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Sulfamerazine: Understanding polymorphic phase-transformation through X-ray synchrotron studies and *ab initio* lattice dynamics

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Abstract Understanding the polymorphism exhibited by organic active-pharmaceutical ingredients (APIs), in particular insight into the relationships between crystal structure and the thermodynamics of polymorph stability, is vital for the production of more stable drugs and better therapeutics, and for the economics of the pharmaceutical industry in general. In this paper, we report a detailed study of the structure-property relationships among the polymorphs of the model API, Sulfamerazine. Detailed experimental characterization using synchrotron radiation is complemented with computational modelling of the lattice-dynamics and mechanical properties, to study the origin of differences in millability and to investigate the thermodynamics of the phase equilibria. Good agreement is observed between calculated phonon density of states curves and mid-infrared and Raman spectra. The presence of slip planes, evident in the low-frequency lattice vibrations, explains the higher millability of Form I compared to Form II. Energy/volume curves for the three polymorphs, together with the temperature dependence of the thermodynamic free energy computed from the phonon frequencies, explains why Form II converts to Form I at high temperature, whereas Form III is a rare polymorph which is difficult to isolate. Moreover, the combined experimental and theoretical approach employed here should be generally applicable to the study of other systems which exhibit polymorphism, potentially helping to deliver better, more active forms of drugs at lower costs.

Introduction

Understanding polymorph transformations is extremely important, both at a fundamental and application (industrial) level. The activity, stability, processability and dissolution kinetics of a drug product depend on the solid-state structure, and so being able to rationalize and predict the most stable form of a system is critical.¹ Polymorphism is a property exhibited by most organic molecular crystals, whereby a given molecule can pack into different crystal lattices, depending on the kinetic and thermodynamic driving forces present at the time of crystallization. For example, different annealing temperatures can provide varying amounts of energy to enable the system to access different polymorphs.² Kinetic products are frequently found to be metastable polymorphs, as the most stable polymorph often takes longer to form. Eventually, however, metastable polymorphs invariably convert to the most stable form, provided the two forms are enantiotropically related. This conversion, under given storage conditions, decides the shelf-life and potentially the activity of a drug. The changes in properties associated with the changes in structure can also have other direct impacts on the economics of the pharmaceutical industry.

A well-known example is the case of the anti-HIV drug Ritonavir (Abbott). The active form of this drug (Form I) is metastable, and eventually converts to the more stable Form II under storage conditions. Form II was not only inactive against HIV, but also inhibited the production of the active form, ultimately leaving the company with a significant financial loss.³ Understanding the structural features which lead to particular polymorphs being favored over competing phases, and which determine physical properties such as processability, is thus of paramount importance.

In this paper, we report a combined experimental and theoretical study of the polymorphism exhibited by the model drug, Sulfamerazine (SMZ). SMZ is a sulfonamide drug, used as an anti-

bacterial agent in the early 20th century. While no longer in clinical use amongst humans, it is still extensively studied as a model polymorphic system,⁴ and for its ability to form co-crystals⁵ and also co-amorphous systems.^{5b} Indeed, a general Google Scholar search reveals that some 300 papers with Sulfamerazine in their title have been published since the 1940s, discussing everything from clinical trials to processability and fundamental properties, while thousands more papers have been published discussing it as a part of other studies.

SMZ has three known polymorphs. Form I is a kinetic product, whose crystal structure was first reported in 1972 by Yang *et al.*, with a more detailed crystallographic study by Caria *et al.* following in 1992.^{4a} Form II is more thermodynamically stable, and was discovered by Acharya *et al.* in 1982.⁶ A less well-known third form, Form III, was discovered in 2006 by Hossain *et al.*;^{4b} however, since this is very difficult to isolate, it has received considerably less attention. Since their discovery, there have been extensive studies of the structure-property relationships between the three polymorphs. The main emphasis has been on the thermodynamics of the polymorph transformations and on mechanical properties such as millability, *etc.*^{5a, 7}

Zhang *et al.* reported that the thermodynamic transformation of Form II to Form I happens between 50-54 °C,^{7m} while in our previous work, we discovered that Form I goes to Form II on ball milling for an hour at room temperature.^{5b}

Experimentally, it has been observed that Form I is more millable than Form II,^{5b} i.e. it amorphises more easily than form II, and this fact has been attributed to the presence of slip planes in the Form I structure.^{5b, 8} Sun *et al.* calculated and compared the attachment energies of different layers in various compounds and their polymorphs, with and without slip planes, using molecular-mechanics codes, and discovered that, while it was possible to model polymorphs with slip planes relatively accurately, they were not able to extend the procedure to the more

stable polymorphs of the compounds.⁸ Beyond this, however, there has been little work done thus far to investigate the fundamental relationship between slip planes and millability.

For understanding both the mechanical properties of a system, and also the thermodynamics of the phase equilibria between polymorphs, *ab initio* lattice-dynamics calculations, carried out e.g. within the density-functional theory (DFT) framework, may be informative. Whereas standard total-energy calculations can provide only differences in the athermal (i.e. 0 K) lattice energies between polymorphs, lattice-dynamics calculations provide access to thermodynamic free energies as a function of temperature, based on the thermal population of the vibrational modes of the system. These calculations allow the temperature dependence of a number of properties to be evaluated from first principles, for example the constant-volume (Helmholtz) or constant-pressure (Gibbs) free energy, the thermal expansion, and the bulk modulus.⁹ Given the often subtle energy differences involved in polymorphism (typically on the order of a few kJ mol⁻¹), differences in zero-point vibrational energy and/or temperature-dependent vibrational internal energy and entropy may be sufficient to overcome differences in lattice energy, and hence to shift the free-energy ordering of competing forms. In addition, knowledge of the vibrational modes of a structure, in particular of the low-frequency collective motions which will be thermally accessible at low-to-moderate temperatures, may provide an insight into which internal motions within the unit cell are particularly low in energy, and hence how the structure may preferentially deform under *e.g.* mechanical shear.

In this study, we have carried out a combined experimental and theoretical characterization of SMZ, using *ab initio* lattice-dynamics calculations in conjunction with modelling of the mechanical properties, to address several important questions about this system: 1) why is Form I more millable than Form II, and 2), how is this related to the presence of slip planes?; 3) Why

does Form II convert to Form I only on heating?; and 4) why is Form III so rare? We evaluate critically the utility of DFT lattice-dynamics calculations in reproducing experimental data, demonstrating good reproduction of the atomic thermal motion and vibrational spectra of SMZ polymorphs, and illustrate how this approach can be used to obtain new insight into polymorphism in molecular crystals.

Experimental methods

Sulfamerazine (SMZ) was purchased from Sigma-Aldrich and used as received. All solvents were used as received, without further purification. SMZ Form I (**CCDC code: SLFNMA02**) was prepared by sublimation *in vacuo* at 160 °C (<200 mbar). Form II (**CCDC code: SLFNMA01**) was prepared according to the procedure in Ref. ^{4a}, by preparing seeds by ball milling Form I for 60 minutes, which were then used to seed a solution of SMZ in an 80:20 mixture of acetonitrile and water once cooled to room temperature after initial heating. We were unable to obtain SMZ Form III (**CCDC code: SLFNMA03**) from dimethylformamide according to the reported method,^{4b} which in our experiments resulted in the crystallization of solvates rather than the pure compound.

Variable-temperature single-crystal studies were carried out using an in-house Agilent Xcalibur S instrument. A full hemisphere of data was acquired in each experiment, using Mo-K α radiation ($\lambda = 0.71069 \text{ \AA}$) with a graphite monochromator. The structures were solved using the SHELXT¹⁰ software, and refined using SHELXL,¹¹ with all non-hydrogen atoms being refined anisotropically. ORTEX plots were generated using OSCAIL software.¹² A more comprehensive set of measurements were performed at the Diamond Light Source, Beamline I19, to obtain measurements of the lattice parameters with a finer temperature resolution. Full

datasets were collected between 150 K and 300 K at 10 K intervals using a source wavelength of 0.68890 Å and a dtrek-CrysAlisPro-abstract goniometer paired with a Rigaku detector. During these experiments, the temperature was ramped at 6 ° per minute, with the sample being allowed to equilibrate for 10 mins at each target temperature before collecting Structures were solved using the same procedure as for the in-house data outlined above.

Combined differential-scanning calorimetry (DSC) and thermogravimetric analysis (TGA) measurements were carried out using a Rheometric Scientific STA 625 (calibrated using an Indium standard) between room temperature and 250 °C, with a heating rate of 5 °C/min, to study the transformations between Form I and II (see supporting information for DSC trace).

Raman and IR spectra of both forms were acquired using a Witec Raman system (785nm laser excitation, <500 mW laser power, 64-scan integration with 0.5 s accumulation time, 4 cm⁻¹ resolution within a 100-1800 cm⁻¹ spectral range) and a Perkin Elmer SpectrumOne (Waltham, Massachusetts; 400-3400 cm⁻¹ range, 4 cm⁻¹ resolution, 32-scan integration), respectively.

Lattice-dynamics calculations

Lattice-dynamics calculations refer generally to the evaluation of the phonon modes of a periodic system. The standard model is to treat a crystal of N atoms as $3N$ independent quantum-harmonic oscillators, which is generally sufficient to describe vibrational properties quantitatively up to moderate temperatures.

The key computation is the evaluation of the interatomic force-constant (IFC) matrices, which capture the change in force on an atom j in response to displacement of an atom i by a small distance from its equilibrium position (eq. 1):

$$\Phi_{\alpha\beta}(il, jl') = -\frac{\partial F_{\alpha}(il)}{\partial r_{\beta}(jl')} \quad (1)$$

The subscripts α and β are the Cartesian directions x , y and z , and the indices l and l' denote the unit cells in which atoms i and j reside relative to one another. In periodic systems, phonons are modelled in reciprocal space, with the wavevector \mathbf{q} describing the propagation and modulation of the atomic-displacement wave across unit cells. The range of the IFCs (values of l and l') which needs to be considered to accurately model the variation (dispersion) of phonon frequencies around the phonon Brillouin zone depends on the number of atoms in the unit cell, with long-range IFCs being most important for treating short-wavelength vibrations.

The force-constant matrices can be obtained either by the “direct” (finite-displacement) method, where symmetry-inequivalent atomic displacements are physically performed and the resulting force hence computed, or by a perturbation-theory approach such as density-functional perturbation theory (DFPT). The latter method can be easily extended to obtain long-range IFCs, whereas to do this in a finite-displacement approach requires performing calculations on a supercell of the initial structure.

The force constants are then used to build up 3×3 blocks of the dynamical matrix for a given \mathbf{q} -vector, diagonalization of which produces eigenvectors and eigenvalues corresponding to the normal-mode coordinates and associated oscillator frequencies, respectively (eq. 2):

$$D_{\alpha\beta}(i, j, \mathbf{q}) = \frac{1}{\sqrt{m_i m_j}} \sum_{l'} \Phi_{\alpha\beta}(i0, jl') \exp[i\mathbf{q} \cdot (\mathbf{r}(jl') - \mathbf{r}(i0))] \quad (2)$$

where m_i is the mass of atom i , and $\mathbf{r}(il)$ is the position of atom i in the l th unit cell. It is worth noting that a dynamical matrix for a given \mathbf{q} -vector can be constructed from IFCs computed to an arbitrary range, allowing phonon modes to be obtained with a fine Brillouin-zone sampling

without requiring explicit calculation of the IFCs in all the unit cells involved in the modulation period.

Harmonic lattice-dynamics calculations also enable the calculation of the constant-volume (Helmholtz) thermodynamic free energy, A , as a function of temperature, which for a periodic system is given by:

$$A(T) = U_L + U_V(T) - TS_V(T) \quad (3)$$

where U_L and U_V are the lattice and vibrational internal energies, respectively, and S_V is the vibrational entropy. We note that the Helmholtz energy is the constant-volume analogue of the more familiar Gibbs free energy.

With knowledge of the phonon frequencies, it is convenient to compute the Helmholtz energy from the partition function, Z , given by:

$$Z(T) = \exp(-U_L/k_B T) \prod_{\mathbf{q}v} \frac{\exp(-\hbar\omega(\mathbf{q}v)/2k_B T)}{1 - \exp(-\hbar\omega(\mathbf{q}v)/2k_B T)} \quad (4)$$

where ω are the phonon frequencies of the v modes at each wavevector \mathbf{q} , and the product captures the statistical occupation of phonon energy levels at a given temperature according to the Bose-Einstein distribution. The Helmholtz energy can then be obtained from the bridge relation:

$$\begin{aligned}
A(T) &= -k_B T \ln Z \\
&= U_L + \frac{1}{2} \sum_{qv} \hbar\omega(\mathbf{qv}) + k_B T \sum_{qv} \ln[1 - \exp(-\hbar\omega(\mathbf{qv})/2k_B T)] \quad (5)
\end{aligned}$$

The RMS of Eq. 5 shows that the Helmholtz energy is a sum of three terms, *viz.* the lattice energy, a sum of the zero-point vibrational energies of each mode, and a temperature-dependent term arising from the population of phonon energy levels, which contains part of U_V plus the entropic contribution to the free energy. It is worth noting that U_L is the only component of the free energy which is available from standard total-energy calculations, and, in this model, the temperature dependence of the free energy is thus available only by evaluating the phonon modes.

In addition to $A(T)$, it is also possible to evaluate the temperature dependence of the internal energy and entropic contributions separately. The former can be evaluated directly according to:

$$U(T) = U_L + U_V(T) = U_L + \sum_{qv} \hbar\omega(\mathbf{qv}) \left[\frac{1}{2} + \frac{1}{\exp(\hbar\omega(\mathbf{qv})/k_B T) - 1} \right] \quad (6)$$

where again the phonon occupation number is obtained from a Bose-Einstein distribution using the vibration frequency. The entropy can be obtained from the standard thermodynamic relation $S = \partial A / \partial T$.

Computational methods

Computational modelling was carried out on the CCDC structures of Forms I, II and III within the density-functional theory (DFT) framework as implemented in QuantumESPRESSO code.¹³ The internal coordinates were optimized using three different DFT functionals, namely the Perdew-Burke-Enzerhof (PBE)¹⁴ functional, the variant of PBE revised for solids (PBEsol),¹⁵ and the dispersion-corrected PBE-D2 functional.¹⁶ All calculations were carried out using projector augmented-wave pseudopotentials¹⁷ with a plane-wave kinetic-energy cut-off of 70 Ry. The Brillouin zones of the Form I and III structures were sampled using Monkhorst-Pack k -point meshes¹⁸ with $1 \times 1 \times 3$ and $1 \times 3 \times 1$ subdivisions, respectively, while the Form II electronic structure was modelled at the Γ point. We found from convergence testing that these parameters were sufficient to converge the absolute total energies to within 1 meV atom⁻¹.

Ab initio lattice-dynamics calculations were performed using the Phonopy package,¹⁹ using a custom-made wrapper around its Vienna *ab initio* Simulation Package (VASP) interface to convert to and from the QuantumESPRESSO file formats. Harmonic-phonon calculations were carried out according to the finite-displacement method with a step size of 0.01 Å. A tolerance of 10⁻³ Å on the atomic positions was applied during the detection of the space group, and the calculated force constants were symmetrized appropriately. We neglected the possibility of long-range interactions between unit cells, and thus carried out the phonon calculations on a single unit cell. However, when constructing the phonon density of states and performing thermodynamic integration during post-processing, the Brillouin zone was sampled with a \mathbf{q} -point mesh with $32 \times 32 \times 32$ subdivisions; whereas this led to little perceptible change to the phonon DOS compared to evaluating only the Γ -point frequencies, we found that the larger mesh was necessary to converge the thermodynamic free energy.

Finally, to study the mechanical properties of the three polymorphs further, we also computed energy/volume curves for each structure with PBE-D2. To do this, the cell shape and internal positions were optimized for a range of fixed volumes about the value in the reported crystal structures. The E/V data was then fitted to the Murnaghan equation of state²⁰ to obtain the equilibrium volume, density and bulk moduli of the three forms.

Results and discussion

Variable-temperature crystallography

Representative structures of the three forms of SMZ from literature data are shown in Figure 1. Form I is in the $Pna2_1$ space group with eight molecules in the unit cell, which form a layered structure along the crystallographic c -axis^{4a}. Form II also has eight molecules in the unit cell, but in this polymorph the molecules adopt a higher-density herringbone structure in the $Pcba$ space group^{4a}. In contrast, Form III has only four molecules in the unit cell, and adopts the $P2_1/c$ space group^{4b}. The three different polymorphs have distinctly different H-bonding patterns, and Forms I and III both contain slip planes.

To provide an experimental reference for the computational modelling, and in particular to obtain insight into the thermally-accessible lattice vibrations from an analysis of the thermal ellipsoids, we performed single crystal X-ray diffraction experiments at variable temperature using both an in-house instrument and synchrotron radiation. Figure 2 shows the density of Forms I and II as a function of temperature, and the corresponding percentage changes in the lattice parameters. Due to the difficulty in obtaining Form III we were not able to carry out similar experiments on Form III crystals.

The difference in the nature of the bonding in the two polymorphs is well reflected in the anisotropic expansion observed along the three crystallographic axes in both unit cells. In Form I, the crystallographic *c*-axis undergoes significantly larger expansion compared to the *a* and *b* axes. From the in-house data, the *a* axis appears to stop expanding beyond 200 K, whereas in the higher-resolution synchrotron data the expansion is roughly linear from 150-300 K with a shallow gradient. In the case of Form II, maximum expansion is observed along the *b* axis, which corresponds to the stacking direction of the herringbone “layers”. Conversely, minimum expansion occurs along the *c* direction, which would require stretching the intermolecular H-bonds. The percentage expansion of the Form II lattice is on the same order as that of Form I, but the latter maintains a lower density throughout the temperature range studied.

Interestingly, while Form I undergoes predictable thermal expansion, indicated by the near-linear decrease in density with temperature, there is a visible break in the thermal expansion of Form II between 150 K and 185 K. This prominent feature is much less evident in the synchrotron data, however, suggesting that it may be crystal dependent, but nonetheless it is the *c*-axis which undergoes contraction in this dataset, which is consistent with its shallow expansion. Aside from this discrepancy, the synchrotron study gave a general trend in good agreement with our in-house collections. We note that the differences in the percentage change in lattice constants and in the densities amount to fairly small variation in the lattice parameters (see supporting information), and so may be due simply to differences between the crystals used in the various data collections, or indeed in the instrument models used during the data reduction. Another potential factor to note is that data collections could be performed in seconds at the synchrotron source, whereas the same experiment took eight hours on the in-house instrument, allowing the structure to equilibrate for much longer at the given temperature. We intend to carry

out further calculations in the future to investigate the thermal expansion in more detail, in particular the potential low-temperature negative expansion of Form II.

A lot of information about the crystal dynamics can be gleaned from studying the thermal ellipsoids at different temperatures (Figure 3). In both polymorphs, there is significant inherent molecular flexibility evident even at 150 K. The carbon atoms on the benzene rings bearing the methyl groups have relatively large thermal ellipsoids compared to the rings bearing the amino groups. With increasing temperature, the size of the thermal ellipsoids on all the atoms increases, but, interestingly, the motion of the ring bearing the methyl group, and also that of the methyl C itself, is anisotropic, suggestive of a “rocking” motion of the ring about the S-C and S-N bonds. There is likewise a considerable increase in the thermal ellipsoids on the atoms in the amino ring with temperature, and these are again anisotropic, suggesting a similar behavior. Form II, in comparison to Form I, appears to have much less flexibility, in particular in the motion of the ring bearing the amino group, with the ellipsoids being more isotropic than those of the methyl ring. This is consistent with the interlayer spacing in Form I, introduced by the slip plane, providing more freedom for the rings to vibrate.

Molecular motion in crystals has been studied in the past using NMR, where the inherent atomic motion and the phase transition in the crystalline form of chloroform were characterized by studying the relaxation times as a function of inverse temperature.²¹ More recently, the thermal motion of organic-molecular crystals has also been studied using lattice-dynamics calculations to predict the thermal ellipsoids and anisotropic-displacement parameters (ADPs) at low temperature, giving generally good correspondence with low-temperature neutron-scattering data.²² In the present work, from our *ab initio* lattice-dynamics calculations we were similarly able to identify numerous soft phonon modes corresponding to the motion of the two rings and

their pendant functional groups, which explains the anisotropy observed in the thermal ellipsoids; this will be discussed further in the following subsections.

Ab-initio lattice-dynamics calculations

We first performed a set of harmonic-phonon calculations on the optimized initial structures with our three chosen functionals. The three sets of initial phonon DOS curves are compared to the experimentally-recorded MIR and Raman spectra in the supporting information, and a general assignment of modes can be found in Refs. ^{5b, 23}. We found that the best agreement between the positions of the peaks in the calculated phonon DOS curves and the measured spectra of Form I and II was obtained with the PBE-D2 functional. The match was found to be especially good in the low-wavenumber and fingerprint regions of the spectrum. A more noticeable offset between the calculated and measured peaks was observed in the high-frequency stretch region of the spectrum between 2500 and 3600 cm^{-1} - we found that this region was better reproduced by PBEsol, but that this functional gave a less good reproduction of the spectrum as a whole. In comparison to both these functionals, we found that PBE yielded a phonon spectrum which was notably red shifted with respect to those obtained from the other two functionals, and also compared to the experimental measurements.

We observed imaginary (negative-frequency) modes in all three of the phonon DOS curves, which are an indicator of structural instability. These modes invariably corresponded to the inherent motion of the crystal visible in the thermal ellipsoids (see Figure 3), which suggests that the room-temperature structures reported in Refs. ^{4, 6} are crystallographic averages over soft phonon modes. To attempt to get to the “true” equilibrium structure, within the constraints of the experimental unit cell, we generated structures with the atoms displaced along the imaginary-

mode phonon coordinates, then re-optimized the internal positions. This mode-following procedure invariably led to a loss of the symmetry of the cell, as a result of which performing additional phonon calculations on these structures required single-point calculations on a considerably larger number of displaced structures. We therefore performed a second phonon calculation with only the PBE-D2 functional.

The all-electron PAW lattice energies of the three polymorphs, obtained with the three functionals before and after following the imaginary modes, are collected in Table 1. For comparison, the calculated zero-point energies obtained from the various phonon calculations are shown in Table 2, while Figure 4 compares the final PBE-D2 phonon DOS curves against the MIR and Raman spectra collected from Form I and Form II samples.

Based on the work in Ref. ^{7m}, we would expect that Form II, as the most thermodynamically stable form of SMZ, should have a lower combined lattice and zero-point energy than Form I. For the lattice energies, this was the case in the PBEsol and PBE-D2 calculations, which predicted Form II to be 0.49 and 6.40 kJ mol⁻¹ per molecule more stable than Form I, respectively. In contrast, however, PBE predicts Form I to be the more stable of the two, by 2.62 kJ mol⁻¹ per molecule. All three functionals predict Form III to have a higher lattice energy and thus to be less stable than both of the other two polymorphs, which provides an explanation as to why it is the most difficult of the three to isolate. Mode following changed some of the energy differences by up to approx. 10 %, but did not change the stability ordering.

Interestingly, the differences in the calculated zero-point vibrational energies (ZPEs) are on the same order as the difference in lattice energies, highlighting the potential importance of considering the free energy when assessing polymorph stability. Before mode following, all three functionals predict Forms II and III to have a higher ZPE than Form I. For PBE-D2, the ZPE

contribution to the free energy at 0 K does not change the relative stability of the polymorphs, although it does reduce the energy difference between Forms I and II by around 30 %. For PBE, on the other hand, the zero-point energy contributions lead to Form III being more stable than Form II at 0 K, while for PBEsol the differences in ZPE are sufficient to raise Form II above Form I in energy. As for the lattice energies, mode following changed the ZPEs obtained with PBE-D2 slightly, but this did not alter the stability ordering of the systems.

To investigate the variation in relative stability with temperature, we compared the Helmholtz free energies and vibrational internal energy and entropy as a function of temperature from 0 to 600 K (Figure 5). The free energies of Forms I and II cross around 8 °C, which is remarkably close to the 50-60 °C phase-transition temperature observed experimentally.^{7m} Even though the difference is large in temperature terms, it corresponds to a few meV in energy units, which is close to the limit of accuracy in the DFT calculations. Despite this limitation, however, the phase transition temperature is predicted with reasonable accuracy, and the trend is consistent with experiment. From Figure 5c, it can be seen that the crossover comes about from a significant difference in the vibrational entropy (S_V) of Form I, which at higher temperature is sufficient to offset the lower lattice energy of Form II. The increased entropy is attributable to soft lattice vibrations, such as are reflected in the thermal ellipsoids, the thermal population of which can increase the entropy of the system without incurring a large internal-energy penalty. From this analysis, the high-temperature stability of Form I may be related to the presence of the slip plane and consequent reduced density, which would allow for lower-energy molecular motions

Interestingly, these calculations predict that Form III remains unstable with respect to the other polymorphs even at high temperature. Although it has a larger entropy than Form II at higher temperatures - which, as for Form I, may be due to its layered structure - it remains above Form I

in energy up to at least 600 K. Furthermore, this entropic stabilization is insufficient to offset the differences in lattice and vibrational internal energy with respect to Form II. If it is indeed the case that Form III is thermodynamically unstable with respect to Forms I and II, these calculations provide a natural explanation for why it is only possible to isolate it under very specific conditions.

Lattice dynamics and slip planes

As noted earlier, form I of SMZ is more millable than form II, making form I easier to process,⁸ due to the presence of slip planes. However, aside from the computational modelling by Sun *et al.* to probe this indirectly *via* calculation of attachment energies,⁸ which gave good results for polymorphs with slip planes, but was less successful for those without (e.g. herringbone structures), little work has been done to link this structural feature to millability. Figure 6 (a) shows the indexed faces of a single crystal of SMZ Form I, with the *c*-axis normal to the hexagonal sheet-like [001] plane. When pressure is applied to the crystal normal to the *c*-axis, the layers readily slip, as can be seen in the photograph in Figure 6(b).

From an analysis of the phonon eigenvectors obtained from the lattice-dynamics calculations, a large number of low-frequency modes related to the "rocking" of the benzene rings in the SMZ molecule about the S-C bond are clearly observed. This explains the origin of the size and, where applicable, the anisotropy of the thermal ellipsoids in the ORTEX plots noted in the previous section (see also Figure 3).

For Forms I and III, which have layered structures, these motions would aid in the separation of the layers, and hence the macroscopic "slip action". We also observed modes corresponding to the layers sliding past one another, which would likewise aid the mechanical slippage. In case of

Form I, the relevant vibrational modes contributing to slipping seen in Figure 6 have frequencies of 230.39, 271.44, 274.81, 286.75 and 290.19 cm^{-1} . The analogous modes in Form III were found to have significantly lower energies of 64.49, 75.31 and 97.25 cm^{-1} (slip along the *b*-axis), and 99.90, 101.51, 113.59-139.31 and 291.73 cm^{-1} (slip along the *c*-axis). The fact that there is a possibility of slipping along two axes, combined with the soft nature of the phonons which would aid in the macroscopic slip action, suggests that Form III may be mechanically, as well as thermodynamically, unstable compared to the competing phases, which could further explain its rarity. We also observed “partial” slip modes in Forms I and III, in which one layer slips while the other displays ring bending, which could also aid in layer separation.

In contrast, Form II, with its herringbone packing, does not lend itself to slipping. Despite this, phonon modes similar to the ones observed in the other two forms were visible at 277.69-330.96 cm^{-1} in this polymorph, although this is generally stiffer than in Form I, implying that such motions are less energetically accessible. A list of the relevant modes observed in the three forms, including their frequencies and assignments, can be found in the supporting information.

Equation of state and mechanical properties

Finally, to investigate further the mechanical properties of the three polymorphs, we also calculated energy/volume curves (Figure 7), which were then fit to an equation of state to obtain equilibrium structural parameters, *viz.* the volume, density and bulk modulus (Table 3). The *E/V* curves reproduce the key features of the system observed experimentally and from the lattice-dynamics calculations presented earlier, *viz.* the higher density of Form II compared to the other polymorphs, and the 0 K stability ordering of Form II < Form I < Form III.

Interestingly, the equation of state suggests that the lattice energies of Forms II and I may come into equilibrium under moderate expansion of Form II. This condition could be met, while also introducing energy to effect the structural rearrangement, by heating, which provides an additional explanation as to why Form II can be converted to Form I on heating. Indeed, we note that, whereas the thermodynamic equilibrium has been reported to be at around 50-54 °C, fast conversion is observed at rather higher temperatures around 160 °C.^{7m} Form III has a higher lattice energy over the complete range of volumes studied in this work, reinforcing its thermodynamic instability with respect to the other SMZ polymorphs.

A further piece of information which can be obtained from the E/V curves is the common tangent between the minima of Forms I and II, which gives the theoretical pressure at which they would be in equilibrium. We calculated this pressure to be around 500 MPa, which may be accessible by mechanical milling, and which would be consistent with the fact that Form I converts to Form II on ball milling at RT for an hour.^{5b} The conversion on milling may also be interpreted based in terms of the higher density of Form II.

Discussion

We close with some general comments on the methodology employed in this work. In general, the *ab initio* lattice-dynamics calculations performed on SMZ have shown good agreement with experiment when compared both to MIR and Raman spectroscopy, which probe the phonon frequencies, and to the thermal ellipsoids from variable-temperature crystallography, which probe indirectly the atomic displacements which characterize the low-frequency phonon modes.

In terms of thermodynamics, our results suggest that differences in zero-point vibrational energy can be on the same order as differences in lattice energy (\sim kJ mol⁻¹), which suggests that

including this contribution to the free energy may be important for analyzing polymorph stability even at low temperature, when the effects of phonon occupation on internal energy and entropy are minimal. In the present work, we were able to use the temperature-dependent Helmholtz energy, computed at the room-temperature lattice parameters, to estimate the thermodynamic transition temperature between Forms I and II with some accuracy. This is in spite of the discrepancy between the calculated and measured frequencies of the high-energy phonons, which may be ascribed to the fact that the low-frequency modes are the ones which are significantly populated at low-to-moderate temperature, and so make the most significant contribution to the temperature dependence of the free energy.

However, it is worth noting that, under most experimental conditions, it is the constant-pressure (Gibbs) free energy, rather than the Helmholtz energy, which is relevant. Within the quasi-harmonic approximation,^{9,24} the lattice temperature is captured by the cell volume, and the Gibbs energy at a given temperature is obtained as the Helmholtz energy computed at the corresponding lattice volume. Therefore, it is likely that the good agreement in the transition temperature is due in part to our fixing the unit-cell parameters at the 300 K values, which in this case happen to be fairly closer to the experimentally-measured transition point. We intend to investigate this further in the future by performing full quasi-harmonic calculations on SMZ.

Finally, it is worth noting that we observed qualitative differences in the stability ordering predicted by the three DFT functionals we tested, *viz.* PBE, PBEsol and PBE-D2, with PBE performing particularly poorly for this system. This indicates that in studies such as the present, which aim to probe subtle energetics, it may important to benchmark several functionals to find the best-performing one for the system under study.

Conclusion

Through the combined experimental and computational study performed in this work, we have obtained a detailed understanding of the polymorphic transformations observed between the forms of SMZ as a model API, and the relationships between the structures and the industrially-relevant mechanical properties.

In spite of a few caveats, *ab initio* lattice-dynamics calculations have enabled an exploration of the soft phonon modes which give rise to the crystal dynamics visible in the thermal ellipsoids obtained from X-ray diffraction experiments. Thermodynamics calculations successfully reproduced the high-temperature phase transition between Forms II and I, which appears to occur primarily due to the higher vibrational entropy of the latter offsetting differences in internal energy, in particular the lattice energy, at finite temperature. This can be attributed to the layered structure of Form I allowing for softer lattice vibrations. The rarity of Form III can be explained by the fact that at low temperature it has a higher internal energy than either of the competing phases, whereas at high temperature its vibrational entropy is not competitive with that of Form I.

From our calculations, we were also able to identify the microscopic reason behind the easier millability/processability of Form I over Form II. We identified vibrational modes in Form I which may aid in the macroscopic slip action, and although some similar modes were observed in Form II, which does not have a slip plane, these were observed to occur at higher frequencies due to the tighter H-bonding network of the latter, which indicates that such motions are energetically more difficult in the denser herringbone structure. The slip action in Form III, on the other hand, appears to be supported by very soft lattice phonons, which may lead to this polymorph being mechanically, as well as thermodynamically, unstable.

A comparison of the calculated equations of state of the polymorphs show that the lattice energies of Form II and Form I may come to equilibrium as the Form II lattice is expanded, providing additional evidence for why the conversion from Form II to Form I happens on heating. On the other hand, this analysis suggests that Form I and II would be in equilibrium at a pressure of around 500 MPa, which, combined with the lower density of Form II, suggests why the conversion of Form I to Form II can be effected by ball milling. The microscopic insight obtained from this work may help to improve processing of sulfamerazine, i.e. milling, compaction, tableting etc., and to direct crystal-engineering approaches to obtain formulations with improved stability and properties

In summary, the findings from this study reinforce the results from previous work in the literature, while providing additional insight which may help to rationalize the relative stabilities of the polymorphs in this and in other pharmaceutically-important systems, and also to aid the design of formulations (e.g. cocrystals) with improved stability and properties. Moreover, the computational methodology explored in this work is general, and could be applied to the study of other, perhaps more challenging, systems.

Figures

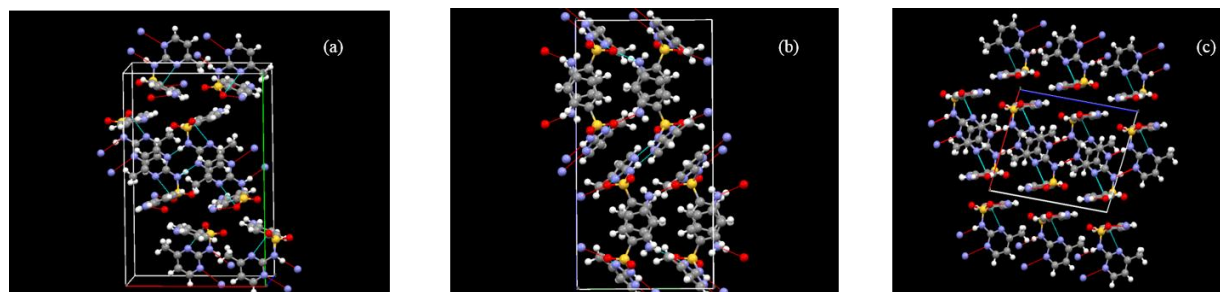


Figure 1. Representative crystal structures of Sulfamerazine Forms I (a), II (b) and III (c), generated from the reported structures^{4, 6} using the Mercury software²⁵. Forms I and Form III both have slip planes, while there is strong H-bonding along all axes in Form II.

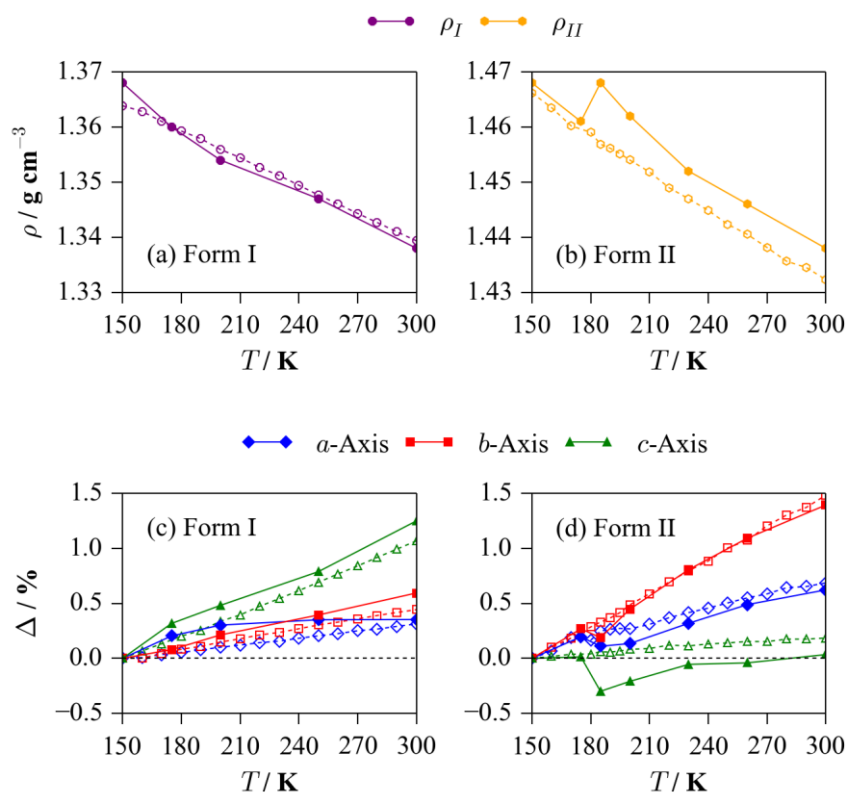


Figure 2. Thermal expansion of Sulfamerazine Forms I and II from single-crystal X-ray diffraction studies. Plots (a) and (b) show the change in the density of Form I (a) and II (b), while plots (c) and (d) show the corresponding % change in lattice constants. On each plot, the open markers/dashed lines represent data collected at the Diamond Light Source, while the filled markers/solid lines show data collected on an in-house diffractometer.

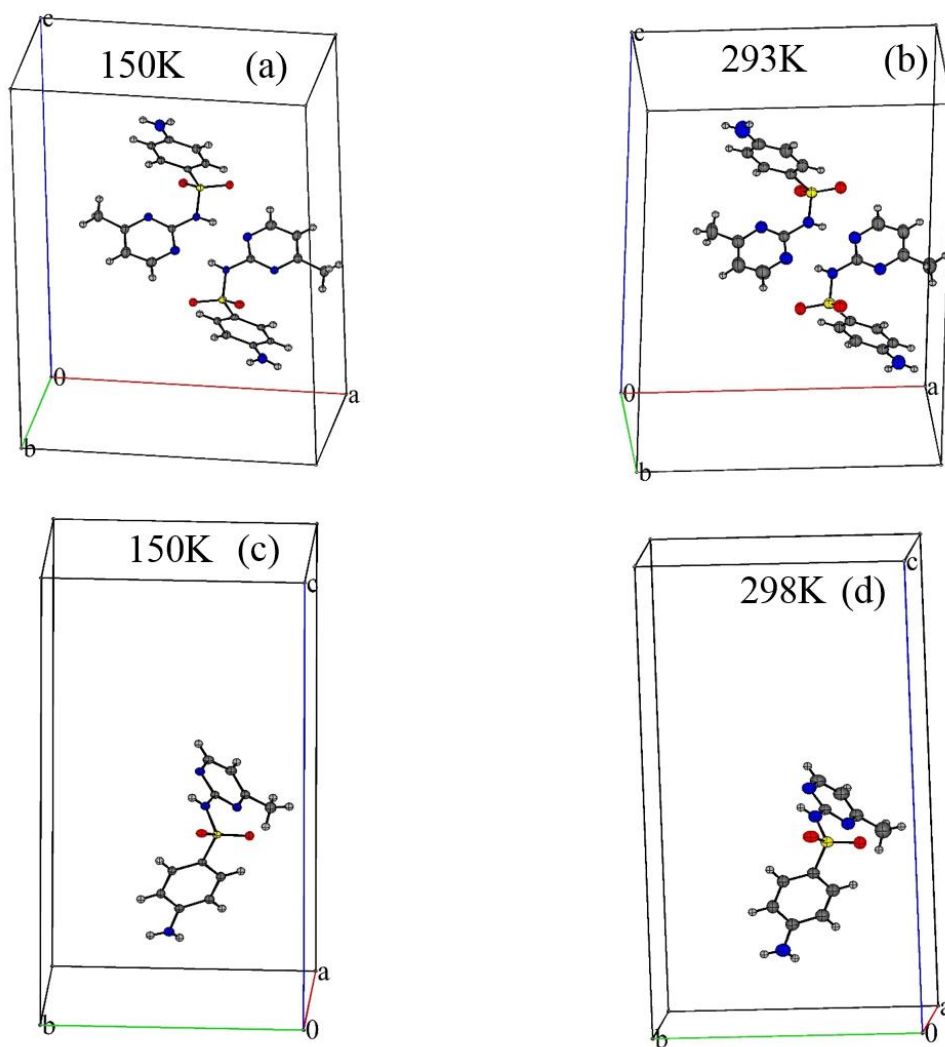


Figure 3. ORTEX plots (30% probability) showing the thermal ellipsoids of Sulfamerazine Form I (a and b) and II (c and d) at the temperatures indicated beside the structures. These structures were obtained from solution and refinement of data collected on an in-house diffractometer. A relative increase in the sizes of the ellipsoids with temperature is observed, as expected, but the pendant rings in both polymorphs exhibit fairly anisotropic ellipsoids, reflecting soft lattice vibrations corresponding to “rocking” of the rings.

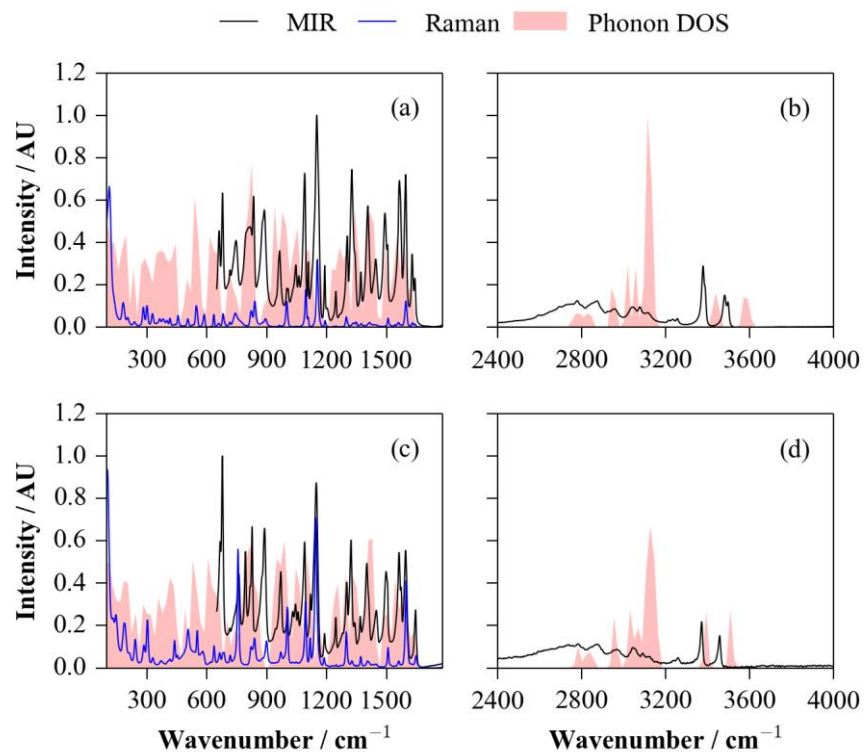


Figure 4. Vibrational spectra of Sulfamerazine Form I (a, b) and Form II (c, d). Plots (a) and (c) compare mid infra-red (MIR) and Raman spectra (785 nm excitation), recorded in the fingerprint region between 100 and 1780 cm^{-1} , to the calculated phonon density of states (DOS). Plots (b) and (d) compare the MIR spectra and phonon DOS between 2400 and 4000 cm^{-1} .

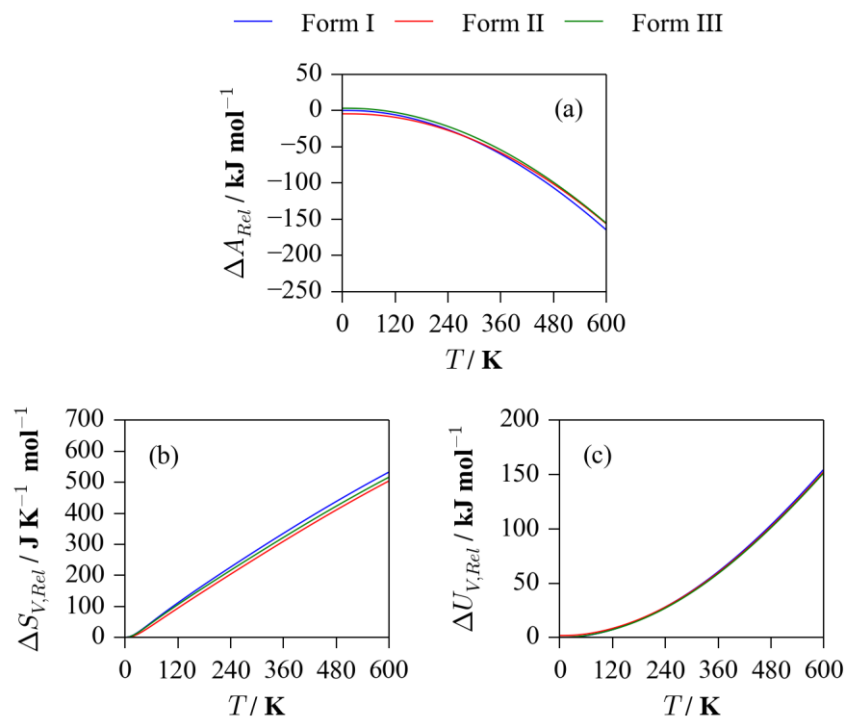


Figure 5. *Ab-initio* thermodynamics of Sulfamerazine Forms I, II and III. The three plots show (a) the calculated constant-volume (Helmholtz) free energy, A , together with the separate contribution from (b) the vibrational entropy, S_V , and (c) the vibrational internal energy, U_V , as a function of temperature, between 0 and 600 K. All four curves are expressed relative to Form I at 0 K.

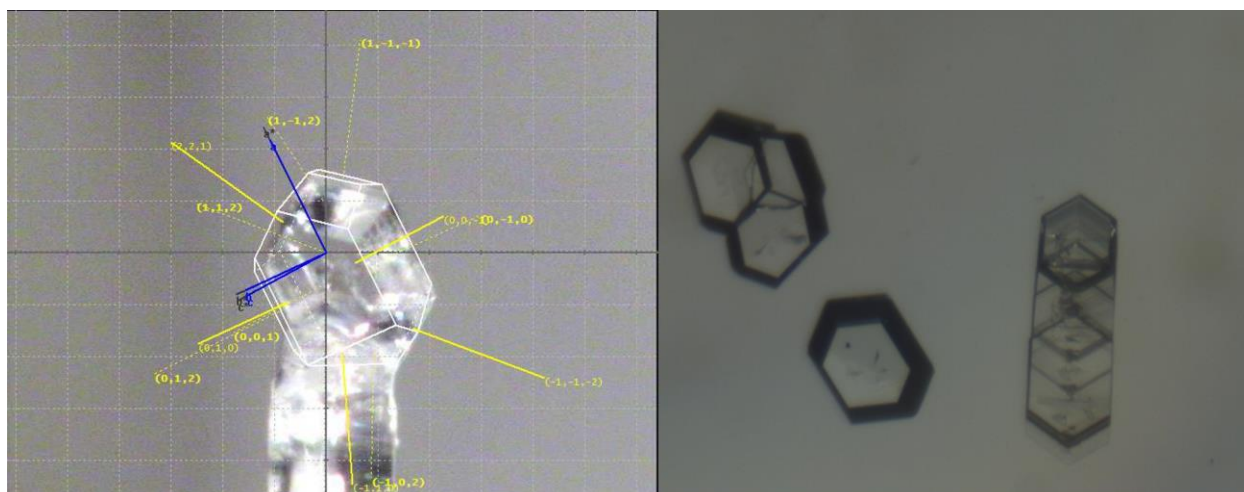


Figure 6. (Left) Indexed faces of the Sulfamerazine Form I crystal. (Right) Layers of Form I formed by slipping along the slip plane normal to the crystallographic c axis.

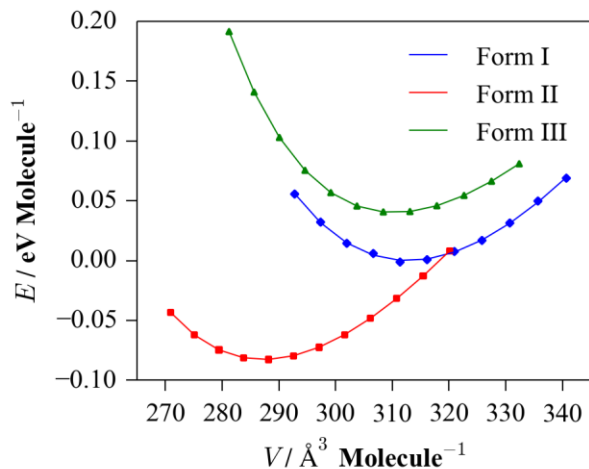


Figure 7. Calculated energy versus volume curves for Sulfamerazine Forms I (blue/diamonds), II (red/squares) and III (green/triangles). The markers are the calculated energies, and the solid lines are fits to the Murnaghan equation of state. The equilibrium volumes, densities and bulk moduli obtained from the fits are given in Table 3. The energies are expressed relative to the fitted equilibrium energy of Form I.

| Functional | $E / \text{eV Molec}^{-1}$ | | | $\Delta E_I / \text{kJ mol}^{-1} \text{Molec}^{-1}$ | |
|-----------------------|----------------------------|-----------|-----------|---|----------|
| | Form I | Form II | Form III | Form-II | Form-III |
| Before Mode Following | | | | | |
| PBE | -2389.848 | -2389.846 | -2389.845 | 2.62 | 3.91 |
| PBEsol | -2382.408 | -2382.408 | -2382.405 | -0.49 | 3.02 |
| PBE-D2 | -2389.975 | -2389.980 | -2389.973 | -6.40 | 2.53 |
| After Mode-Following | | | | | |
| PBE | -2389.849 | -2389.846 | -2389.845 | 2.77 | 4.18 |
| PBEsol | -2382.408 | -2382.408 | -2382.405 | -0.39 | 3.30 |
| PBE-D2 | -2389.975 | -2389.980 | -2389.973 | -6.52 | 2.80 |

Table 1. Calculated per-molecule all-electron (PAW) lattice energies for the three polymorphs of Sulfamerazine, computed with three different DFT functionals, before and after the mode-following procedure performed to attempt to remove imaginary phonon modes from the structures (see text). The first three columns give the absolute values in eV, while the last two give (Form - Form I) energies in kJ mol^{-1} .

| Functional | $U_{ZP} / \text{kJ mol}^{-1} \text{Molec}^{-1}$ | | | $\Delta U_{ZP,I} / \text{kJ mol}^{-1} \text{Molec}^{-1}$ | |
|-----------------------|---|---------|----------|--|----------|
| | Form I | Form II | Form III | Form-II | Form-III |
| Before Mode Following | | | | | |
| PBE | 589.31 | 591.34 | 590.10 | 2.04 | 0.79 |
| PBEsol | 585.73 | 587.58 | 586.14 | 1.85 | 0.41 |
| PBE-D2 | 586.63 | 588.81 | 587.10 | 2.18 | 0.47 |
| After Mode-Following | | | | | |
| PBE-D2 | 586.90 | 588.78 | 293.57 | 1.88 | 0.24 |

Table 2. Calculated per-molecule vibrational zero-point energies of Sulfamerazine Forms I, II and III, obtained from phonon calculations with three different DFT functionals. For PBE-D2, the values after the mode following are also given. As in Table 1, the first three columns give the absolute values (in kJ mol^{-1}), while the last two give the energy differences relative to Form I.

| Polymorph | $V_0 / \text{\AA}^3 \text{ Molec}^{-1}$ | $\rho_0 / \text{g cm}^{-3}$ | B_0 / GPa |
|------------------|---|-----------------------------|--------------------|
| Form I | 312.77 | 1.404 | 11.44 |
| Form II | 287.26 | 1.528 | 10.99 |
| Form III | 310.39 | 1.415 | 11.09 |

Table 3. Calculated equilibrium volumes, densities and bulk moduli of the three forms of Sulfamerazine, obtained by fitting E/V curves to the Murnaghan equation of state (see Figure 7).

Supporting Information. Contains the DSC curves and the unit-cell parameters recorded in the in-house and synchrotron single-crystal X-ray diffraction measurements. Also has assignments for the various phonon modes which relate to the slip action observed in the different polymorphs of sulfamerazine, as discussed in the text. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Abbreviations

SMZ - Sulfamerazine, DSC - differential scanning calorimetry, TGA - thermogravimetric analysis, IR - infra-red

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