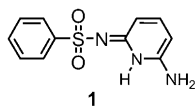# Unmasking a Third Polymorph of a Benchmark Crystal-Structure-Prediction Compound**
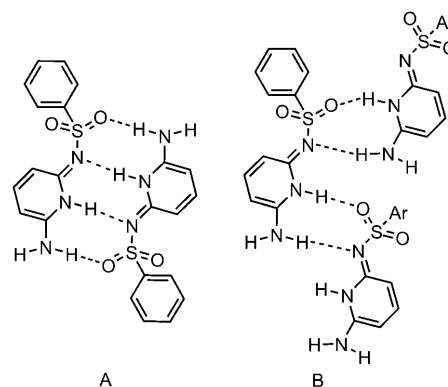
*Saikat Roy and Adam J. Matzger**

The ability of a chemical substance to adopt more than one crystal structure is known as polymorphism,[1] a phenomenon which can be both beneficial and problematic.[2] Serendipity often plays a key role in the discovery of new forms, because no general methodology exists for producing new forms of a given compound. Understanding the origin of polymorphism and controlling the outcome of crystallization processes to avoid undesired forms is therefore a current goal.[3] A closely related challenge is the prediction of a crystal structure from a given chemical structure. This process, which involves generating and energetically ranking many hypothetical polymorphs, is referred to as crystal-structure prediction (CSP).[4] The importance of CSP has been recognized through the "blind tests" conducted by the Cambridge Crystallographic Data Center (CCDC). However, even simple rigid molecules in common space groups present a considerable challenge,[5,6] and prediction of flexible molecule crystal structures is even more difficult owing to the much larger parameter space to be explored.[7,8] Examination of kinetic and thermodynamic issues in crystallization can provide insight into the mechanism of nucleation and aid development of better methodologies for CSP. In this spirit, we undertook the study of 6-amino-2-phenylsulfonylimino-1,2-dihydropyridine (**1**, Scheme 1), which was part of the second CCDC blind test in 2001 (molecule VI)[5b] and then subjected to additional scrutiny after the contest.[9]

The dihydropyridine **1** prediction exercise ended with disappointment, as none of the participants of the blind test were able to predict the crystal structure correctly.[5b] Further study[9,10] yielded a second polymorph of molecule **1**, claimed to be the thermodynamic form; form II contained dimer hydrogen-bonding four-point synthon A (Scheme 2). It was proposed[9] that because form I contains two-point synthon B, it facilitates 1D growth and that this polymorph was the kinetically favored form. This rationale neatly explained why

Scheme 1. Chemical structure of blind-test molecule **1**.

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Scheme 2. The four-point synthon A and two-point synthon B.

thermodynamic predictions of polymorph stability employed in most CSP approaches failed to find this form and implicated the initial crystallization conditions in leading to an unstable form.
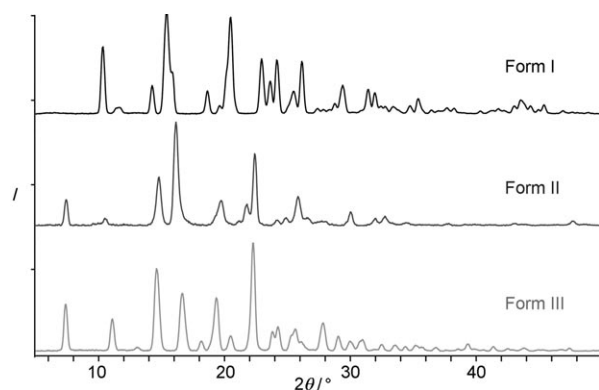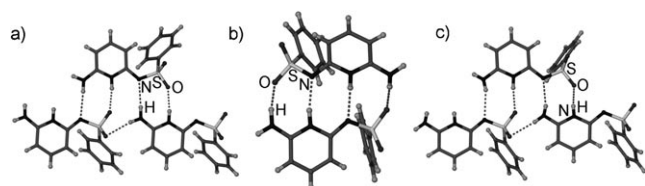
Because polymorphism is so common in sulfonamides,[11] we were encouraged to reopen the investigation of molecule **1** utilizing functionalized cross-linked polymers as heteronuclei to reveal new regions of polymorph space.[3a] Polymer-induced heteronuleation (PIHn) is a strategy that has proven effective for a wide range of compounds.[12] Crystals of molecule **1** were grown from ethanol using PIHn (see the Supporting Information). Three types of crystal morphologies were observed: block-like crystals of form I, needle-type crystals of form II, and hexagonal plates (Figure S1 in the Supporting Information). Raman spectroscopic analysis of these crystals revealed three distinct forms with characteristic Raman spectra (Figure S2 in the Supporting Information), and the hexagonal plates where denoted as form III. The powder X-ray diffraction (PXRD) patterns of these three forms are distinct (Figure 1), and block-like form I and needle-like form II closely match predicted patterns based on the previously reported forms of molecule **1**.[9] However, form III, although distinct (Table S2 in the Supporting Information), has some similarities in PXRD profile with form II, and this finding necessitated further study by single-crystal X-ray diffraction.

The earlier reported structures[9] of form I and form II revealed the presence of synthon B and synthon A (Scheme 2) as building blocks of the crystal lattices with one and two molecules in the asymmetric unit, respectively. Form III is orthorhombic[13] with one molecule in the asymmetric unit. Moreover, form III exhibits two-point synthon B, similar to form I (Figure 2c). Form I and form III have a similar catemer synthon with N−H···N hydrogen bonds

**Figure 1.** Experimental powder X-ray diffraction pattern of form I, form II, and form III.

Figure 2. Hydrogen-bonding synthons in a) form I (synthon B), b) form II (synthon A), and c) form III (synthon B).


Figure 3. a) *Anti* arrangement of phenyl rings in catemers of form I. *Syn* orientation of phenyl rings in stacked layers of b) dimer in form II and c) catemer of form III.

of an amine with an imine N atom and N−H···O hydrogen bonds between secondary ring amine and the O atom of a sulfonyl moiety. Both form I and form III possess N−H···O interactions between translationally related molecules along the *b* axis. However, form II is quite different structurally, with N−H···N and N−H···O hydrogen bonding between two symmetry-independent molecules to make a dimer (Figure 2b). In form II, these 0D dimers are connected by N−H···O hydrogen bonds to make 2D sheet arrangements. Although form I and form III share the same synthon in their structures, orientations of phenyl rings are different, resulting in completely different packing (Figure 3a,c). The phenyl groups of the molecule in the dimer of form II are also in a *syn* orientation, as in form III, which leads to similar stacks of layered structures in both the forms (Figure 3b,c). Conformational analysis of the four symmetry-independent molecules in the three forms of molecule **1** reveals that they each have distinct molecular conformations (Figure 4). This conformational polymorphism arises from the flexibility along C-C-S-N, C-S-N-C, and S-N-C-N torsion angles.

It was previously proposed[9] that synthon A in form II is more preferred because of its shorter and more linear hydrogen bonding. Moreover, a lattice energy calculation (CVFF95) on the crystal structures suggested that form II is more stable by 0.86 kcal mol^{-1}. The Hirshfeld surfaces[14] of the polymorphs of molecule **1** (Figure 5) reveal that form I has a greater contribution from O···H (26.1%) and lesser N···H bonding (8.2%) than form II (21.5% and 10.4%, respectively). In form III, the contribution of O···H hydrogen bonds is less (21.1%), because it does not contain C−H···O interactions, unlike form I. Overall, the analysis suggests that form II has a higher contribution from N···H bonds than
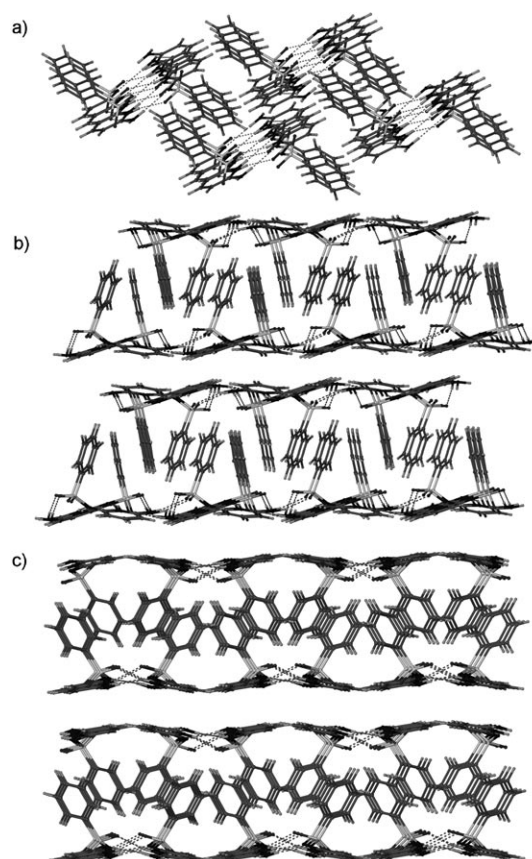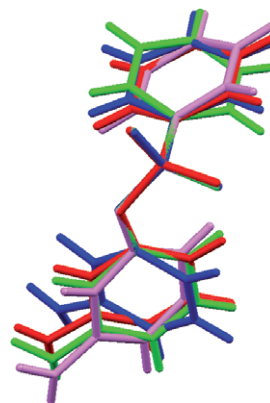
Figure 4. Overlay of symmetry-independent molecules of form I (pink), form II molecule A (green), form II molecule B (blue), and form III (red).

form I and form III. Hirshfeld surface fingerprint plots (Figure S4 in the Supporting Information) show the presence of close O···H contacts in form I and close N···H interactions in form II.

Thermomicroscopy and differential scanning calorimetry (DSC) experiments confirm that form I and form III have approximately 12°C higher melting point than form II
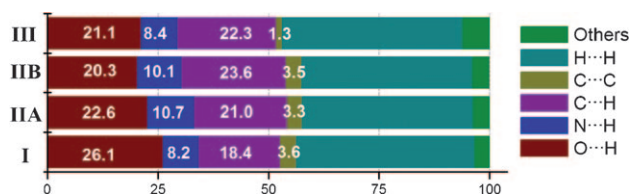
Figure 5. Relative contribution to the Hirshfeld surface for the various intramolecular contacts for the molecules in form I, form II molecule A, form II molecule B, and form III.

(Figure S5 in the Supporting Information). Moreover, it is observed that form II has a lower enthalpy of melting ($\Delta H = 9.56\ kcal\,mol^{-1}$) than form I ($\Delta H = 11.81\ kcal\,mol^{-1}$) and form III ($\Delta H = 10.92\ kcal\,mol^{-1}$). The higher enthalpy of form I indicates more favorable packing energy than for form II and form III (Figure 3).

Previous lattice-energy calculations[9] predicted that form II is more stable by about $1\ kcal\,mol^{-1}$ than form I and, along with synthon energy computational results, concluded that form II is thermodynamically favored, while form I is kinetically favored. Our experimental results led us to reexamine this issue with a computational procedure based on the COMPASS force field that has been demonstrated to agree well with experiment for a range of polymorphic pharmaceuticals.[15] However, this method incorrectly predicts that form II is the lowest-energy arrangement, thus highlighting the challenge of applying computational approaches to this molecule.

Enthalpic measurements alone cannot predict which form is most stable at room temperature. To determine the relative free energy relationships, solvent-assisted polymorphic transformation experiments were carried out by combining polymorphs pairwise in ethanol; both form II and form III convert to form I, thus demonstrating that the crystal structure originally reported as the blind-test solution is the thermodynamically most favorable one at room temperature. To quantify these differences, relative free energies were determined (see the Supporting Information).[12d] Form I is the most stable at 299 K and is more stable than form II by $0.44\ kcal\,mol^{-1}$ and than form III by $0.23\ kcal\,mol^{-1}$. These experiments demonstrate that form I is the thermodynamically favored form and that form II is least stable among the three polymorphs. In this context, the results of all teams in the 2001 blind prediction trial were reexamined. The two most stable forms, forms I and III, were absent from all submitted structure predictions.

In conclusion the thermochemical and physiochemical relationship among the polymorphs of a conformationally flexible blind-test molecule has been established based on experimental findings. Moreover, a third novel form has been found for this important benchmark compound. These results demonstrate that though form I is the thermodynamic form, it was beyond prediction; this result highlights the importance in improvements of computational methodology for CSP. Finally, 20 years ago Maddox commented that the lack of success in CSP is a "continuing scandal" and noted that the "X-ray crystallographer need not worry—yet".[16] After two decades, although improvements have been made, there is still considerable job security for the experimental chemist and crystallographer.

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[13] Crystal data for form III: $C_{11}H_{11}N_3O_2S$, $M_r = 249.29$, crystal dimensions $0.30 \times 0.20 \times 0.04$ mm³, orthorhombic, space group *Pbca*, $a = 10.6177(2)$, $b = 9.31782(19)$, $c = 23.0558(5)$ Å, $V = 2280.99(8)$ Å³, $Z = 8$, $\rho_{calcd} = 1.452$ g cm⁻³, $T = 95$ K, 9473 measured, 1948 independent, 1492 observed $[(I) > 2\sigma(I)]$ reflections, $R_{int} = 0.0872$, $R_1 = 0.0591$, $wR_2 = 0.1878$ [for $(I) > 2\sigma(I)$], $S = 1.110$. CCDC 736451 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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