Cite this: New J. Chem., 2012, 36, 2242-2252

www.rsc.org/njc

Adventures in co-crystal land: high Z', stoichiometric variations, polymorphism and phase transitions in the co-crystals of four liquid and solid cyclic carboxylic acids with the supramolecular reagent isonicotinamide[†]‡

Andreas Lemmerer* and Manuel A. Fernandes

Received (in Montpellier, France) 9th March 2012, Accepted 11th July 2012 DOI: 10.1039/c2ni40186i

The supramolecular reagent isonicotinamide (isonico) was used to co-crystallize with three liquid carboxylic acids, cyclopropanecarboxylic acid (C_3A), cyclobutanecarboxylic acid (C_4A) and cyclopentanecarboxylic acid (C_5A), and a solid carboxylic acid, cyclohexanecarboxylic acid (C_6A). A total of six co-crystal structures resulted, which are an illustration of the co-crystal space observed in the ever-expanding research on co-crystallization of multiple molecular components. Co-crystal 1, (C_3A) (isonico), has a crystal structure with one of the highest reported Z' values. 12 acid and 12 isonico molecules combine in the asymmetric unit to give a Z' = 12, all forming 1-D ribbons. Co-crystals **2a** and **2b**, both having a formula of $(C_4A)_2$ (isonico), having, respectively, a Z' of 1 and 2, illustrate both stoichiometric variation as well as polymorphism, resulting in different packing architectures. Co-crystals (C_5A) (isonico) **3** and (C_6A) (isonico) **4** have isostructural structures at low temperature, and both show phase transitions above room temperature. For (C_6A) (isonico), we determined the structure of both the low temperature phase, 4a, as well as a high temperature phase, 4b, by single crystal X-ray diffraction, and monitored the transition of 3 by variable temperature powder X-ray diffraction. In all of the compounds reported here, synthesized from two components that are not necessarily solids at ambient conditions and which we have called co-crystals, the primary hydrogen bonded interaction is the carboxylic acid · · · pyridine hydrogen bond.

Introduction

The crystal engineering discipline of co-crystals is defined as the deliberate pursuit to create a new solid entity that incorporates two distinct molecular entities.1 One of the most encompassing definitions of co-crystals was coined by Bond as a "multicomponent molecular complex".² Under this umbrella, solvates, hydrates and clathrates are also defined as co-crystals, although few researchers would include the serendipitous inclusion of a solvent molecule during the crystallization process as the deliberate creation of a co-crystal. On the other hand, if the intent was to include a molecule such as methanol or those in a liquid state under ambient conditions into a new crystalline

Molecular Sciences Institute, School of Chemistry, University of the Witwatersrand, Johannesburg 2050, South Africa.

E-mail: Andreas.Lemmerer@wits.ac.za; Fax: +27 11 717 6749; Tel: + 27 11 717 6711

entity with a second molecule, either a solid or liquid, and the result was successful, then this compound can be rightly called either a co-crystal or a solvate. In the past, some researchers have rigorously defined a co-crystal as being made up of two or more different molecules that are all solids under ambient conditions in their pure state, as given in Table $1^{2,3}$ This is a very narrow definition, and has been disputed by Bond by examining the very similar chemical and physical behaviour of a series of complexes made up of gaseous Cl₂, liquid Br₂ and solid I₂ together with dioxane.² Due to the differences in their pure physical state, only the latter compound would be classified as a co-crystal, for example, according to the majority of definitions given in Table 1. Boese and co-workers have produced co-crystals (in our opinion) of two molecules that are gaseous at ambient conditions by cryo-cooling both of them in a sealed capillary.⁴ On a less extreme front (and which will be the focus of this study), we have in the past made a series of co-crystals using solid isonicotinamide, and chiral carboxylic acids that were either in a solid state or in a liquid state at ambient conditions depending on whether the racemate or the optically pure enantiomer was used.⁵ Regardless, a conventional solvent molecule (methanol) was used to "dissolve" a

[†] Dedicated to Professor Demetrius C. Levendis.

[‡] Electronic supplementary information (ESI) available: Hydrogen bonding table for 1, measured PXRD patterns for 1, 2a, 3, and 4a; IR traces for 1-4a, and DSC trace for 1, as well as cif files for all compounds. CCDC 860999-861004. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2nj40186j

Fable 1	Some	definitions	of	co-crystal	in	the	literature ^t	
---------	------	-------------	----	------------	----	-----	-------------------------	--

Senior author ^a	Definition	Ref.
G. P. Stahly	"In general, cocrystals can be considered unique crystalline solids containing multiple components"	3a
A. Nangia	"multi-component solid-state assemblies of two or more compounds held together by any type or combination of intermolecular interactions"; "The starting components in their pure form are generally solids at ambient conditions, but liquid and gaseous states are within the scope of accepted co-crystal definitions."	3b
S. L. Childs	"A cocrystal is a crystalline material made up of two or more compounds, usually in a stoichiometric ratio, each component being an atom, ionic compound or molecule"	3c
C. B. Aakeröy	"Only compounds constructed from discrete neutral molecular species will be considered co-crystals. Conse- quently, all solids containing ions, including complex transition-metal ions, are excluded." "Only co-crystals made from reactants that are solid at ambient conditions will be included." "A co-crystal is a structurally homogenous crystalline material that contains two or more neutral building blocks that are present in definite stoichiometric amounts"	3d
A. Bond	"co-crystal is used only as a synonym for 'multi-component molecular crystal'."	2
W. Jones	"A cocrystal may be thought of as a crystalline complex of two or more neutral molecular constituents bound together in the crystal lattice through noncovalent interactions, often including hydrogen bounding."	3e
M. J. Zaworotko	"The primary difference is the physical state of the isolated pure components: if one component is a liquid at room temperature, the crystals are referred to as solvates; if both components are solids at room temperature, the products are referred to as co-crystals."	3f
^{<i>a</i>} Defined as the cor	responding author. ^b Adapted from ref. 3g.	

stoichiometric amount of both the solid and liquid components, and co-crystals grown by slow evaporation. The observed hydrogen bonded interactions as well as the packing architectures were the same for both the racemate and optically pure enantiomers, which allows us to call all compounds thus synthesized co-crystals.

In this report, we use a series of cyclic alkyl carboxylic acids and isonicotinamide, shown in Scheme 1. The acids were chosen deliberately as the first three, cyclopropanecarboxylic acid, cyclobutanecarboxylic acid and cyclopentanecarboxylic acid, are all liquids at room temperature, whereas cyclohexanecarboxylic acid is a solid.⁶ The aim is to show that it is not necessary to have a solid-only definition of co-crystal starting materials to be able to classify the product as co-crystals, and also to show that many of the phenomena observed in singlecomponent solids, such as asymmetric units with $Z' \gg 1$,⁷ polymorphism⁸ and phase transitions⁹ are just as prevalent in co-crystals. The possibility of stoichiometric variation allows this phenomenon to be studied in the crystal space of co-crystals.¹⁰

Experimental

Syntheses

All reagents were purchased from commercial sources and used without further purification. All solvents were of AP-grade.

(Cyclopropanecarboxylic acid) (isonicotinamide), **1**. 0.200 g of isonicotinamide (1.64 mmol) and 0.141 g of cyclopropanecarboxylic (1.64 mmol) were dissolved in 10 ml of hot methanol. The solution was left to cool to room temperature and colourless, opaque crystals with a block morphology were obtained after a few days by slow evaporation. For grinding experiments, 0.400 g of isonicotinamide (3.28 mmol) and 0.282 g of cyclopropanecarboxylic acid (3.28 mmol) were ground together in a pestle and mortar with drop-wise additions of methanol for 20 minutes.

(Cyclobutanecarboxylic acid)₂·(isonicotinamide) Form I, **2a**. 0.200 g of isonicotinamide (1.64 mmol) and 0.164 g of cyclobutanecarboxylic (1.64 mmol) were dissolved in 10 ml of hot methanol. The solution was left to cool to room temperature and colourless, soft crystals with a plate morphology were obtained after a few days by slow evaporation. For grinding experiments, 0.400 g of isonicotinamide (3.28 mmol) and 0.656 g of cyclobutanecarboxylic acid (6.55 mmol) were ground together in a pestle and mortar with drop-wise additions of methanol for 20 minutes. Diffraction quality crystals were obtained by recrystallizing the ground powder from methanol by slow evaporation.

(Cyclobutanecarboxylic acid)₂·(isonicotinamide) Form II, **2b**. A single prism-shaped crystal was selected from among the bulk plate-like crystals obtained from the first crystallization experiment of **2a**.

(Cyclopentanecarboxylic acid) (isonicotinamide) Form II, **3.** 0.200 g of isonicotinamide (1.64 mmol) and 0.187 g of cyclopentanecarboxylic (1.64 mmol) were dissolved in 10 ml of hot methanol. The solution was left to cool to room temperature and colourless block-like crystals were obtained after a few days by slow evaporation. For grinding experiments, 0.400 g of isonicotinamide (3.28 mmol) and 0.374 g of cyclopentanecarboxylic acid (3.28 mmol) were ground together in a pestle and mortar with drop-wise additions of methanol for 20 minutes.

(Cyclohexanecarboxylic acid) (isonicotinamide) Form II, 4. 0.200 g of isonicotinamide (1.64 mmol) and 0.210 g of cyclohexanecarboxylic (1.64 mmol) were dissolved in 10 ml of hot methanol. The solution was left to cool to room temperature and colourless block-like crystals were obtained after a few days by slow evaporation. For grinding experiments, 0.400 g of isonicotinamide (3.28 mmol) and 0.420 g of cyclohexanecarboxylic acid (3.28 mmol) were ground together in a pestle and mortar with drop-wise additions of methanol for 20 minutes.

Single crystal X-ray diffraction (SCXRD)

Intensity data for all compounds were collected on a Bruker APEX II CCD area detector diffractometer with graphite monochromated MoK α_1 radiation (50 kV, 30 mA) at different temperatures using an Oxford Cryostream 600 cooler. The collection method involved ω -scans of width 0.5°. Data reduction was carried out using the program *SAINT*+, version 6.02¹¹ and empirical absorption corrections were made using the program *SADABS*.¹² Space group assignments were made using *XPREP*¹¹ on all compounds.



Scheme 1 The four carboxylic acid molecules and the supramolecular reagent isonicotinamide showing the two heteromeric and one homomeric interactions used to assemble the molecules of the co-crystals 1–4 studied here.

In all cases, the structures were solved in the $WinGX^{13}$ Suite of programs, with direct methods for all compounds except **1** using *SHELXS*-97¹⁴ and refined using full-matrix least-squares/difference Fourier techniques on F^2 using SHELXL-97.¹⁴ The structure of **1** was solved by using Sir-2010¹⁵ and refined using SHELXL-97.¹⁴ All non-hydrogen atoms were refined anisotropically. Thereafter, all hydrogen atoms attached to N and O atoms were located in the difference fourier map for all compounds, and their coordinates refined freely (except for **1** and **4b** which were refined as riding), with isotropic parameters 1.5 times those of their parent atoms. All C–H hydrogen atoms with isotropic parameters 1.2 times those of their parent atoms.

In 3, the disorder of the cyclopentane ring with carbon atoms C(7), C(8), C(9), C(10) and C(11) was resolved by finding alternate positions from the difference Fourier map for the respective atoms. These atoms were then refined anisotropically with site occupancies such that the sum of the occupancies for the two alternate atom positions equalled one. The bond length and angles were restrained using the SADI instruction in SHELX, and the atomic displacement parameters of atoms were restrained using similarity and 'rigid bond' restraints. Hydrogen atom positions were then calculated for the respective atoms using a riding model.

In **4b**, the disorder of the cyclohexane ring with carbon atoms C(7), C(8), C(9), C(10), C(11) and C(12) was resolved by finding alternate positions from the difference Fourier map for the respective atoms. These atoms were then refined anisotropically with equal site occupancies of 0.5. The bond length and angles were restrained using the DFIX and DANG instructions in SHELX, and their atomic displacement parameters of atoms were restrained using similarity and 'rigid bond' restraints. Hydrogen atom positions were then calculated for the respective atoms using a riding model.

Diagrams and publication material were generated using *ORTEP-3*,¹⁶ *PLATON*,¹⁷ *DIAMOND*¹⁸ and *MERCURY*.¹⁹ Experimental details of the X-Ray analyses are provided in Table 2.

Powder X-ray diffraction (PXRD)

Powder X-ray diffraction data were collected at 293 K on a Bruker D2 Phaser diffractometer which employed a sealed tube Cu X-ray source ($\lambda = 1.5406$ Å), operating at 30 kV and 10 mA, and LynxEye PSD detector in Bragg-Brentano geometry. Powder X-ray diffraction confirmed that the single crystal structures of 1 (Fig. S1 and S2 in ESI^t), 3 (Fig. S5 and S6 in ESI[‡]) and 4a (Fig. S7 and S8 in ESI[‡]) were representative of the bulk material. The peak positions are shifted owing to the different temperatures at which the measured sample was carried out compared with the calculated pattern. The peak intensities vary, perhaps due to microcrystalline orientation and/or texture effects. PXRD for the phase transition of 3 was recorded by placing powder in a sealed capillary, and recording powder rings on the APEX II detector by performing 2 minute, $360^{\circ} \phi$ -rotations at 5 or 10 °C intervals. Integration of images to powder patterns was done using the APEX2 software.¹¹

Differential scanning calorimetry (DSC)

Differential Scanning Calorimetry data were collected on a Mettler Toledo 822^{e} at a scan rate of 10 K min⁻¹ in sealed aluminium pans under air. The temperature and the energy calibration were performed with pure indium (purity 99.999%, mp 156.6 °C, heat

Table 2	Crystallographic	data for all	compounds
---------	------------------	--------------	-----------

	1	2a Form I	2b Form II	3 Form II	4a Form II	4b Form I
Empirical formula	(C ₄ H ₆ O ₂)·	$(C_5H_8O_2)_2$ ·	$(C_5H_8O_2)_2$ ·	$(C_6H_{10}O_2)$	$(C_7H_{12}O_2)$ ·	$(C_7H_{12}O_2)$.
	$(C_6H_6NO_2)$	$(C_6H_6NO_2)$	$(C_6H_6NO_2)$	$(C_6H_6NO_2)$	$(C_6H_6NO_2)$	$(C_6H_6NO_2)$
Molecular weight	208.22	322.36	322.36	236.27	250.29	250.29
Crystal size/mm	$0.66 \times 0.15 \times 0.04$	$0.50 \times 0.20 \times 0.10$	$0.43 \times 0.16 \times 0.10$	$0.29\times0.25\times0.07$	$0.27 \times 0.26 \times 0.09$	$0.88 \times 0.53 \times 0.47$
Crystal system	Triclinic	Monoclinic	Triclinic	Triclinic	Triclinic	Triclinic
Space group	ΡĪ	$P2_1/c$	$P\overline{1}$	$P\bar{1}$	$P\bar{1}$	ΡĪ
T/K	173(2)	173(2)	173(2)	173(2)	173(2)	343(2)
a/Å	8.7790(2)	16.1822(11)	10.5050(8)	6.9305(7)	6.9910(1)	6.9587(4)
b/Å	24.3199(6)	4.8068(3)	12.843(1)	8.9843(8)	8.9810(1)	9.0375(5)
c/Å	30.6605(8)	21.7053(15)	13.081(1)	10.836(1)	11.2980(1)	12.3302(8)
$\alpha/^{\circ}$	71.677(2)	90	101.339(3)	113.556(3)	67.479(1)	68.763(3)
$\beta'/^{\circ}$	84.871(2)	102.360(4)	90.243(3)	95.236(3)	81.065(1)	76.211(3)
$\gamma/^{\circ}$	83.430(2)	90	101.687(3)	97.390(3)	83.458(1)	82.636(3)
$V/\text{\AA}^3$	6163.5(3)	1649.21(19)	1692.7(2)	605.75	651.877(13)	701.20(7)
Z'/Z	12/24	1/4	2/4	1/2	1/2	1/2
$r_{\rm (calc)}/{\rm g}~{\rm cm}^{-3}$	1.346	1.298	1.265	1.295	1.275	1.185
μ/mm^{-1}	0.101	0.097	0.094	0.094	0.091	0.085
F(000)	2640	688	688	252	268	268
Scan range $(\theta)/^{\circ}$	0.70 to 28.00	1.92 to 28.00	1.59 to 28.00	2.08 to 28.00	1.95 to 28.00	1.81 to 25.12
Total reflections	77 934	15863	25 540	7078	8121	6918
Unique reflections	29 233 [0.0457]	3972 [0.0676]	8163 [0.0754]	2929 [0.0462]	3138 [0.0422]	2485 [0.0208]
[R(int)]						
No. data with $I \geq$	15677	2246	3718	1960	2112	1259
$2\sigma(I)$						
Parameters	1622	220	439	209	175	217
Restraints	0	0	0	178	0	184
$R_1 \left[I > 2\sigma(I) \right]$	0.0627	0.0517	0.0574	0.0491	0.0389	0.0739
wR2 (all data)	0.2002	0.1403	0.1592	0.1451	0.1063	0.2788

of fusion 28.45 J g^{-1}). Measurements of onset temperature and heat of fusion were done either in duplicate or triplicate.

Infrared spectroscopy (IR)

IR spectra where recorded on a Bruker Vertex 70 equipped with a Harrick ATR device on a diamond crystal.

Results and discussion

The primary concern in synthesizing co-crystals is to have complementary functional groups from a hydrogen bonding perspective, in order to have the "glue" that will link the individual molecules and prevent them from undergoing homomeric interactions and crystallizing out in their pure states. A heteromeric interaction that the crystal engineer can utilize is the carboxylic acid ... pyridine hydrogen bond, shown in Scheme 1 in its most basic form.^{20a} This interaction has been used in a large number of co-crystallization experiments, and is one of the reasons that isonicotinamide is considered to be an ideal supramolecular reagent. In addition, isonicotinamide can also form a heteromeric dimer with the acid, providing an additional attachment point.^{20b,c} Regardless of whether the second molecule is a liquid or a solid, these two hydrogen bonded interactions can successfully create co-crystals, as will be shown in this report. We will now present some aspects of co-crystals in a simple system of molecules, illustrating the many solid state phenomena that exist in co-crystals.

Preliminary characterization of co-crystals was carried out using FT-IR spectroscopy. The O–H····N hydrogen bond that will constitute the primary interaction between our two molecules appears as a characteristic broad stretch centred around 2500 and 1900 cm⁻¹.²¹ Table 3 lists these selected IR bands of the spectra given in the ESI.[‡]

Table 3 Selected IR bands indicative of intermolecular O–H \cdots N hydrogen bonds in all co-crystals stable at room temperature

	Acid	Band 1	Band 2
1	Cyclopropanecarboxylic acid	1853	2428
2a	Cyclobutanecarboxylic acid	1856	2524
2b	Cyclobutanecarboxylic acid	1880	2455
3	Cyclopentanecarboxylic acid	1899	2469
4a	Cyclohexanecarboxylic acid	1856	2462

The formation of a neutral complex, *i.e.* a co-crystal instead of a molecular salt, can often hinge on the difference in pK_a of the hydrogen bonding groups found on the two distinct molecules. By calculating the value for the $\Delta p K_a = p K_a$ (base) – pK_a (acid), a prediction can be made. In general, a $\Delta pK_a > 3$ will be expected to form a salt, while a $\Delta p K_a < 0$ almost certainly results in a neutral co-crystal, while the range between 0 and 3 does not lend itself to a clear answer and it is only once the result is known can one be certain if proton transfer occurred.²² The pK_a (acid) values for cyclopropanecarboxylic, cyclobutanecarboxylic, cyclopentanecarboxylic and cyclohexanecarboxylic acid are, respectively, 4.8(1), 4.8(2), 4.8(2) and 4.9(1).²³ The pK_a (base) for the pyridine group on the isonicotinamide is 3.4(3).²³ Hence, a negative value for $\Delta p K_a$ results for all four combinations, and the resulting neutral co-crystals described below all confirm that no proton transfer occurred.

(Cyclopropanecarboxylic acid) (isonicotinamide) 1: a very high Z' structure

The co-crystal formed between cyclopropanecarboxylic acid (abbreviated C_3A) and isonicotinamide (isonico), (C_3A).

(isonico) (1), is an example of the sometimes perplexing phenomena of molecules crystallizing with a large number of symmetry independent units in the crystallographic asymmetric unit (ASU). Single-component compounds or crystals have been observed to crystallize with a Z' > 2 with a slightly increasing frequency²⁴ over time, as seen in the Cambridge Structural Database. This increase is partly due to improvements in the devices used to measure diffraction data and increased computational power over time, which has allowed the structural determination of difficult structures to become more routine. Nonetheless, this shows us that nature will sometimes not be able to construct a close packed arrangement using only a single molecular entity together with packing efficient symmetry relations such as glide planes, centers of inversion and screw axes.²⁵ Similarly, in a binary co-crystal for example, the simplest case has two molecules in the Z' = 1 case if the mole ratio is 1:1 (other stoichiometric ratios are possible and will be discussed in co-crystal 2). The base unit for co-crystals reported here consists of one molecule of acid hydrogen bonding in some fashion to the isonico molecule. However, in co-crystal 1, the ASU consists of no less than 12 such entities (an entity being an isonico and C₃A molecule), all showing hydrogen bonding using the carboxylic acid. pyridine hydrogen bond. These 12 entities, labelled from A-K and consisting of one molecule of C₃A and isonico each, are grouped together in six pairs, where each isonico molecule hydrogen bonds to each other using the homomeric amide ... amide dimer. Hence, a more accurate description of the ASU is of six four-molecule units, consisting of A-A = B-B, C-C = D-D, E-E = F-F, G-G = H-H, I-I = J-J, K-K = L-L combinations (see Fig. 1), where a single dash '-' indicates the acid \cdots pyridine hydrogen bond and a double dash '=' the amide ... amide dimer (see Table S1 in the ESI[‡] for a complete listing of all hydrogen bonds). Furthermore, the six pairs can be further subdivided into two groups: Group A/B, G/H, and K/L are all aligned in about the same direction, while C/D, E/ F and J/J are all aligned similarly but significantly orthogonally to the former group (Fig. 2). All 12 isonico and 12 C₃A molecules have similar conformations, being restricted to only rotate around a single C-C single bond, as summarized in Table 4. The four-molecule units are linked by the anti H of the amide group hydrogen bonding to the carbonyl O atom on the carboxylic acid group of adjacent units, forming 1-D ribbons along the a-axis, an example of which is shown in Fig. 3 for the A/B unit. Hence, six unique ribbons are formed, all created by translation symmetry only. The relative packing of the ribbons is shown in Fig. 4, and are coloured by symmetry equivalents. As there is unlikely to be any packing frustration, we believe that these crystals could be remnants of the early nucleation process, as seen in other high Z' crystal structures.²⁶ A possible additional explanation has been proposed by Anderson et al.,²⁷ and postulates that by having more than one strongly directional hydrogen bonded interaction, or supramolecular synthon, as well as additional unique chemical moieties in a system, that these two factors can lead to crystal structures with Z' > 1. In this particular set of co-crystals, where the acid...pyridine and amide...amide dimer are so dominant, this is a plausible factor. Also, C₃A is the smallest and least flexible of the acid molecules used here, and there has been a

correlation that these two factors contribute towards an increase in Z' > 1 occurrence.²⁸

When trying to reproduce the solution crystallization experiments by mechanochemical means, the same high Z' structure is obtained. In this case, liquid-assisted grinding is done by adding a few drops of methanol to an equimolar ratio of isonico and C₃A, and grinding all three together in a pestle and mortar for 10 minutes. The measured PXRD of the resulting powder compared to the calculated pattern from the single crystal structure are in good agreement (Fig. S2 in ESI‡). Finally, the thermal behaviour of this co-crystal was investigated using DSC, and shows a melting point of 91.5(2) °C with a fusion enthalpy of 31(1) kJ mol⁻¹.

(Cyclobutanecarboxylic acid) (isonicotinamide) (2): stoichiometric variation and polymorphism

The second carboxylic acid in the series is cyclobutanecarboxylic acid, C₄A, and is also a liquid. The initial solution crystallization experiments resulted repeatedly in plate-like crystals, that were very soft and laminar, and did not lead to diffraction quality single crystals suitable for SCXRD. Repeated experiments after a year revealed that the bulk of the crystals were of this type, however a few small prism-like crystals were found within the bulk material. SCXRD experiments of these crystals were successful and gave a co-crystal with a 1:2 ratio of isonico to C_4A , 2b. These prism-shaped crystals of (isonico) (C_4A)₂ have a Z' = 2 (Fig. 5). Later, we obtained a structure that is representative of the initial bulk material by recrystallizing the product of a liquid-assisted grinding (LAG) experiment. The plate-like crystals also have a 1:2 ratio, but with a Z' = 1 (2a) (Fig. 5), and hence both structures are polymorphs of each other, designated as form I (2a) and form II (2b), as the latter is the minor product in terms of bulk quantity obtained. The two polymorphs have identical hydrogen bonded interactions, but result in different packing architectures.

This stoichiometric variation, where either 1:1 or 1:2 ratios are formed, is seen often in isonico co-crystals with acids,^{20a} and is enabled by the fact that isonico has two access points for carboxylic acid functional groups. The acid · · pyridine as seen in co-crystal 1 is the most commonly encountered interaction as it matches up the best donor with the best acceptor, in accord with Etter's rules.²⁹ The second access point is the carboxylic amide functional group, which is structurally related to a carboxylic acid functional group. As a consequence, a heteromeric acid · · · amide dimer can be formed instead of the usual homomeric amide ... amide dimer (Scheme 1). In this case, this allows for two acid molecules to be incorporated into a new crystalline phase with isonico. The formation of 1:2 co-crystals is surmised to be due to increased stabilization of the acid ... amide heteromeric dimer over the acid...pyridine heterosynthon when weak carboxylic acids are used.^{20a} However, in the acids used here, the pK_a values are relatively similar and hence that argument is not applicable.

The asymmetric unit of form I (2a) consists of two molecules of C₄A and one molecule of isonico, all on general positions. Hence, 2a has the most basic asymmetric unit, with Z' = 1, and a *single* three-molecule unit. There are a total of four hydrogen bond donors within the unit, and three of them



Fig. 1 The atomic numbering scheme of the six four-molecule units, *i.e.* of the 24 total symmetry independent molecules in the asymmetric unit of **1**. The six units are all shown to be normal to the plane defined by the amide dimer, and show similar conformations relative to each other. Displacement ellipsoids are shown at the 50% probability level. H atoms not involved in hydrogen bonding interactions are omitted for clarity.

are used to connect the three unique molecules, by using the $acid \cdots pyridine$ and $acid \cdots amide$ hydrogen bonds (Table 3). The fourth donor, the *anti* H, then hydrogen bonds to the carbonyl O atom of a C₄A molecule of an inversion related

second unit to form centrosymmetric dimers (Fig. 6a). The dimers then stack on top of each other along the *b*-axis and are stabilised by C==O··· π interactions (*d*(O···Cg): 3.124(2) Å). This form is present as the major phase in all crystallization experiments.



Fig. 2 The complete asymmetric unit of **1** showing the relative positions of the six pairs of four-molecule units. Displacement ellipsoids are shown at the 50% probability level.

 Table 4
 Absolute values of comparative torsion angles in the 24 molecules in the asymmetric unit, grouped together into six four-molecule units

Molecular entity	C(2)-C(1)-C(6)-N(1)	C(8)-C(7)-C(10)-O(2)
A	11.3(4)	31.4(4)
В	16.7(3)	36.7(3)
С	19.0(3)	32.0(3)
D	12.8(4)	34.2(3)
E	22.3(3)	37.8(3)
F	12.7(3)	33.4(3)
G	11.4(3)	34.6(3)
Н	21.1(3)	29.2(3)
Ι	12.1(3)	33.0(3)
J	17.0(3)	39.1(3)
K	13.5(3)	36.9(4)
L	17.5(3)	30.6(3)



Fig. 3 The hydrogen bonded ribbon formed by the A/B pair (see Fig. 1). The same ribbons are formed by the other pairs.

In contrast, the asymmetric unit of form II (2b), has two threemolecule units in its asymmetric unit, Z' = 2. The two units are connected by the same N-H···O hydrogen bond from the *anti* H to the carbonyl O as seen in form I (Fig. 5 and 6b), but in this case forms an infinite chain of these units along the *a*-axis by hydrogen bonding to adjacent units (Fig. 6c), instead of the isolated centrosymmetric dimers as in the former case of **2a**. The individual members within the chains are stabilised by $\pi \cdots \pi$ (*d*(Cg···Cg): 3.817(1) Å) and C=O··· π (*d*(O···Cg): 3.364(2) and 3.381(2) Å) interactions.

The initial solution experiments were all carried out in a ratio of 1:1, and hence the formation of a 1:2 co-crystal



(a)



Fig. 4 (a) The packing diagram of **1** using a wireframe model generated using the program *MERCURY*. The diagram shows the positions of the six unique hydrogen bonded ribbons formed, shown using different colours. (b) The same packing diagram, however using a space-filling model.

was unexpected. The PXRD pattern of the solution experiments gives a mixed phase, incorporating some of the unreacted isonico (Fig. S3 in ESI[‡]). Grinding experiments using methanol gave a more phase pure result, with the same bulk phase as calculated for **2a** (Fig. S4 in ESI[‡]).

(Cyclopentanecarboxylic acid) (isonicotinamide) (3) and (cyclohexanecarboxylic acid) (isonicotinamide) (4): reversible temperature-dependent phase transitions

Until now we have seen how two very closely structurally related carboxylic acids, both being liquids at ambient conditions, give different packing architectures, and can morph from a 1:1 complex to a 1:2 complex, an example of stoichiometric variation, by making use of the additional hydrogen bonded interactions possible of the isonico molecule. Now we illustrate a case where two further acids, one of them a liquid, cyclopentanecarboxylic acid (C_5A), and one of





Fig. 5 The asymmetric units of the two polymorphs 2a (form I) and 2b (form II), showing the atomic numbering scheme. Displacement ellipsoids are shown at the 50% probability level.

them a solid, cyclohexanecarboxylic acid (C₆A), result in isostructural co-crystals **3** and **4**, which have identical hydrogen bonded interactions, packing architectures and similar temperature dependent phase transitions. This ultimately shows that the physical state of a co-crystal former is not important or a criterion in classifying what is co-crystal. In fact, the room temperature phases of the two co-crystals are isostructural.

The structure of co-crystal (isonico)·(C₅A) (**3**) has one molecule of isonico and C₅A in the asymmetric unit, and forms a similar hydrogen bonded unit as seen in any of the 12 entities in **1** (Fig. 7). The C₅A molecule, which shows disorder of its cyclopentane ring, hydrogen bonds to the pyridine of isonico. The isonico molecule then forms a dimer with centrosymmetrically related units, which then hydrogen bond to each other to give similar ribbons as seen in **1** (Fig. 8 and Table 5). Adjacent ribbons are stabilised using a C–H··· π interaction ($d(H \cdots Cg)$: 2.77(1) Å; \angle (C–H···Cg): 158°). In other words, the asymmetric unit seen in **3** was what we expected to see in **1** and in general in this study, on the basis of isonico co-crystals seen in the literature.³⁰ This structure of **3**, stable at room temperature, is designated as form II.

The phase transition from II to I was observed by performing a DSC scan from room temperature to the melting point. Fig. 9 (run 1, heating scan) shows an exotherm with an average onset of $68.0(3)^{\circ}$ C and with a transition enthalpy of 4.7(6) kJ mol⁻¹. This phase transition is reversible as the same exothermic event is observed upon heating again (run 3, heating) but the transition event back from I to II is not readily observed in the corresponding cooling scan (run 2). However, a broad peak is observed repeatedly in all the second heating runs, and is presumed to be the missing reverse transition. The melting of form I finally occurs at 95.1(9) °C with a fusion enthalpy of 23.4(4) kJ mol⁻¹.







Fig. 6 (a) The isolated centrosymmetric dimers (composed of two ASUs) of form I (2a). (b) The same hydrogen bonding interactions as seen in 2a are observed in form II (2b), but form a chain of molecules down the *a*-axis (c). H atoms not involved in hydrogen bonding are omitted for clarity.

We tried to follow the phase transition using SCXRD, but the chosen single crystals did not remain intact after the transition event. Nonetheless, we were able to confirm the phase transition by recording variable temperature PXRD patterns using powdered **3** sealed in a capillary on the single crystal diffractometer (Fig. 10). The resulting powder patterns show only a small change with increasing temperature, indicative of only minor structural arrangements occurring, as will be described for the related case of (isonico) (C_6A) (**4**).

The structure of co-crystal (isonico) (C_6A) (4a) has one molecule of isonico and C_6A in the asymmetric unit (Fig. 11),



Fig. 7 The asymmetric unit of **3** (form II), showing the atomic numbering scheme. Displacement ellipsoids are shown at the 50% probability level. Only the major occupied site of the disorder is shown.



Fig. 8 The hydrogen bonded ribbons formed in 3. Note the similarity to the ribbons shown in Fig. 11 for 4a. H atoms not involved in hydrogen bonding are omitted for clarity.

similar to 3, and has the same form stable at room temperature, namely form II. The only difference to form II of 3 is that the cyclohexane ring is ordered in 4a. The hydrogen bonding has the acid...pyridine hydrogen bond and very similar hydrogen

Table 5 Geometrical parameters for hydrogen bonds in 2a-4b

bonded ribbons are formed as in **3** (Fig. 12a). Adjacent ribbons are stabilised again using a C–H··· π interaction (d(H···Cg): 2.98(1) Å; \angle (C–H···Cg): 140°).

The DSC trace of **4** shows very similar behaviour to **3** (Fig. 13). There is a transition from form II to I ($61.9(1) \degree C$; $6.9(3) \text{ kJ mol}^{-1}$), which is followed by melting of form I ($110.5(2) \degree C$; $31.0(5) \text{ kJ mol}^{-1}$). When cooling the sample immediately after the phase transition, the reversibility of the transition is clearly seen in an endotherm ($61.5(1) \degree C$; $2.7(1) \text{ kJ mol}^{-1}$).

In the case of co-crystal 4, we were able to transform a single crystal by heating it up in a capillary sealed in paratone oil (to reduce sublimation and loss of sample during data collection), and to determine the crystal structure of form I (4b). The unit cell volume has slightly increased by 50 Å³, mainly due to an expansion along the c-axis parameter by 1 Å. The crystal structure shows the same hydrogen bonded interactions, as well as ribbon architecture as observed in form II. However, a significant change is in the conformation of the cyclohexane ring to the carboxylic acid group. Form II has a torsion angle of $-140(1)^{\circ}$ measured through the O(2)-C(13)-C(7)-H(7) sequence. Form I has a disorder of the entire cyclohexane ring, whereupon 50% of the ring is unchanged in conformation (O(2)-C(13)-C(7A)-H(7A): $-140(1)^{\circ}$) and another 50% is rotated almost perpendicular $((O(2)-C(13)-C(7B)-H(7B): -53(1)^{\circ}))$. The relative positioning of the two cyclohexane sites is seen in Fig. 12b. By comparing the two packing diagrams of 4a and 4b, one can identify the additional space between adjacent ribbons that allows for the rotation of the cyclohexane ring and the required increase in c-axis length and unit cell volume as a consequence.

Conclusions

Hydrogen bonds make up an integral part of the structures reported here with neither co-crystal molecular moiety being

D–H···A	<i>d</i> (D–H)/Å	$d(\mathbf{H}\cdot\cdot\cdot\mathbf{A})/\mathrm{\AA}$	$d(\mathbf{D}\cdot\cdot\cdot\mathbf{A})/\mathrm{\AA}$	${\scriptstyle \angle (D\!-\!H\!\cdot\cdot\cdot A)/^\circ}$	Symmetry transformations
2a					
$N(1)-H(1S)\cdots O(5)$	0.92(2)	2.10(2)	2.993(2)	165(2)	_
$N(1)-H(1A)\cdots O(3)$	0.89(2)	2.06(2)	2.941(2)	170(2)	-x + 1, -y + 2, -z + 1
$O(2)-H(2)\cdots N(2)$	1.06(2)	1.58(3)	2.635(2)	173(2)	
$O(4) - H(4) \cdots O(1)$	1.08(3)	1.54(3)	2.612(2)	174(2)	
2b					
$N(1A)-H(1AS)\cdots O(5A)$	0.92(2)	2.00(3)	2.910(3)	174(2)	
$N(1A) - H(1AA) \cdots O(3B)$	0.91(3)	1.98(3)	2.873(3)	166(2)	
$O(2A) - H(2A) \cdots N(2A)$	0.96(3)	1.68(3)	2.635(3)	173(3)	
$O(4A) - H(4A) \cdots O(1A)$	0.88(3)	1.76(3)	2.618(2)	163(3)	
$N(1B) - H(1BS) \cdots O(5B)$	0.91(3)	2.01(3)	2.908(3)	170(2)	
$N(1B)-H(1BA)\cdots O(3A)$	0.98(3)	1.93(3)	2.880(3)	165(2)	x - 1, v, z
$O(2B)-H(2B)\cdots N(2B)$	0.87(3)	1.78(3)	2.638(3)	170(3)	
$O(4B) - H(4B) \cdots O(1B)$	0.83(3)	1.79(3)	2.611(2)	169(3)	
3					
$N(1)-H(1S)\cdots O(1)$	0.94(2)	1.98(2)	2.916(2)	177(2)	-x, -v + 3, -z + 2
$N(1) - H(1A) \cdots O(3)$	0.90(2)	1.99(2)	2.860(2)	1634(2)	x, y + 1, z
$O(2)-H(2)\cdots N(2)$	0.91(3)	1.75(3)	2.653(2)	170(2)	
4a					
$N(1)-H(1S)\cdots O(1)$	0.90(2)	2.01(2)	2.910(1)	178(1)	-x + 2, -v + 2, -z + 2
$N(1) - H(1A) \cdots O(3)$	0.89(2)	2.00(2)	2.861(1)	164(1)	x, y + 1, z
$O(2)-H(2)\cdots N(2)$	0.99(2)	1.65(2)	2.635(1)	174(2)	
4b					
$N(1)-H(1S)\cdots O(1)$	0.86	2.07	2.925(6)	176	-x + 2, -v + 2, z + 2
$N(1) - H(1A) \cdots O(3)$	0.86	2.10	2.918(7)	158	x, y + 1, z
$O(2)-H(2)\cdots N(2)$	0.82	1.86	2.661(7)	166	



Fig. 9 DSC traces of a series of three subsequent heating/ cooling runs starting with form II of 3, showing the phase transition from II to I, the reverse phase transition from I to II (broad peak), and the fusion endotherm of form I. The heating and cooling rates are 10 K min^{-1} .



Fig. 10 The variable temperature PXRD recorded by using the single crystal detector to record the powder rings in the range from 3 to 17° 2 θ (Mo radiation, $\lambda = 0.7107$ Å) for 3. Note the change in peaks between 7° and 9° .

an accidental guest. The common basic hydrogen bonding motifs in co-crystals 1, 3, 4a and 4b, regardless of whether the



Fig. 11 The asymmetric units of the two polymorphs 4a (form II) and 4b (form I), showing the atomic numbering scheme. Displacement ellipsoids are shown at the 50% probability level for 4a and 20% for 4b.

co-crystals were synthesised from liquid or solid starting materials, suggest that any definition insisting that a co-crystal can only be synthesised from solid starting materials is too strict. This work indicates that perhaps a better way to judge the formation of a co-crystal is to look at the interactions between the components making up the crystal. More interestingly, this work also shows that other phenomena usually reported for single-component crystals can also occur in co-crystals. Phenomena reported here include a structure with one of the highest recorded Z' values, as well as two pairs of co-crystal polymorphs. An additional phenomenon, stoichiometric variation, allows for a diverse range of structures differing in hydrogen bonding patterns (co-crystals 2a and 2b have different hydrogen bond motifs compared with the rest of the structures presented here) and crystal packing to be obtained from the same starting materials. These results



Fig. 12 Comparative packing diagrams of the two polymorphs of 4: (a) shows the phase stable below 61.9(1) °C and (b) above. The two conformations of the cyclohexane rings are shown as light and dark grey spheres in form I. H atoms not involved in hydrogen bonding are omitted for clarity.



Fig. 13 DSC traces of a series of three subsequent heating/cooling runs starting with form II of **4**, showing the phase transition from II to I, the reverse phase transition from I to II, and the fusion endotherm of form I. The heating and cooling rates are 10 K min⁻¹.

suggest that a crystal engineer has much to gain by working in the area of co-crystals.

Acknowledgements

The University of the Witwatersrand and the Molecular Sciences Institute are thanked for providing the infrastructure and financial support to do this work. Dr Clive Oliver is thanked for solving the crystal structure of **1**. AL thanks the Friedel Sellshop Grant for additional financial support.

Notes and references

- (a) V. Bertolasi, L. Pretto, P. Gilli, V. Ferretti and G. Gilli, New J. Chem., 2002, 26, 1559–1566; (b) C. B. Aakeröy, N. Schultheiss, J. Desper and C. Moore, New J. Chem., 2006, 30, 1452–1460; (c) K. K. Arora, M. S. Talwelkar and V. R. Pedireddi, New J. Chem., 2009, 33, 57–63; (d) H. F. Clausen, M. S. Chevallier, M. A. Spackman and B. B. Iversen, New J. Chem., 2010, 34, 193–199; (e) J. Martí-Rujas, B. M. Kariuki, C. E. Hughes, A. Morte-Ródenas, F. Guo, Z. Glavcheva-Laleva, K. Taştemür, L.-L. Ooi, L. Yeo and K. D. M. Harris, New J. Chem., 2011, 35, 1515–1521.
- 2 A. D. Bond, CrystEngComm, 2007, 9, 833-834.
- 3 (a) G. P. Stahly, Cryst. Growth Des., 2007, 7, 1007–1026; (b) B. R Bhogala and A. Nangia, New J. Chem., 2008, 32, 800–807;
 (c) S. L. Childs and K. I Hardcastle, Cryst. Growth Des., 2007, 7, 1291–1304; (d) C. B. Aakeröy and D. J. Salmon, CrystEngComm, 2005, 7, 439–448; (e) W. Jones, W. D. Motherwell and A. V. Trask, MRS Bull., 2006, 341, 875–879; (f) Ö. Almarsson and M. J. Zaworotko, Chem. Commun., 2004, 1889–1896;
 (g) N. Schultheiss and A. Newman, Cryst. Growth Des., 2009, 9, 2950–2967.
- 4 R. Boese, D. Bläser and G. Jansen, J. Am. Chem. Soc., 2009, 131, 2104–2106.

- 5 A. Lemmerer, N. B. Báthori and S. A. Bourne, Acta Crystallogr., Sect. B: Struct. Sci., 2008, 64, 780–790.
- 6 C₃A: 14–17 °C; C₄A: –7.5 °C; C₅A: 3–5 °C and C₆A: 30 °C.
- 7 (a) B. Sarma, S. Roy and A. Nangia, Chem. Commun., 2006, 4918–4920; (b) K. M. Anderson, K. Afarinkia, H.-W. Yu, A. E. Goeta and J. W. Steed, Cryst. Growth Des., 2006, 6, 2109–2113; (c) K. M. Anderson, A. E. Goeta, K. S. B. Hancock and J. W. Steed, Chem. Commun., 2006, 2138–2140; (d) G. S. Nichol and W. Clegg, Cryst. Growth Des., 2006, 6, 451–460; (e) K. M. Anderson, M. R. Probert, C. N. Whiteley, A. M. Rowland, A. E. Goeta and J. W. Steed, Cryst. Growth Des., 2009, 9, 1082–1087.
- 8 (a) I. Halasz, M. Rubčić, K. Užarević, I. Đilović and E. Meštrović, *New J. Chem.*, 2011, **35**, 24–27; (b) A. Mukherjee and G. R. Desiraju, *Chem. Commun.*, 2011, **47**, 4090–4092.
- 9 H.-Y. Ye, J.-Z. Ge, F. Chen and R.-G. Xiong, *CrystEngComm*, 2010, **12**, 1705–1708.
- 10 S. Karki, T. Friščić and W. Jones, *CrystEngComm*, 2009, 11, 470–481.
- 11 Bruker, SAINT+, Version 6.02 (Includes XPREP and SADABS), Bruker AXS Inc., Madison, Wisconsin, USA, 2004.
- 12 G. M. Sheldrick, SADABS, Universität Göttingen, Germany, 2004.
- 13 L. J. Farrugia, J. Appl. Crystallogr., 1999, 32, 837-838.
- 14 G. M. Sheldrick, Acta Crystallogr., Sect. A: Found. Crystallogr., 2008, 64, 112–122.
- 15 M. C. Burla, R. Caliandro, M. Camalli, B. Carrozzini, G. L. Cascarano, L. De Caro, C. Giacovazzo, G. Polidori, D. Siliqi and R. Spagna, J. Appl. Crystallogr., 2007, 40, 609–613.
- 16 L. J. Farrugia, J. Appl. Crystallogr., 1997, **30**, 565.
- 17 A. L. Spek, J. Appl. Crystallogr., 2003, 36, 7-13.
- 18 K. Brandenburg, *Diamond, Version 2.1e*, Crystal Impact GbR, Bonn, Germany, 1996–2001.
- 19 C. F. Macrae, P. R. Edgington, P. McCabe, E. Pidcock, G. P. Shields, R. Taylor, M. Towler and J. van de Streek, *J. Appl. Crystallogr.*, 2006, **39**, 453–457.
- 20 (a) P. Vishweshwar, A. Nangia and V. M. Lynch, Cryst. Growth Des., 2003, 3, 783–790; (b) M. Du, Z.-H. Zhang, X.-G. Wang, H.-F. Wu and Q. Wang, Cryst. Growth Des., 2006, 6, 1867–1875; (c) M. Du, Z.-H. Zhang, X.-J. Zhao and H. Cai, Cryst. Growth Des., 2006, 6, 114–121.
- 21 C. B. Aakeröy, A. B. Grommet and J. Desper, *Pharmaceutics*, 2011, **3**, 601–614.
- 22 S. L. Childs, G. P Stahly and A. Pak, *Mol. Pharmaceutics*, 2007, 4, 323–338.
- 23 As calculated using the ACD Labs module in SciFinder. For comparison, the pK_a values of their acyclic isomers show the same trend and relative values.
- 24 (a) T. Steiner, Acta Crystallogr., Sect. B: Struct. Sci., 2000, 56, 673–676; (b) K. M. Anderson and J. W. Steed, CrystEngComm, 2007, 9, 328–330.
- 25 (a) J. W. Steed, CrystEngComm, 2003, 5, 169–179;
 (b) G. R. Desiraju, CrystEngComm, 2007, 9, 91–92.
- 26 D. Das, R. Banerjee, R. Mondal, J. A. K. Howard, R. Boese and G. R. Desiraju, *Chem. Commun.*, 2006, 555–557.
- 27 K. M. Anderson, A. E. Goeta and J. W. Steed, *Cryst. Growth Des.*, 2008, 8, 2517–2524.
- 28 K. M. Anderson, M. R. Probert, A. E. Goeta and J. W. Steed, CrystEngComm, 2011, 13, 83–87.
- 29 M. C. Etter, Acc. Chem. Res., 1990, 23, 120-126.
- 30 N. B. Báthori, A. Lemmerer, G. A. Venter, S. A. Bourne and M. R. Caira, *Cryst. Growth Des.*, 2011, 11, 75–87.