

New polymorphs of isonicotinamide and nicotinamide†

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For each of the well-known co-crystal formers, isonicotinamide and nicotinamide, a new polymorph, obtained during attempted co-crystallisation experiments, has been fully characterized and its stability relationship with previously reported forms established.

Isonicotinamide (pyridine-4-carboxamide) and nicotinamide (pyridine-3-carboxamide) (Fig. 1) are two popular co-formers used as partner molecules with active pharmaceutical ingredients (APIs) in co-crystal preparation.^{1–3} The crystal structures of two polymorphs of isonicotinamide were reported in 2003,^{4,5} but their thermodynamic relationship was not determined. These two forms, herein designated Iso1 (CSD refcode EHO-WIH02)⁴ and Iso2 (CSD refcodes EHOWIH,⁵ EHOWIH01),⁴ were evidently the only known polymorphs of isonicotinamide, despite the successful incorporation of this molecule into 51 co-crystals whose single crystal X-ray structures were reported between 2001 and 2010.⁶ A third polymorph, designated Iso3,‡ first obtained during our attempts to form a co-crystal with an anti-tubercular API (isoxyl, Fig. 1), is described in this report.

The single crystal X-ray structure of nicotinamide (Nic1) was first reported in 1954,⁷ a more accurate determination appearing in 1999 (CSD refcode NICOAM01).⁸ The polymorphism of nicotinamide was first discussed in 2001⁹ based on the evidence obtained from DSC analysis. However, during the period 1950–2010, although the structures of 27 co-crystals containing nicotinamide were successfully determined,⁶ the structure of only one nicotinamide polymorph was known. The new polymorph of nicotinamide,§ isolated and characterised in this study, and obtained exclusively during an attempt to co-crystallise nicotinamide and the anti-tubercular API, has been designated Nic2.

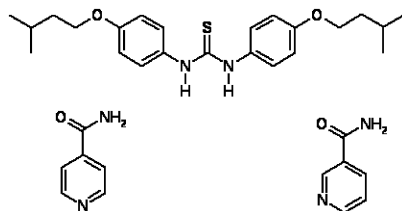


Fig. 1 Structures of isoxyl (top), isonicotinamide (bottom, left) and nicotinamide (bottom, right).

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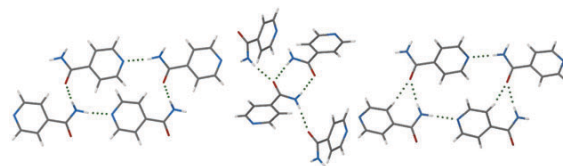


Fig. 2 Hydrogen bonded motifs in Iso1 (left), Iso2 (centre) and Iso3 (right).

Single crystal X-ray diffraction analysis of the new polymorphic form Iso3 (*Pbca*, $Z = 8$)§ revealed that its hydrogen bonding motif bears some resemblance to that in Iso1 (*P2₁/c*, $Z = 8$) (Fig. 2), while Iso2 (*P2₁/c*, $Z = 4$) features a completely different motif. Iso1 contains two crystallographically independent molecules A and B, molecule A being hydrogen bonded to other symmetry-generated molecules A only, and molecule B being likewise hydrogen bonded to symmetry-generated B molecules only. In polymorph Iso3, a weak intermolecular hydrogen bond C2–H2...O1ⁱ ($i = 1/2 + x, 1/2 - y, 2 - z$, C...O = 3.205(2) Å) occurs within the motif. This is associated with the different pyridine ring orientations in the hydrogen bond motifs of Iso1 and Iso3. An analogous interaction (not shown) occurs in Iso1 with, however, slightly less favourable geometry.

In the crystal of Iso1, the two symmetry-independent molecules A and B form two independent hydrogen-bonded layers A and B, (Fig. 3, left). The unit cell thus contains eight symmetry-related molecules arranged in four layers (A, B, A' and B') which extend infinitely, parallel to the *c*-axis. In the crystal of Iso3, there are instead eight symmetry-related molecules in the unit cell, arranged in two layers which extend infinitely parallel to the *a*-axis, Fig. 3 (right). Layers A and B of Iso1 differ in the relative inclinations of the pyridine rings comprising them, whereas layers A and A' in Iso3 are related to one another by a centre of inversion. No interlayer hydrogen bonding interactions occur in either of these polymorphs.

All three isonicotinamide polymorphs were carefully examined by differential scanning calorimetry (DSC), hot

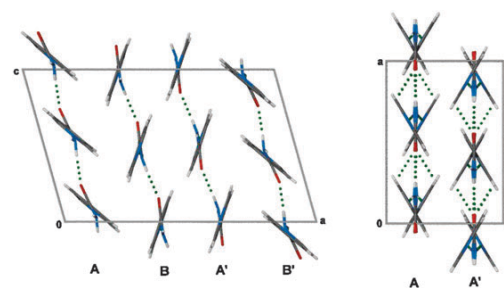


Fig. 3 Crystal packing diagrams for Iso1 viewed along the *b*-axis (left) and Iso3 viewed along the *c*-axis (right).

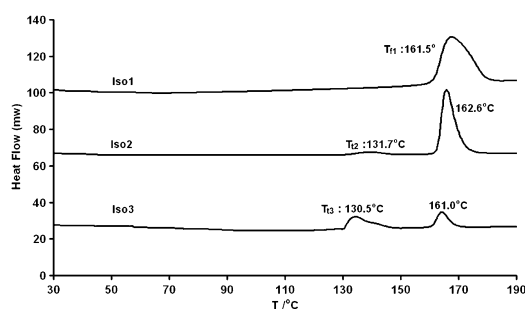


Fig. 4 DSC traces of Iso1, Iso2 and Iso3 (heating at 70 K min⁻¹) with the onset temperature of each thermal event.

stage microscopy (HSM) and variable temperature powder X-ray diffraction (PXRD). Fig. 4 shows the DSC results for these crystalline phases heated at 70 K min⁻¹ (this high heating-rate having been selected after several trials to enhance the appearance of endotherms for transitions other than melting). The DSC trace for Iso1 exhibited a single endothermic peak representing fusion. For both Iso2 and Iso3, the DSC traces exhibited an initial endothermic peak, followed by a second endothermic peak. These were interpreted as indicating that both Iso2 and Iso3 underwent solid–solid phase transitions into modified forms which subsequently melted.

The fact that the fusion temperatures for all three forms are very similar suggests complete phase transformation of both Iso2 and Iso3 to Iso1 on heating. Variable temperature PXRD profiles (not shown) were recorded to confirm the above conclusions. Specifically, the PXRD pattern of Iso2 heated above ~120 °C and that of Iso3 heated above ~110 °C corresponded to that of Iso1. (These temperatures are somewhat lower than those for the transitions in the DSC and are attributed to the different sample arrangements in the DSC and PXRD experiments *viz.* sample holders closed and open to the atmosphere, respectively.) Furthermore, no indication of a phase change between Iso2 and Iso3 was evident. Therefore, Iso1 is enantiotropically related to Iso2 and Iso3, while Iso2 and Iso3 are monotropically related. These represent the fundamental data needed for constructing a semi-quantitative energy–temperature diagram (Fig. 5).

According to the density rule,^{10,11} the thermodynamically stable form at 0 K has the highest density. From the *E/T*

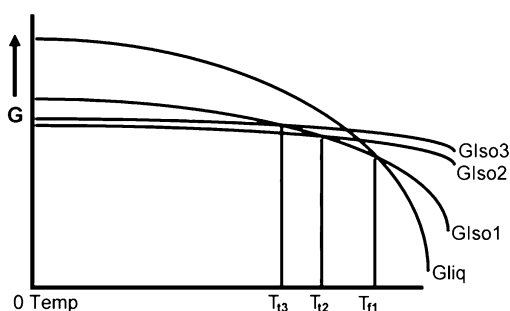


Fig. 5 A schematic *E/T* diagram for the three polymorphs of isonicotinamide. T_{13} and T_{12} are the temperatures for the respective transitions Iso3 → Iso1 and Iso2 → Iso1; T_{11} represents the melting point of Iso1. (Note that the interval $T_{13} \rightarrow T_{12}$ is highly exaggerated.)

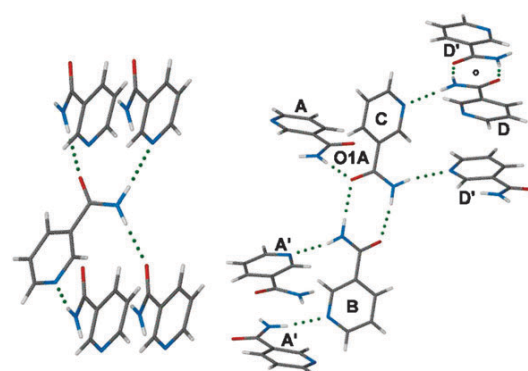


Fig. 6 The hydrogen bond interactions in Nic1 (left) and Nic2 (right).

diagram, it can be predicted that the density order below T_{13} is: Iso2 > Iso3 > Iso1. The respective calculated densities at 173 K are 1.402, 1.374 and 1.354 g cm⁻³. It can also be predicted from the *E/T* diagram that these polymorphs would have a solubility order at room temperature: Iso2 < Iso3 < Iso1.

The crystal polymorphism of nicotinamide is simpler than that of isonicotinamide, the available data indicating a dimorphic system. There are four crystallographically independent molecules (A, B, C, D) in the asymmetric unit of the newly isolated form Nic2. Fig. 6 shows relevant hydrogen bond interactions. A noteworthy observation is that the oxygen atom in molecule A is not involved in any hydrogen bonding while all the O and N atoms in molecules B, C and D engage in H-bonding. Molecule D forms a hydrogen-bonded homomeron (having graph-set descriptor $R_2^2(8)$) with an inversion-related molecule.

As for the polymorphs of isonicotinamide, those of nicotinamide were likewise investigated by thermal analysis methods in this study. DSC analysis was performed on Nic1 and Nic2 at a heating rate of 10 K min⁻¹ (Fig. 7). Both DSC traces exhibited a single endotherm corresponding to fusion. The melting peak for Nic2 displays both a shoulder and a peak. This is attributed to the fact that an intact crystal (1.03 mg) of Nic2 was used for this analysis with consequent non-uniform heat transport through this abnormally thick specimen. (Any possibility of inducing a phase transformation in Nic2 by grinding was eliminated by the use of a single crystal as the sample for DSC.)

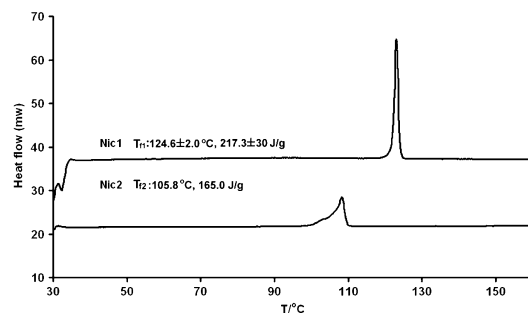


Fig. 7 DSC traces of Nic1 and Nic2 (heating rate 10 K min⁻¹) with the onset temperature and heat of fusion of each thermal event indicated.

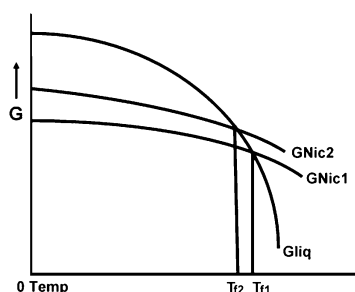


Fig. 8 A schematic E/T diagram for the two polymorphs of nicotine; T_1 and T_2 represent the melting points of Nic1 and Nic2, respectively.

Based on the Burger and Ramberger Heat of Fusion rule,¹¹ the fact that the lower-melting form (Nic2) has the smaller enthalpy of fusion leads to the conclusion that Nic1 and Nic2 are monotropically related. Variable temperature PXRD profiles (not shown) were used to confirm the above conclusion. Specifically, the distinctive PXRD patterns of these polymorphs were maintained when they were heated from 30 °C to their respective melting points. Hence, a simple energy–temperature diagram for the nicotine polymorphs (Fig. 8) was constructed.

From the E/T diagram, it can be predicted that Nic1 is the thermodynamically stable form between absolute zero and its melting point while Nic2 is the thermodynamically metastable form between absolute zero and its melting point. Also, in this temperature range, the densities of the two polymorphs would be in the order: Nic1 > Nic2 (respective calculated ρ values in g cm^{-3} are 1.446 [150 K] and 1.355 [173 K]), while the solubilities of the two forms would be in the order: Nic1 < Nic2.

Given the current high level of interest in co-crystallisation phenomena worldwide and the frequent choice of both isonicotinamide and nicotine as potential co-crystal formers, we draw the readers' attention to the possibility of these new polymorphic forms being induced to crystallise preferentially during failed co-crystallisation experiments. The experimental and computed PXRD patterns of the new polymorphs of isonicotinamide (Iso3) and nicotine (Nic2) (ESI†) are provided to enable their identification and especially to distinguish these phases from putative co-crystals.

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Notes and references

† Iso3 and Nic2 precipitated serendipitously during attempts to prepare co-crystals of the API isoxyl, an antitubercular thiourea drug (also known as Tiocarlide, *N,N'*-[4-(3-methylbutoxy)-phenyl]thiourea) with isonicotinamide and nicotine respectively. Under the specific conditions employed in the experiments described here, the appearance of Iso3 crystals did not depend on the presence of isoxyl while that of Nic2 crystals did, as explained below. A physical mixture of 38 mg (0.31 mmol) of isonicotinamide [Sigma-Aldrich Chemie GmbH (Steinheim, Germany)] and 20 mg (0.05 mmol) of isoxyl [Sapphire (Redfern NSM, Australia)] was dissolved in 2 ml chloroform at 45 °C. The solution was stirred for 10 min and filtered (0.45 μm nylon filter) while hot. It was then placed in a Dewar flask containing water at ~45 °C. The Dewar flask was covered with an insulating material to allow slow cooling. The water in the Dewar flask returned to ambient temperature over a period of one and a half days. Crystals of all three polymorphic

forms of isonicotinamide were present after this period. Because their morphologies were not sufficiently distinctive, the requisite amount of Iso3 for the various analyses was accumulated by direct verification of the unit cell data for several crystals of this species on the diffractometer. It was subsequently found that the above crystallisation outcome occurred also in the absence of added API. A physical mixture of 19 mg of nicotine (0.15 mmol) [Sigma-Aldrich Chemie GmbH (Steinheim, Germany)] and 9 mg (0.02 mmol) of isoxyl was dissolved in 2 ml ethyl acetate at 54 °C. The solution was stirred for 10 min and filtered (0.45 μm nylon filter) while hot. It was then placed in a Dewar flask containing water at ~54 °C. Rapid cooling was prevented by using an insulating material to cover the flask. Two days were required for the water in the Dewar flask to cool to ambient temperature. The solution was then allowed to evaporate slowly and crystallise under ambient conditions. Crystallisation occurred within two weeks of standing. A mixture of the polymorphs Nic1 and Nic2 resulted. It should be noted that in attempting to check reproducibility, using this procedure repeatedly resulted in random outcomes as far as the precipitation of Nic2 is concerned. Nic2 crystals were, however, never observed to crystallise in the absence of the API. DSC experiments were performed using a Perkin Elmer PC7-Series System under a dry N_2 atmosphere and the instrument was calibrated using standard materials. Samples, which ranged in mass between 0.3 and 10 mg, were placed in crimped, vented aluminium pans with lids. Intensity data for both crystals were collected on a Nonius Kappa CCD diffractometer. Unit cell determinations were carried out both at ambient temperature (294 ± 2 K) as well as low temperature (173 ± 2 K) in order to test whether there were any phase changes during the cooling process; none was evident. The structures of Iso3 and Nic2 were solved routinely using SHELXS-97¹² and refined against F^2 with SHELXH-97.¹³

§ Crystal data for Iso3: $\text{C}_6\text{H}_6\text{N}_2\text{O}$, $M = 122.13$, orthorhombic, space group $Pbca$ (no. 61), $a = 10.1603(7)$, $b = 7.3231(5)$, $c = 15.8720(6)$ Å, $V = 1180.95(12)$ Å³, $Z = 8$, $D_c = 1.3736$ g cm^{-3} , $F_{000} = 512$, Mo-K α radiation, $\lambda = 0.71073$ Å, $T = 173(2)$ K, $2\theta_{\text{max}} = 26.37^\circ$, $\mu = 0.098$ mm^{-1} , 2126 reflections collected, 1188 unique ($R_{\text{int}} = 0.0286$). Final GooF = 1.120, $R_1 = 0.0453$, $wR_2 = 0.1086$, R indices based on 896 reflections with $I > 2\sigma(I)$ (refinement on F^2), 82 parameters. CCDC 794755. Crystal data for Nic2: $\text{C}_6\text{H}_6\text{N}_2\text{O}$, $M = 122.13$, monoclinic, space group $P2_1/n$ (no. 13), $a = 15.0634(5)$, $b = 10.6976(4)$, $c = 15.2067(5)$ Å, $\beta = 102.188(2)^\circ$, $V = 2395.21(14)$ Å³, $Z = 16$, $D_c = 1.3545$ g cm^{-3} , $F_{000} = 1024$, Mo-K α radiation, $\lambda = 0.71073$ Å, $T = 173(2)$ K, $2\theta_{\text{max}} = 26.37^\circ$, $\mu = 0.096$ mm^{-1} , 88974 reflections collected, 4881 unique ($R_{\text{int}} = 0.1173$). Final GooF = 1.101, $R_1 = 0.0499$, $wR_2 = 0.1241$, R indices based on 3492 reflections with $I > 2\sigma(I)$ (refinement on F^2), 325 parameters. CCDC 794756.

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