment (*ca.* 13.8 J of mechanical energy) and, by 60 minutes of treatment (*82.8 J*), a product mixture containing only the novel phase is observed. Within this interval, at approximately 45 minutes (*ca.* 62.1 J) both product phases are observed. Of further note is the fact that, regardless of the product phase, only minimal amounts can be produced; a phenomenon that will be discussed in Section III.III. It must be mentioned that as each sample was prepared independently, sample mixing may differ and as such the quoted energy values may only be indicative of the general process. Regardless, the immense time and energy gaps between these notable events in the evolution of the system suggest that minor discrepancies in the mixing will have negligible effects on the outcome.

A further caution must be mentioned with respect to the working of the impact device. While the impact device induces mechanical action through impact motion, it is critical to acknowledge that energy is not necessarily translated in an identical fashion through the sample mixture, as will be discussed in section III.III.

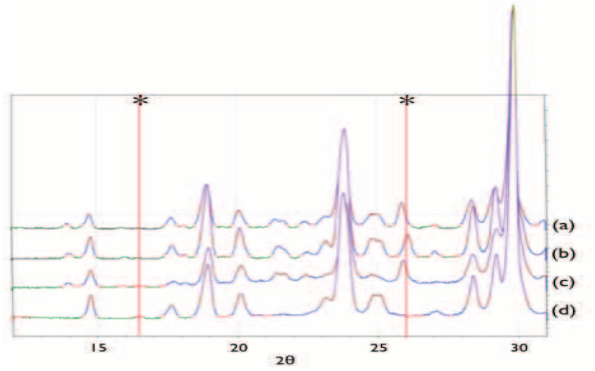

Fig. 2 *XRPD of a series of impact experiments conducted on 3:1 $\alpha-glycine+\beta$-malonic acid mixtures. For clarity, only the major peaks of the product phases are indicated (*) at 16.5° (novel phase) and* 26.0° *(GSM). Treatment duration was (a) 20 minutes, (b) 30 minutes, (c) 45 minutes and (d) 60 minutes. These data demonstrate the conversion of GSM to novel phase upon sufficient impact treatment.*

3.1.2 Isolated Treatment - Shear.

Similar to impact studies, 3:1 mixtures of α-glycine + β-malonic acid were used for shear treatment studies. A sample was submitted for 3 minutes of shearing treatment, resulting in a sticky substance. Quickly solidifying, XRPD of the sample indicated complete conversion of all available malonic acid to GSM, with no indications of the novel phase being present, Figure 3. This sample was subsequently resubmitted for a further 20 minutes of shear treatment, with no observable change. Of note here was the fact that the product mixture of the second treatment was not noticeably sticky, suggesting the formation of a liquid phase intermediate, perhaps through a eutectic melt, between initial reactants. It is interesting to compare the product yield obtained through shear treatment with that of impact treatment. The largely improved yield of the shearing device is likely the result of continued particle mixing throughout the treatment and inhibition of tablet formation.

Curious to observe the effect of shear treatment on the novel phase, a product mixture containing noticeable quantities of the novel phase was produced by vibratory treatment and submitted to successive bouts of 30 minute shearing, Figure 4. Analysis of the resulting product mixtures clearly indicates that shear treatment greatly favours formation of GSM, while leading to loss of the novel phase, which is no longer observable following 90 minutes of shear treatment.

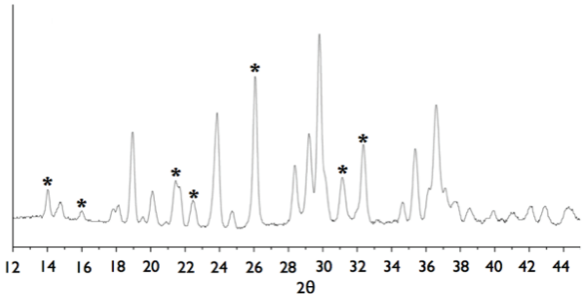

Fig. 3 *XRPD resulting from shear treatment of mixtures of 75 mol% $\alpha-glycine+25\%\ \beta-malonic\ acid$. Sample was treated for 3 minutes. Labelled peaks (*) indicate GSM, with remaining peaks belonging to α-glycine. Small peaks at 27°and $33-34°$ may indicate traces of β-malonic acid. It appears that shear treatment leads to a nearly complete conversion of available reactants to the product phase.*

3.1.3 Milling Studies.

A comparison of the effects of isolated treatments on the α-glycine + β-malonic acid system to the observed reaction under ball milling was particularly intriguing. The trend of product formation upon milling appears to be most similar to that observed under impact treatment, *viz.* initial production of GSM followed by conversion to the novel phase, Figure 5. Interestingly, however, the rate of this conversion differs drastically. While the GSM $\rightarrow$ novel phase transition occurs rather slowly under impact treatment – with an intermediate composition containing both GSM and the novel phase – this process occurs very abruptly under milling treatment. This is perhaps not surprising considering the intensity and frequency associated with each treatment. However, the question remains as to whether milling treatment can then be thought of as acting in the same, or a similar, way as impact treatment.

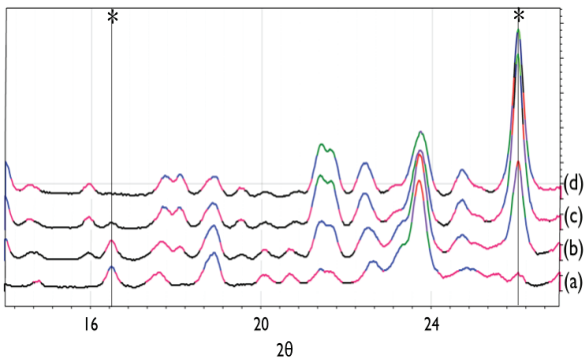

Fig. 4 *XRPD of sample prepared by vibratory treatment, subsequently treated by successive bouts of shear treatment. For clarity, the product phases can be monitored by their most prominent peaks, indicated (*) at 16.5° (novel phase) and 26° (GSM). (a) Initial mixture, (b) 30 minutes shear, (c) 60 minutes shear and (d) 90 minutes shear. It is clear that shear treatment favours GSM formation, leading to the loss of the novel phase.*

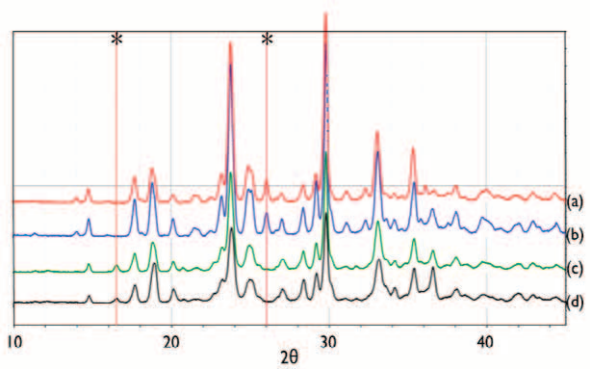

Fig. 5 *Milling (24 Hz) α-glycine + β-malonic acid mixture of equimolar composition. For clarity, the two product phases can be monitored by their most intense peaks at 16.5° (novel phase) and 26.0° (GSM salt), indicated by (*). (a) Milling 30 min, (b) milling 45 min, (c) milling 60 min and (d) milling 90 min. Milling treatment initially leads to GSM formation, transitioning to novel phase production after sufficient treatment.*

3.1.3.1 Reactive Regions in a Ball Mill.

In an attempt to understand the relationship between impact, shear and mill treatments it proved interesting to consider the fact that general mechanoreactors act upon their samples in a variety of ways within the reaction vessel. In the case of the Retsch cryo-mill ball mill used in these studies, two unique reaction zones were in fact observed, Figure 6. Sampling from the walls of the milling vessel indicates the presence of GSM, with no signs of the novel phase. In contrast, sampling from the milling jar ends (a tablet), indicates signs of the novel phase, with minimal amounts of GSM. The presence of two unique zones of reactivity within the milling jar is clear, with the walls being consistent with the previously demonstrated shearing product and the ends being consistent with the previously demonstrated impact product. The existence of these two regions may prove of grave importance to both academia and industry, in which, over time, e.g. on storage, small traces of undesired product may induce a complete conversion of desired product into this undesired phase.

It is important to note here that different ball mills will act differently on their samples, depending largely on the orientation of the milling jar to the displacement axis and the displacement path followed by the milling jar. In addition, factors including the ratio of sample to milling bodies and regime of treatment may also affect the outcome.

3.2 Thermal Studies - A Mechanism for GSM Formation

Despite having demonstrated the selective effects of shearing and impact treatment, little can so far be said regarding the mechanisms involved in the apparent ”solid-state” reaction. Substantial work has been done attempting to understand the mechanisms by which solids react.[52–55] At present a number of common mechanisms have been proposed. These consist of (1) liquid phase intermediates, including from liquids present in the initial mixture (*e.g.* moisture or residual solvent)[16,35,56–61] or by formation of a eutectic melt,[56,57,62–66] (2) gas phase intermediates of a single or multiple reactant components[37,56,66–69] and (3) solid-solid mass transfer. It is not difficult to comprehend mechanisms involving either (1) or (2), however, the feasibility of (3) remains highly debated, in particular when considering non-spherical, bulky organic molecules. At present, arguments in favour of (3) include highly mobile intermediate phases, such as amorphous solids,[70] which can potentially ease solid-phase diffusion processes. It is widely accepted that mechanical treatment induces a certain level of heating, whether this be the result of shear heating or so-called ”hot spots.” Therefore, the low melting point, eutectic and volatile nature of organic crystals makes them prime systems to expect these heating effects to be of potential consequence, with mechanisms (1) and (2) being very easy to imagine possible.

3.2.0.2 Identifying Thermal Character of Reactant Compounds.

DSC of β-malonic acid identifies two thermal events, the first occurring at *ca.* 97 °C, with the second at *ca.* 132 °C. The latter is consistent with both literature and TGA data (shown below), corresponding to melting. The former event, however, offers an interesting query. Previous experiments have suggested this phase transition to occur at 79 °C[71] and 87 °C[72], both measured by DSC. Experimental protocol for ref [71] indicates that prior to DSC measurements malonic acid was

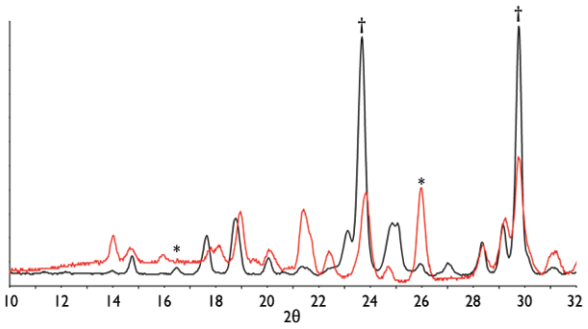

Fig. 6 *XRPD patterns of milling equimolar α-glycine + β-malonic acid 24 Hz, 3 × 20 min, with no intermittent mixing. Sample was tested from the milling jar ends (black) and milling jar walls (red). For clarity, the products (∗) can be identified by their major peaks at 16.5 (novel phase) and 26° (GSM). Similarly, the relative amounts of reactant (†) can be monitored by their major peaks at 30° (glycine) and 23.8° (malonic acid); their intensities coincide with the observed product formation. It is evident that zones with distinct reactivity exist within a single milling jar.*

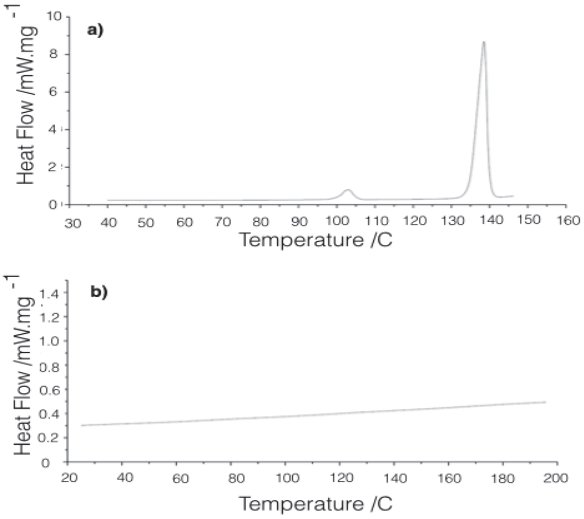

Fig. 7 *DSC data of reactant compounds, (a) β-malonic acid, (b) α-glycine*

re-crystallised from aqueous solution. It is possible that this process may have introduced contaminants or moisture to the sample, which would account for a largely decreased temperature for the phase transition as compared to the current and other literature data. One might also consider the effects of variations in particle size between experiments, a factor known to have strong effects on DSC data[73–76]. Consistent with previous works[76,77] on α-glycine, DSC displayed no thermal events below its decomposition temperature, Figure 7.

Through mechanochemical experiments under no conditions did mechanoreactors become warm to the touch. As such, it is difficult to imagine that temperatures corresponding to the melting temperatures would be reached at a global level within any of the tested systems. It was therefore interesting to investigate the possibility of eutectic melting at inter-particle contacts for the system of study. As an initial test system, 3:1 mixtures consistent with those used in mechanochemical studies were used for DSC experiment, Figure 8. The initial endothermic peak, taken to correspond to melting of the system, is seen to occur at *ca.* 88°C, well below the melting temperature of either reactant component. This peak is followed by a shallow exothermic event, likely recrystallisation of GSM salt. The second endothermic event occurring at *ca.* 112 °C is consistent with the melting temperature of GSM[78]. Testing systems of equimolar composition show this melting temperature to drop to as low as *ca.* 60°C. It is therefore clear that the system expresses substantial eutectic character. While these temperatures are still well above what would be expected for a reactor that does not feel warm to the touch, it is possible that they may be indicative of the energy equivalent attainable at mechanochemical hot spots. This combination of thermal data with mechanochemical studies offers an intriguing opportunity to study the character of hot spots in depth.

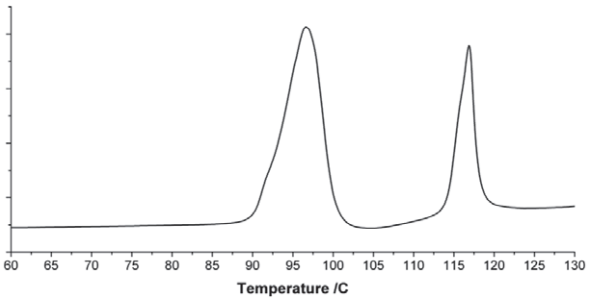

Fig. 8 *DSC curve for 25mol% β-malonic acid + 75mol% α-glycine mixture. The initial endothermic peak corresponds to reactant melting, followed by an exothermic recrystallisation step. The second endothermic peak is consistent with GSM melting.*

3.2.0.3 The Nature of the Intermediate Fluid Phase: Gas or Liquid?

Observing that heat is sufficient to induce formation of GSM from an initial α-glycine + β-malonic acid mixture the question remains as to the nature of this phase.

Analysis of β-malonic acid suggests two thermal events, the first at *ca.* 132°C, with the second event being characterized by a gradual onset, with a maximum gradient following *ca.* 142°C. The former is consistent with the melting temperature of β-malonic acid, at which point there is obvious volatilisation (mass loss > 0.05 mg), with the latter being taken as the evaporation of the substance. In contrast, α-glycine displays

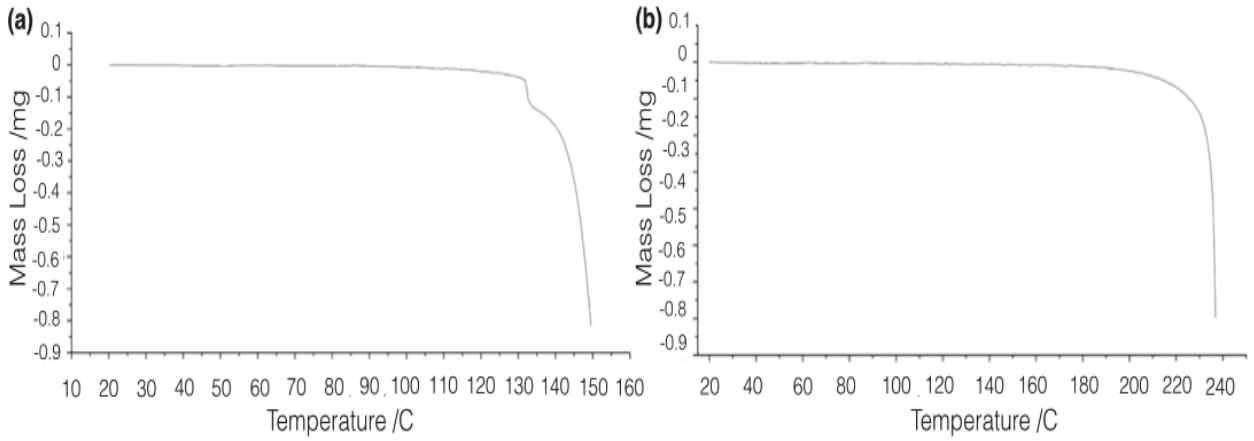

Fig. 9 *TGA analysis of reactant components. (a) β-malonic acid system; (b) α-glycine. It does not appear that volatilization of reactant components occurs at sufficiently low temperatures to support a gas-phase mechanism for GSM formation, which itself melts at ca. 112°C.*

only a single thermal event, taken to correspond to the sublimation of the substance with loss (> 0.05 mg) occurring from 214 °C. The decomposition point is clearly visible, occurring at (232 °C) at which point rate of mass loss drastically hastens. This result is consistent with previously reported temperatures for the decomposition of glycine.[79]

By comparison of these results, it follows that for a gas-phase intermediate to have any notable impact on the mechanochemical reaction, energies within the mechanoreactor would be required to reach the equivalent of *ca.* 132 °C. From DSC it is known that GSM is formed well below 132 °C and thus, a gas-phase intermediate does not appear to be a plausible mechanism. It is important to note here that, while it is obvious a gas-phase intermediate is not *required* for the formation of GSM, its role in the overall mechanism of GSM formation cannot be completely discounted when considering mechanical conditions. It is possible that hot spots may in fact induce temperatures required for volatilisation, or perhaps impact may lead to a "loosening" of surface molecules, thus favouring volatilisation at reduced temperatures.
It is important to reiterate that, under no circumstances through the mechanochemical studies did any mechanoreactors become warm to the touch, indicating, at least at a global level, these volatilisation temperatures were not obtained.

3.3 Insights into Mechanisms of Novel Phase Synthesis: The Physical Basis of Consectutive Products

Having discussed the effects of impact and shear on the α-glycine + β-malonic acid system, as well having shed some light on the processes occurring within a simple ball mill, it becomes interesting to consider the time-dependence of the observed reaction pathway, i.e. the existence of consecutive products. It is clear from the aforementioned experiments that GSM results from shear treatment − which, in accordance with section III.II is likely the result of shear heating − with the novel phase obtainable only *via* impact treatment. This thus demands answers to (1) why the novel phase does not appear immediately upon submission of a sample to impact treatment, (2) why the novel phase is favoured by impact treatment, and (3) the ultimate fate of GSM. In considering this we present here an extension to the mechanochemical model of Section III.II, presenting initial evidence supporting a route to the novel phase that requires the existence of the mechanochemically produced tablet and its corresponding conditions.

3.3.0.4 Tableting: A 'Switch' to Novel Phase Synthesis. From section III.I it appears that all treatment initially favours GSM formation, while the novel phase can only be obtained after sufficient impact treatment. An explanation for this may be found in considering the processes involved under impact treatment, a treatment that ultimately yields formation of a solid powder tablet. Initial stages of this tableting process are characterised by loose particles being thrust past one another by the impacting body. With particles thrusting past one another there is undoubtedly substantial shearing between particles. As vacant space within the tablet is reduced, the intensity and length of shearing across particles decreases, ultimately yielding a densely packed tablet consisting of particles incapable of further motion. At this point one could imagine that nearly all incident impact force would be transferred through the tablet as particle-particle impact and minimal shearing, Figure 10. Therefore, one could imagine implementing such a system as α-glycine + β-malonic acid to measure tableting rates and the forces and energies required. For example, 3:1 mixtures of the present system appears to undergo this transi-

tion between 45 and 60 minutes of treatment – i.e. between 62.1 J and 82.8 J energy.

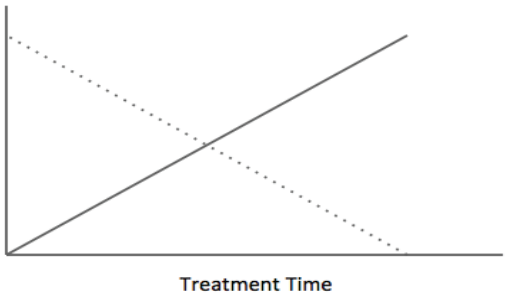

Fig. 10 *Diagramatic Representation of the change in tablet free space (dashed) and % impact (solid) as a function of treatment time.*

It is of interest here to point out that a mechanism involving tablet formation for novel phase production would offer a convincing explanation as to the minute maximum quantities of obtainable product. It is important to note that mechanical treatment of GSM does not form solid tablets; it is likely that mechanically induced melting of the initial reactant components leads to tableting.

3.3.0.5 The Importance of Tableting on Reactivity.
To investigate the role of tablet formation on the mechanochemical product, alternative milling protocols were implemented, Figure 11. Experiment 1, in which the tablet was manually destroyed at intermittent points in the milling cycle, yielded substantial quantities of GSM, with no notable indications of the novel phase. In contrast, the product mixture obtained from Experiment 2, in which the tablet was left intact, indicated no signs of GSM, with observable quantities of the novel phase. It is therefore clear that the existence of this tablet plays a crucial role in specifying the resulting product and may offer an explanation for the observed selectivity of shear and impact treatment; both of which may induce melting, but only the latter of which does so within the presence of a tablet framework, yielding nucleation under constrained conditions.

Alternatively, one may suggest that Experiment 1 is characterised by substantial amounts of shear treatment as a result of the aforementioned tableting process being repeated. In contrast, Experiment 2 allows full tablet formation, at which point the relative quantities of shear and impact transferred through the tablet by the mechanoreactor differ substantially.

3.3.0.6 Consecutive Mechanochemical Products
This concept of tablet formation as a requirement for novel phase growth presents an intriguing starting point for an underlying mechanism of formation. There remains, however, a rather pressing issue: what happens to GSM? From experiment it is obvious that the initial stages of treatment lead to formation of GSM salt, and one might expect that this product would persist, irrespective of continued treatment. This, however, is not the case. Initially it could be suggested that continued treatment may induce GSM degradation (either to the novel phase or reversion to reactants), amorphisation or melting, all of which would lead to the loss of the XRPD pattern corresponding to GSM. In other works,[40,78] however, evidence was presented against these possibilities as routes to the novel phase, with further evidence discounting the possibility of mechanically-induced GSM phase transition as the underlying culprit.

Here we suggest an alternative explanation, rooted in a theory of the mechanical energy available in the system.
In mechanochemical studies, the total excess energy of a system (E) can be defined as the sum of the current energy of the system (E_i) plus some input energy from the mechanical pulse (ΔE), accounting for the loss of energy due to relaxation of the system (ΔE_R) Equation 1.

$$E = E_i + \Delta E - \Delta E_r \quad (1)$$

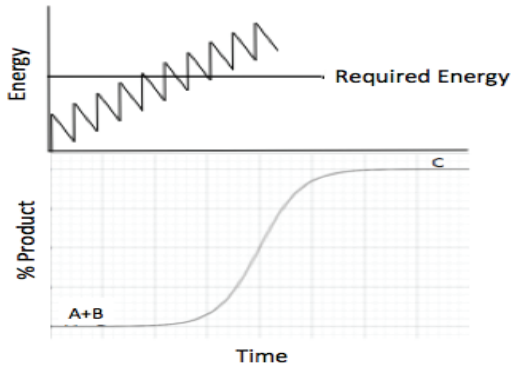

Fig. 12 *Diagramatic representation of a systems energy under mechanical treatment (top) and the corresponding reactant (A+B) → product (C) conversion (bottom). The repetitive increase and decrease of the energy of the system is caused by the interplay between mechanical action and the relaxation of the system. The time between successive mechanical action (increasing energy) can be controlled, thus allowing tuning of the rate of energy accumulation. The rate of relaxation (decreasing energy) is a property of the system of study.*

One might therefore expect the rate of product accumulation to follow a sigmoidal trend, Figure 12. In such a system, the interplay between mechanically induced increases in energy and the decrease in energy resulting from relaxation lead to a gradual increase in the total energy of the system provided the rate of successive bouts of mechanical stressing exceeds the rate of relaxation. As the overall energy of the system increases, there exist, initially, momentary periods of time in

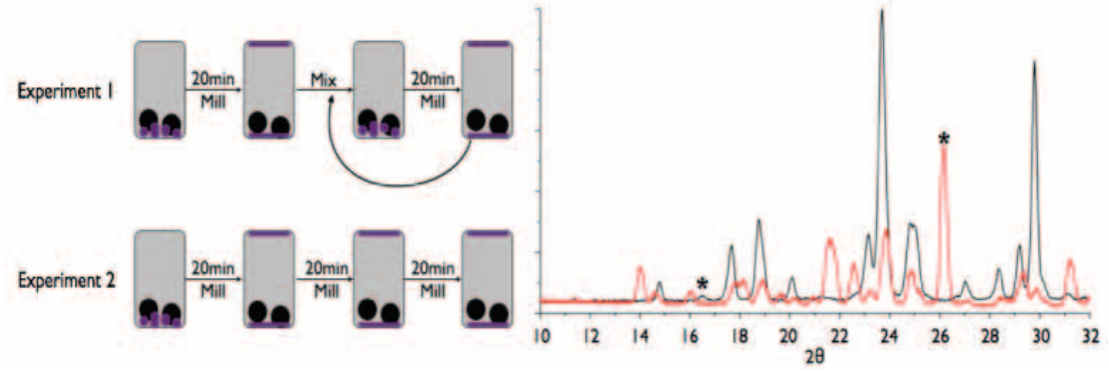

Fig. 11 *(Left) Schematic of experimental protocol implemented. (Right) PXRD of resulting products from experiment 1 (red) and experiment 2 (black).(*) Indicates the most intense peak of each product phase: Novel phase (16.5°) and GSM (26°). It is clear that these two very similar protocols yield drastically different products as a result of mechanical treatment.*

which sufficient energy is present to overcome a reaction energy barrier. With prolonged treatment, this period of time increases rapidly, yielding the sigmoidal trend. The observed rate of GSM to novel phase transition is consistent with such a model, with initial decline in GSM followed by its rapid disappearance, Figure 13. In addition, this model accounts for the extended time required for full conversion of products observed upon impact treatment as compared to milling treatment; weaker and slower impulses lead to a slower increase in energy, Section III.I.III.

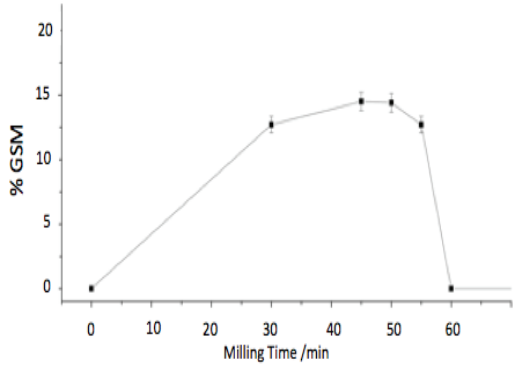

Fig. 13 *Percent of glycinium semi-malonate observed in the product mixture following neat milling over a range of duration of milling treatment. The loss of GSM appears to occur initially between 50-55 minutes, accelerating greatly between 55-60 minutes, by which point GSM is no longer detectable. This trend is consistent with a sigmoidal increase in mechanically induced energy or pressure in the reacting system.*

This model demands two major requirements:

1. The rate of treatment must exceed that of the relaxation process.
2. The rate of treatment must exceed that of nucleation or growth.

This model therefore would offer an exciting opportunity to experimentally measure the rate of relaxation processes and crystal nucleation and growth. By extension of this model, two mechanisms can be suggested to explain consecutive mechanochemical products:

1. The products are directly competitive at the nucleation stage and nuclei can be converted with sufficient energy. *i.e.* one nucleation process to both products.
2. The products are competitive in that they require the same reactants, but nucleation is controlled by the type of energy applied and/or the environment in which nucleation occurs. Loss of GSM results not from conversion to the novel phase, but from loss of crystallinity of the product. *i.e.* two different nucleation processes take place, each to a unique product.

Much work has been done to study relaxation processes in inorganic crystal,[80] however, at present, similar work remains to be performed on organic crystals. Of particular interest is the lifetime of metastable states in crystals, estimated at $10^{-2} - 10^{-3}$ s.[80] Given that inorganic crystals are based on strong interatomic interactions, while organic crystals are stabilised by weak intermolecular forces, it is feasible to assume that similar processes may be longer-lived – *i.e.* relax at slower rates – in organic systems. Assuming all blows strike the same sample, the impact device used in these studies applies mechanical stressing every 0.435 seconds, with the milling device doing the same every 0.0417 seconds. It is thus not infeasible, in particular in sight of tablet frameworks discussed below, to suggest that such an interplay of energetic process may be occurring in the α-glycine + β-malonic acid system.

As demonstrated in Section III.II, GSM appears to be the result of shear-induced melting and re-crystallisation in the absence of a tablet. Initial stages of re-crystallisation may be characterised by a metastable product, as suggested for the nucleation of reactant glycine crystals,[81–83] which can be inhibited from full relaxation – for example by hindering self-assembly processes – to the GSM product nuclei whilst treatment is continued. If sufficient treatment is provided, an energy barrier can be overcome, causing conversion of this hypothetical metastable phase (which may simply be characterised by nanometer metastable nuclei[83]) to an alternative phase, either the novel or an amorphous GSM state. Studies demonstrating the increased ductility of organic substances under tabletting conditions – provided a low-temperature phase transition exists, such as in GSM[78]– lend support to the theory of an amorphous state,[84] with addition evidence for the amorphisation of GSM from experiments with shear treatment.

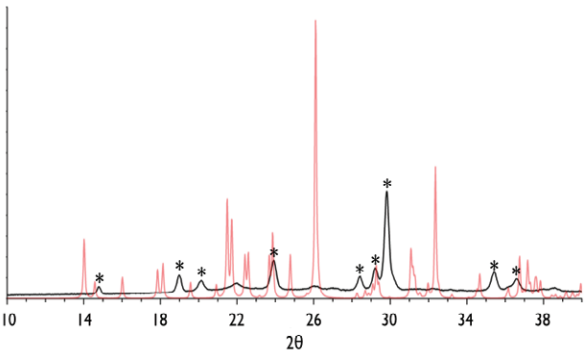

Fig. 14 *XRPD resulting from shear treatment of mixtures of 75 mol% α−glycine + 25% β−malonic acid. Sample was subjected to 25 minutes of continuous shearing treatment. The experimental pattern (black) is compared against the theoretical pattern for GSM (red). Labelled peaks (*) indicate -glycine, with no obvious signs of malonic acid. Minor, broad features suggest amorphisation of GSM as the resulting product.*

Provided sufficient, continuous shear treatment is applied, shearing of pure reactants leads to formation of an apparent partially amorphous GSM product, Figure 14. It is therefore plausible that continued treatment may convert a metastable product to an amorphous state, thus leading to a disappearance of GSM product under continued treatment. Such an effect may be similar to the observation of mechanical amorphisation of sulphathiazole reported previously.[85] It is interesting here to reiterate that conducting any form of mechanical treatment on mixtures initially containing GSM have, to date, proved incapable of producing this effect of disappear products, and may be the result of providing reaction mixtures with initial, stable GSM nuclei. Consistent with the above model, this suggests that once nucleation has relaxed through an initial metastable state to the stable GSM product it is no longer susceptible to mechanical amorphisation under these experimental conditions, therefore further offering an explanation as to why mechanical treatment of pure GSM yields no effect.[40]

3.3.0.7 Tablet Conditions to Novel Phase Formation. In a mill we can realistically assume that reactants will only react at jar walls and ends, i.e. where a three-body collision between reactants and milling body occurs with any substantial force. When this takes place at jar walls, the shearing product, GSM, is produced, with no indications of the ability to yield either the novel phase or amorphisation as observed in the shearing device. In contrast, when this collision occurs at the end of a milling jar it compresses and begins to form a tablet. We have demonstrated how truly continuous (*i.e.* with the shearing device) treatment can lead to GSM amorphisation and here extend this concept to discontinuous treatments such as impact and milling by considering the concept of a tablet.

A comparison of milling series conducted across 3 : 1 and equimolar mixtures, Figure 15 offers interesting evidence towards the role of a tablet. While the product transition for equimolar mixtures occurs between 55 and 60 minutes of treatment, that for 3 : 1 mixtures occurs instead between 40 and 45 minutes, a marked discrepancy with a minimum difference of 10 minutes. It is known that, within a solid, the rate – and potentially feasibility – at which a product forms is, to some extent, dependent on the stress this transformation has on the surrounding environment.[53] In its simplest form a pellet can be considered as an extended solid structure and thus it is a not great stretch to propose similar effects within a tablet.

Adopting a measure for crystal density, ρ, as a ratio of the crystal void space (CVS) and unit cell volume (UCV), Equation 2, a simple comparison, Table 1, shows that, while the free space available within malonic acid and the product phase, GSM, are nearly identical, that available in the glycine unit cell is substantially less. Thus, with increasing quantity of glycine, the amount of free space available in the tablet decreases and the stress of relaxation to produce the product phase likely also increases. In addition, decreasing available void space would also decrease the space available for molecular reorganisation required for re-crystallisation.

It should be noted here that when extending this measure of void space from a crystal to a tablet, an additional term must be added to account for inter-grain void spaces within the tablet itself. Given that in the current system the tablet appears sufficiently strong to induce its effect even under the low frequency, low intensity impact treatment on both 3:1 and equimolar mixtures, it can be approximated that, for this system, composition has negligible effects on tabletability. As such, this additional inter-grain void space term can be taken as a constant and therefore can be disregarded for the purposes

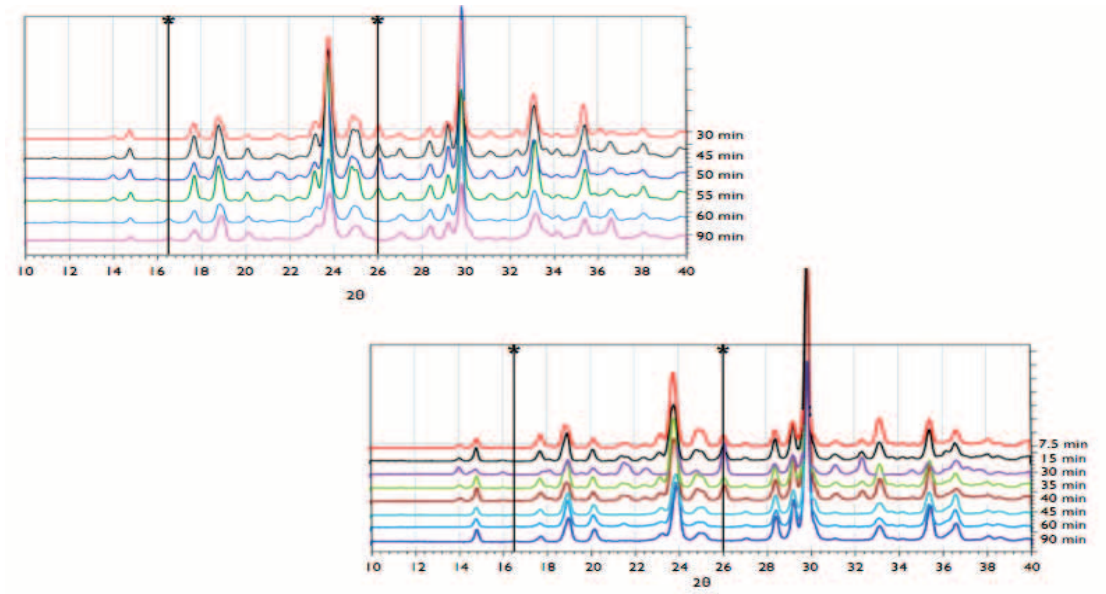

Fig. 15 *XRPD resulting from milling at 24 Hz over a series of times. Similar series were conducted for equimolar mixtures (top) and 3:1 mixtures (bottom) of α-glycine + β-malonic acid. For clarity, only the major peak of each product phase is indicated (*) at 16.5° (novel phase) and 26.0° (GSM). Both compositions exhibit the same trend of GSM to novel phase conversion upon sufficient treatment. However, this transition occurs under notably less treatment for 3:1 mixtures as compared to equimolar mixtures.*

of this model. It is critical to emphasise that this approximation will not hold for all systems, as it is known that excipients can have drastic consequence on compressibility[86]

$$\rho = \frac{CVS}{UCV} \times 100 \qquad (2)$$

Table 1 *Unit cell volume (UCV) and and crystal void space (CVS) dimensions of reactant and products involved in mechanochemical reactions*

Substance	UCV /$\AA^3$	CVS /$\AA^3$	CVS/UCV
α-glycine	310.122	5.25	1.70%
β-malonic acid	213.836	19.15	8.96%
GSM	751.201	62.47	8.32%

Continued mechanical treatment will therefore strengthen/compress the tablet framework and thus work in opposition to the relaxation, expansion and formation of the GSM phase, thereby offering a mechanism by which the aforementioned metastable phase could be maintained. This further reduces the effective value gap between the rate of successive mechanical action and the life-time of metastable states, discussed above, by elongating the lifetime of the metastable state. Further, it follows that extra resistance against relaxation offered by the tablet in such a scheme will likely increase relaxation rates of mechanically induced stresses. Therefore, for a system in which this resistance is larger, e.g. by means of a denser pellet – such as the 3:1 mixture – the rate of increase of the energy in the system will hasten, therefore decreasing the time required to induce GSM amorphisation. This is consistent with experiment, Figure 15.

Under the present model, access to the novel phase is obtained through a unique nucleation event occurring within the constrained, elevated-pressure conditions of the tablet framework, and is not a product of an energetic conversion of nuclei, but instead an alternative nucleation event directed by this framework. This can be easily visualised by altering the axes of Figure 12, bottom, such that the vertical axis represents the fraction of tablet environments at or exceeding the required transformation pressure. Therefore, the initial production of the novel phase would not necessarily be indicative of completion of the tableting process, but instead of the point at which sufficient stress exists in the tablet to induce a change of crystallisation product. Relaxation processes within the tablet would largely be composed of the relaxation of pressure, upon which nucleation can then occur.

An additional interpretation for the effect that altering reactant mixture composition may have on the rate of the GSM → novel phase transition may be proposed based on the stoichiometries of the reaction products. While it is known that altering mixture composition under mechanochemical conditions can induce control on the outcome of product stoichiometry,[87] this effect would simply be expected to alter the relative

proportions of product phases obtainable. This is largely due to the fact that the novel phase can only be formed within a tablet, an environment in which particle mixing is no longer a factor. It therefore follows that the composition will affect the amount of product attainable by altering the relative amount of heterogeneous particle interfaces capable of reaction. As outlined in Section III.II, a global melt is not attainable within the mechanoreactors and as such any reaction will occur solely at these heterogeneous interfaces. The total mixture composition will therefore have minimal effect on the *effective* concentration of the reaction.

While one might alternatively propose a concept borrowed from fluid phase chemistry as an alternative to the above, attempting to explain why alterations in reactant mixture composition may influence the rate of the reaction by means of increasing reactant concentrations, this argument is rendered invalid once tableting is considered.

With this completed model in mind, one could imagine that both altering the rate of tablet formation and allowing tablet relaxation at intermittent points throughout a mechanochemical experiment would alter the amount and type of product obtained. In the event that a tablet is formed slowly, the majority of nuclei would be expected to form as GSM-type and therefore continued treatment would simply result in conversion to an amorphous state. This is simply to say that the vast majority of nuclei will be formed during the tableting process, not within the tablet, with *some* nuclei forming as novel phase-type. In contrast, rapid formation of tablets would ensure that a larger proportion of nucleation processes occur *within* a tablet and will therefore be of novel phase-type.

To test this, two experiments were performed, (1) milling experiments with altered intermittent relaxation processes, testing GSM formation and (2) a comparison of novel phase formation with tableting rate.

In the first set of experiments a sample was milled for three consecutive 20-minute bouts of treatment, altering relaxation time between successive bouts, Figure 16. Noting that 60 minutes of continuous treatment yields no signs of GSM formation, these data demonstrate an interesting trend. Indeed, it appears that allowing elongated relaxation times between treatments does increase GSM formation. Unfortunately, due to the immobility of tableted particles, this experimental protocol is only capable of producing small quantities of GSM. As such, elongation beyond 6 minutes showed no notable increase in GSM production. The observed trends are consistent with the model proposed here, suggesting that the tablet framework is capable of suspending nucleation processes in the, perhaps, the proposed metastable state.

Choosing two forms of mechanical treatment at either end of the range of tableting rate, *i.e.* impact (2.1 Hz) and vibratory treatment (50 Hz), the second set of experiments comparing tableting rate and product formation was performed, Figure 17. Interestingly, consistent with the proposed model, increasing tableting rate drastically increases the observed amount of novel phase. An alternative explanation for these results may reside in the number of tablets observed (noting that vibrational treatment creates many small tablets distributed about the milling body) however this logic would imply that a larger sample, such as that used in milling studies, would also yield substantially larger quantities of the novel phase; this is not observed over milling studies on mixtures of equivalent composition to impact and vibrational studies.

These results further suggest that GSM and the novel phase cannot be two products that are competitive from the same nucleation process – if this were the case, the rate of tablet formation should not affect the amount of the product observed. Instead, one would expect that slower tablet formation, such as in the mill or impact device, would yield a mixture of the two observable product phases, GSM and the novel phase.

Further investigation into the processes that underpin the mechanochemical reactivity of the α-glycine + β- malonic acid system may allow exciting opportunities to study the kinetics and energetics of mechanical processes in relation to organic systems.

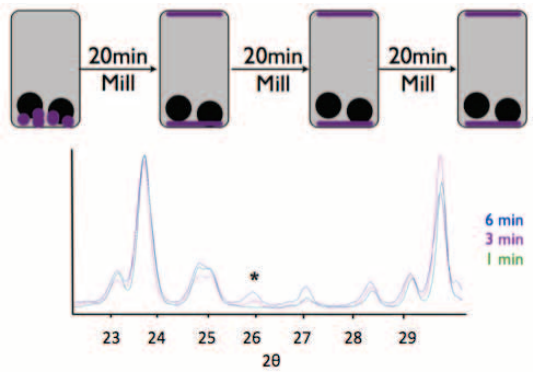

Fig. 16 *(Top) Milling protocol used. (Bottom) XRPD of resulting mixtures, showing an increase in the amount of GSM present with increasing wait times between successive 20-minute milling cycles. The major peak of GSM is indicated (*). It appears that increasing tablet relaxation time at intermittent intervals leads to a detectable increase in GSM growth.*

4 Liquid Assisted Grinding

Liquid assisted grinding (LAG) is becoming an increasingly popular variation of mechanical treatment, offering in many cases substantial improvement and increased control over traditional approaches.[14,15,88] In fact, studies have demonstrated the ability of liquids to have an impressive level of control of mechanochemical processes, in some cases specific solvents favouring a particular product, with other cases showing that a

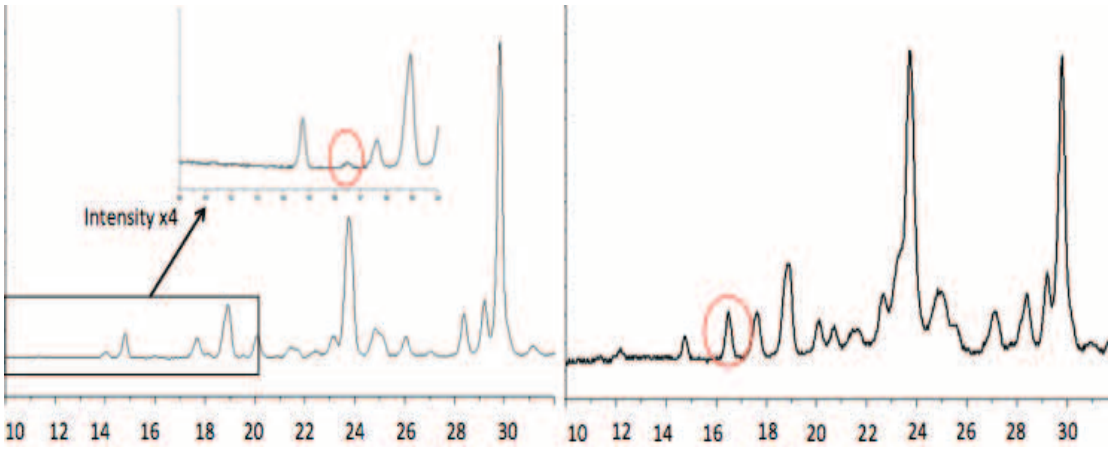

Fig. 17 *XRPD patterns resulting from (left) 60 minutes impact treatment and (right) 8 minutes vibratory treatment of a 3:1 α-glycine + β-malonic acid system. Highlighted peak corresponds to the novel phase. It can be suggested that the intensity of treatment, and thereby the rate of energy or pressure increase in the system, has a positive correlation with the amount of the novel phase attainable.*

solvent is crucial for the reaction to occur at all.[12,16,33,61,88–91] With these potential benefits, the applications and mechanisms governing LAG have been the focus of numerous studies, however, at present there remains no substantiated theory describing the full workings of this mechanochemical variation. Current theories have suggested a number of roles for the liquid under LAG conditions, including acting as a lubricant to ameliorate component mixing, a medium to facilitate tableting or affecting dielectric permeability, polarizing or even ionizing components, or acting as a solvent, dissolving one or more components thereby allowing the reaction to occur in solution.[12?] Current trends in mechanistic LAG studies involve comparison of identical reactions in the presence of a range of solvents. In doing so one can often begin eliminating possible interpretations for the effect of a liquid on the mechanochemical reaction of choice. For example, if liquids that do not dissolve any reactant component still exhibit an effect on co-grinding, one can obviously exclude transition to a solution phase reaction.[61]

Following this methodology, a series of solvents were tested for the α-glycine + β-malonic acid system, Figure 18. The formation of GSM appears to be facilitated by polar liquids, which dissolve the reactant components to a great extent. This is consistent with the aforementioned hypothesis that the formation of this salt proceeds more easily through a fluid state, either a eutectic or, in the case of LAG, through solution at the inter-particle contacts. Examining the effects of non-polar solvents, however, also exhibits an intriguing effect. In the early stages of treatment, these solvents appear to increase (albeit to a much lesser amount as compared to polar solvents) the quantity of GSM produced, as compared to neat grinding. In addition, the GSM → novel phase transition point is also elongated. Following from section III.III, one might therefore suggest that non-polar solvents, which do not dissolve reactant components, may instead induce their effects by affecting tablet formation. Inhibiting tablet densification would greatly reduce the stabilising capabilities of the tablet framework on the hypothetical metastable state, thereby hastening the stabilisation of GSM nuclei and subsequent growth: *i.e.* increased quantities of GSM. In addition, longer treatment times would be required to achieve sufficient conditions within the tablet to yield the novel phase, thereby explaining the elongation of this GSM → novel phase transition point.

Further studies are required to continue to gain deeper insights into this very complex problem. However, such studies will be dramatically simplified by first obtaining a detailed understanding of mechanochemical mechanisms of the system in question.

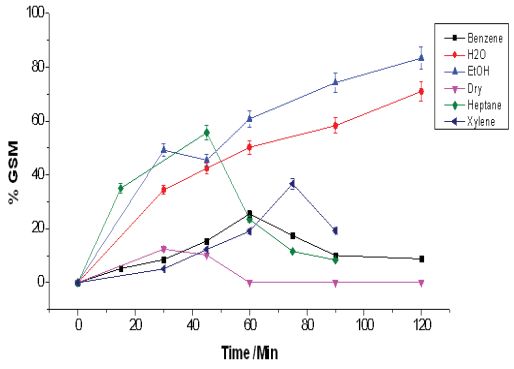

Fig. 18 *Rate of formation of GSM under neat and LAG milling experiments over a range of solvents.*

5 Conclusion

The α-glycine + β-malonic acid system has to date displayed an immense level of mechanochemical complexity. Under treatment in an SPEX-8000 mill[38,39] the resulting product of mechanical treatment is selective to control of the initial reactant mixture composition, demonstrating an $\alpha \rightarrow \gamma$-glycine phase transition or formation of GSM salt low mol% malonic acid and equimolar mixtures, respectively. We add to this complexity by demonstrating a second divergent reaction pathway, dependent on the type of mechanical treatment applied to the system of study. Specialty devices allowed for segregation of basic mechanical actions, impact and shearing. Impact treatment was observed to ultimately yield formation of a novel phase, at present unobtainable by any other crystallisation methods, whereas shear treatment induced GSM salt formation. This selectivity was independent of reactant mixture composition. Combination of these observations to mechanical treatment in a common ball mill demonstrated the existence of two unique reaction regions; sampling from the milling jar ends showed novel phase synthesis, while sampling from milling jar walls showed GSM formation. These results could be of drastic consequence to academia and industry, with particular importance to the pharmaceutical industry where small quantities of undesired product may induce a transformation following packing, thereby having consequence on such factors as bioavailability or patent protection.

The importance of tableting for the formation of the novel phase, *i.e.* as a mechanism for the effect of impact treatment, was explored. It was demonstrated that the existence of a tablet is crucial for novel phase synthesis, with further studies suggesting the role of a tablet to be in altering crystallisation conditions. We propose a model in which the two products, GSM and the novel phase, diverge at the initial nucleation stage. Under continuous treatment *e.g.* shearing, GSM nuclei are inhibited from relaxing to a stable crystalline state, eventually adopting a non-crystalline state. In contrast, whereas the tablet framework is evidenced to maintain this GSM metastable state, initial crystallisation within this framework leads to novel phase-type nucleation, ultimately responsible for novel phase formation. Considering shearing studies, in which shear treatment (likely shear melting and recrystallisation) under ambient conditions demonstrated a clear novel phase $\rightarrow$ GSM transition, it can be suggested that, even with novel phase seeds present, GSM is the favoured crystal product. However, whether this be thermodynamic or kinetic, as in the case of the kinetic preference for α-glycine under ambient conditions,[76] remains to be studied.

6 Acknowledgements

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