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Authors	Eccles, Kevin S.;Deasy, Rebecca E.;Fábián, László;Braun, Doris E.;Maguire, Anita R.;Lawrence, Simon E.
Publication date	2011-01
Original Citation	Eccles, Kevin S., Deasy, Rebecca E., Fabian, Laszlo, Braun,Doris E., Maguire, Anita R., Lawrence, Simon E. (2011) 'Expanding the crystal landscape of isonicotinamide: concomitant polymorphism and co-crystallisation'. CrystEngComm, 13 (23):6923-6925. doi: 10.1039/c1ce06320k
Type of publication	Article (peer-reviewed)
Link to publisher's version	http://pubs.rsc.org/en/Content/ArticleLanding/2011/CE/c1ce06320k - 10.1039/c1ce06320k
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Download date	2024-04-28 05:07:34
Item downloaded from	https://hdl.handle.net/10468/942

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

COMMUNICATION

Expanding the crystal landscape of isonicotinamide: concomitant polymorphism and co-crystallisation

Kevin S. Eccles,^a Rebecca E. Deasy,^a László Fábián,^b Doris E. Braun,^c Anita R. Maguire^d and Simon E. Lawrence^{*a}

Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX

DOI: 10.1039/b000000x

Attempts to co-crystallise 3-arylbutanoic acid derivatives with isonicotinamide have led to co-crystals and novel polymorphs of the isonicotinamide co-former appearing under similar crystallisation conditions.

Isonicotinamide (Fig. 1) is used widely in co-crystallisation studies,¹⁻⁷ and has recently been investigated in relation to anti-inflammatory activity and Huntington's disease.^{8,9} It has three structurally characterised forms,¹⁰⁻¹² as well as two hydrates and an unidentified anhydrous form.¹³ The known forms contain amide...amide [N-H...O=C] hydrogen-bonds which are prevalent in biomolecules,¹⁴ as well as amide...pyridine [C(O)N-H...N] hydrogen-bonds. These result in 2-D layers in forms **II** and **III**, and a 3-D array in form **I**.

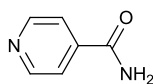


Fig. 1 The structure of isonicotinamide.

Co-crystallisation involves forming novel materials containing two or more neutral molecules (co-formers) in a crystalline array. Isonicotinamide is routinely investigated as a possible co-former because it forms robust and predictable hydrogen-bonded arrays with carboxylic acids, involving amide...amide and acid...pyridine hydrogen-bonds (Fig. 2). This has been exploited many times for co-crystal formation.¹⁻⁷

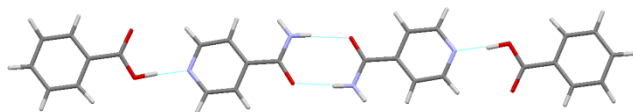


Fig. 2 The amide...amide and acid...pyridine hydrogen-bonds seen in co-crystals of isonicotinamide with carboxylic acids, shown here for benzoic acid.¹

During our studies into developing co-crystallisation as a tool for determining the absolute stereochemistry of materials which are hard to crystallise,⁷ we found that subtle changes in the solvent composition had a dramatic effect on the crystallisation outcome. For the successful co-crystallisation of substituted 3-

arylbutanoic acids with isonicotinamide, it was necessary to use a 70:30 solvent mixture of acetonitrile and acetone, respectively.

The use of pure acetone as solvent gave rise to two new forms of isonicotinamide, denoted **IV** and **V** (Fig. 3). Form **IV** was initially identified by its powder diffraction (PXRD) pattern, and form **V** discovered in subsequent crystallisation experiments.

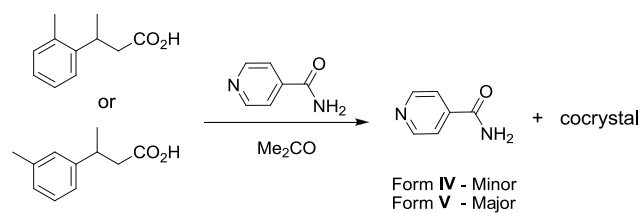


Fig. 3 Co-crystallisation of isonicotinamide with 3-arylbutanoic acid derivatives leads to new forms of isonicotinamide and/or the co-crystal, depending on crystallisation conditions.

The new forms were obtained by dissolving the co-formers in acetone and allowing the solution to stand at ambient temperature. Crystals were harvested from the side of the container before complete evaporation of the solvent, with form **V** (major product) isolated in a band of crystalline material above form **IV** (minor). When the solvent is allowed to completely evaporate, a complex mixture of the additive, the co-crystal and forms **I**, **II** and **IV** was isolated. Note that liquid assisted /solvent-drop grinding using acetone produces the co-crystal.

Repeating this procedure in the absence of the substituted 3-arylbutanoic acid results in the concomitant formation of forms **IV** and **II** on the side of the container before the solvent completely evaporates. Pure form **I** precipitates on the base of the container after the acetone completely evaporates. A wide variety of different crystallisation conditions were tried in efforts to separate form **IV** from form **II**. However, in this work the forms **I**, **II**, **IV** and **V** were isolated as laths at all times and could not be distinguished visually. Therefore, the individual crystals were separated and single crystal analysis was performed on each crystal. Unsurprisingly, the PXRD pattern always showed mixtures of both forms **IV** and **II**. For form **V** yields were often poor, typically 10%, and in some cases it could not be obtained. Similar reproducibility issues were reported by Cairn when investigating form **III**.¹²

Single crystal analysis of form **IV** (Pc , $Z' = 3$) reveals that it possesses a similar hydrogen-bonding network to that observed in forms **II** and **III**, namely amide chains held in 2-D sheets via amide...pyridine hydrogen-bonding (Fig. 4). The three molecules in the asymmetric unit are independent of each other, meaning that each molecule is hydrogen-bonding only with symmetry related molecules, giving rise to an ABC stacking of isonicotinamide layers. Overall, the packing in form **IV** is similar to that seen in form **II**. The hydrogen-bonded layers are identical in both forms, corresponding to the similarity of the b and c cell parameters. The stacking of these layers is such that three layers of both forms can be virtually superimposed, but there is a significant difference in the shift/reorientation of subsequent layers along the b -axis (Fig. 5). Thus, forms **II** and **IV** can be considered as polytypes.

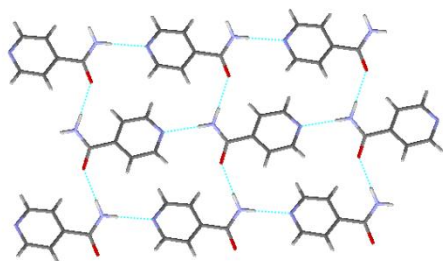


Fig. 4 The 2-D hydrogen-bonded sheets present in form **IV**.

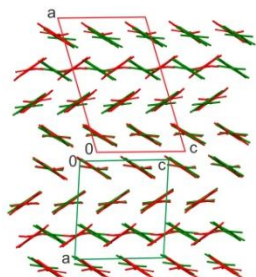


Fig. 5 Overlay of forms **IV** (green) and **II** (red).

Form **V** ($P2_1/c$, $Z' = 1$) has similar hydrogen-bonding to those observed in forms **II**, **III** and **IV** (Fig. 6). However, there is a significant difference: neighbouring molecules are almost perpendicular to each other, resulting in infinite zigzagging sheets (Fig. 7). There is a weak C-H...O hydrogen bond between the pyridyl ring and the neighbouring carbonyl group (not shown). Comparison of the PXRD data for forms **IV** and **V** with the unidentified anhydrous form¹³ is ambiguous.

Differential Scanning Calorimetry measurements (DSC) are widely used to investigate crystal forms and to gain insight into their stability using Burger-Ramberger rules.^{15,16} The melting points of forms **I** and **II** are in the range 155–157 °C.¹⁰ The DSC data for form **III** were obtained at a fast heating rate of 70 °Cmin⁻¹, and show a **III**→**II** phase transition followed by melting of **II**.¹² To ensure the correct form was used during the DSC experiment, the unit cell of each crystal was checked on a single crystal diffractometer and then several crystals were combined to make the DSC sample. The DSC data were collected at 2 °Cmin⁻¹

and indicate good purity (Fig. 8). The data for form **V** has two extra features: a step in the baseline at 125–130 °C, of unknown origin; and a broadening of the melting endotherm, which is normally indicative of impurity. All forms **I**, **II**, **IV** and **V** have a melting point between 154 – 158 °C, under the conditions used, meaning it is not easy to distinguish the new forms using DSC.

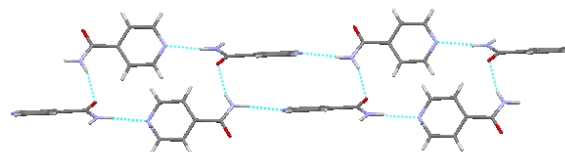


Fig. 6 The 2-D hydrogen-bonded sheets present in form **V**, showing the almost perpendicular alignment of neighbouring molecules.

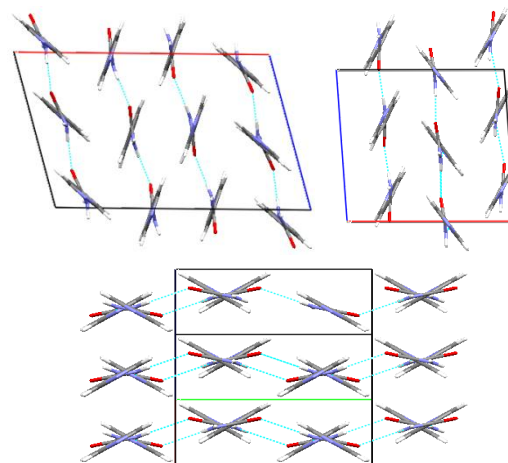


Fig. 7 The packing of layers forms infinite parallel sheets in form **II** (top left) and in form **IV** (top right) and zigzagged sheets in form **V** (bottom).

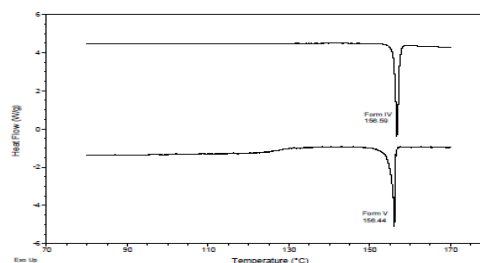


Fig. 8 DSC traces of forms **IV** (top) and **V** (bottom) heated at 2 °Cmin⁻¹.

Form **IV** of isonicotinamide converts into form **II** relatively quickly (~20 h) during single crystal analysis, at both 291 and 100 K. Thus, it was possible to collect a full dataset using Mo radiation, however, the sample transformed during the longer time taken for data collection using Cu radiation. The transformation could be followed in the experiment, with the appearance of elongated diffraction spots signifying the onset of the phase transition. Interestingly, this is not seen in the PXRD analysis and the material is stable even after a total exposure time of ~20 h over an extended period (~72 h) at room temperature. Similar behaviour was observed for the single crystal experiment

for form **V**; the diffraction spots begin to elongate after ~4 h, with a halo due to many small crystallites evident after ~8 h. The crystal retains its exterior morphology during this transformation. Form **V** transforms to form **I** when ground for PXRD analysis. The PXRD data for unground samples of form **V** exhibit severe preferred orientation effects.

One very interesting feature is the importance of the methyl group on the aryl ring of the acid co-former: the formation of form **V** occurred only when the methyl group was present, and using the un-substituted acid forms the co-crystal. The formation of a new form of isonicotinamide depending on such a small structural change, a CH₃ replacing a H, is of real significance for those involved in experimental solid form screening, particularly since it suggests the importance of templating effects in determining crystallisation outcomes.

Isonicotinamide is used extensively as a co-former for tuning the physical properties of drug molecules, e.g. bioavailability, and is being investigated for Huntington's disease and anti-inflammatory activity. Therefore, it is crucial to have a thorough understanding of its crystal landscape. This work shows that crystallisation of a simple molecule which contains robust and reliable supramolecular synthons can still surprise us, and understanding the organic solid state is very much a work in progress.

This publication has emanated from research conducted with the financial support of: Science Foundation Ireland under Grant Numbers 08/RFP/MTR1664, 07/SRC/B1158, 05/PICA/B802 TIDA 09 and 05/PICA/B802/EC07; IRCSET and Eli Lilly.

Notes and references

[†] Department of Chemistry, Analytical and Biological Chemistry Research Facility, University College Cork, Cork, Ireland;

[‡] School of Pharmacy, University of East Anglia, Norwich Research Park, NR4 7TJ, U.K;

[§] Department of Chemistry, University College London, London, WC1H

0AJ, U.K;

[#] Department of Chemistry and School of Pharmacy, Analytical and Biological Chemistry Research Facility, University College Cork, Cork, Ireland.

[†] Electronic Supplementary Information (ESI) available: PXRD data of forms **IV** and **II** formed concomitantly, single crystal data of forms **IV** and **V**, photographs and views of the diffraction frames of form **V** before and after the single crystal experiment.

[‡] Isonicotinamide was obtained from Sigma Aldrich and used without further purification (form **II** by PXRD). (±) 3-(*o*-tolyl)butanoic acid and (±) 3-(*m*-tolyl)butanoic acid were prepared as described previously.¹⁷ Single crystal X-ray diffraction data were collected on a Bruker APEX II DUO diffractometer (form **IV**) and a Bruker SMART X2S diffractometer (form **V**), as described previously.¹⁸ All calculations and refinement were made using the APEX software.^{19,20} PXRD data were collected using a Stoe Stadi MP diffractometer with Cu Kα₁ radiation (λ = 1.5406 Å) at 40 kV and 40 mA in transmission mode using a linear PSD over the 2θ range (3.5 – 60°) with a step size equal to 0.5° and step time of 60 s. DSC data were recorded on a TA Instruments Q1000 Differential Scanning Calorimeter. Samples (0.2–4 mg) were crimped in non-hermetic aluminium pans and scanned from 30 to 170 °C at a heating rate of 2 °Cmin⁻¹ under a continuously purged dry nitrogen atmosphere.

Care is required since Caira *et al.*¹³ refer to Form **I**¹⁰ (CSD refcodes EHOWIH, EHOWIH01, Z' = 1, P2₁/c) as Iso2 and Form **II** (EHOWIH02, Z' = 2, P2₁/c) as Iso1. There is a form **III** (NICOAM04, Z' = 1, Pbcu).

Crystal data for form **IV**: C₆H₆N₂O, *M* = 122.13, monoclinic, space group *Pc*, *a* = 11.0819(6), *b* = 7.9976(4), *c* = 9.9850(5) Å, β = 94.0480(10)°,

V = 882.75(8) Å³, *Z* = 6, *D*_c = 1.378 g cm⁻³, *F*₀₀₀ = 384, Mo Kα radiation, λ = 0.71073 Å, *T* = 100(2) K, 2θ_{max} = 26.45°, μ = 0.098 mm⁻¹. 10209 reflections collected, 3601 unique (*R*_{int} = 0.024). Final GooF = 1.17, *R*₁ = 0.035, *wR*₂ = 0.092 (obs. data: *I* > 2σ(*I*)); *R*₁ = 0.039, *wR*₂ = 0.094 (all data). CCDC 844552.

Crystal data for form **V**: C₆H₆N₂O, *M* = 122.13, monoclinic, space group *P2*₁/c, *a* = 5.1923(11), *b* = 9.466(3), *c* = 12.259(3) Å, β = 91.217(7)°, *V* = 602.4(3) Å³, *Z* = 4, *D*_c = 1.347 g cm⁻³, *F*₀₀₀ = 256, Mo Kα radiation, λ = 0.71073 Å, *T* = 300(2) K, 2θ_{max} = 25.010°, μ = 0.096 mm⁻¹. 3129 reflections collected, 1048 unique (*R*_{int} = 0.029). Final GooF = 1.35, *R*₁ = 0.037, *wR*₂ = 0.092 (obs. data: *I* > 2σ(*I*)); *R*₁ = 0.055, *wR*₂ = 0.101 (all data). CCDC 844553.

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