Template for Submission of Manuscripts to American Chemical Society Journals

Word 2010, single-column, double-spaced (2013)

This template is a guide to be used to prepare manuscripts for submission. Please consult the Instructions to Authors or a recent issue of the journal for detailed guidelines and procedures for submission. This template is intended to benefit to the author in that the entire manuscript (text, tables, and graphics) may be submitted in one file. Inserting graphics and tables close to the point at which they are discussed in the text of the manuscript can also be a benefit for the reviewer.

When you submit a manuscript using this template, you will not actually see the page formatting that appears in the printed journal. This will occur as part of the editorial production process. Abbreviated instructions for using the template follow. Consult the documentation for your specific application and version for more information. Additional instructions can be found in the readme file at the web page where you downloaded this template.

Using the template

In ACS publications there are many different components of a manuscript (i.e., title, abstract, main text, figure captions, etc.) that are represented in the template. See the Guide, Notes, Notice, or Instructions for Authors on the journal's homepage to determine which parts should be included for the manuscript that you are preparing

1. If typing your manuscript directly into the template, select (highlight) the text of the template that you want to replace and begin typing your manuscript (i.e., select the Title section for typing in your title).
2. If you have already prepared your document in a Word file, you will need to attach the template to your working document in order to apply the Word Style tags. Further instructions can be found in the readme file at the web page where you downloaded this template.
    a. Go to the Add-Ins tab and you will see all the Word Styles from the template that has now been imported into the current document. A Styles toolbar has been generated that will display the different Styles for you to choose from. If this is not present, type in the following command (Alt+Ctrl+Shift+S) and it should appear. You can close this at any time and then reopen it when needed.
    b. Click in the sentence or paragraph and then go to the Add-Ins tab and select the relevant Word Style. This will apply the Word Style to the entire text (sentence or paragraph). Do this for all sections of the manuscript.
3. To insert graphics within the text or as a figure, chart, scheme, or table, create a new line and insert the graphic where desired. If your graphic is not visible, ensure that the Word Style is "Normal" with an automatic height adjustment. If the size of the artwork needs to be adjusted, re-size the artwork in your graphics program and re-paste the artwork into the template (maximum width for single-column artwork, 3.3 in. (8.5 cm); maximum width for double-column artwork, 7 in. (17.8 cm)). **NOTE**: If you are submitting a Table of Contents graphic, please insert the graphic at the end of the file.
4. Ensure that page numbers are present on all pages before submitting your manuscript.
5. Delete these instructions and any sections that are not needed.
6. Save the file with the graphics in place: select **Save As** (**File** menu) and save it as a document file (not a .dot template file).
7. Proof the manuscript to ensure that all parts of the manuscript are present and clearly legible.

On the application of strong magnetic fields during organic crystal growth

*Jason Potticary[1], Charlie Hall[1,2], Rui Guo[3], Sarah L. Price[3] and Simon R. Hall[1]**

[1]Complex Functional Materials Group, School of Chemistry, University of Bristol, Bristol BS8 1TS, UK.

[2]Centre for Doctoral Training in Condensed Matter Physics, HH Wills Physics Laboratory, Tyndall Avenue, Bristol, BS8 1TL, UK.

[3] Department of Chemistry, University College London, 20 Gordon Street, London WC1H 0AJ, U.K.

KEYWORDS: Crystallization; Magnetic field; Pharmaceutical; Organic crystal; Kinetics

ABSTRACT: We investigate the effect of crystal growth within a magnetic field for three polymorphic pharmaceuticals, using an experiment where the magnetic field can be varied in strength without altering other crystallization conditions. In the case of carbamazepine, fields above 0.6 T produce the metastable form I and for flufenamic acid, there is an increased propensity to crystallize metastable form I around 1 T. In contrast, the magnetic field has no effect on the crystallization of mefenamic acid, a closely related molecule. The growth of the metastable β- polymorph of coronene within a magnetic field at ambient temperature is difficult to reproduce, but has been seen as a minor component, consistent with this transformation to the

more stable form being facile, depending on the particle size. Calculations of the diamagnetic susceptibility tensors of the polymorphs and their morphologies, provide semi-quantitative estimates of how the diamagnetic susceptibilities of the crystallites differ between polymorphs and explain why mefenamic acid crystallization is unaffected. As the onset of crystallization of carbamazepine and coronene, as defined by changes in turbidity, occur at lower temperatures and hence greater supersaturations in certain ranges of magnetic field strength, this suggests that the field causes precipitation of the metastable form through Ostwald's rule of stages.

INTRODUCTION: The relationship between the specific crystal structure (polymorph),[1, 2] its physical properties, suitable crystallization processes and the performance of the final product is fundamental[3] to the development and manufacture of pharmaceuticals, food stuffs, dyes, explosives and functional organic materials such as organic semiconductors.[4] Industry tries to find all polymorphs and hydrates of a speciality chemical, and a range of automated and manual methods have been developed,[5] but this approach often has to be tailored to the individual molecules.[6, 7] The polymorph screening cannot be restricted to the crystallization conditions suitable for manufacture, as the sudden appearance of a more stable form can lead to the loss of control of crystallization of a previously apparently stable form (disappearing polymorphs),[8] and once seeds of a novel polymorph are available, other methods of crystallization may be found. Hence, computational crystal structure prediction (CSP)[9, 10] is being developed as a complementary tool[11, 12] to polymorph discovery to determine the expected range of polymorphs and their properties.[13] Once the polymorphs have been discovered, then the crystallization of pure phases may require adapting the relative rates of nucleation and growth of the polymorphs, through careful exploration of the variables of the solution, sublimation[14] or ball-milling[15] crystallization process. Many factors can vary the polymorph produced in a crystallization

experiment,[16, 17] from pressure,[18] additives,[19] surface templating,[20, 21] nanoconfinement[22] to laser-induced nucleation[23], and so be appropriate methods for polymorph discovery or control.

A less established method of affecting which polymorph is formed could be the application of a magnetic field during crystal growth.[24, 25] The effects of a magnetic field on a crystallizing system is a topic that has been sporadically explored over the past few decades mainly on inorganic salts and proteins.[26-30] The influence that an applied field has on such dynamic systems is unknown with numerous, often contradictory, hypotheses, and remains to this day, largely, a scientific curio.[31-33] That being said, interesting observations and results keep the subject fresh in the literature, as unquantified as it is. Recently, we found that a magnetic field had an unexpected effect on the crystallization behavior of the polyaromatic hydrocarbon coronene[34] (Figure 1). Under 1 T of applied magnetic field, a second polymorph (β form) was found to grow under ambient conditions. After an investigation into the thermodynamic stability, it was established that the γ form spontaneously transforms into the β form at low temperatures via an enantiotropic transition.[35,36, 37]

The reports of a magnetic field influencing the crystallization of three distinct organic molecules (2,2':6',2''-terpyridine[24], isoxazolone dye[25] and coronene[34]) are intriguing. The cause is not thermodynamic, as even with a molecule with as large an anisotropic magnetic susceptibility as coronene, there is only an energy difference of 10^{-3} J mol^{-1} between alignment perpendicular and along a magnetic field of 1 T, which is so much smaller than k_BT\ at 298 K that the field cannot be affecting the orientational distribution of single molecules in solution. It is not until a molecular cluster of the order of 10^7 coronene molecules is reached that a 1 T magnetic field could produce an energy difference of k_BT at 298 K for different orientations of the molecules. A magnetic field can be used to orientate crystallites of diamagnetic organic

molecules, to aid determination of the structure by powder X-ray diffraction (PXRD),[38] but by this particle size, an internal rearrangement of the molecules within the crystal is unlikely.

The implication is that the magnetic field is affecting the kinetics of either nucleation or growth, or both. It has been previously reported that higher supersaturations of coronene solutions were attainable under an applied magnetic field, detectable through undercooling of the system[34]. It is also emerging that deviations from classical nucleation theory are observed for many organic molecules, with liquid-like/disordered/densified clusters (without polymorph identity but of a size that would be influenced by a magnetic field) being observed even in undersaturated solutions.[39-41] Thus there is the potential for a magnetic field to be influencing behavior within the pre-nucleation clusters.

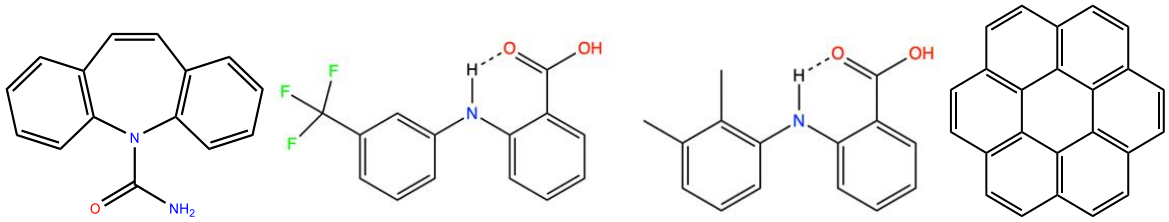


Figure 1. The molecular structures of carbamazepine (CBZ), flufenamic acid (FFA), mefenamic acid (MFA) and coronene.

In this work we determine the effect of strong magnetic fields on the crystallization of three molecular systems that are more typical of pharmaceuticals, namely carbamazepine, flufenamic acid and the closely related mefenamic acid (Figure 1). These results, and more insights into the effect of the magnetic field on the crystallization of coronene, are illuminated by the differences in relative stability and magnetic susceptibility tensors of the competing polymorphs. Experiments on the effects of the field on the crystallization temperature inform the discussion as

to the predictability of whether a magnetic field is able to modify the crystallization of organic molecules.

Methods

The magnetic field crystallization experiments.

A saturated solution of each system was prepared by dissolving the solute in a solvent specific to that molecule (details in SI section I.A). Solute was added to a solvent which was then held at an elevated temperature. Once an equilibrium had been reached between dissolved and undissolved solute, 3 ml of the solution was extruded through a 0.22 μm PTFE filter to remove any potential nucleation centers or undissolved seeds[42] into a quartz cuvette. For CBZ, FFA and MFA the cuvette was then placed inside a copper block pre-heated to 70 °C, situated between magnetic poles (Fig S1) and left to equilibrate for 1 hr. After equilibration, the horizontal linear magnetic field was applied, and the temperature was lowered from 70 to −10 °C at a rate of 1 °C min^{-1}. For coronene, the cuvette was placed in a sample holder (Figure S4) pre-heated to 90 °C and lowered into the sample space of the Bitter magnet (High Field Magnet Laboratory (HFML), cell 3). A vertical linear magnetic field was applied and, after an equilibration time of 30 mins, the temperature was lowered at a rate of 1 °C min^{-1}. Initially, the polymorphic form was established by comparison of the PXRD pattern with those of the known forms. After which, the morphology was used as an identifier, with PXRD used as an occasional control.

Calculation of diamagnetic susceptibility tensors and lattice energies.

All crystal structures in this paper were first optimized with CASTEP[43] using the PBE functional[44] and Tkatchenko and Scheffler's (TS) dispersion correction scheme,[45] a methodology that is widely used for modelling crystal structures of pharmaceutical molecules,[46, 47] particularly in CSP studies.[10] On-the-fly ultra-soft pseudopotentials were used and plane wave cut-off energies and *k*-point grids were carefully selected for the polymorphs of each molecule to ensure

convergence of the total energy (ESI Section II). The optimized structures were converged to a maximum force of less than 0.001 eV/Å. The relative energies for these structures were recalculated using the MBD* dispersion correction,[48] to establish the sensitivity of the relative lattice energies to the dispersion model.

The crystal diamagnetic susceptibilities $\boldsymbol{\chi}^{\mathrm{cryst}}$ of the polymorphs were calculated using this charge distribution, using a sum-over-states perturbation expansion for the susceptibility for a magnetic field with finite wavevector, with the macroscopic $\boldsymbol{\chi}^{\mathrm{cryst}}$ being the limit for a field of infinite wavelength (i.e. uniform $\boldsymbol{B}$),[49] as previously described.[50] The calculated magnetic susceptibility tensors were diagonalized to find the three eigenvalues, $\chi_{\mathrm{i}}^{\mathrm{cryst}}$. From these, the isotropic term, $\chi_{\mathrm{iso}}^{\mathrm{cryst}} = (\sum \chi_{\mathrm{i}}^{\mathrm{cryst}})/3$, and anisotropy (the difference between the largest and smallest eigenvalue), $\Delta\chi_{\mathrm{an}}^{\mathrm{cryst}}$, were calculated. The diamagnetic susceptibility tensor (per molecule within the crystal structure) was overlaid to show its orientation relative to the crystal packing and the main crystal faces, estimated from the crystal structure by the BFDH morphology model[51] calculated using Mercury.[52]

Effect of magnetic field on temperature of crystallization

In an attempt to quantify the extent to which higher supersaturations were attainable under an applied magnetic field,[34] the temperature of crystallization (C_T) was determined spectroscopically (ESI section I.B.). The samples were prepared as for the crystallization experiments. Once in position, the sample was observed spectroscopically using a deuterium-halogen lamp and monitored using an Ocean Insight Flame USB-spectrometer, with C_T being defined at the maximum of the first derivative of the transmission, as a function of temperature (Fig S3). The C_T of coronene in toluene was observed under a range of magnetic fields from 0 to 20 T, in a similar setup in HFML cell 3 (Fig S4), starting at 90 °C at a cooling rate of 1.25 °C

min^{-1}. In order to investigate the parameter space where the effect was maximal, further experiments with a toluene-hexane mixed solvent using the same experimental parameters were carried out at 0.7 T, 0.8 T, 0.9 T, 1.0 T, 1.1 T and 1.2 T in the apparatus shown in Fig S1. Similarly, CBZ was crystallized from ethanol under a range of applied magnetic fields. For flufenamic acid, undercooling experiments were attempted but the extremely high concentrations required resulted in erratic C_T values, and no reliable results were obtained.

Results

Carbamazepine

Carbamazepine (CBZ) (5*H*-dibenz[*b,f*]azepine-5-carboxamide) (Figure 1), an anti-epilepsy and trigeminal neuralgia drug, is a well-established polymorphic system and has five known experimental anhydrous forms and a plethora of solvates, though form IV[53] and form V[54] are yet to be produced in solution screening. CBZ has been shown to manifest as either form II or III based on the supersaturation and temperature of the solution from which it was grown.[55]

CBZ III ($P2_1/c$) has been reported to be the most thermodynamically stable form at atmospheric pressure between 12 K and room temperature.[56, 57] Form I (P-1, Z'=4) is highly metastable, and has a close structural relationship[58] with the void-channel-containing CBZ II, whose growth is stabilized by solvent inclusion.[59] When crystallized from ethanol at RT, form III is grown from a less saturated solution and form II from a more saturated solution.[55] A region of concomitant growth is also observed as the concentration increases from one region to the other.[55] The pharmaceutically used form III is routinely obtained via evaporation, or cooling of an anhydrous ethanol solution. Form I can be accessed from a melt and CBZ III and I are enantiotropically related with a transition temperature at 78 °C,[60] so form III is the thermodynamically stable of these forms during our crystallization experiments.

When saturated solutions of CBZ in ethanol were cooled in a magnetic field between 0 and 0.4 T, the expected form III is routinely found (95% over approx. 65 experiments). When a magnetic field of > 0.5 T is applied, form I is by far the most commonly observed polymorph (88% over approx. 120 experiments) (Figure 2).

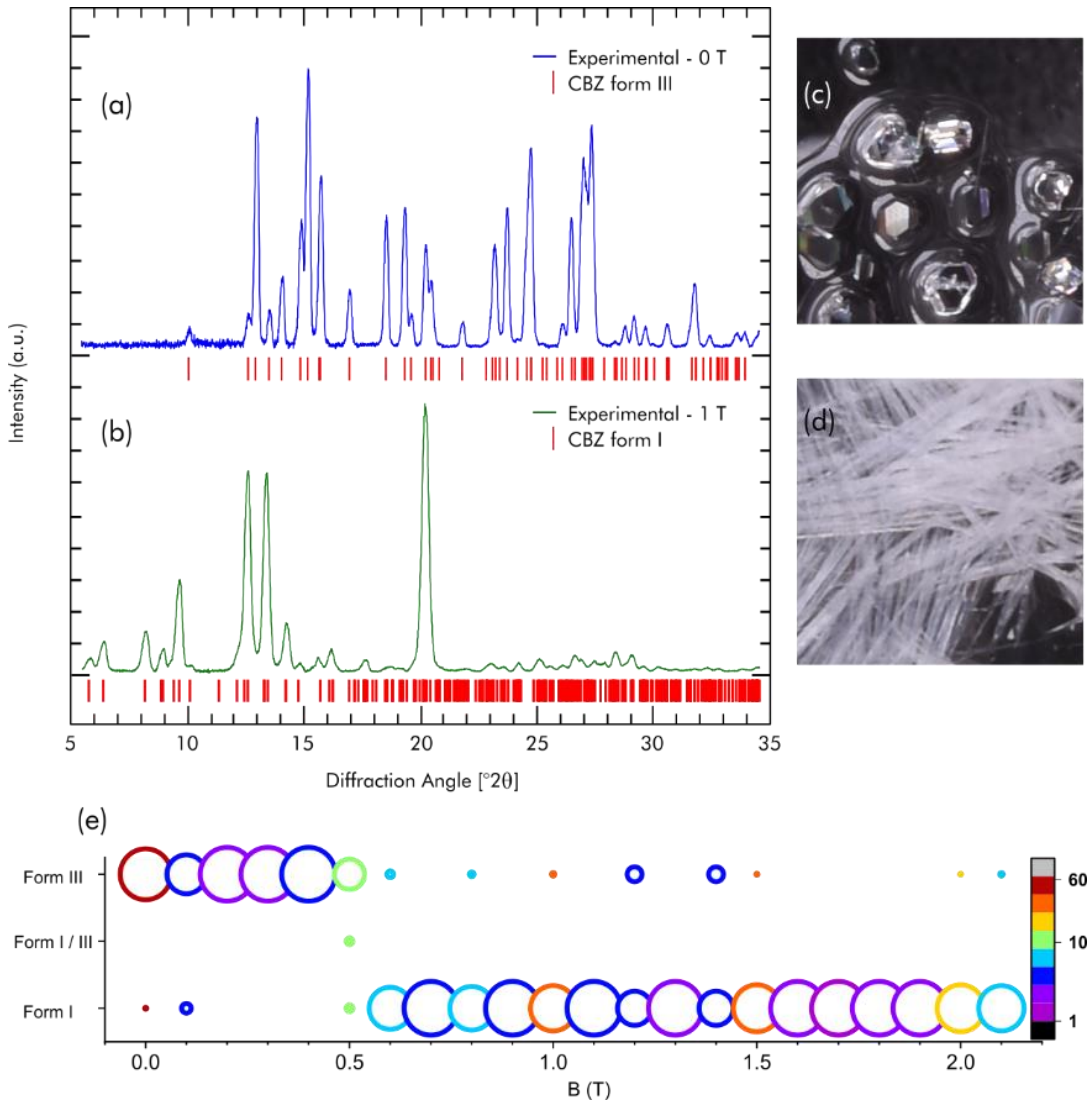
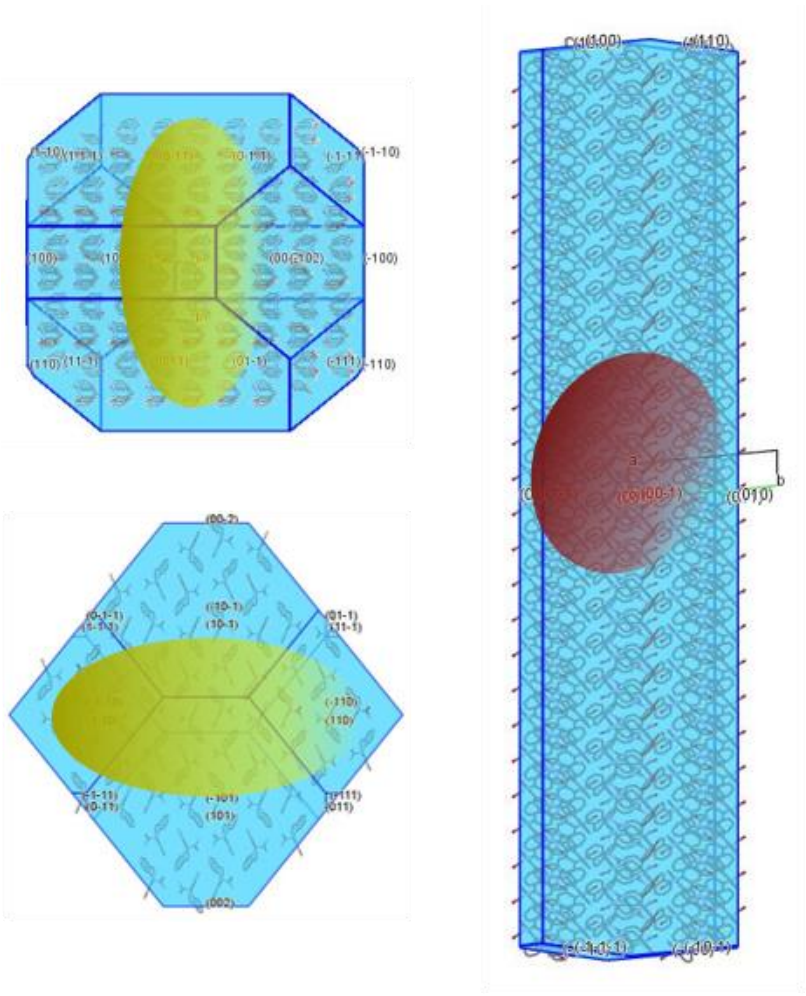


Figure 2. The changes in the polymorph of carbamazepine crystallized from ethanol in varying magnetic fields. Characteristic experimental powder diffraction patterns of (a) form III grown under no field and (b) form I grown at B = 1 T. Optical images of the characteristic morphology of (c) form III and (d) form I. (e) The results of the multiple repeats of the crystallization

experiments at each magnetic field strength, colour coded by number of experiments, with the size of the circles representing the relative proportion of the experiments which resulted in the form or mixture specified in the vertical axis.

Analysis of the diffraction data of the samples crystallized under different fields shows no sign of concomitant polymorphism when the field is under 0.4 T (with most experiments returning pure form III) or over 0.6 T (with most experiments returning pure form I). However, when CBZ crystallizes under an applied field of 0.5 T, some samples were a mixture of forms I and III, though some experiments did give phase-pure form I or phase-pure form III. Furthermore, there is a very strong tendency for a magnetic field above 0.6 T to produce the metastable form I, which rarely occurs at low magnetic fields, with an intermediate field strength sometimes producing a mixed phase.



Form III	Form I
Stable below 351 K	Stable above 351 K
ΔE_{latt} (TS) = 0.00 kJ mol^{-1}	ΔE_{latt} (TS) = 5.13 kJ mol^{-1}
ΔE_{latt} (MBD*) = 0.00 kJ mol^{-1}	ΔE_{latt} (MBD*) = 5.53 kJ mol^{-1}
χ_{iso}^{cryst} = -140 cgs-ppm	χ_{iso}^{cryst} = -140 cgs-ppm
$\Delta\chi_{an}^{cryst}$ = -96 cgs-ppm	$\Delta\chi_{an}^{cryst}$ = -32 cgs-ppm
χ_{i}^{cryst} = -103, -117, -198	χ_{i}^{cryst} = -129, -131, -161

Figure 3. Calculated properties of the observed carbamazepine polymorphs, illustrated by the BFDH morphology of form I and III of CBZ, overlaid with the orientated diamagnetic susceptibility tensor χ ellipsoids, per molecule in the crystal. The properties are calculated with the PBE functional, with the relative lattice energies using the two specified dispersion corrections. Experimental temperature range of stability from ref. 60.

The only polymorph, other than the expected form III, that was observed in the experiments was form I, which is metastable at ambient temperature, with the relative stability changing markedly with temperature. The structure is very different from that in form III, as although both CBZ I and III are based on CBZ hydrogen bonded dimers, the packing of the aromatic rings is significantly different, giving rise to differences in the anisotropy of the diamagnetic susceptibility tensors (Figure 3). The CBZ I packing is based on "translation stacks" of molecules, while CBZ III is based on so-called "inversion cups", formed by two CBZ molecules.[58] The morphology of the crystals is also very different (Figure 2(c,d)), so although the anisotropy of diamagnetic susceptibility per molecule within the crystals is smaller for form I, the maximum eigenvector has a significant component along the needle axis (Figure 3), and so a sufficiently large crystallite of form I would have a larger diamagnetic anisotropy than form III.

Flufenamic acid

Flufenamic acid (FFA, N-(3-Trifluoromethylphenyl)anthranilic acid) (Figure 1) is a fluorinated member of the fenamate group of nonsteroidal anti-inflammatory drugs. It is known to be highly polymorphic,[61] with a number of polymorphs being crystallized at room temperature and pressure in the presence of polymer additives. At room temperature the two most stable polymorphs, form I and form III, are close in energy, with form III being the most stable structure below 42 °C and form I above this temperature, up to the melting point of the solid.[62] Both polymorphs are accessible via solvent cooling experiments.[63, 64]

When FFA crystals are grown from ethanol, the polymorph produced can be affected by the magnetic field (Figure 4), but the outcome is not as reliable as for CBZ (Figure 2). Under zero-field conditions, FFA crystallized as Form III 85.7 % of the time with the remaining 14.3 % of experiments resulting in form I. As the field is increased to 0.5 T, form I crystallizes more

frequently in 66.7 % of the experiments, with similar results at 1.0 T. At 2.0 T however, the appearance of form I becomes less common, reducing to 33.3 % of experiments. Although this data is compelling, the extremely high concentration of FFA required for these experiments (600 mg/ml) along with the elevated temperatures, made avoiding any crystallization occurring during solution preparation and transferring extremely challenging, and the FFA experiments are the most likely to be affected by some nucleation occurring prior to switching on the field.

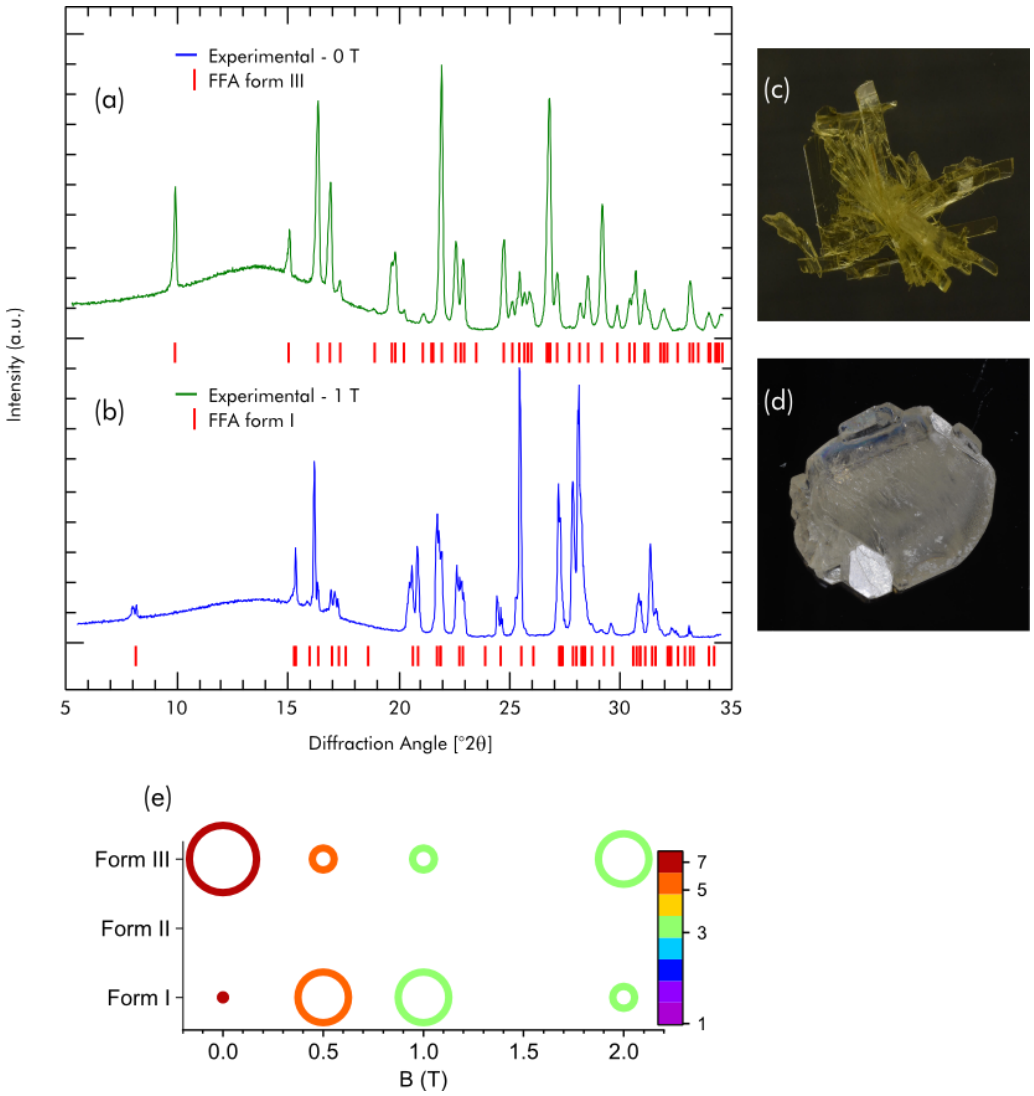


Figure 4. The changes in the polymorph of flufenamic acid crystallized from ethanol in varying magnetic fields. Characteristic powder diffraction patterns of (a) form III, most likely to be

grown in field-free conditions and (b) form I which usually crystallized at B > 0.5 T. Characteristic morphologies in optical images of (c) form III and (d) form I morphology. (e) The results of the multiple repeats of the crystallization experiments at each magnetic field strength, colour coded by number of experiments, with the size of the circles representing the relative proportion of the experiments which resulted in the form or mixture specified on the vertical axis.

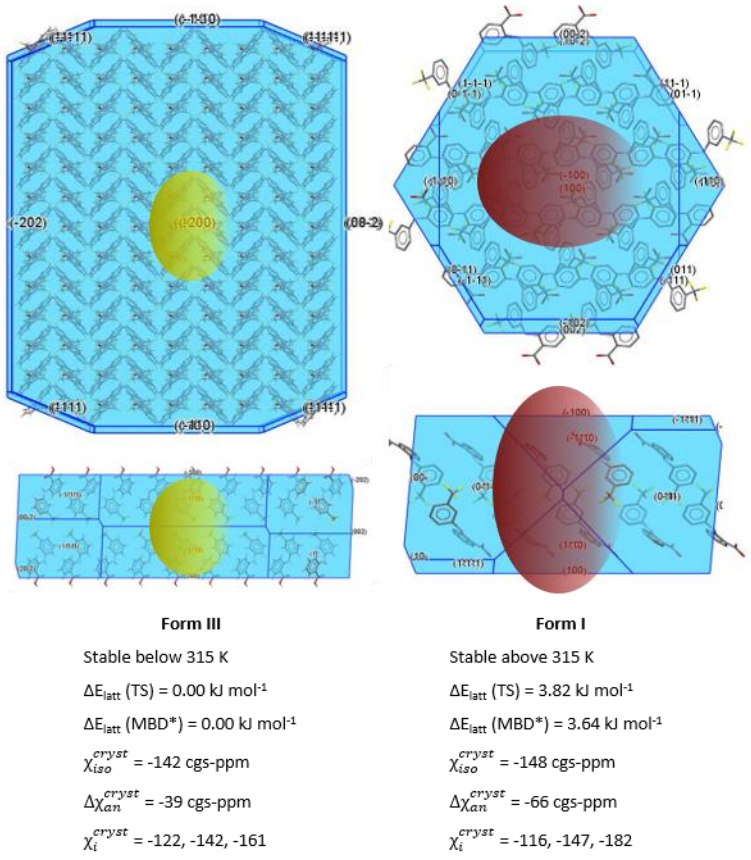


Figure 5. Calculated properties of the observed flufenamic acid polymorphs, illustrated by the BFDH morphology of form III and I of FFA, overlaid with the orientated diamagnetic susceptibility tensor χ ellipsoids, per molecule in the crystal. The properties are calculated with the PBE functional, with the relative lattice energies including the two specified dispersion corrections. Experimental temperature range of stability from ref. 62.

The diamagnetic susceptibility tensor of flufenamic acid is more anisotropic per molecule when in the packing and conformation of form I than form III. There is also a marked difference between the BFDH predicted and observed morphologies (contrast Figure 4 & Figure 5) relative to the difference between the observed morphologies, so it is uncertain how the shape of a growing crystal would determine the anisotropy of the diamagnetic susceptibility of the crystallite. However, FFA molecules adopt very different conformations in the crystals of form I and III,[50] separated by a sizable energy barrier (i.e. forms I and III are conformational polymorphs[65]), which also contributes to the difference in magnetic susceptibility.

Mefenamic acid

Mefenamic acid (MFA, 2-[(2,3-dimethylphenyl)amino]benzoic acid) is similar to FFA being another anthranilic acid derivative but MFA has only three polymorphs,[66] with form III being highly metastable and found in an attempted cocrystallization experiment with adenine.[66] Form II is stable at elevated temperatures (the transition temperature is 86.6 °C[60]) and form I is the most stable at ambient. Form I crystallizes from most solvents, though form II forms on rapid cooling of DMF solutions, and crystals of form II suitable for structure determination have been prepared by slow evaporation from chloroform in less humid conditions.[66] Form II has also been produced in a high pressure crystallization experiment.[67] When templated by specific self-assembled monolayers,[68] the nucleation of mefenamic acid from ethanol and methanol shows a preference for form II.[68] Subjected to the same experimental conditions as the previous compounds in this study, MFA showed no polymorph selectivity whatsoever, always crystallizing as form I from ethanol, at any applied magnetic field strength tested (ESI section I.A.1). The diamagnetic susceptibility tensors for form I and form II (Figure 6) and all other observed crystal structures of mefenamic acid (ESI IIA) are very similar. This is because the

crystal magnetic susceptibility of a polymorph is largely determined by the relative orientations of the aromatic rings, regardless of whether they are in the same molecule or not, which are similar in all three MFA polymorphs. The MFA conformational polymorphs differ by an approximately 180° change in the torsion angle determining the methyl position, and hence the molecular contribution to $\boldsymbol{\chi}^{\mathrm{cryst}}$ is similar. Thus, mefenamic acid polymorphs or their nuclei are likely to be affected in similar ways by a magnetic field.

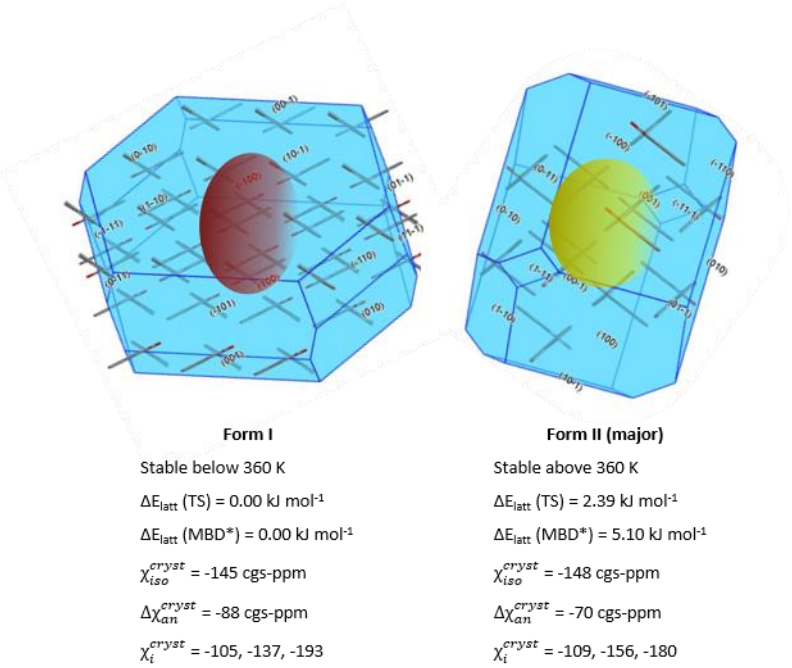
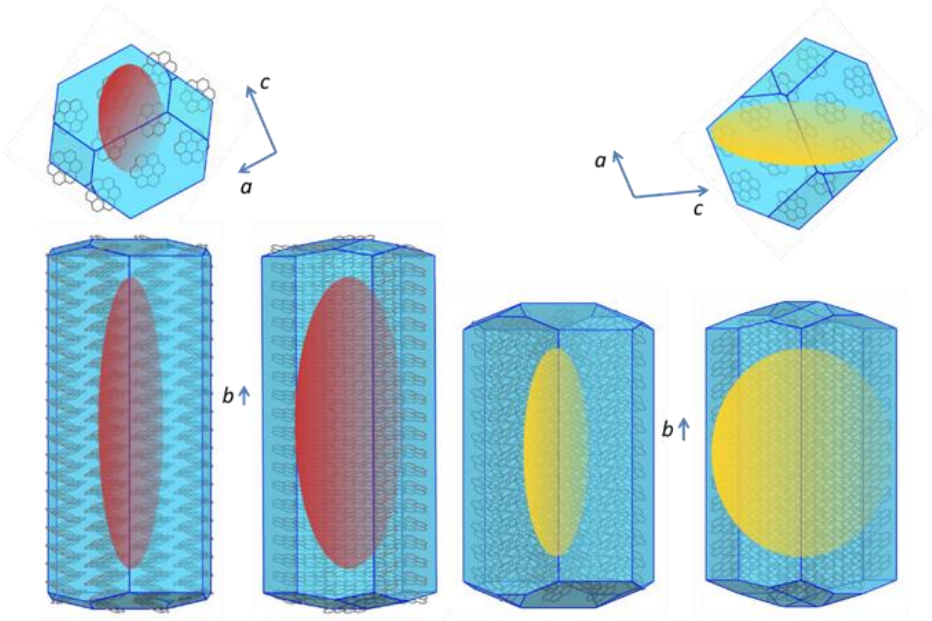


Figure 6. Calculated properties of the observed mefenamic acid polymorph, form I, and the alternative polymorph form II which has been seen in competition with form I in other studies,[68] illustrated by the BFDH morphology, overlaid with the orientated diamagnetic susceptibility tensor χ ellipsoids, per molecule in the crystal. The structure for disordered form II is that of its major component; the results for the minor component of form II and form III are in SI Table S3. The properties are calculated with the PBE functional, with the relative lattice energies including the two specified dispersion corrections. The experimental temperature range of stability is from ref. 60

Coronene

The size of a β coronene crystal grown under a magnetic field[34] was sufficient to establish its structure by single crystal X-ray diffraction. Calculation of the Raman spectra of the two forms has shown that the β form is the more stable phase of coronene at low temperatures,[36, 37] which had not previously been characterized because the γ crystals shatter on cooling. Examination of the phase transition in different samples, (ESI section I.D) shows that the polymorphic transformation is dependent on crystal size. As this is a first order transformation, the degree of hysteresis in the transition is expected to be very dependent on the quality of the crystal, its size and the cooling rate. The unprecedented growth of a large single crystal of β coronene at ambient in a magnetic field gave a crystal that was sufficiently large and perfect that it could be cooled to 80 K for structure determination.

Unfortunately, the reproducibility of the growth of β coronene from solution at room temperature is difficult, despite repeated attempts for this work, β coronene has only been observed as small crystallites grown concomitantly with γ a small number of times in the alternative apparatus (ESI figure S4) at the High Field Magnet Laboratory. Periodic DFT-D calculations vary in the relative lattice energies and stability order of the two forms with dispersion correction (Figure 7 with more values in SI Table S4) but phonon calculations (ESI section II.C) show that increasing temperature favours the γ form. However, the experimental evidence is clear that β is the low temperature form, enantiotropically related to the γ form. Crucially, the growth of a single crystal of β in a magnetic field was under conditions when it was metastable. Hence the inability to reproducibly grow the metastable β polymorph in a magnetic field at ambient seems to be another case of the common phenomenon of "disappearing polymorphs".



Form β

Stable below 160 K

ΔE_{latt} (TS) = 0.00 kJ mol^{-1}

ΔE_{latt} (MBD*) = 0.02 kJ mol^{-1}

ΔE_{latt} (D3BJ) = 0.00 kJ mol^{-1}

χ_{iso}^{cryst} = -267 cgs-ppm

$\Delta\chi_{an}^{cryst}$ = -392 cgs-ppm

χ_{i}^{cryst} = -111, -188, -503

Form γ

Stable above 160 K

ΔE_{latt} (TS) = 6.79 kJ mol^{-1}

ΔE_{latt} (MBD*) = 0.00 kJ mol^{-1}

ΔE_{latt} (D3BJ) = 2.90 kJ mol^{-1}

χ_{iso}^{cryst} = -262 cgs-ppm

$\Delta\chi_{an}^{cryst}$ = -249 cgs-ppm

χ_{i}^{cryst} = -111, -315, -359

Figure 7. Calculated properties of the coronene polymorphs, illustrated by the BFDH morphology overlaid with the orientated diamagnetic susceptibility tensor χ ellipsoids, per molecule in the crystal. The properties are calculated with the PBE functional, with the relative lattice energies including the three specified dispersion corrections. The experimental temperature range of stability is from ref. 37.

Effect of magnetic field on supersaturation/point of crystallization

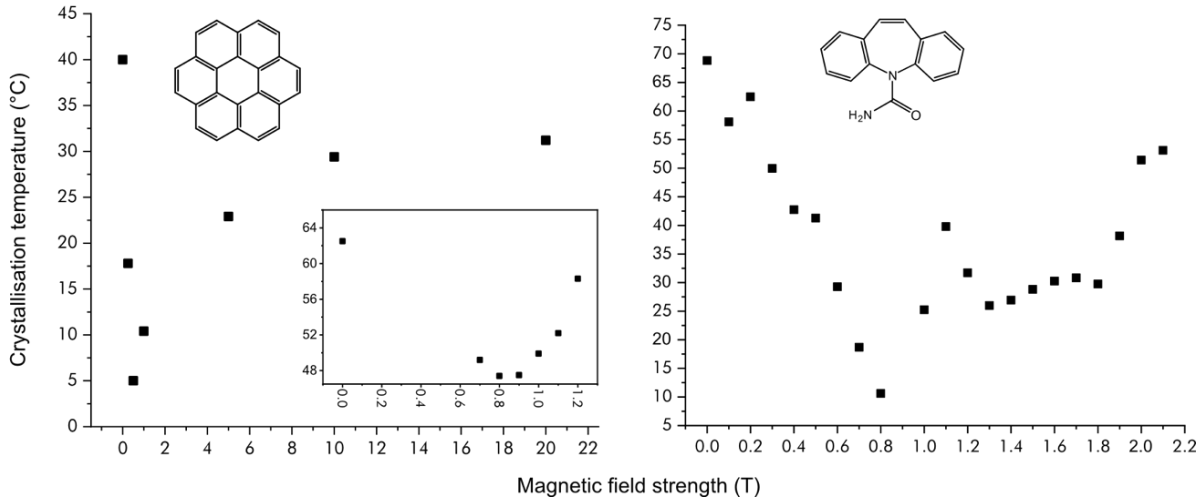


Figure 8. Suppression of crystallization in (left) coronene-toluene system as a function of B up to 20 T. Inset shows a fine variation of B around the inflection point conducted using a toluene-hexane mixed solvent from 0 to 1.2 T, in order to increase the crystallization temperature. (Right) Suppression of crystallization of the CBZ ethanol system as a function of B.

As can be seen from Figure 8, regardless of field strength, the crystallization temperature, C_T, of coronene in toluene is suppressed when compared to zero applied field (C_T = 40 °C). When a linear magnetic field is applied during the cooling of the system, a dramatic change in C_T is observed until a maximum ΔC_T at 0.5 T. This initial, approximately linear suppression of crystallization changes when the field is increased beyond 1.0 T and moves asymptotically towards ΔC_T = 10 °C. This complex behavior suggests more than one physical attribute of crystallization is being affected by the magnetic field with the most pronounced effect for coronene in toluene occurring between 0.5 T and 1.0 T. As the C_T of a saturated solution of coronene in toluene was depressed to 6 °C, a single degree higher than the lowest temperature of which the equipment is capable, a toluene-hexane mixed solvent with a ratio of 1:10 was used to

make a saturated solution in which coronene is slightly less soluble, and this was also investigated. The C_T is 21 °C higher in the hexane-toluene mixed solvent than in pure toluene under 0 T (Figure 8, left insert and Figure S5). The trend in the mixed solvent system looks similar to that of the toluene-only system, but the largest ΔC_T was considerably smaller (15 °C) than in pure toluene (35 °C), though seen within a similar range of magnetic fields (0.8 – 1.0 T and 0.5 – 1.0 T).

As with the coronene, CBZ was crystallized under a range of applied magnetic fields inside smaller magnets (ESI Figure S1) to look for differences in C_T (Figure 8, right). An increase in applied magnetic field also has a 'suppressive' effect on the C_T of CBZ crystals. There is a dramatic change in crystallization temperature with field up to 0.8 T giving a maximum ΔC_T of 59 °C. At higher fields the suppression of crystallization reduces erratically.

Discussion

In this work, we investigated the polymorphic outcome in solution cooling crystallizations for four different organic molecules under the influence of an applied magnetic field. CBZ crystallizes in a metastable form in higher applied fields, FFA has a higher rate of crystallizing in a metastable form in fields around 1 T, coronene has been found to crystallize in a metastable form[34] or as a phase impurity (ESI Figure S7) in a field, while the crystallization of MFA is unaffected by the field. All three pharmaceutical molecules have a much smaller average diamagnetic susceptibility per molecule in their polymorphs (χ_{iso}^{mol} between –140 and –150 cgs-ppm) compared with coronene (about –265 cgs-ppm) as might be expected from the smaller aromatic systems (Figure 1). Nevertheless, for two of the model pharmaceuticals, crystallizing in certain magnetic fields produces a metastable polymorph, in experiments that yield the stable form when the field is not switched on. Thus we have shown that a magnetic field can influence

the polymorphic outcome of pharmaceutical molecules. The anisotropy of the diamagnetic susceptibility tensor differs significantly between the polymorphs, except in the case of mefenamic acid, the case where the field does not affect the polymorph observed.

Additional investigations have shown that adjusting the field strength affects the temperature at which a cooling solution crystallizes, showing an 'undercooling' effect in coronene and CBZ systems, implying supersaturations greater than those reached when no field is applied. A given concentration is less supersaturated with respect to the metastable form than the stable form, so the undercooling effect would not favor the metastable product. However, Ostwald's rule of stages[69-71] suggests the metastable form nucleates first, and a greater supersaturation would lead to it crystallizing from solution once the stochastic nucleation process has started, reducing the opportunity for transformation to the more stable form.

If the effect of the magnetic field is merely to suppress nucleation, allowing the metastable form to crystalize, then the nucleation will be stochastic reflecting the variations in molecular level dynamics. Although our experimental set-up has been designed to try to make the experiments only differ in the application of a field, it is perhaps not surprising[72] that it was not possible to reproduce the growth of β coronene under ambient conditions except as a minor phase in a magnetic field, or gain reproducible results with flufenamic acid. For coronene, the transition between the two forms is relatively facile, though dependent on sample size (ESI section I.D) and so, only crystals of the β form that have grown to a sufficient size and structural purity not to rapidly transform to the stable γ form at ambient could be observed by the time the sample was analyzed by PXRD. In contrast, CBZ does not readily transition between the two forms observed here,[57] which is why we observe the metastable product in abundance. Flufenamic acid, as one of the archetypal polymorphophores,[73] has such a tendency to be trapped

in metastable structures[61] that the competition between form I and form III may be influenced by competition with many other polymorphs.

We have no evidence for the magnetic field affecting the polymorphic outcome in a more specific way than altering the relative kinetics of nucleation and growth to favor known metastable forms. Within classical nucleation theory, in which the spherical nucleus has the final structure, its response to a magnetic field will differ between polymorphs, as reflected in the calculated diamagnetic susceptibility anisotropy. However, the polymorph favored by the field is not always the one with the largest magnetic anisotropy. Furthermore, a spherical nanocluster of diameter more than 100 nm with the structure of CBZ III, containing 3 x 10^6 molecules, would be required before the energy difference between aligning the classical spherical nucleus perpendicular or along a field of 1T would be comparable to k_BT at ambient temperature. Hence, a magnetic field would not be expected to affect the polymorph formed within classical nucleation theory (CNT). However, we do observe that a magnetic field can affect the crystallization temperature and polymorphic outcome implying that CNT does not correctly describe these systems.

The magnetic susceptibility of a crystallite is affected by its size and shape, as it is tensorially additive, and some of the competing polymorph pairs differ in morphology. Orientated or rotating growing crystallites could modify the approach of solute growth units to the nascent crystallite, and possibly affect the growth spirals. Magnetic fields with gradients can suppress the surface convections, thus slowing down the growth of protein crystals,[74, 75] though our experiments are in a uniform field. If the field is affecting the structure of the surface layer and local supersaturation, then this can affect the relative thermodynamic stability of the polymorphs at small nuclei/crystallite sizes.[76] Although it is plausible that the field differentially affects

crystallite growth, it seems more likely that the field is affecting the formation of pre-nucleation clusters in which there is an increased density of solute molecules but the cluster is still liquid-like. In this type of two-step nucleation, there are many factors that can influence which polymorph emerges, such as the presence of surfaces.[77] It is conceivable that the field may make a difference to the organization of the molecules within the dense solvent-solute cluster, but elucidating the mechanism would require more experimental work.[39, 40] With a molecular level model of a nucleating cluster, it would be feasible to estimate its magnetic susceptibility, assuming tensorial addition of the molecular susceptibility, which is a good approximation for crystals.[50]

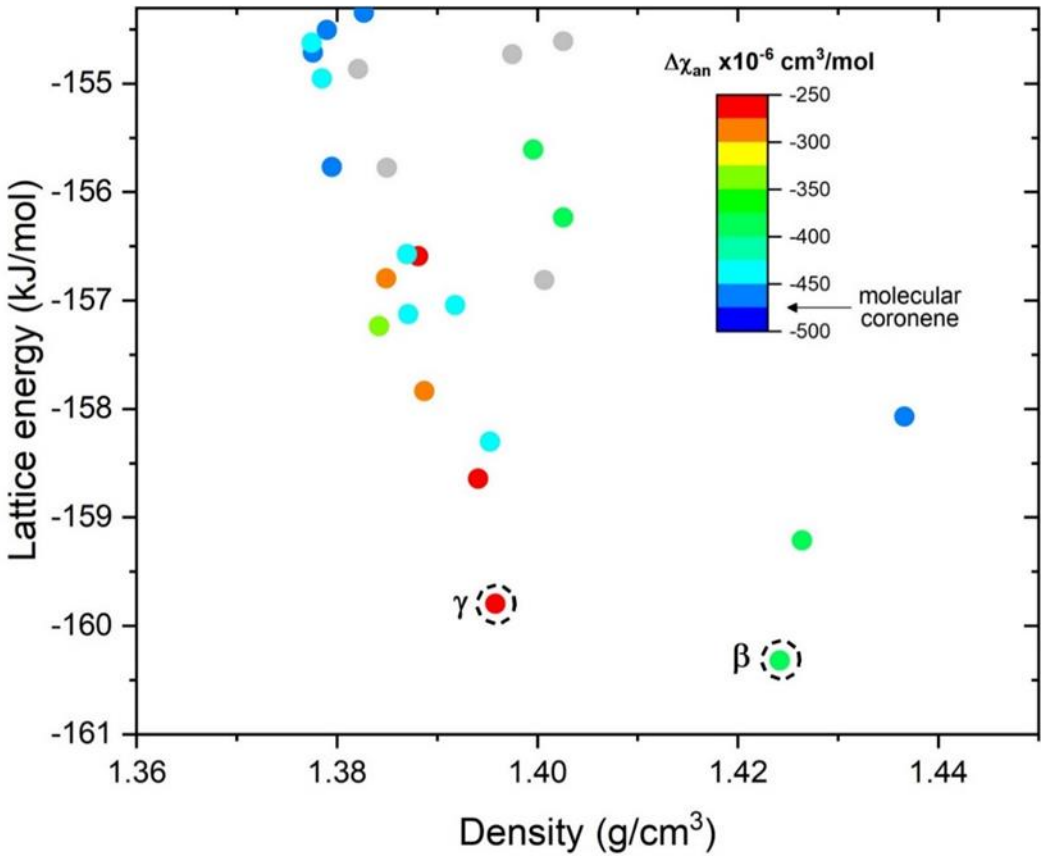


Figure 9. The summary of the output of a CSP study on coronene, where each symbol represents a minimum in the lattice energy, colored by the anisotropy in the diamagnetic susceptibility.

If the magnetic field always favors metastable polymorphs, then it may be a useful additional tool in polymorph control when a metastable form is needed. There is also the potential of combining crystal structure prediction studies with the estimate of the magnetic susceptibility tensor to produce energy-structure-$\Delta\chi_{an}^{cryst}$ maps[50] to determine whether there are unobserved structures that are energetically competitive with the known forms, whose crystallization could be more favorable in a magnetic field. Such a map is shown in Figure 9 for coronene, where it is clear that the β form is not only close in energy to the γ form that is usually crystallized at ambient but also will be more affected by a magnetic field, suggesting that magnetic field-induced polymorph change is a distinct possibility. The magnetic field could not affect the polymorphic outcome if the diamagnetic susceptibility tensor was the same for each polymorph (as found for mefenamic acid (Figure 6)), so such property crystal energy landscapes can at least show when there are no thermodynamically competitive unseen structures whose nucleation may be affected by a magnetic field.

In summary, crystallization in a magnetic field is a technique that may affect polymorphic outcome and so could be considered as a route to finding more polymorphs. This effect needs consideration when an applied field is necessary during analysis (e.g. in most Transmission Electron Microscopes).[78] However, far more needs to be understood about the nucleation of organic molecules before it can be considered as a reliable route to polymorph control for specific pharmaceutical systems.

Conclusion

We have demonstrated that a magnetic field can affect the polymorphic outcome of crystallization of model pharmaceutical molecules, containing typical aromatic systems,

provided that they are packed to give a significant difference in the anisotropy of the diamagnetic susceptibility tensor. For carbamazepine, the crystallization of metastable form I at fields greater than 0.6 T is reasonably reproducible (Figure 2). In the case of flufenamic acid, there is a switch in whether form III or I is preferred over a range of fields. On the basis of this limited range of compounds, it seems that the magnetic field can help stabilize the nucleation of the metastable form. This is likely to occur from the magnetic field suppressing nucleation, leading to a higher supersaturation when crystallization occurs. More work is needed to understand crystallization in a magnetic field, but calculations can establish when a magnetic field could not distinguish between polymorphs as shown for mefenamic acid.

ASSOCIATED CONTENT

Supporting Information.

The following files are available free of charge.

Referenced data S1 – S10, detailed experimental information and computational methods (PDF)

AUTHOR INFORMATION

Corresponding Author

Simon R. Hall

Email: simon.hall@bristol.ac.uk

Author Contributions

S.R.H. initiated and supervised the project. J.P. and C.H. performed the crystallization and structural characterization experiments at Bristol. R.G. performed the CASTEP calculations

under the supervision of S.L.P. All authors contributed to the discussion of the results, analysis of the materials and to manuscript preparation.

Funding Sources

Any funds used to support the research of the manuscript should be placed here (per journal style).

Notes

The authors declare that they have no competing interests.

ACKNOWLEDGMENT

This work is supported by MagnaPharm, a collaborative research project funded by the European Union's Horizon 2020 Research and Innovation programme under Grant Agreement Number 736899. S.R.H., J.P. and C.H. acknowledge the Engineering and Physical Sciences Research Council UK (grants EP/L015544/1), and the Bristol Centre for Functional Nanomaterials and the Centre for Doctoral Training in Condensed Matter Physics for project funding. Part of the computational work was carried out on ARCHER, UK National Supercomputing Service (http://www.archer.ac.uk) via our membership of the UK's HEC Materials Chemistry Consortium, which is funded by EPSRC (EP/L000202). R.G. acknowledges the help of Prof. Jonathan Yates, Dr. Simone Sturniolo, and CCP-NC, Collaborative Computational Project for NMR Crystallography, for carrying out magnetic property calculations with CASTEP.

REFERENCES

1. Bernstein, J., *Polymorphism in Molecular Crystals*. 2nd ed.; Clarendon Press: Oxford, 2020.

2. Hilfiker, R.; von Raumer, M., *Polymorphism in the Pharmaceutical Industry, solid form and drug development*. 2 ed.; Wiley-VCH: Weinheim, Germany, 2019.

3. Sun, C. C., Material Science Tetrahedron-A Useful Tool for Pharmaceutical Research and Development. *Journal of Pharmaceutical Sciences* **2009,** *98*, 1671-1687.

4. Yang, Y.; Rice, B.; Shi, X. Y.; Brandt, J. R.; da Costa, R. C.; Hedley, G. J.; Smilgies, D. M.; Frost, J. M.; Samuel, I. D. W.; Otero-De-La-Roza, A.; Johnson, E. R.; Jelfs, K. E.; Nelson, J.; Campbell, A. J.; Fuchter, M. J., Emergent Properties of an Organic Semiconductor Driven by its Molecular Chirality. *Acs Nano* **2017,** *11* (8), 8329-8338.

5. Pfund, L. Y.; Matzger, A. J., Towards Exhaustive and Automated High-Throughput Screening for Crystalline Polymorphs. *ACS Combinatorial Science* **2014,** *16* (7), 309-313.

6. Newman, A., Specialized Solid Form Screening Techniques. *Organic Process Research & Development* **2013,** *17* (3), 457-471.

7. Bhardwaj, R. M.; McMahon, J. A.; Nyman, J.; Price, L. S.; Konar, S.; Oswald, I. D. H.; Pulham, C. R.; Price, S. L.; Reutzel-Edens, S. M., A Prolific Solvate Former, Galunisertib, under the Pressure of Crystal Structure Prediction, Produces Ten Diverse Polymorphs. *Journal of the American Chemical Society* **2019,** *141* (35), 13887-13897.

8. Bucar, D. K.; Lancaster, R. W.; Bernstein, J., Disappearing Polymorphs Revisited. *Angewandte Chemie-International Edition* **2015,** *54* (24), 6972-6993.

9. Reilly, A. M.; Cooper, R. I.; Adjiman, C. S.; Bhattacharya, S.; Boese, A. D.; Brandenburg, J. G.; Bygrave, P. J.; Bylsma, R.; Campbell, J. E.; Car, R.; Case, D. H.; Chadha, R.; Cole, J. C.; Cosburn, K.; Cuppen, H. M.; Curtis, F.; Day, G. M.; DiStasio Jr, R. A.; Dzyabchenko, A.; van Eijck, B. P.; Elking, D. M.; van den Ende, J. A.; Facelli, J. C.; Ferraro, M. B.; Fusti-Molnar, L.; Gatsiou, C.-A.; Gee, T. S.; de Gelder, R.; Ghiringhelli, L. M.; Goto, H.; Grimme, S.; Guo, R.; Hofmann, D. W. M.; Hoja, J.; Hylton, R. K.; Iuzzolino, L.; Jankiewicz, W.; de Jong, D. T.; Kendrick, J.; de Klerk, N. J. J.; Ko, H.-Y.; Kuleshova, L. N.; Li, X.; Lohani, S.; Leusen, F. J. J.; Lund, A. M.; Lv, J.; Ma, Y.; Marom, N.; Masunov, A. E.; McCabe, P.; McMahon, D. P.; Meekes, H.; Metz, M. P.; Misquitta, A. J.; Mohamed, S.; Monserrat, B.; Needs, R. J.; Neumann, M. A.; Nyman, J.; Obata, S.; Oberhofer, H.; Oganov, A. R.; Orendt, A. M.; Pagola, G. I.; Pantelides, C. C.; Pickard, C. J.; Podeszwa, R.; Price, L. S.; Price, S. L.; Pulido, A.; Read, M. G.; Reuter, K.; Schneider, E.; Schober, C.; Shields, G. P.; Singh, P.; Sugden, I. J.; Szalewicz, K.; Taylor, C. R.; Tkatchenko, A.; Tuckerman, M. E.; Vacarro, F.; Vasileiadis, M.; Vazquez-Mayagoitia, A.; Vogt, L.; Wang, Y.; Watson, R. E.; de Wijs, G. A.; Yang, J.; Zhu, Q.; Groom, C. R., Report on the sixth blind test of organic crystal structure prediction methods. *Acta Crystallographica Section B* **2016,** *72* (4), 439-459.

10. Price, S. L., Is zeroth order crystal structure prediction (CSP_0) coming to maturity? What should we aim for in an ideal crystal structure prediction code? *Faraday Discussions* **2018,** *211*, 9-30.

11. Price, S. L.; Reutzel-Edens, S. M., The potential of computed crystal energy landscapes to aid solid-form development. *Drug Discovery Today* **2016,** *21* (6), 912-923.

12. Nyman, J.; Reutzel-Edens, S. M., Crystal structure prediction is changing from basic science to applied technology. *Faraday Discussions* **2018,** *211*, 459-476.

13. Musil, F.; De, S.; Yang, J.; Campbell, J. E.; Day, G. M.; Ceriotti, M., Machine learning for the structure-energy-property landscapes of molecular crystals. *Chemical Science* **2018,** *9* (5), 1289-1300.

14. Kamali, N.; O'Malley, C.; Mahon, M. F.; Erxleben, A.; McArdle, P., Use of Sublimation Catalysis and Polycrystalline Powder Templates for Polymorph Control of Gas Phase Crystallization. *Crystal Growth & Design* **2018,** *18* (6), 3510-3516.

15. Kamali, N.; Gniado, K.; McArdle, P.; Erxleben, A., Application of Ball Milling for Highly Selective Mechanochemical Polymorph Transformations. *Organic Process Research & Development* **2018,** *22* (7), 796-802.

16. Llinas, A.; Goodman, J. M., Polymorph Control: past, present and future. *Drug Discovery Today* **2008,** *13* (5/6), 198-210.

17. Lee, E. H., A practical guide to pharmaceutical polymorph screening & selection. *Asian Journal of Pharmaceutical Sciences* **2014,** *9* (4), 163-175.

18. Fabbiani, F. P. A.; Pulham, C. R., High-pressure studies of pharmaceutical compounds and energetic materials. *Chemical Society Reviews* **2006,** *35* (10), 932-942.

19. Bucar, D. K.; Day, G. M.; Halasz, I.; Zhang, G. G. Z.; Sander, J. R. G.; Reid, D. G.; MacGillivray, L. R.; Duer, M. J.; Jones, W., The curious case of (caffeine).(benzoic acid): how heteronuclear seeding allowed the formation of an elusive cocrystal. *Chemical Science* **2013,** *4* (12), 4417-4425.

20. Solomos, M. A.; Capacci-Daniel, C.; Rubinson, J. F.; Swift, J. A., Polymorph Selection via Sublimation onto Siloxane Templates. *Crystal Growth & Design* **2018,** *18* (11), 6965-6972.

21. Case, D. H.; Srirambhatla, V. K.; Guo, R.; Watson, R. E.; Price, L. S.; Polyzois, H.; Cockcroft, J. K.; Florence, A. J.; Tocher, D. A.; Price, S. L., Successful Computationally Directed Templating of Metastable Pharmaceutical Polymorphs. *Crystal Growth & Design* **2018,** *18* (9), 5322-5331.

22. Ward, M. D., Perils of Polymorphism: Size Matters. *Israel Journal of Chemistry* **2017,** *57* (1-2), 82-91.

23. Clair, B.; Ikni, A.; Li, W. J.; Scouflaire, P.; Quemener, V.; Spasojevic-de Bire, A., A new experimental setup for high-throughput controlled non-photochemical laser-induced nucleation: application to glycine crystallization. *Journal of Applied Crystallography* **2014,** *47*, 1252-1260.

24. Honjo, S.; Yokota, M.; Doki, N.; Shimizu, K., Magnetic Field Influence on the Crystal Structure of 2,2′:6′,2″-Terpyridine. *Kagaku Kogaku Ronbunshu* **2008,** *34* (3), 383-387.

25. Aret, E. Growth of Organic Dye Crystals Morphology and Polymorphism. Radboud, Radboud University, 2013.

26. Kuschel, F.; König, A. N.; Gropp, R., Crystal Growth in Magnetic Fields (I) Crystallization of Me (NH4)2(SO4)2 · 6 H2O (Me = Zn, Cu, Ni, Fe) from Aqueous Solutions in Moderate Magnetic Fields. *Crystal Research and Technology* **1982,** *17* (7), 793-799.

27. Freitas, A. M. B.; Landgraf, F. J. G.; Nvltý, J.; Giulietti, M., Influence of Magnetic Field in the Kinetics of Crystallization of Diamagnetic and Paramagnetic Inorganic Salts. *Crystal Research and Technology* **1999,** *34* (10), 1239-1244.

28. Wakayama, N. I., Effects of a Strong Magnetic Field on Protein Crystal Growth. *Crystal Growth & Design* **2003,** *3* (1), 17-24.

29. Tai, C. Y.; Wu, C.-K.; Chang, M.-C., Effects of magnetic field on the crystallization of CaCO3 using permanent magnets. *Chemical Engineering Science* **2008,** *63* (23), 5606-5612.

30. Rodzevich, A. P.; Kuzmina, L. V.; Gazenaur, E. G.; Sugatov, E. V.; Krasheninin, V. I., The Effect of Magnetic Field on Crystallization and some Properties of Silver Azide Crystals. *Materials Science Forum* **2018,** *938*, 18-26.

31. Amiri, M. C.; Dadkhah, A. A., On reduction in the surface tension of water due to magnetic treatment. *Colloids and Surfaces A: Physicochemical and Engineering Aspects* **2006,** *278* (1), 252-255.

32. Wang, Y.; Zhang, B.; Gong, Z.; Gao, K.; Ou, Y.; Zhang, J., The effect of a static magnetic field on the hydrogen bonding in water using frictional experiments. *Journal of Molecular Structure* **2013,** *1052*, 102-104.

33. Cai, R.; Yang, H.; He, J.; Zhu, W., The effects of magnetic fields on water molecular hydrogen bonds. *Journal of Molecular Structure* **2009,** *938* (1), 15-19.

34. Potticary, J.; Terry, L. R.; Bell, C.; Papanikolopoulos, A. N.; Christianen, P. C. M.; Engelkamp, H.; Collins, A. M.; Fontanesi, C.; Kociok-Kohn, G.; Crampin, S.; Da Como, E.; Hall, S. R., An unforeseen polymorph of coronene by the application of magnetic fields during crystal growth. *Nature Communications* **2016,** *7*.

35. Potticary, J.; Boston, R.; Vella-Zarb, L.; Few, A.; Bell, C.; Hall, S. R., Low temperature magneto-morphological characterisation of coronene and the resolution of previously observed unexplained phenomena. *Scientific Reports* **2016,** *6*, 38696.

36. Bannister, N.; Skelton, J.; Kociok-Kohn, G.; Batten, T.; Da Como, E.; Crampin, S., Lattice vibrations of gamma- and beta-coronene from Raman microscopy and theory. *Physical Review Materials* **2019,** *3* (12).

37. Salzillo, T.; Giunchi, A.; Masino, M.; Bedoya-Martinez, N.; Della Valle, R.; Brillante, A.; Girlando, A.; Venuti, E., An Alternative Strategy to Polymorph Recognition at Work: The Emblematic Case of Coronene. *Crystal Growth & Design* **2018,** *18* (9), 4869-4873.

38. Kimura, F.; Kimura, T., Magnetically textured powders-an alternative to single-crystal and powder X-ray diffraction methods. *Crystengcomm* **2018,** *20* (7), 861-872.

39. Warzecha, M.; Safari, M. S.; Florence, A. J.; Vekilov, P. G., Mesoscopic Solute-Rich Clusters in Olanzapine Solutions. *Crystal Growth & Design* **2017,** *17* (12), 6668-6676.

40. Cookman, J.; Hamilton, V.; Hall, S.; Bangert, U., Non-classical crystallisation pathway directly observed for a pharmaceutical crystal via liquid phase electron microscopy. *Scientific Reports* **2020,** *10* (1).

41. Cookman, J.; Hamilton, V.; Price, L.; Hall, S.; Bangert, U., Visualising early-stage liquid phase organic crystal growth via liquid cell electron microscopy. *Nanoscale* **2020,** *12* (7), 4636-4644.

42. Kuhs, M.; Zeglinski, J.; Rasmuson, Å. C., Influence of History of Solution in Crystal Nucleation of Fenoxycarb: Kinetics and Mechanisms. *Crystal Growth & Design* **2014,** *14* (3), 905-915.

43. Clark, S. J.; Segall, M. D.; Pickard, C. J.; Hasnip, P. J.; Probert, M. J.; Refson, K.; Payne, M. C., First principles methods using CASTEP. *Zeitschrift fur Kristallographie* **2005,** *220* (5-6), 567-570.

44. Perdew, J. P.; Burke, K.; Ernzerhof, M., Generalized gradient approximation made simple. *Physical Review Letters* **1996,** *77* (18), 3865-3868.

45. Tkatchenko, A.; Scheffler, M., Accurate Molecular Van Der Waals Interactions from Ground-State Electron Density and Free-Atom Reference Data. *Physical Review Letters* **2009,** *102* (7), 073005.

46. van de Streek, J.; Neumann, M. A., Validation of experimental molecular crystal structures with dispersion-corrected density functional theory calculations. *Acta Crystallographica Section B - Structural Science* **2010,** *66*, 544-558.

47. Beran, G. J. O., Modeling Polymorphic Molecular Crystals with Electronic Structure Theory. *Chemical Reviews* **2016,** *116* (9), 5567-5613.

48. Ambrosetti, A.; Reilly, A. M.; DiStasio, R. A.; Tkatchenko, A., Long-range correlation energy calculated from coupled atomic response functions. *J Chem Phys* **2014,** *140* (18), 18A508.

49. Mauri, F.; Louie, S. G., Magnetic Susceptibility of Insulators from First Principles. *Physical Review Letters* **1996,** *76* (22), 4246-4249.

50. Guo, R.; Uddin, M. N.; Price, L. S.; Price, S. L., Calculation of Diamagnetic Susceptibility Tensors of Organic Crystals: From Coronene to Pharmaceutical Polymorphs. *The Journal of Physical Chemistry A* **2020,** *124* (7), 1409-1420.

51. Docherty, R.; Clydesdale, G.; Roberts, K. J.; Bennema, P., Application of Bravais-Friedel-Donnay-Harker, attachment energy and Ising models to predicting and understanding the morphology of molecular crystals. *Journal of Physics D* **1991,** *24* (2), 89-99.

52. Macrae, C. F.; Sovago, L.; Cottrell, S. J.; Galek, P. T. A.; McCabe, P.; Pidcock, E.; Platings, M.; Shields, G. P.; Stevens, J. S.; Towler, M.; Wood, P. A., Mercury 4.0: from visualization to analysis, design and prediction. *Journal of Applied Crystallography* **2020,** *53*, 226-235.

53. Florence, A. J.; Johnston, A.; Price, S. L.; Nowell, H.; Kennedy, A. R.; Shankland, N., An automated parallel crystallisation search for predicted crystal structures and packing motifs of carbamazepine. *Journal of Pharmaceutical Sciences* **2006,** *95* (9), 1918-1930.

54. Arlin, J. B.; Price, L. S.; Price, S. L.; Florence, A. J., A strategy for producing predicted polymorphs: catemeric carbamazepine form V. *Chemical Communications* **2011,** *47* (25), 7074-7076.

55. Parambil, J. V.; Poornachary, S. K.; Tan, R. B. H.; Heng, J. Y. Y., Influence of solvent polarity and supersaturation on template-induced nucleation of carbamazepine crystal polymorphs. *Journal of Crystal Growth* **2017,** *469*, 84-90.

56. Grzesiak, A. L.; Lang, M. D.; Kim, K.; Matzger, A. J., Comparison of the four anhydrous polymorphs of carbamazepine and the crystal structure of form I. *Journal of Pharmaceutical Sciences* **2003,** *92* (11), 2260-2271.

57. Brandenburg, J. G.; Potticary, J.; Sparkes, H. A.; Price, S. L.; Hall, S. R., Thermal Expansion of Carbamazepine: Systematic Crystallographic Measurements Challenge Quantum Chemical Calculations. *Journal of Physical Chemistry Letters* **2017,** *8* (17), 4319-4324.

58. Gelbrich, T.; Hursthouse, M. B., Systematic investigation of the relationships between 25 crystal structures containing the carbamazepine molecule or a close analogue: a case study of the XPac method. *CrystEngComm* **2006,** *8* (6), 448-460.

59. Cruz-Cabeza, A. J.; Day, G. M.; Motherwell, W. D. S.; Jones, W., Solvent inclusion in form II carbamazepine. *Chemical Communications* **2007,** (16), 1600-1602.

60. Park, K.; Evans, J. M. B.; Myerson, A. S., Determination of solubility of polymorphs using differential scanning calorimetry. *Crystal Growth & Design* **2003,** *3* (6), 991-995.

61. Lopez-Mejias, V.; Kampf, J. W.; Matzger, A. J., Nonamorphism in Flufenamic Acid and a New Record for a Polymorphic Compound with Solved Structures. *Journal of the American Chemical Society* **2012,** *134* (24), 9872-9875.

62. Li, H.; Wen, H.; Stowell, J. G.; Morris, K. R.; Byrn, S. R., Crystal Quality and Physical Reactivity in the Case of Flufenamic Acid (FFA). *Journal of Pharmaceutical Sciences* **2010,** *99* (9), 3839-3848.

63. Delaney, S. P.; Smith, T. M.; Korter, T. M., Conformational origins of polymorphism in two forms of flufenamic acid. *Journal of Molecular Structure* **2014,** *1078*, 83-89.

64. Krishna Murthy, H. M.; Bhat, T. N.; Vijayan, M., Structure of a new crystal form of 2-{[3-(trifluoromethyl)phenyl]amino}benzoic acid (flufenamic acid). *Acta Crystallographica Section B* **1982,** *38* (1), 315-317.

65. Cruz-Cabeza, A. J.; Bernstein, J., Conformational Polymorphism. *Chemical Reviews* **2014,** *114* (4), 2170-2191.

66. SeethaLekshmi, S.; Guru Row, T. N., Conformational Polymorphism in a Non-steroidal Anti-inflammatory Drug, Mefenamic Acid. *Crystal Growth & Design* **2012,** *12* (8), 4283-4289.

67. Abbas, N.; Oswald, I. D. H.; Pulham, C. R., Accessing Mefenamic Acid Form II through High-Pressure Recrystallisation. *Pharmaceutics* **2017,** *9* (2), 16.

68. Yang, X.; Sarma, B.; Myerson, A. S., Polymorph Control of Micro/Nano-Sized Mefenamic Acid Crystals on Patterned Self-Assembled Monolayer Islands. *Crystal Growth & Design* **2012,** *12* (11), 5521-5528.

69. Cardew, P.; Davey, R., The Ostwald Ratio, Kinetic Phase Diagrams, and Polymorph Maps. *Crystal Growth & Design* **2019,** *19* (10), 5798-5810.

70. Threlfall, T., Structural and thermodynamic explanations of Ostwald's rule. *Organic Process Research & Development* **2003,** *7* (6), 1017-1027.

71. Ostwald, W. Z., Studies on the formation and transformation of solid phases. *Zeitschrift fur Physikalische Chemie-International Journal of Research in Physical Chemistry & Chemical Physics* **1897,** *22*, 289-330.

72. Threlfall, T., Crystallisation of polymorphs: Thermodynamic insight into the role of solvent. *Organic Process Research & Development* **2000,** *4* (5), 384-390.

73. Lopez-Mejias, V.; Matzger, A. J., Structure-Polymorphism Study of Fenamates: Toward Developing an Understanding of the Polymorphophore. *Crystal Growth & Design* **2015,** *15* (8), 3955-3962.

74. Heijna, M. C. R.; Poodt, P. W. G.; Tsukamoto, K.; de Grip, W. J.; Christianen, P. C. M.; Maan, J. C.; Hendrix, J. L. A.; van Enckevort, W. J. P.; Vlieg, E., Magnetically controlled gravity for protein crystal growth. *Applied Physics Letters* **2007,** *90* (26), 264105-264105.

75. Poodt, P. W. G.; Heijna, M. C. R.; Tsukamoto, K.; de Grip, W. J.; Christianen, P. C. M.; Maan, J. C.; van Enckevort, W. J. P.; Vlieg, E., Suppression of convection using gradient magnetic fields during crystal growth of NiSO4·6H2O. *Applied Physics Letters* **2005,** *87* (21), 214105-214105.

76. Belenguer, A. M.; Lampronti, G. I.; Cruz-Cabeza, A. J.; Hunter, C. A.; Sanders, J. K. M., Solvation and surface effects on polymorph stabilities at the nanoscale. *Chemical Science* **2016,** *7* (11), 6617-6627.

77. Warzecha, M.; Guo, R.; Bhardwaj, R. M.; Reutzel-Edens, S. M.; Price, S. L.; Lamprou, D. A.; Florence, A. J., Direct Observation of Templated Two-Step Nucleation Mechanism during Olanzapine Hydrate Formation. *Crystal Growth & Design* **2017,** *17* (12), 6382–6393.

78. Ngo, D.-T.; Kuhn, L. T., In situ transmission electron microscopy for magnetic nanostructures. *Nanoscience and Nanotechnology* **2016,** *7* , 045001.

BRIEFS (Word Style “BH_Briefs”). If you are submitting your paper to a journal that requires a brief, provide a one-sentence synopsis for inclusion in the Table of Contents.

SYNOPSIS (Word Style “SN_Synopsis_TOC”). If you are submitting your paper to a journal that requires a synopsis, see the journal’s Instructions for Authors for details.