

Minimizing polymorphic risk through cooperative computational and experimental exploration

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ABSTRACT: We combine state-of-the-art computational crystal structure prediction (CSP) techniques with a wide range of experimental crystallization methods to understand and explore crystal structure in pharmaceuticals and minimize the risk of unanticipated late-appearing polymorphs. Initially, we demonstrate the power of CSP to rationalize the difficulty in obtaining polymorphs of the well-known pharmaceutical isoniazid and show that CSP provides the structure of the recently discovered, but unsolved, Form III of this drug despite there being only a single known form for almost 70 years. More dramatically, our blind CSP study predicts a significant risk of polymorphism for the related iproniazid. Employing a wide variety of experimental techniques, including high-pressure experiments, we experimentally obtained the first three known non-solvated crystal forms of iproniazid, all of which were successfully predicted in the CSP procedure. We demonstrate the power of CSP methods and free energy calculations to rationalize the observed elusiveness of the third form of iproniazid, the success of high-pressure experiments in obtaining it, and the ability of our synergistic computational-experimental approach to “de-risk” solid form landscapes.

Introduction

The significance of late-appearing polymorphism

Polymorphism is the existence of multiple crystal structures with identical chemical compositions for a particular chemical compound.^{1–3} Many pharmaceutical drugs display polymorphism and the different structures have different physicochemical properties such as solubility, hydration stability, *etc.*, which can markedly impact on the overall drug efficacy.⁴ In addition, factors such as crystal morphology and particle size can influence the drug’s formulation and processing properties.⁵ Thus, a thorough understanding of the solid form landscape of a particular compound provides the opportunity to fine-tune material properties.

Polymorph screening, using a wide range of experimental parameter and or procedures, has become routine across the solid-state sciences. Famously, McCrone stated that “the number of forms known for a given compound is proportional to the time and energy spent in research on that compound.”⁶ Indeed, there are many compounds for which an extraordinary number of forms have been discovered. For instance, the tenth form of galunisertib⁷, the twelfth form of aripiprazole⁸ and sixteenth polymorph of ROY^{9,10} have all been reported. Such a high degree of polymorphism is uncommon, however, and some compounds

are monomorphic, *i.e.* they have only one known crystal structure *e.g.* Pigment Yellow 74,¹¹ fenamic acid¹² and the bromo derivative of ROY.¹³ In the ideal case, this is achieved through close packing to give a dense crystal with all potential directional intermolecular interactions being optimal, with no alternatives of comparable stability.¹⁴

However, it can be premature to assume that a compound is monomorphic, as there exist many examples of late-appearing polymorphs of compounds previously considered to have only a single form, sometimes with significant consequences. Until very recently, isoniazid (ISN) was thought to be monomorphic,¹⁵ but despite the molecule being known for almost 70 years, two new forms were recently discovered by *via* crystallization from the melt.¹⁶ The most famous case of late-appearing polymorphism is that of ritonavir, an antiretroviral drug synthesized by Abbott Laboratories with a late-appearing polymorph that resulted in a two-year halt in production and \$250 million in lost sales.^{1,17,18} Bučar *et al.* have discussed 10 other cases of elusive or disappearing polymorphs.¹ For example, the dopamine agonist rotigotine, first produced in 1985, was only known to exist in one crystal structure.¹⁹ However, almost 30 years after its discovery, the appearance of a new crystalline form in the Neupro® patches stopped its clinical use. The patches were eventually reformulated as a

stable amorphous matrix, but during this process, patches were unavailable for four years. Clearly, it is extremely desirable to avoid these late-appearing forms and to be confident that all likely polymorphs of a compound have been discovered and, ideally, fully characterized.

The late appearance of thermodynamic forms may be due to unfavourable crystallization kinetics, but once an energetically preferred form crystallizes it can inhibit the formation of previously known metastable forms.²⁰ Interestingly, both ritonavir and rotigotine are examples of conformational polymorphism, in which different conformations are adopted in the polymorphs and the need for conformational change may contribute to the nucleation barrier for a particular form.

The discovery of novel forms is aided by increasingly sophisticated crystallization techniques. For instance, the templating of the catemeric Form V of carbamazepine *via* sublimation onto the isostructural dihydrocarbamazepine,²¹ the crystallization of novel β -coronene under an external magnetic field²² and the crystallization of two novel forms of adefovir dipivoxil in ionic liquids.²³ These kinds of experiments are unlikely to feature in a traditional polymorph screen and hence combined experimental and computational modelling approaches using a broad range of techniques are needed to minimize the risk of a late-occurring, stable solid form.

It is in this context that computational methods for crystal structure prediction (CSP) can be employed to understand these risks.^{24–27} At a basic level, predicting, enumerating, and ranking the stable crystalline forms of a given molecule can provide a picture of what crystal forms are possible and whether the most highly ranked structures (by a chosen scoring function, typically the lattice energy) have all already been experimentally characterized. The results of CSP can, therefore, motivate additional effort in exploring crystallization conditions.²⁸ At a more sophisticated level, there is the possibility of guiding the experimental polymorph search, both by predicting new forms' existence and by suggesting conditions under they might be produced – either to streamline efforts to obtain them or to highlight conditions that should be avoided to minimize the risk of their formation.

Computational approaches can also offer insight into the likelihood of the formation of novel polymorphs under non-ambient conditions, particularly high pressure, as was performed *post hoc* for 2-fluorophenol and 4-chlorophenol,²⁹ and more recently used *a priori* to predict high-pressure polymorphs of the pharmaceutical dalce-trapib.²⁰ However, experimental crystallization of high-pressure polymorphs is often not thermodynamically-controlled,³⁰ frustrating direct comparison between computed high-pressure thermodynamics and high-pressure crystallization experiments. Calculation of crystal structure free energy rather than static lattice energy,^{31–34} can close the gap between the simulation environment and experimental conditions, but these require expensive and sensitive dynamical calculations.

It is well-known that the “energy landscapes” provided by CSP – the set of predicted stable crystal structures, ranked by their static lattice energy – feature many more unique structures than have been observed even for high-

ly-polymorphic molecules like ROY.³⁵ Clearly, not every structure predicted by a CSP procedure is a feasible polymorph, so to be useful, CSP must suggest which structures are in the “danger zone” on the landscape, *i.e.* those that are likely to crystallize alongside or instead of the known or desired form(s).

Rationalizing polymorph risk through computed energetics

To define this “danger zone”, previous work has demonstrated that computed lattice energy differences between experimentally-observed polymorphs for a wide range of organic molecules are usually smaller than 2 kJ/mol, and less than 7.2 kJ/mol in 95% of cases.³¹ The statistics from this study can be applied to assess the probabilities of observing predicted polymorphs of a target molecule based on their lattice energy difference to the global energy minimum, which is always assumed to be an observable crystal structure. However, to make any confident prediction of monomorphism (or completely characterized polymorphism), the sampling of possible structures must be sufficiently extensive to have found all the relevant (low-energy) candidates and the method for obtaining their relative energies must be sufficiently accurate.²⁴

The sampling problem is one of the biggest challenges of CSP due to the high dimensionality of the search space and is made even more difficult when molecular flexibility adds to the number of degrees of freedom. A routine, rudimentary approach for treating flexibility is to sample the crystal packing possibilities of multiple molecular conformers generated from isolated-molecule optimizations. This approach is based on the assumption that the in-crystal conformation is nearly equivalent to a stable gas-phase conformer, but allows for less stable conformers that might lead to more favourable packing interactions to be considered in the CSP procedure. The advantage of this CSP approach is that the cost of the procedure increases only linearly with the number of conformers considered; the disadvantage is that it does not allow for significant conformational distortions of a gas-phase minimum that might be stabilized (or kinetically-trapped) by subsequently favourable packing arrangements.

The severity of this rigid-molecule approximation can be relieved by optimizing the final crystal structures using a method that allows intramolecular degrees of freedom to relax. The most commonly-employed such method is periodic density functional theory (DFT).²⁴ Refinement of predicted structures with DFT also often provides improved energetic rankings and computed properties of the structures compared to the force fields used in the initial structure generation and minimization, albeit at a considerably increased computational cost.

In this work, we combine computational CSP with both traditional and non-traditional experimental crystallization approaches to explore the polymorphism of two related molecules, ISN and iproniazid (IPN). Until very recently,¹⁶ ISN was thought to have a single obtainable non-solvated structure, although it forms a number of cocrystals.³⁶ The recent work of Zhang *et al.*¹⁶ has located two additional, metastable forms (Forms II and III) of ISN *via*

crystallization from the melt. Only Form II’s structure could be fully solved, while a unit cell was proposed for Form III from powder X-ray diffraction data.

In contrast, the structural analogue IPN has no reported crystal structures, except for a phosphate salt,³⁷ and therefore it is an ideal candidate with which to undertake a fresh combined experimental and computational polymorph screen.

We aim to predict and characterize the solid form landscapes for these compounds as completely as possible. We begin by predicting “blindly” (*i.e.* with no prior crystal structure information) the CSP landscape of ISN and IPN. Armed with this knowledge, we attempt to crystallize all the forms that appear to be experimentally accessible from the CSP landscape using a wide range of experimental techniques – typical solvent screening methods, templated sublimations, gel-phase crystallizations and high-pressure experiments. Finally, we combine the information from both approaches to characterize the observed forms and assess the risk of late-appearing polymorphism for both compounds.

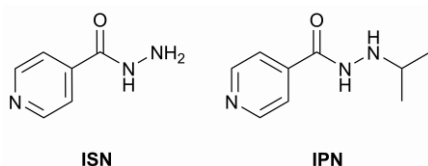


Figure 1: Molecular structures of isoniazid (ISN) and iproni-azid (IPN).

Computational Methods and CSP Procedure

Generation of hypothetical structures *via* CSP

Initial molecular conformers for both molecules were generated *via* a combined molecular mechanics sampling and DFT optimization procedure (described more fully in the ESI). This procedure yielded a single conformer for ISN, and for IPN a set of five conformers labelled A through E in order of decreasing relative stability (see ESI for diagrams). All five conformers lay within 5 kJ/mol of the global gas-phase minimum – *i.e.* with conformational energies well within the expected energy bounds for observed crystal structures.³⁸

For each conformer of each molecule, hypothetical crystal packing arrangements were generated with rigid molecular geometries, in our global lattice energy explorer method,³⁹ details of which are described fully in previous work. The search was restricted to the 25 most common space groups (see ESI) observed in the Cambridge Structural Database⁴⁰ for one molecule in the asymmetric unit ($Z'=1$) and, for isoniazid, also $Z' = 2$. Such restrictions on the complexity of the asymmetric unit are a crucial assumption in CSP for maintaining tractable computational cost – however, it precludes the identification of higher Z' structures and those in unusual space groups. The recently discovered ISN Form II has unusually low symmetry, with four independent molecules in the asymmetric unit ($Z'=4$) and represents a considerable challenge for any CSP effort, due to the number of independent degrees of free-

dom. Given that there was no evidence of any polymorphs of ISN at the outset of our work, a search up to $Z'=2$ represents a reasonable compromise between exploration and affordability.

The hypothetical packing arrangements were optimized in a multi-stage process of successively higher-accuracy energy minimization methods, progressing from rigid-molecule pairwise force field models using the DMACRYS software⁴¹ (see ESI for a complete description) to a periodic DFT optimization and ranking of the most stable structures. Duplicate structures were removed by automated comparison of computed PXRD patterns obtained *via* the PLATON⁴² program. For final optimization in periodic DFT, we used the PBE functional⁴³ and Grimme’s D3 dispersion correction⁴⁴ with Becke-Johnson damping (GD3BJ)⁴⁵ and a plane-wave basis set, using the VASP^{46–49} software package. All atomic degrees of freedom and unit cell parameters were relaxed in the final stage of the procedure, which introduces a description of the molecular flexibility in response to the crystal packing arrangement.

Predicting free energies

The energy landscapes obtained *via* the above methods are computed under the assumption of a static crystal structure – no thermal effects or zero-point energy are included. This is a significant approximation, but necessary to manage computational cost. Once a sufficiently small number of plausible structures have been identified, it becomes tractable to predict free energy differences. For ordered crystal structures, the most important contribution to free energies beyond the static energy arises from the dynamics of the crystal structure: the zero-point vibrational energy and the phonon modes populated at finite temperature, which contribute the vibrational term $F_{\text{vib}}(T)$ to the Helmholtz free energy $A(T)$:

$$A(T) = E_{\text{latt}} + F_{\text{vib}}(T)$$

$F_{\text{vib}}(T)$ is calculated from the phonon frequencies derived from DFT (PBE-GD3BJ). We employed the Phonopy⁵⁰ package to obtain the phonon frequencies *via* finite displacements, calculating energies in VASP for a supercell of each structure; the supercell dimensions are chosen to correspond to sampling reciprocal space q-points of at most $0.12 \text{ \AA}^{-1}$ spacing, which has been demonstrated^{31,32} to be sufficiently converged for polymorph vibrational energy differences. Phonopy employs a variant of the Parlinski-Li-Kawazoe method⁵¹ for interpolating between explicitly sampled q-points. It is critical to ensure that structures are at true minima to obtain reliable frequencies of vibration about the atomic equilibrium positions; hence structures were reoptimized with significantly more stringent convergence criteria (1000 eV basis set cut-off, 0.005 eV/Ång in forces) before the dynamical matrix was calculated.

Free energy calculations were improved by employing the Debye model to describe the acoustic mode contribution to the phonon density of states from the Brillouin zone centre to the nearest sampled q-point.³² We obtain the elastic tensor from the DFT calculations and calculate an orientationally-averaged velocity of sound in the crystal, from which a Debye frequency was determined and used

to calculate a correction term for long-wavelength acoustic contributions to $F_{\text{vib}}(T)$. Details are provided in our previous work.³²

Experimental Methods

Solution crystallizations and gel phase crystallizations

Solution crystallizations were performed by the heating of a saturated solution of either ISN or IPN and leaving the well-dissolved solution to cool slowly in a heating block. These were carried out in parallel with gel-phase crystallizations under the same conditions, but in which the heated solution was used to dissolve the gelator (1 w/v%). Then the solutions were also left to cool slowly in the heating blocks.

Templated sublimations

The powder of the sample being sublimed was placed on a glass slide and then on a Linkam LTS420 heating stage. The templating crystal was affixed to a borosilicate glass coverslip with a small amount of Vaseline and then separated from the glass slide with a small rubber o-ring. The powders were then heated to a temperature to achieve sublimation, 131 °C for IPN and 141 °C for ISN at either 5 or 10°C/min for 6 hours for to ensure that all the sample sublimates and then the sample was left overnight to allow for crystal growth.

High-pressure experiments

High-pressure experiments were conducted by compressing crystals that were grown at ambient pressure in a Merrill-Bassett diamond anvil cell (DAC)⁵² using Fluorinert™ FC-70 as an inert pressure transmitting fluid. A 250 μm thick stainless steel gasket was pre-indented to ca. 150 μm and drilled with a 300 μm precision hole to create the sample chamber between the two diamond anvils, culet size of 800 μm . The pressure inside the cell was measured after equilibration using a ruby sphere included in the sample chamber by the R_1 ruby fluorescence method.⁵³ The diamond anvil cell was directly attached to a goniometer head and mounted on the diffractometer. Data were collected using the XIPHOS II diffractometer at Newcastle University, a four-circle Huber Eulerian goniometer with offset chi cradle fitted with a Bruker APEXII CCD area detector and an Ag- $K\alpha$ $\text{I}\mu\text{S}$ generator. Data collections of crystals in DACs is poor at locating H-atom positions due to shading by the gasket and DAC, which reduces the completeness of the dataset.^{54–56}

Novel polymorphs of iproniazid Forms I and II were produced by slow cooling and Form III was produced by high-pressure experiments. A more detailed analysis of these novel forms, as well details on gelator synthesis, characterization methods and computational processes (molecular conformer generation, Space group selection for structure generation and structure minimization) and further results of the free energy calculations are all available in the ESI.

Results and Discussion

Isoniazid: crystal structure prediction

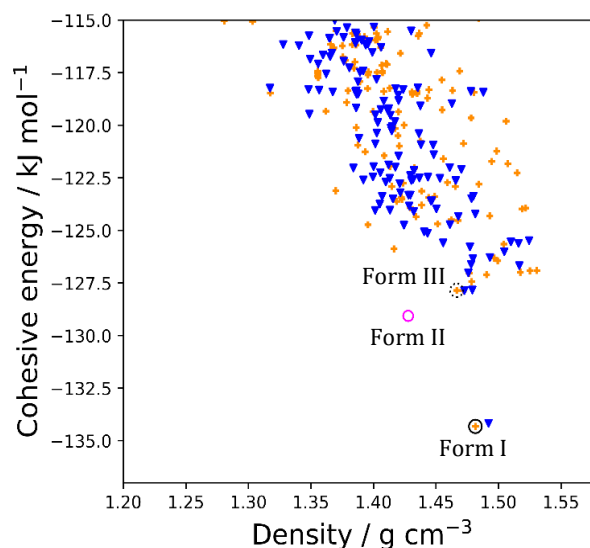


Figure 2: The CSP landscape for isoniazid, in which the lowest-energy predicted structure (circled in solid black) matches the longest-known experimentally-observed form and is separated by more than 6 kJ/mol from any other predicted minima. Orange crosses indicate structures generated assuming only one isoniazid molecule in the asymmetric unit ($Z'=1$), while blue triangles indicate $Z'=2$. The pink circle indicates where the recently-discovered $Z'=4$ Form II lies when optimized using the same methods, while the broken circle indicates the CSP structure whose lattice parameters and computed PXRD pattern closely match those of the unsolved Form III. Energies and densities are obtained from PBE+GD3BJ periodic DFT.

The CSP results for isoniazid are shown in Figure 2: The CSP landscape for isoniazid, in which the lowest-energy predicted structure (circled in solid black) matches the longest-known experimentally-observed form and is separated by more than 6 kJ/mol from any other predicted minima. Orange crosses indicate structures generated assuming only one isoniazid molecule in the asymmetric unit ($Z'=1$), while blue triangles indicate $Z'=2$. The pink circle indicates where the recently-discovered $Z'=4$ Form II lies when optimized using the same methods, while the broken circle indicates the CSP structure whose lattice parameters and computed PXRD pattern closely match those of the unsolved Form III. Energies and densities are obtained from PBE+GD3BJ periodic DFT. The pronounced global minimum energy structure accurately reproduces the observed, thermodynamically most stable structure Form I, known since 1954. All of the other structures generated by CSP lie at least 6.5 kJ/mol higher, at the upper limits of the expected energy range for polymorphism. The global minimum of the $Z'=2$ search is also isostructural to Form I, but in a lower-symmetry space group.

Such a clear thermodynamic preference for an experimentally observed structure in a CSP landscape is unusual.^{57,58} The absence of any energetically competitive structures for isoniazid at this level of theory and within the space groups and Z' values considered explains the previ-

ously long-held empirical conclusion that this molecule had only one accessible crystal structure. If ISN were a novel compound undergoing screening, we would suggest on this basis that the risk of late-appearing, stable polymorphs would be low.

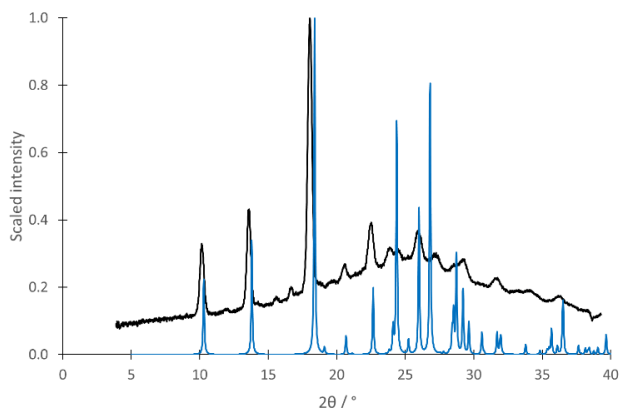


Figure 3: Comparison of experimental PXRD pattern (black, originally presented by Zheng *et al.*) for Form III of ISN and the computed PXRD pattern (blue) for the second-lowest energy CSP structure. Intensities of each pattern have been scaled to the value of the largest peak in each case.

The recent work of Zhang *et al.*¹⁶ in obtaining two new isoniazid polymorphs (Forms II and III) occurred contemporaneously with the present study, and refutes these previous conclusions of monomorphism. The second-lowest energy predicted structure, *i.e.* the most plausible polymorphic candidate in a blind CSP run (**Error! Reference source not found.**, broken circle, 6.5 kJ/mol above the global minimum), has lattice parameters ($a = 3.751$ Å, $b = 17.164$ Å, $c = 9.692$ Å, $\beta = 95.67^\circ$, $P2_1/c$, $Z' = 1$) that are in good agreement with those reported for Form III (3.931(2) Å, 9.754(5) Å, 8.568(4) Å), apart from cell doubling in the **b** direction.¹⁶ Form III is a highly metastable polymorph that proved too short-lived for full characterization. The computed PXRD pattern for this CSP structure is also in good agreement with the experimental pattern (**Error! Reference source not found.**). Hence, we propose that this predicted structure corresponds to the experimental Form III.

Form II, with $Z' = 4$, would be unlikely to be found in a typical blind CSP attempt. Lattice energy minimization places Form II 5.5 kJ/mol above the global minimum (**Error! Reference source not found.**, pink circle), within the expected energy range for polymorphism. The high calculated energies of Forms II and III, relative to Form I, agree with the experimentally observed metastability of these polymorphs, which transform rapidly to Form I, and the energetic ordering agrees with the room temperature stability ranking ($I > II > III$) from experiment.¹⁶

Iproniazid: crystal structure prediction

The CSP results for IPN, with $Z' = 1$ structures generated for 5 distinct molecular conformers, are shown in **Error! Reference source not found.** Unlike its simpler analogue

ISN, IPN displays a more diverse CSP landscape that is more typical of small organic molecules, with multiple low-lying minima within a few kJ/mol of each other, in different space groups and with different molecular conformations.

As is common in blind CSP, we posit that the global minimum energy structure (in space group $P2_1/c$), which is also the global density maximum, is the most likely to be observed experimentally.²⁵ A close-lying predicted structure (space group $P2_1$) approximately 1 kJ/mol higher in energy is likely as an accessible polymorph, followed by a gap, then a more varied, nearly continuous distribution of possible structures starting approximately 5 kJ/mol above the global minimum. There are 13 unique structures within 7.2 kJ/mol, all but two of which feature either the gas-phase minimum conformer A or the 4th-lowest energy conformer D, indicating that the latter can compensate for its higher conformational energy with improved intermolecular interactions or denser packing. Indeed, the global minimum energy (and maximum density) crystal structure features conformer D. Given the small energy difference between the two lowest energy structures, the accessibility of multiple structures within 5 kJ/mol, and the prevalence of only two conformers in many of these predicted structures, it is likely that iproniazid can readily form multiple polymorphs and carries a substantial risk of late-appearing polymorphism.

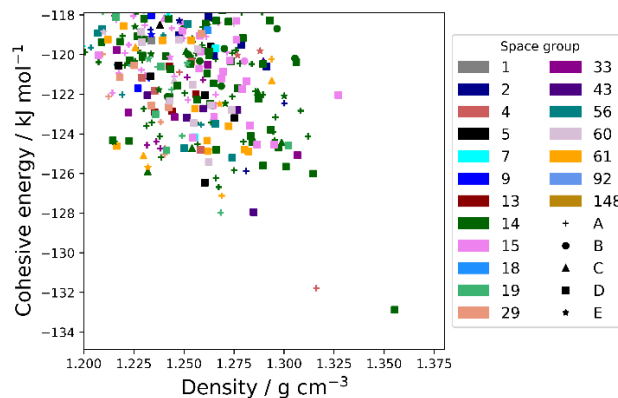


Figure 4: The CSP landscape for IPN. Data point colour denotes space group, while the shapes of points indicate the gas-phase conformer used to generate the initial crystal structure, A being the gas-phase global minimum conformation. Energies and densities are obtained from PBE+GD3BJ periodic DFT.

Comparison of predicted hydrogen bond motifs

Isoniazid: The global minimum structure of ISN from the CSP landscape, which matches the experimental structure Form I, features hydrogen bonding between the pyridyl group of one ISN molecule and the terminal amine group of another, forming a $C_1^1(8)$ chain (**Error! Reference source not found.a**). These chains are in turn linked to each other with N-H $\cdots$ N bonds between the terminal amine and the hydrazide nitrogen atom in an adjacent molecule. However, the carbonyl group does not participate in any H-bonding in Form I.

The CSP structure matching Form III, in contrast, features the same terminal amine N-H $\cdots$ N(pyridyl) chains

instead linked by (hydrazide)N-H...O(carbonyl) bonds (**Error! Reference source not found.c**). While this and several of the predicted higher-energy structures feature H-bonding motifs that involve the carbonyl group as an acceptor (always in a carbonyl-hydrazide H-bond, sometimes sharing the oxygen atom with a carbonyl-amine H-bond), it appears that involving the carbonyl is unnecessary to form a particularly stable crystal structure of ISN, in opposition to what might be expected based on Etter's rules.⁵⁹

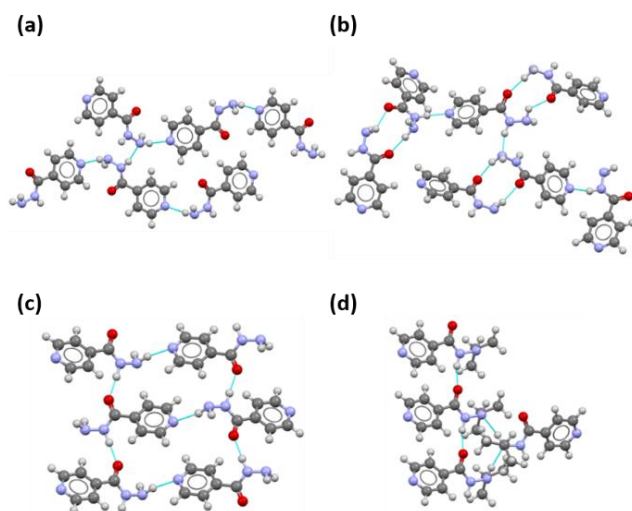


Figure 5: Hydrogen bonding for (a) ISN-I, (b) ISN-II, (c) ISN-III and (d) the global minimum energy structure of IPN. Blue lines indicate intermolecular hydrogen bond interactions.

Form II of ISN displays noticeably different hydrogen bonding to Form I or Form III in a more complex arrangement, owing to its low symmetry ($Z'=4$). Only 2 of the 4 symmetry-inequivalent molecules exhibit pyridyl-acceptor H-bonding, both *via* a neighbouring hydrazide N-H donor rather than pyridyl-amine chains. However, in all 4 molecules the H-bonding involves all the available protons (terminal amine and hydrazide), and the carbonyl oxygen (**Error! Reference source not found.b**).

Iproniazid: In contrast with ISN, all predicted structures except one of IPN within 7.2 kJ/mol of the global minimum (*i.e.* 12 of 13) display hydrogen bonding involving the carbonyl group (most commonly to the hydrazide N-H). The one structure that does not involve the carbonyl is at the upper limit (7.0 kJ/mol) of this energy bound, making it of lesser concern in terms of polymorphic risk than others and suggesting that the carbonyl acting as an acceptor is energetically optimal.

The variety of H-bonding patterns available in predicted structures of IPN is reduced compared to ISN by the lack of the accessible terminal amine group, *e.g.* the pyridyl group appears less likely to participate in H-bonding due to the isopropyl group precluding the formation of end-to-end molecular chains. Instead the second N-H typically H-bonds to other infinite H-bonding chains of IPN (**Error! Reference source not found.d**).

Experimental crystallization of ISN and IPN

The crystallization of ISN was carried out in 26 solvents *via* slow cooling of saturated solutions and through the

slow evaporation of ISN solutions. In all cases, the known form of ISN was produced, as first reported in 1954.⁶⁰ As a result, sublimation experiments were also undertaken as they have previously been used to crystallize the formation of metastable forms.^{61–63} ISN was sublimed by heating on a microscope stage below its melting point (171.4°C) at relatively high heating rates (5 and 10 °C/min). A borosilicate glass coverslip was placed above the sample and the ISN vapour crystallized on the colder coverslip. However, no new forms were obtained.

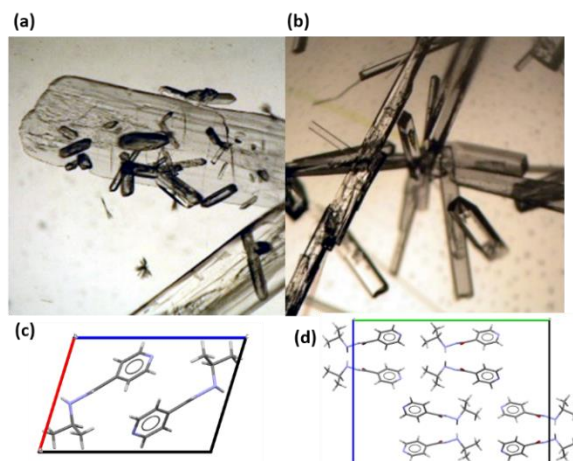


Figure 6: Photos of IPN crystals (a) Form I grown from slow cooling a saturated nitrobenzene solution and (b) Form II produced via the sublimation of IPN powder on a borosilicate coverslip. Unit cell (c) Form I and (d) Form II.

For iproniazid, slow cooling and slow evaporation in 22 solvents resulted in 14 samples exhibiting diffraction quality crystals. The crystals are all colourless and plate-like (Figure 6). Single crystal X-ray diffraction shows that all of the crystals are of the same, new form, designated Form I (IPN-I), in the monoclinic space group $P2_1$.

In one instance, crystallization from slow cooling of a saturated toluene solution of IPN produced a second form of IPN, designated Form II (IPN-II), in space group $Pbca$; as with IPN-I, the structure has $Z'=1$. Despite multiple attempts, it was not possible to reproduce this form through solvent crystallization methods, suggesting that IPN-II is likely to have a high barrier to nucleation in solution, is metastable with respect to or is outgrown by IPN-I.⁶⁴ Indeed, slurry experiments, in which both forms were added to a saturated solution, resulted in only IPN-I, as confirmed by PXRD (Fig. S1), demonstrating that IPN-I is the more stable form under ambient conditions. IPN-II was, however, reproducibly obtained by the sublimation of IPN powder onto borosilicate coverslips.

Comparison of the structural information and geometric overlays using Mercury⁶⁵ (Fig. S2) of both IPN Forms I and II with the CSP structures reveals excellent matches with two predicted structures, both within 7.2 kJ/mol of the global minimum. Therefore, both these forms of IPN were correctly predicted blind in our CSP procedure, both with energy rankings within the experimentally accessible range. The metastable IPN-II resides towards the upper limit of the “at risk” region of the energy landscape (+5.8 kJ/mol versus the global minimum), while IPN-I matches

the second-lowest energy predicted structure (+1.1 kJ/mol); the energetic ordering of these two forms is consistent with the experimental observation that IPN-I is more readily obtained and more stable than IPN-II.

However, these solution and sublimation crystallization experiments did not yield crystals corresponding to the global energy minimum on the CSP landscape. Furthermore, the landscape (**Error! Reference source not found.**) contains multiple structures that are of very similar energy to IPN-II. It is not apparent why IPN-II is experimentally observed while similarly metastable structures and the global minimum are not obtained. Both observations indicate that the risk of late-appearing polymorphism of IPN remains after conventional solvent screening and sublimation.

Gel-phase crystallizations

Gel phase crystallization is an emerging technique for expanding the polymorphism search space^{66,67} and was undertaken for ISN and IPN with a series of gelators (**Error! Reference source not found.**). Gelator **1** mimics the structure of ISN and IPN and parallels the use of other drug-mimetic mimic gelators that have previously been shown to stabilize metastable forms over the thermodynamically favoured polymorph,⁶⁶ as well as resulting in the discovery of new solvates.⁶⁸ Gelators **2** and **3** were chosen to mimic co-formers known to form co-crystals with ISN. The co-crystals of ISN are polymorphic and exhibit different H-bonding motifs with the carbonyl and pyridyl groups both being H-bond acceptors.^{36,69,70} Thus, these gelators may be able to template forms with different H-bonding motifs. Gelator **4** forms gels in aromatic solvents and therefore was chosen in an attempt to recover Form II in toluene.

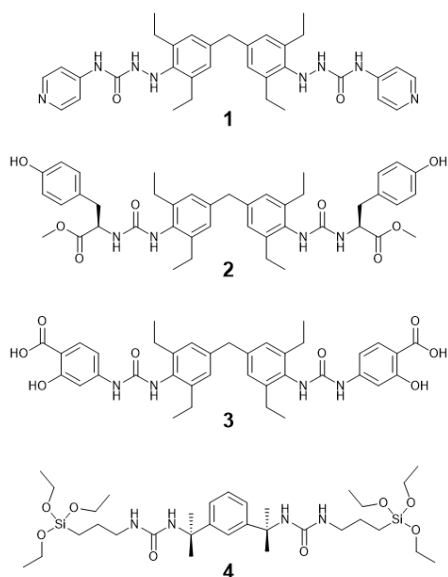


Figure 7: Chemical structures of gelators used in this study.

These experiments were carried out at the same solute concentration as the slow cooling crystallizations. For each experiment, either ISN or IPN and then the gelator were dissolved with heating and sonication, and left to cool under ambient conditions. In all cases, Form I of both ISN and IPN were obtained, demonstrating the strong preference

for these forms to crystallize over any other predicted structures.

Templated sublimations

Previous work has demonstrated that it is possible to template the growth of a particular form and discover new polymorphs by subliming onto different surfaces, *e.g.* polycrystalline powders,⁷¹ siloxane-coated glass⁶¹ and crystals with related structure.^{32,33} Both Forms I and II of IPN display different hydrogen bonding patterns to the known form of ISN and hence crystals of one compound could be used to template the growth of new forms of the other analogue.

In the CSP landscapes, the lowest energy IPN structure with ISN-like H-bonding is 7.0 kJ/mol above the global minimum. Conversely, on the ISN landscape, the lowest energy structure displaying IPN-like H-bonding (*i.e.* involving the carbonyl group) is the CSP structure that we propose matches Form III of ISN, 6.5 kJ/mol higher in energy than Form I. While these energy differences are towards the upper limit of the energy range of expected polymorphism, they remain plausible risks. This assessment is borne out in the case of ISN with the recent experimental production of Form III, but is also significant for IPN, as the observable Form II is only 1.2 kJ/mol more stable than the aforementioned lowest-energy ISN-like structure.

Sublimation of each compound was attempted using crystals of either ISN or IPN as a template for the other by crystallization directly from the vapour phase. Crystals of both compounds did grow on top of the surface of the parent template (Fig. S3) but in both cases the same polymorph was produced (Form I ISN or Form II IPN) as sublimation crystallization in the absence of template. These experiments further qualify the risk of further metastable forms of ISN/IPN with unusual H-bonding pattern; these calculated forms -- along with the global minimum form of IPN -- appear to be inaccessible through these methods.

An elusive high-density form of iproniazid

The calculated global energy minimum form of IPN is notably denser than either of the forms experimentally obtained. While it is not unprecedented that the most accessible structure is not the global minimum on a CSP landscape, the significantly greater density of the IPN global minimum compared to the experimental forms is noteworthy. A higher-density polymorph should become comparatively even more stable under higher pressure, suggesting high pressure crystallization as a means to obtain this form experimentally.

Geometry optimizations under pressure show that the energy difference between IPN-I and the global minimum CSP structure widens from -0.7 at zero applied pressure to -7.6 kJ/mol at $P = 2.4$ GPa (**Error! Reference source not found.**). This is expected, as the global minimum is already the densest predicted structure and therefore no “cross-over” in ranking is expected with increased pressure. While this trend agrees with physical intuition, it provides no clarity as to why this global minimum structure is not found in conventional crystallization experiments. Evidently, static lattice energy calculations alone are not

enough to rationalize the elusiveness of the high-density form.

Computed free energies of iproniazid

Given the possibility of obtaining the elusive high-density predicted structure of IPN under elevated pressures, a more useful quantity to compute is the free energy change as a function of both temperature and pressure. However, the latter is a computationally expensive proposition, as each step in pressure requires new phonons to be calculated as the crystal structure is compressed. To provide some estimate of the free energy difference between the forms under higher pressure, we make the approximation that the pressure and vibrational effects are independent and purely additive, *i.e.* we compute vibrational contributions to the free energy only for the ambient pressure structures, and add these to the *PV* contribution. These approximate Helmholtz free energies are shown in **Error! Reference source not found.**

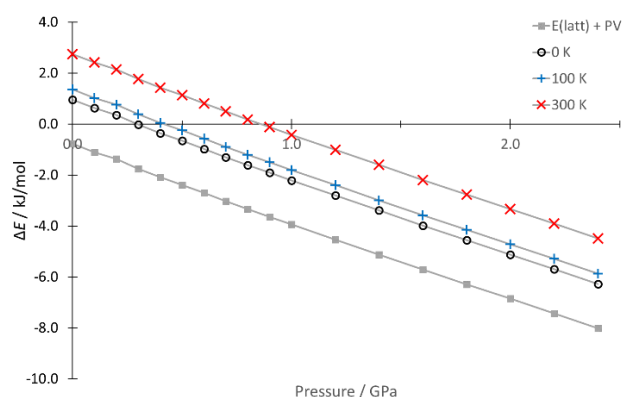


Figure 8: The computed energy difference, ΔE , between IPN-I and the global minimum in lattice energy as a function of pressure. Grey squares are static lattice energies including the *PV* contribution; the remaining data are Helmholtz free energies presented at three different temperatures: 0 K (black circles) *i.e.* only ZPE contributions, 100 K (blue crosses), and 300 K (red diagonal crosses). Values were calculated via periodic PBE+GD3BJ; vibrational contributions were corrected with a Debye model for low-frequency modes.

With dynamical effects incorporated into the calculations, the static CSP global minimum becomes metastable with respect to IPN-I at ambient pressure, being 2.8 kJ/mol higher in free energy at 300 K. In fact, the missing high-density form of IPN is computed to be higher in free energy at ambient pressure than IPN-I across all temperatures; the vibrational zero-point energy (ZPE) difference of 1.8 kJ/mol between the two forms re-ranks them even before any thermal contributions. It is known that vibrational ZPE can be important in relative polymorph ranking, particularly for some hydrogen-bonded species.^{72,73} In these cases, an accurate treatment of lattice dynamics is necessary to obtain an estimate of the ZPE and hence polymorph rankings that are consistent with experimental observations, as appears to be the case for IPN.

Having considered both temperature and pressure, the elusiveness of the high-density form is more easily ex-

plained – this structure is metastable at standard temperature and pressure with respect to IPN-I, with a considerably larger energy difference between structures than the static calculations alone indicated. As expected, increased pressure stabilizes this high-density form, with higher temperatures requiring higher applied pressures to make it more favourable than IPN-I. While our approximation of additivity of the vibrational and *PV* terms compounds the uncertainty in the free energy, the results indicate that at 300 K an applied pressure in excess of 1.0 GPa would be required to make the high density structure most favourable.

Assessing the polymorphic risk of the IPN landscape now based on calculated free energies, the global minimum is now less of a risk than indicated by the static calculations alone. This demonstrates the power of computational work to identify risks in crystallization processes, but also highlights the importance of thorough, rigorous application of advanced methods to provide accurate insight. If assessments of risk are made on the basis of “black-box” CSP approaches alone, using static lattice energies (as in **Error! Reference source not found.**), then this maximal density structure would be perceived as a serious risk as a late appearing, stable polymorph because it is the global minimum on such a landscape. This risk is diminished when free energy (including quantum vibrational effects) is considered, as dynamical contributions re-rank the two structures and suggest IPN-I is in fact most stable. However, the free energy difference between the two remains within the “danger zone” of polymorphism at ambient pressure, and hence it is prudent to explore whether high-pressure experiments can indeed obtain this form as the free energy trends in **Error! Reference source not found.** indicate.

High-pressure experiments

The global minimum on the IPN landscape contains the molecule in a less-stable conformation than that of IPN-I or IPN-II. This conformation may have a sufficiently high nucleation barrier that it cannot be crystallized by solution phase, gel phase or sublimation screening as its crystallization is kinetically hindered. Similar observations were made for ritonavir and rotigotine whereby the thermodynamically favoured forms were conformationally different from the metastable forms and were not discovered for many years.

As the CSP static global minimum structure is significantly denser than IPN-I and IPN-II, it is stabilized by higher pressures, due to the smaller pressure-volume contribution to the free energy; this is shown by the free energy calculations (**Error! Reference source not found.**). High-pressure experiments are known to be capable of effecting conformational change in crystal structures.^{74,75} Thus, both high-pressure recrystallization and compression of crystals grown at ambient pressures were undertaken in Merrill-Bassett diamond anvil cells (DACs).

All attempts to recrystallize IPN from solution at various pressures produced polycrystalline samples. This may be due to the many surfaces on which nucleation can occur inside the DAC, *e.g.* the ruby spheres, the edge of the tung-

sten gasket, or the faces of the diamond.⁷⁶ As a result we turned to compression of crystals grown at ambient pressure.

At lower pressures (≤ 0.3 GPa), only slight reductions in the unit cell dimensions were observed for IPN-II (Table S1). However, the compression is anisotropic, affecting mostly the *b* axis. At higher pressures (*ca.* 0.5–0.8 GPa), the crystal breaks perpendicular to the longest axis, indicating that this form is unable to compress further or transform to relieve the stress caused by the elevated pressure.

When IPN-I was compressed up to *ca.* 2.1 GPa, no changes to the crystal habit could be observed visually. However, single crystal X-ray diffraction confirmed that under hydrostatic pressure IPN-I ($P2_1$) undergoes a single crystal-to-single crystal transformation to produce a new structure, IPN-III ($P2_1/c$). Pressure-mediated transformations without the destruction or dissolution of the crystal are rare but can be achieved for molecules with conformational flexibility.⁷⁶ Single crystal-to-single crystal transformations have been achieved for other organic molecules through conformational changes, *e.g.* β -glycine to δ -glycine,⁷⁷ glutathione-I to glutathione-II,⁵⁴ and di-*p*-tolyl disulphide α form to β form.⁷⁸ In the present case this transformation results in a conformational change such that the structure closely matches the predicted conformer D. Structural overlay (Fig. S4) confirms that this new form corresponds to the predicted global minimum structure of IPN.

Upon decompression to ambient pressure, the crystallinity of the sample was significantly reduced because of damage to the crystal from the compression, decompression and X-ray irradiation. However, it proved possible to obtain an ambient pressure structure determination which, while of low precision and data completeness, unambiguously identifies the sample as Form III (Table S2). This key result indicates that Form III represents a considerable risk as a late-appearing polymorph, if created in an industrial setting under milling conditions, for example.

Crystal packing analysis

Differences in the packing of the polymorphs of IPN explain why Form I rather than Form II transforms to Form III and why Form III is the densest polymorph. The three IPN polymorphs exhibit a similar H-bonding motif - a $C_1^1(4)$ chain with the carbonyl group as an acceptor and the donor being the N-H adjacent to the carbonyl of the next molecule (Figure 9Figure 10: H-bonding sheets of IPN visualized perpendicular H-bonding chains with alternative sheets coloured red and blue. Blue lines represent interactions between IPN molecules. (a) IPN-I, (b) IPN-III and (c) IPN-III.). These are the shortest contacts for all forms, and appear as two spikes on the 2D fingerprint plots of the IPN Hirshfeld surfaces (Figs. S5 and S6), which were used to visualize the differences in intermolecular interactions. For IPN-I the H-bonding chains run parallel to the *b*-axis and only a small compression of the *b*-axis is observed upon transition to IPN-III. This is commensurate with only a small reduction in the H-bond length in IPN-III (Table S2). Similarly, these chains run parallel to the *a*-axis for IPN-II and only a modest reduction of this axis is recorded after

compression in the DAC (Table S1). This is in line with previous studies that the shortest contacts remain unchanged and transformations instead rely on a rearrangement of longer contacts.^{82,83}

Accordingly, there are some subtle differences between forms in the interactions of the pyridyl groups in adjacent H-bonding chains. All IPN forms exhibit a short contact between the pyridyl groups *via* a (pyridyl)C-H...N(pyridyl) interaction. For IPN-I and IPN-II these are $C_1^1(3)$ chains, which stack in a herringbone-like manner. These contacts in IPN-II are longer than in IPN-I (Table S3), indicating poorer packing. The compression of IPN-I significantly reduces the *a*-axis (the *c*-axis in IPN-III), such that the pyridyl groups are less offset from one another. The conformational change also results in the two pyridyl rings becoming nearly coplanar. These changes transform these contacts in IPN-III to $R_2^2(6)$ rings which are noticeably shorter than in the other forms (Fig. S8g, Table S3); further, the H-bonding chains now run anti-parallel to one another (Figure 9).

Table 1: Crystallographic data for the three polymorphs of IPN

Crystal Form	Form I	Form II	Form III
Formula	C ₉ H ₁₃ N ₃ O	C ₉ H ₁₃ N ₃ O	C ₉ H ₁₃ N ₃ O
Molecular weight /g mol ⁻¹	179.219	179.219	179.219
Crystal System	Monoclinic	Orthorhombic	Monoclinic
Space Group	$P2_1$	$Pbca$	$P2_1/c$
T/K	120	120	291
Pressure/ GPa	ambient	ambient	2.21
<i>a</i> /Å	8.1440(8)	4.9971(7)	11.240(5)
<i>b</i> /Å	5.0966(5)	16.831(3)	5.043(3)
<i>c</i> /Å	11.7207(13)	22.850(3)	15.171(14)
α /°	90	90	90
β /°	107.122(4)	90	109.14(7)
γ /°	90	90	90
<i>V</i> /Å ³	464.93(8)	1921.7(5)	812.4(10)
<i>Z</i>	2	8	4
<i>Z'</i>	1	1	1
ρ_{calc} /g cm ⁻³	1.280	1.239	1.465
independent reflections	3067 [$R_{\text{int}}=0.0731$]	1577 [$R_{\text{int}}=0.0918$]	287 [$R_{\text{int}}=0.0851$]
goodness-of-fit	1.024	1.060	1.082
final <i>R</i> indexes [$I \geq 2\sigma(I)$]	$R_1 = 0.0501$	$R_1 = 0.0398$	$R_1 = 0.0987$
	$wR_2 = 0.1033$	$wR_2 = 0.0857$	$wR_2 = 0.2524$
final <i>R</i> indexes [all data]	$R_1 = 0.0719$	$R_1 = 0.0612$	$R_1 = 0.1434$
	$wR_2 = 0.1111$	$wR_2 = 0.0945$	$wR_2 = 0.2863$
CCDC code	2011025	2011026	2011027

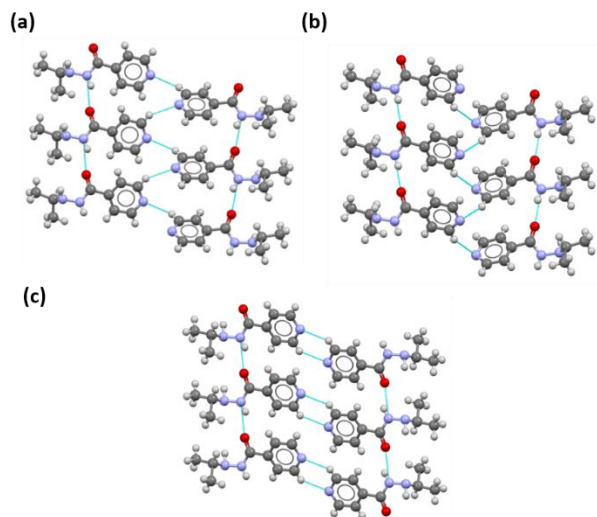


Figure 9: Hydrogen bonding for (a) IPN-I, (b) IPN-II and (c) IPN-III. Blue lines indicate interactions between molecules.

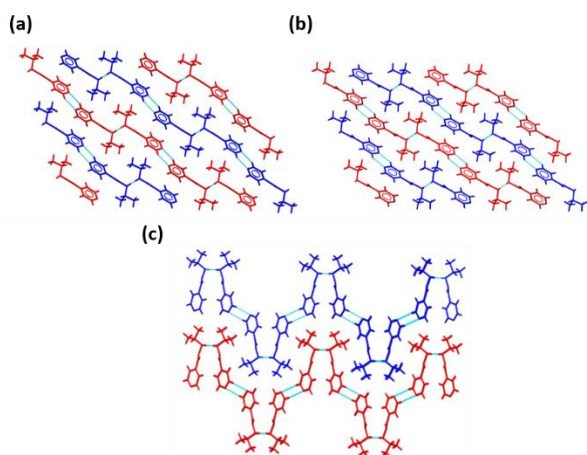


Figure 10: H-bonding sheets of IPN visualized perpendicular H-bonding chains with alternative sheets coloured red and blue. Blue lines represent interactions between IPN molecules. (a) IPN-I, (b) IPN-III and (c) IPN-III.

Together, the H-bonding chains and the pyridyl-pyridyl contacts produce sheets that connect the IPN molecules (Figure 10: H-bonding sheets of IPN visualized perpendicular H-bonding chains with alternative sheets coloured red and blue. Blue lines represent interactions between IPN molecules. (a) IPN-I, (b) IPN-III and (c) IPN-III.) in all three forms. These sheets are additionally held together by (hydrazine)N-H...N(hydrazine) H-bond interactions (Fig. S9a and S10). The shorter pyridyl-pyridyl contacts in IPN-III allow the sheets to stack closer together, while the anti-parallel chains and the conformational change allows rotation of the isopropyl group for denser packing within these sheets (Fig S9d); both effects contribute to IPN-III being the densest. Further analysis of the packing and presentation of the Hirshfeld fingerprint plots can be found in the ESI.

In IPN-II, the b-axis is normal to the plane of these sheets (Fig. S10), and it is this axis along which IPN-II compresses before breaking under pressure. It is speculated that these

sheets compress together rather than the H-bonding chains to accommodate the pressure increases.

Though all three forms contain these H-bonded sheets, the shape of the sheets in IPN-I and IPN-III is notably different from those in IPN-II. The sheets of both Forms I and III are relatively planar, with gentle undulations. In contrast, those of Form II are more corrugated, having an increased roughness (rugosity) with neighbouring sheets interpenetrating more (Figure 10: H-bonding sheets of IPN visualized perpendicular H-bonding chains with alternative sheets coloured red and blue. Blue lines represent interactions between IPN molecules. (a) IPN-I, (b) IPN-III and (c) IPN-III.). As these sheets in IPN-II are very different to those in IPN-III, there is no obvious route for transformation to IPN-III, in contrast to IPN-I which only needs to undergo a comparatively small change in the sheet structure. Topological rugosity has been linked to slip planes for crystals which affect the mechanical properties and thus the tableability of different forms.^{84,85} Therefore, it is expected that the different forms of IPN may behave differently during formulation, particularly if tableting pressures cause the transformation from IPN-I to IPN-III that can persist at ambient pressure. Given the structural differences, however, we do not expect IPN-II to transform due to pressure during the tableting process.

Conclusions

We have demonstrated the power of computational CSP methods to rationalize the difficulty in obtaining polymorphs of isoniazid, due to the absence of any competitive predicted thermodynamic minima (assuming $Z' \leq 2$). Solvent and sublimation based crystallization methods did not reveal any further forms beyond the long-known Form I, consistent with previous screening.¹⁵

The contemporaneous discovery by Zhang *et al.* of two new forms from melt crystallization¹⁶ is remarkable, but consistent with our computational findings in both cases. Form II would not be predicted in a typical CSP due to its high Z' making a search prohibitively expensive in the general case. However, the structure of Form II is ranked favourably in energy when treated with our computational methods. In contrast, the second-lowest energy CSP structure of ISN lies just at the bounds of likely polymorphic energy range and matches the PXRD pattern of Form III, which could not be fully characterized experimentally. Therefore, although our initial assumptions precluded our CSP procedure from predicting Form II, Form III was predicted as the most likely polymorphic structure, albeit with an energy that suggests it would be challenging to isolate (and arguably agreeing with its experimental instability). Thus, our approach successfully predicted the only other $Z'=1$ structure of ISN yet discovered, and has revealed its crystal structure.

More significantly, a blind CSP of the analogue iproniazid predicted a polymorphic system with at least two notably low-energy structures and several metastable ones. An exhaustive experimental screening process, including solvent-based, gel-phase and sublimation crystallization, successfully obtained two of the predicted structures: the stable Form I and metastable Form II. However, the global minimum on the static energy landscape, the densest pre-

dicted structure, remained elusive despite its predicted thermodynamic stability. It was only through diamond anvil compression experiments that this structure, Form III, was obtained experimentally. Detailed free-energy calculations representing the state-of-the-art in CSP techniques rationalize the stability relationship between Forms I and III. Form III is not the global energetic minimum when thermal effects are considered but is obtainable when experimental searching is guided by CSP. Once formed by compression, Form III persists at ambient pressure and hence CSP has revealed a high-risk late appearing polymorph and indicated the conditions under which it is formed.

This work demonstrates the power of combining exhaustive experimental screening with modern CSP methods to elucidate the risk of late-appearing polymorphism. We emphasize the synergy between the two fields; the blind CSP of iproniazid suggested a significant risk of polymorphism, which justified a thorough experimental screening that obtained Forms I and II. When the most likely structure according to CSP eluded this screening, further computational analysis *via* free energy calculations rationalized its elusiveness, while high-pressure experiments motivated by the predicted maximal density of this structure successfully yielded Form III. The crystallization and characterization of three polymorphs of iproniazid, for which no pure crystal structure was previously available, is tangible evidence of the value of this combined approach for exploring and “de-risking” solid form landscapes.

ASSOCIATED CONTENT

Extended description of experimental procedures (sublimation, gelator synthesis, and high-pressure experiments); extended description of computational CSP procedure (conformer generation and space group sampling); crystallographic data and analysis (PXRD patterns, Hirshfeld and packing analysis); crystal structure files (CIF format).

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Notes

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