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Putting pressure on elusive polymorphs and solvates**


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Supporting information:
† Electronic Supplementary Information (ESI) available: X-ray powder diffraction patterns of malonamide up to 5.0 GPa. Experimental and simulated X-ray powder diffraction patterns of malonamide (forms I and II) and maleic acid (form II). See http://dx.doi.org/10.1039/B814471K

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Abstract

The reproducible crystallisation of elusive polymorphs and solvates of molecular compounds at high pressure has been demonstrated through studies on maleic acid, malonamide, and paracetamol. These high-pressure methods can be scaled-up to produce ‘bulk’ quantities of metastable forms that can be recovered to ambient pressure for subsequent seeding experiments. This has been demonstrated for paracetamol form II and paracetamol monohydrate. The studies also show that the particular solid form can be tuned by both pressure and concentration.

Introduction

The importance of polymorphism and solvate formation in the crystallisation of organic compounds is widely recognised within the industrial and academic communities. The solid-state properties (and hence crystal structure) of a compound can affect other properties such as the bioavailability of a drug compound, the colour of a pigment, and the shock-sensitivity of an explosive. Intellectual property can also become an issue for pharmaceutical companies who develop and market new drug products, where challenges to patents have been made on the basis of the discovery of a new polymorph or solvate. Substantial effort is therefore deployed in order to explore fully the polymorphic behaviour of emerging drug products. Generally the techniques used for polymorph screening involve recrystallisations from a wide range of solvents under a variety of conditions, and high-throughput robotic screening is increasingly being used. One of the aims of such studies is to identify the controlled conditions required to ensure that a particular polymorph or solvate can be reproducibly obtained. However, Dunitz and Bernstein have highlighted several examples where this reproducibility has been shown to be very difficult to achieve and cite examples where apparent loss of control of the crystallisation procedure results in an inability to obtain the desired form even though this form had previously been routinely obtained over long periods of time. The authors discussed the concept of “disappearing” or elusive polymorphs and described situations where a polymorph may only be observed once before a new, more thermodynamically stable polymorph is crystallised. The crystallisation of the second form results in the ‘disappearance’ of the previous polymorph and repeated attempts to grow the original polymorph are unsuccessful despite using the same crystallisation conditions. Several of the examples of ‘disappearing’ polymorphs given in their review illustrated the importance of seed crystallites in the formation of the stable polymorph—once seed crystallites of the more stable form were present in the laboratory it proved impossible to obtain the other polymorphs. The example of benzocaine picrate was one where the original polymorph could be found again, but at a cost of cleaning the entire laboratory and waiting 8–12 days. Another example was that of 1,2,3,5-tetra-O-acetyl-β-D-ribofuranose, which warned that the loss of a particular polymorph can be a global problem and not just restricted to a one specific laboratory. There are numerous other examples of compounds where, although not impossible, it is often difficult to obtain one polymorph at the expense of another. It is for this reason that various crystallisation strategies have been
developed. These include: crystallisation in the presence of additives,\textsuperscript{6–10} co-crystallisation,\textsuperscript{11–13} flash cryocrystallisation,\textsuperscript{14} and hydrothermal methods.\textsuperscript{15}

Another method that has proved to be successful for the exploration of polymorphism in molecular compounds is the use of high pressure.\textsuperscript{16} Examples include simple alcohols\textsuperscript{17,18} and carboxylic acids,\textsuperscript{19,20} mineral acids and their hydrates,\textsuperscript{21,22} polycyclic aromatic hydrocarbons,\textsuperscript{23} chloroalkanes and chlorosilanes,\textsuperscript{24,25} pharmaceutical compounds such as paracetamol and piracetam,\textsuperscript{26,27} amino acids,\textsuperscript{28–30} explosives,\textsuperscript{31} and inorganic coordination compounds.\textsuperscript{32} Nevertheless, the study of molecular systems using high pressure remains as an emerging field, and at this stage its true potential as a tool for the control of polymorphism and solvate formation has yet to be fully realised.

In this paper we use three examples to demonstrate how high-pressure methods can be used to obtain apparently elusive crystalline forms. We also show how these methods can be scaled up to recover to ambient pressure “bulk” quantities of these phases. The three examples (see Figure 1 for molecular structures) are maleic acid, malonamide and paracetamol (acetaminophen). Our attention was drawn to these compounds not only by the difficulty in obtaining the elusive form, but also by the densities of the various forms. For all three compounds the crystal density (calculated from the X-ray diffraction parameters at similar temperatures) of the elusive polymorph was significantly greater than the densities of the other more prevalent polymorph(s). Since high-pressure conditions frequently favour the formation of higher density forms, our intention was to discover whether the application of high-pressure techniques could be used to obtain these elusive polymorphs in a reproducible manner.

\textbf{Figure 1}. Molecular structures of maleic acid, malonamide, and paracetamol.

\textbf{Results and discussion}

\textbf{Example 1 - maleic acid}

Maleic acid is used widely in the pharmaceutical industry as a salt-forming agent and so is a good example of a compound that has been recrystallised from solution literally thousands of times. The results of all structural
studies up to 2006 strongly suggested that the compound was monomorphic.\textsuperscript{33,34,35} However, Day \textit{et al.} recently obtained and characterised a new polymorph (form II) by dissolution in chloroform of the 1 : 2 adduct formed between maleic acid and caffeine, followed by slow evaporation.\textsuperscript{36} With admirable honesty, the authors reported that unfortunately they were unable to obtain this new form again and remarked that “...this is possibly another e of disappearing polymorphism...”.

Both forms of maleic acid contain identical, hydrogen-bonded, polar sheets (Figure 2) in which the carbonyl groups point in similar directions. The difference between the forms lies in the relationship between adjacent sheets. In form I, the sheets that are formed above and below are aligned in the opposite direction from the central sheet (see Figure 2). This results in the adoption of a centrosymmetric space group ($P2_1/c$). In form II (see Figure 3), each sheet is pointing in the same direction resulting in the adoption of a non-centrosymmetric space group ($Pc$). The densities of forms I and II at 180 K are 1.643 and 1.661 g cm$^{-3}$, respectively.\textsuperscript{36}

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{figure2.png}
\caption{View of crystal structure of maleic acid form I showing adjacent layers aligned in opposite directions.}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{figure3.png}
\caption{View of crystal structure of maleic acid form II showing adjacent layers aligned in the same direction.}
\end{figure}
X-Ray powder diffraction patterns were recorded at 293 K over a series of pressures up to 4.2 GPa for a polycrystalline sample of form I contained in a Merrill-Bassett diamond-anvil cell (DAC) with Fluorinert-FC75 acting as a pressure-transmitting medium. These measurements showed that there was no transition to form II. Instead, a smooth (~12%) decrease in unit-cell volume was observed over this pressure range, with the largest decrease being along the direction of the $a$-axis. This is parallel to the hydrogen-bonded chains within the layers (see Figure 4). This result supports the suggestion by Day et al. that stress-induced interconversion between forms I and II would be unlikely on account of their different stacking patterns which would result in a significant barrier to transformation.\(^{36}\)

![Figure 4. View of hydrogen-bonded layer of maleic acid form I showing the direction of greatest compression along the $a$-axis.](image)

Subsequent experiments using a range of concentrations of aqueous maleic acid solutions showed that the presence of ice-VI was in fact not required in order to precipitate form II; crystallisation at pressures above ~0.5 GPa invariably gave form II. It also proved possible to grow a single crystal from this precipitate at 0.5 GPa by cycling the temperature of the DAC. Care was required during this process in order to avoid temperature-induced isomerism to the thermodynamically more stable (and significantly less soluble) fumaric
acid, especially as there was some evidence that this isomerisation occurred more readily under elevated pressures. This is consistent with an early study involving the thiocyanate-catalysed isomerism of maleic acid at pressures up to 0.5 GPa which showed that the rate of this reaction increased with increasing pressure. Single-crystal X-ray diffraction measurements identified the crystal as maleic acid form II. On decompression to ambient pressure the single crystal was observed to dissolve, in line with the increased solubility of maleic acid at lower pressure. Similar observations were made on decompression of polycrystalline samples and it was only possible to recover solid to ambient pressure when the DAC was loaded with super-saturated solutions. On these occasions, X-ray powder diffraction showed that at high pressure (>0.5 GPa) only form II was produced. Form II persisted on decompression to lower pressures (~ 0.2 GPa), but when the pressure was completely released such that the DAC was no longer sealed, additional diffraction peaks attributable to form I were observed. We suspect that this form was produced by partial evaporation of the solution from the edge of the gasket. Judging from the diffraction patterns recorded after several hours, there appeared to be no change in the relative proportions of the two forms or in the texture of the powder patterns. This was rather surprising since although direct interconversion is hindered, the presence of water should allow a solvent-mediated transition if form I is appreciably more stable than form II. Hence one possible interpretation is that under these conditions both forms have almost equal thermodynamic stabilities. Support for this comes from the calculated lattice energy difference between the two forms of 0.15 kJ mol$^{-1}$ obtained by Day et al. On the other hand, it could be that in the absence of stirring the process of interconversion is kinetically slow, and so complete conversion to the more stable form does not occur over this relatively short time period.

![Figure 5](image.png)

**Figure 5.** Powder X-ray diffraction pattern recorded for maleic acid form II at 0.6 GPa using radiation of wavelength 0.44397 Å. Note that the preferred orientation of the sample, combined with the small size of the incident X-ray beam, has a significant impact on the relative intensities of the Bragg peaks.
Not surprisingly, given the similarities in structural motif, the Raman spectra of both polymorphs in the range 200–3000 cm$^{-1}$ are almost indistinguishable, although there is a variation in the relative intensities of the two bands near 1700 cm$^{-1}$. However, one distinct difference was observed in the region near 300 cm$^{-1}$ (Figure 6)—form I displays three well defined bands whilst at the same pressure two of these bands overlap in the spectrum of form II.

![Raman spectra of form I (upper) and form II (lower) of maleic acid](image)

**Figure 6.** Raman spectra of form I (upper) and form II (lower) of maleic acid.

**Example 2 - malonamide**

Three crystalline forms of malonamide have been identified and structurally characterised. The monoclinic form I can be obtained by recrystallisation from warm water and was first structurally characterised in 1970; it is this form that is commercially available (Sigma-Aldrich). A tetragonal form II, obtained from the alkaline hydrolysis of 4,6-dihydroxypyrimidine, was recently discovered and structurally characterised by Nichol and Clegg. However, after the original batch of crystals had been misplaced, it proved impossible, despite numerous attempts, to reproduce this form. Instead, a third orthorhombic form III was obtained and the authors speculated that this might be an example of the phenomenon of “disappearing polymorphs.” The densities of forms I, II, and III at 150 K calculated from X-ray diffraction measurements are 1.426, 1.546 and 1.427 g cm$^{-3}$, respectively. Hence high-pressure methods might be expected to favour the elusive tetragonal form II.
X-Ray powder diffraction patterns were recorded at 293 K over a series of pressures up to 5.0 GPa for a polycrystalline sample of the monoclinic form of malonamide contained in a Merrill-Bassett diamond-anvil cell with 4 : 1 methanol/ethanol acting as a pressure-transmitting medium. Figure 7 shows the sequence of diffraction patterns in the order in which they were recorded. All of the patterns up to 0.9 GPa could be indexed to the monoclinic form with a smooth decrease in unit-cell volume. At 1.3 GPa the pattern became more complex with the growth of new peaks and a reduction in intensity of some of the original peaks, suggesting a mixed phase powder pattern. At the next pressure point (1.8 GPa), the pattern simplified considerably and could be indexed to the elusive tetragonal form with lattice parameters $a = 5.2183(3)$ and $c = 14.9944(13)$ Å. No further phase transitions were observed up to 5.4 GPa. Progressive decompression showed that the tetragonal form II persisted to ambient pressure. The presence of both phases at 1.3 GPa allows a direct comparison of the molar volumes of the monoclinic and tetragonal forms at this pressure, and shows that the tetragonal form II is 6% more dense at this pressure.

*Figure 7.* Sequence of X-ray powder diffraction patterns recorded for form I of malonamide with increasing pressure showing the transition to form II at 1.3 GPa and subsequent recovery of form II to ambient pressure (wavelength = 0.44397 Å).

It also proved possible to grow a single crystal of malonamide contained in a diamond-anvil cell by recrystallisation from an aqueous solution at a pressure of 0.4 GPa. Figure 8 shows the optical image of this crystal and single-crystal X-ray diffraction confirmed that this was also the tetragonal form. The significantly
lower pressure required for the phase transition in the solution recrystallisation experiments reflects how the barriers to solid–solid phase transitions may be substantially reduced by high-pressure recrystallisation from solution. These observations strongly suggest that form II is the thermodynamically more stable form at elevated pressures.

**Figure 8.** Optical image of single crystal of tetragonal form II malonamide grown at 0.4 GPa.

A previous DSC study had demonstrated that a metastable form of malonamide with a lower melting point and lower enthalpy of fusion could be obtained by quench cooling the melt from 443 K to 300 K. We used X-ray powder diffraction to identify this form and showed that it was in fact the tetragonal form II that formed under these conditions. These results therefore suggest that although form II is not as elusive as originally reported, high pressure is a useful tool for changing the relative thermodynamic stabilities of polymorphs and hence providing access to metastable forms. This will be demonstrated more fully in the next example.

**Example 3 - paracetamol**

Paracetamol (acetaminophen) is a widely used analgesic drug for which two polymorphic forms have been identified and structurally characterised. A third form has also been observed, but is so unstable that its crystal structure remains unknown, although a possible structure has been suggested on the basis of powder diffraction measurements and theoretical predictions. Under ambient conditions the thermodynamically most stable polymorph is the monoclinic form I, first described by Haisa et al. and followed more recently by more precise structural determinations at low temperature. A metastable orthorhombic form II was also
first described by Haisa et al., but subsequent attempts by other workers to obtain single crystals of this form using Haisa's method were unsuccessful, although polycrystalline material in this phase can be grown from the melt. Interest in the selective production of form II stems from its property of undergoing plastic deformation upon compaction, thereby presenting some potential processing advantages over form I. Nichols et al. showed that single crystals of form II can be grown by seeding a super-saturated solution of paracetamol in methylated spirit with a micro-crystal of form II derived from melt-crystallised paracetamol, but highlighted the fact that solvent-mediated interconversion to form I was very facile. The densities of forms I and II calculated from X-ray diffraction measurements are 1.297 and 1.336 g cm\(^{-3}\) at 298 K, respectively. Form II has also been crystallised preferentially from aqueous solutions in the presence of selected polymers, and also via a process that involves pre-treatment of a glass vessel with an alkaline solution followed by recrystallisation over a period of weeks. Both of these methods highlight the importance of surface nucleation and/or the presence of additives in directing the crystallisation process. Very recently it has been shown that small quantities of form II can be selectively crystallised by evaporation from the edge of an aqueous solution I a process termed “contact line crystallisation”. It is clear from all of these studies that whilst the reproducible preparation of samples of form II is possible, it is not at all straightforward.

Within the field of high pressure, Boldyreva et al. have demonstrated that the application of pressures in excess of 4 GPa to solid form I resulted in conversion to form II, but conversion was incomplete. Our own studies involving recrystallisation of paracetamol from various solutions under high pressure gave a 1 : 1 methanol solvate at 0.6 GPa and a dihydrate at 1.1 GPa. Crystallisation from ethanol at 1.1 GPa gave the orthorhombic form II, and this prompted us to explore (a) the extent to which high-pressure methods could reproducibly be used to produce form II, and (b) whether this metastable form could be prepared in larger quantities at high pressure with subsequent recovery to ambient pressure. Initial experiments involved repeated high-pressure recrystallisations in diamond-anvil cells of solutions of paracetamol in acetone (at 0.2 GPa), 1,4-dioxane (at 0.3 GPa), and water (at 0.25 GPa) to give single crystals that were all subsequently identified by single-crystal X-ray diffraction to be form II. Experiments were then performed using a larger volume pressure vessel (UniPress U101) capable of pressurising samples of volume \(~4\text{ cm}^3\) up to 1.2 GPa. Such a vessel is used routinely in the pressure-induced enhancement of Diels–Alder and Michael-addition reactions. Thus a series of experiments were performed, which involved pressurisation of aqueous solutions (\(~3\text{ cm}^3\)) of paracetamol spanning a range of concentrations (10–150 g dm\(^{-3}\)) contained in smooth Pyrex ampoules sealed with a thin Teflon membrane. The warm ampoules were loaded into the UniPress apparatus, pressurised to between 0.5 and 1.0 GPa, and were then allowed to stand at pressure for a period of 10–20 min. Over this time period the temperature of the ampoules equilibrated with the temperature of the press, \(i.e. \sim 293\text{ K}\). On depressurisation to ambient pressure, the ampoules containing the more
concentrated solutions (>20 g dm\(^{-3}\)) were observed to contain a polycrystalline, white precipitate, with the quantity of the precipitate being dependent on the concentration of the solution (see Figure 9).

Figure 9. (a) Aqueous solution of paracetamol prior to loading in pressure vessel, (b) precipitate of metastable phase recovered after pressurisation.

The morphology of the crystallites varied depending on the concentration—at concentrations >140 g dm\(^{-3}\) the crystallites displayed a prismatic or plate-like habit that is characteristic of the monoclinic form of anhydrous paracetamol and this was confirmed by X-ray powder diffraction. At concentrations <20 g dm\(^{-3}\), no precipitate was observed. By contrast, at intermediate concentrations, crystallites formed as very fine needles that transformed to prisms and plates over a period of several hours at 298 K. These prisms and plates were also identified by X-ray powder diffraction as being the monoclinic form of anhydrous paracetamol. Attempts to isolate the first-formed crystalline material by filtration at ambient temperature for subsequent analysis by X-ray powder diffraction invariably led to poor-quality powder patterns that were dominated by the monoclinic anhydrous form I, although there was some tentative evidence for the presence of an additional phase. It was clear that the processes of filtration and subsequent manipulation were causing rapid transformation of the recovered material. For this reason, it was decided to perform an experiment that would minimise the degree of sample manipulation and hence reflect more accurately the initial composition of the sample. Since it had also been observed that the rate of transformation of the needles to monoclinic form I could be substantially slowed by cooling the suspension to 275–280 K, an additional requirement of the experiment was the ability to cool the sample. Although powder neutron diffraction would perhaps not be an obvious choice to study this system, the larger sample volumes required for neutron studies combined with the low absorption of thermal neutrons by many materials often allows a much more flexible sample environment for neutron scattering experiments compared to X-ray experiments. For this reason we opted to use the POLARIS diffractometer at the UK spallation neutron source, ISIS, located at the STFC Rutherford Appleton Laboratory, UK. Owing to the very high incoherent scattering associated with H-containing materials it was
necessary to use solutions of perdeuterated paracetamol-\(d_9\) in D\(_2\)O for these experiments. Inevitably this raises the question as to whether deuteration significantly affects the relative stabilities of the two forms, but experiments at ambient pressure showed no indication of this – recrystallisation from water and other solvents (methanol, ethanol, acetone) under a range of cooling conditions and concentrations invariably produced form I. Highly supersaturated solutions of paracetamol-\(d_9\) in D\(_2\)O (100 and 133 g dm\(^{-3}\)) were loaded into Suprasil (quartz) ampoules (external diameter 10 mm and wall thickness 0.25 mm) sealed with a thin Teflon membrane. Each ampoule contained \(~4\) cm\(^3\) of solution and was pressurised to between 0.5 and 1.0 GPa using the UniPress U101. After maintaining this pressure for a period of 10–20 min, the sample was depressurised and transferred immediately into a standard vanadium can cooled to 280 K. The vanadium can containing the sample was then transferred directly into the POLARIS diffractometer, which was maintained at a temperature of 280 K throughout the experiment. For each of the samples no changes in the powder diffraction patterns were observed over the period of data collection (2–6 h). Figure 10 shows the powder pattern obtained when the more concentrated sample had been pressurised to 1.0 GPa. The broad background is caused by scattering from liquid D\(_2\)O, but Bragg peaks from the precipitated solid are clearly visible. It proved possible to index and refine very satisfactorily the pattern to the anhydrous form II of paracetamol. No other solid forms were detected in the pattern. A similar result was obtained when the less concentrated solution was pressurised to 0.5 GPa. At the end of the experiment the ampoule was removed and after standing at ambient temperature for a period of days, large block-shaped crystals were obtained. These were subsequently identified by single-crystal X-ray diffraction as form II.

**Figure 10.** Neutron powder diffraction pattern recorded for the recovered orthorhombic form II of paracetamol-\(d_9\) on the POLARIS instrument. Tick marks indicate predicted Bragg peaks. The large hump is caused by scattering from liquid D\(_2\)O.

By contrast, when the less concentrated sample was pressurised to 1.0 GPa, a very different diffraction pattern was observed, which corresponded exclusively to paracetamol monohydrate. This hydrate has been prepared previously by flash cooling an aqueous solution of paracetamol containing sodium fumarate, and although
stable at low temperatures the monohydrate readily dehydrates under ambient conditions to give the anhydrous form I. A possible explanation for the formation of the monohydrate at high pressure can be suggested by an examination of the phase diagram of water. This shows that compression of water at 298 K to 1.0 GPa results in the formation of ice-VI. Thus it may be that the presence of ice is responsible for the nucleation of paracetamol monohydrate at elevated pressures. Analogous behaviour has been observed for piracetam dihydrate, which nucleated in the presence of ice-VI when aqueous solutions were compressed to 1.3 GPa. Formation of ice under these conditions might be expected to encourage crystallisation by two mechanisms: (i) removal of water as solid ice will cause the local concentration of the solution to increase, and (ii) the formation of ice crystallites provides many more potential nucleation sites.

It also proved possible to seed at ambient pressure a cold, saturated, aqueous solution of paracetamol with a few crystallites of the monohydrate or form II recovered from the high-pressure experiments. This produced several grams of crystalline material which displayed either the characteristic needle-like morphology of the monohydrate or the block-like morphology of form II, respectively. This illustrates how the methodology of high-pressure crystallisation on a relatively small scale can be used to generate metastable forms for use in seeding experiments at ambient pressure, thus removing the need for expensive, very large-volume pressure vessels.

These studies show that pressure-induced precipitation from aqueous solution can be used to prepare and recover to ambient pressure significant quantities (up to ~0.3 g) of metastable forms of paracetamol, and that control over which form is produced can be achieved by variation of both concentration and pressure. These results demonstrate for the first time the preparation of form II paracetamol from aqueous solution without the requirement for any additives or surface treatment of the glass. They are also in agreement with the observation that the orthorhombic form II is the thermodynamically stable form at elevated pressures. Support for this comes from the results of recent high-pressure DSC measurements, which identified the I-II-liquid triple point at $P = 0.259$ GPa and $T = 489.6$ K. These experimental results are also in good agreement with inferences drawn from topological $P-T$ and $V-T$ phase diagrams, which estimated the pressure for the I-II equilibrium at 298 K to be 0.299 GPa.

**Conclusions**

The results of this study have shown that the application of high pressure to molecular compounds can be used to obtain in a reproducible way polymorphs and solvates that are often found to be elusive using ambient-pressure techniques and which may be metastable under ambient conditions. This appears to be particularly true for metastable polymorphs that have higher densities. In such cases pressure would be expected to favour denser forms by changing the relative thermodynamic stabilities of the various forms. Based on the results of high-pressure DSC measurements this is clearly the situation for paracetamol, and it seems likely that it is
also the situation for maleic acid and malonamide. Thus the use of pressure has the potential to enhance our control over crystallisation processes and hence reduce the occurrence of “disappearing” or elusive polymorphs and solvates.

The examples selected here are relatively simple molecules, which do not have the complexity of many modern pharmaceutical compounds. However, we see no reason why our methodologies should not be applicable to more complex compounds; indeed our experience to date suggests that the substantial conformational flexibility of many of these more complex molecules may result in significantly richer pressure-induced polymorphic behaviour.

Part of the success of the solution crystallisation method used to obtain these metastable forms must also reflect the confined nature of the diamond-anvil cell or larger volume pressure vessel. Both provide an environment in which it is possible not only to exclude atmospheric seed crystallites of more stable forms, but also ensure that any remaining seed crystallites in solution can be completely dissolved. Such a strategy is crucial in view of the well documented difficulties experienced in crystallisation processes where the presence of even trace amounts of a more stable form in the atmosphere or on laboratory glassware may prevent the crystallisation of the metastable form.4

Finally, we have shown that appreciable quantities of metastable forms can be generated by crystallisation at elevated pressure with subsequent recovery to ambient pressure. These recovered forms can then be characterised at ambient pressure or can be used in seeding experiments at ambient pressure, thus removing the need for expensive, very large-volume pressure vessels. This has the potential to make high-pressure crystallisation a very useful tool in materials discovery.

**Experimental**

High-pressure X-ray experiments were performed using a Merrill-Bassett diamond anvil cell69 equipped with 600 µm culets and a tungsten gasket with a 300 µm hole. A 4:1 mixture of methanol/ethanol or Fluorinert-FC75 was used as a hydrostatic pressure medium with a ruby chip acting as the pressure calibrant. Single-crystal and powder diffraction data were collected at the STFC Daresbury Laboratory, UK on Stations 16.2SMX and 9.5HPT,61 respectively. Single-crystal data were processed according to the procedure described by Dawson et al.62 X-Ray powder diffraction images were processed using FIT2D,63 and data were manipulated using PowderCell (version 2.3).64 Neutron powder diffraction data were collected at 280 K using the POLARIS diffractometer65 at the UK spallation neutron source, ISIS, located at the STFC Rutherford Appleton Laboratory. Neutron diffraction data were manipulated using GSAS.66 Paracetamol-\(d_9\) was prepared by the reaction between acetic anhydride-\(d_6\) (QMX Laboratories) and 4-aminophenol-\(d_7\) (QMX Laboratories) in \(D_2O\) according to a procedure described in ref. 67. Larger volume experiments were performed using a UniPress U101, with heptane as a pressure-transmitting medium.
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