Unusual co-crystal of isonicotinamide: the structural landscape in crystal engineering

BY SRINU TOTHADI AND GAUTAM R. DESIRAJU*

Solid State and Structural Chemistry Unit, Indian Institute of Science, Bangalore 560 012, India

The idea of a structural landscape is based on the fact that a large number of crystal structures can be associated with a particular organic molecule. Taken together, all these structures constitute the landscape. The landscape includes polymorphs, pseudopolymorphs and solvates. Under certain circumstances, it may also include multi-component crystals (or co-crystals) that contain the reference molecule as one of the components. Under still other circumstances, the landscape may include the crystal structures of molecules that are closely related to the reference molecule. The idea of a landscape is to facilitate the understanding of the process of crystallization. It includes all minima that can, in principle, be accessed by the molecule in question as it traverses the path from solution to the crystal. Isonicotinamide is a molecule that is known to form many co-crystals. We report here a 2 : 1 co-crystal of this amide with 3,5-dinitrobenzoic acid, wherein an unusual N–H···N hydrogen-bonded pattern is observed. This crystal structure offers some hints about the recognition processes between molecules that might be implicated during crystallization. Also included is a review of other recent results that illustrate the concept of the structural landscape.

Keywords: crystal engineering; hydrogen bond; crystallization

1. Introduction

Beyond the crystal are the issues that underlie the formation of crystals from solution or the melt. Elucidating the mechanism of crystallization of an organic compound is one of the key issues in crystal engineering and supramolecular chemistry [1,2]. Crystallization is a supramolecular reaction [3]. The starting materials are the solute and solvent molecules. The crystal nucleus, which is possibly a partially ordered entity with or without solvent, may be likened to the transition state in that it corresponds to the highest energy along the reaction coordinate that takes one from the entropy-dominated situation in solution to the enthalpy controlled one in the crystal. The products are the crystals that are obtained. These generally cascade along an energy gradient according to Ostwald’s Rule of Stages [4], and several kinetic (that is metastable) crystals

*Author for correspondence (gautam_desiraju@yahoo.com).

One contribution of 14 to a Theme Issue ‘Beyond crystals: the dialectic of materials and information’.
ultimately give way to the final thermodynamic global minimum. Very little is known about the events that take place during crystallization of organic solids, a non-equilibrium process that occurs under conditions of supersaturation \[5\]. Crystallization has been likened, in the earlier mentioned description, to a chemical reaction. But the energies involved in crystallization are much smaller than those involved in a covalent-bond-making or covalent-bond-breaking process. Therefore, there is a chance that the intermediate species that are involved in crystallization have a better chance of being detected than a transition state and the reaction intermediates in a chemical reaction.

Generally, information that offers hints about the mechanism of crystallization is obtained with spectroscopy, computation or crystallography. Spectroscopy gives information about the early stages of the crystallization reaction. Davey et al. \[6\] demonstrated, with Fourier transform infrared spectroscopy, a direct relationship between molecular self-association of tetrolic acid in solution and H-bonded patterns in the subsequently crystallized solid phases. This work is important because it shows that the supramolecular synthons that are present in the final crystal have an existence in solution prior to crystallization. The course of crystallization may also be monitored with computation. Gavezzotti has recently described a new algorithm for the simulation of the events that lead from an isotropic liquid to a crystal \[7\]. The liquid-to-solid transformation in \(n\)-hexane was simulated with a pseudo-Monte Carlo technique that starts with the liquid with a significant population of gauche molecular conformations, and gives a crystalline molecular assembly with parallel all-trans aliphatic chains and which is very similar to the real crystal structure. Crystallography gives information on the late stages of crystallization; it can be used to image high-energy structures that have been obtained fortuitously under conditions that favour kinetic crystallization. Such structures include solvates, high \(Z'\) forms, unstable polymorphs and co-crystals. Along these lines, Desiraju and co-workers determined the crystal structure of sodium saccharin dihydrate, \(\text{Na(sac)}-(\text{H}_2\text{O})_{1.875}\), and argued that this heavily hydrated structure is a good model for the nucleus in the crystallization of the lower hydrate \(\text{Na}_3(\text{sac})_3(\text{H}_2\text{O})_2\). Essentially, this complex structure resembles a metastable high-energy intermediate \[8\]. More recently, a \(Z' = 6\) structure of phenylacetylene was isolated by Desiraju and co-workers \[9\]. This new \(\gamma\) polymorph of the compound was described as a bridging structure between the known \(\alpha\) and \(\beta\) forms of the compound on the one hand, and the liquid on the other. Interestingly, this high \(Z'\) form was obtained by sudden quenching of the neat liquid, and corresponds to a structure that occurs earlier in the reaction coordinate than the two stable polymorphs \(\alpha\) and \(\beta\).

All related crystal forms in a particular chemical system, when taken collectively, constitute a kind of landscape \[4\]. The idea of the structural landscape is recent and is based on the fact that a large number of crystal structures can be associated with a particular organic molecule. The idea of a landscape was originally intended to be an energy profiling of the final stages of crystallization, and it was referred to as a crystal energy landscape that consisted of polymorphs of a compound. However, it is also convenient to include pseudopolymorphs and solvates along with polymorphs because crystallization of an organic compound could also involve solvated forms as intermediates. Under these circumstances, one obtains a structural landscape with which one can also consider slightly earlier stages of crystallization \[10\]. The structural landscape may also include
multi-component crystals that include the reference molecule as one of the components. The co-crystal may allow one to sample certain variations—for example, a high-energy conformation that is not normally accessible. Under still other circumstances, the landscape may include the crystal structures of molecules that are closely related to the reference molecule—for example, substitutional variations. The idea of a landscape is to facilitate the understanding of the process of crystallization. The landscape includes all minima that can, in principle, be accessed by the molecule in question as it traverses the pathway from solution to the crystal.

Isonicotinamide (IN) is a primary amide that contains multiple hydrogen bond donor and acceptor sites. IN has been widely used to obtain co-crystals—in other words, multi-component molecular crystals—with other compounds that contain hydrogen bond functionalities [11–18]. Around 80 fully organic co-crystals of IN are known. In a routine co-crystal screening of this compound, we obtained a 2:1 adduct of IN with 3,5-dinitrobenzoic acid (DNBA). The unusual crystal structure of this 2:1 co-crystal could provide some hints about the mechanism of crystallization. Also included is a brief review of other recent crystal structure studies that report possibly metastable structures that might occur during the crystallization process. This includes some crystal structures where \( Z' > 1 \). These structures are discussed in the context of crystallization mechanisms.

The concept of the supramolecular synthon has been widely accepted in crystal engineering and it facilitates the description of crystal structures and crystallization intermediates [19]. A synthon is a structural unit that encapsulates important recognition information between functional groups in molecules that interact during crystallization [3]. In the context of acid/amide recognition in general and IN in particular, the following synthons are of relevance. IN is a heavily studied system in the context of co-crystallization and, in this sense, is some sort of a benchmark. So we examined it more closely.

2. Results and discussion

There are two competing hydrogen bond acceptor sites in IN: the heterocyclic N-atom and the amide carbonyl O-atom. The former is the better acceptor.
Let us consider the co-crystallization of IN with a monocarboxylic acid. In the system \((\text{IN})(\text{RCO}_2\text{H})\), the acid and amide H-atoms are potential donors, and the heterocyclic and carbonyl groups in either the amide or the acid or both are acceptors. Etter’s generalization that the best hydrogen bond donor associates with the best acceptor [20] is illustrated in this case, and it may be anticipated that the carboxyl H-atom of the acid would hydrogen bond to the heterocyclic N-atom of IN (best donor to best acceptor) as shown in synthon I, leaving the amide groups of IN to hydrogen bond to each other in an amide···amide homosynthon II (second best donor to second best acceptor). The basic structural unit is therefore a tetramer; this tetramer consists of an amide dimer that is hydrogen bonded to a carboxylic acid molecule at each of the two heterocyclic N-atoms. Such an outcome was predicted and realized by Aakeröy et al. [21].

A Cambridge Structural Database (CSD) search shows that hydrogen bonding between the carboxyl group and the pyridine N-atom is overwhelmingly preferred (29/30) in 1 : 1 co-crystals of monocarboxylic acids and IN. Alkanedicarboxylic acids invariably form carboxyl···pyridine \(\text{O} - \text{H} \cdots \text{N}\) hydrogen bonds in their co-crystals with IN. But Nangia and co-workers [22] found variations that depend on the amide:acid stoichiometry. The 2 : 1 co-crystals strictly follow the hierarchical model and the amide homosynthon II is formed. In the 1 : 1 co-crystals, however, any particular diacid is hydrogen bonded to a pyridine N-atom and an amide \(\text{C}=\text{O}\) group at each end and consequently, the acid–amide heterosynthon III is formed. To summarize, many diacid:IN co-crystals occur in both 1 : 1 and 1 : 2 acid–amide stoichiometries, but all contain the acid–pyridine interaction [23]. Hierarchical modes of hydrogen bonding are advantageous in crystal design strategies and these arguments were subsequently extended to the design of ternary co-crystals, a normally difficult task [24].

A CSD analysis (v. 5.32, November 2010) of IN-containing crystals gives a total of 79 structures. Among these, 48 correspond to multi-component crystals of IN with various acids. Synthon I occurs 44 times and, in all cases, these are co-crystals as opposed to salts. In the remaining four, two are salts and two are co-crystals. Additional to the most favoured acid···pyridine synthon, there is the additional occurrence of amide···amide homodimers II in 34 cases and amide···acid heterodimers in 12 cases.

Phil. Trans. R. Soc. A (2012)
With this background, we now consider the co-crystallization of IN with 3,5-DNBA and 3,5-dinitrosalicylic acid (DNSA). When IN and DNBA are taken in MeOH in equimolar amounts, a 1:1 amide–acid binary crystal is obtained ($P\bar{1}$, $Z'' = 2$). (The study of Nichol & Clegg [25] refers to the concept of $Z''$ proposed earlier (see, van Eijck & Kroon [26]). We note that $Z''$ may often be a more meaningful parameter than $Z'$ in multi-component molecular crystals.) The asymmetric unit consists of one molecule of IN and one molecule of DNBA. The structure is illustrated in figure 1. The normal acid···pyridine hydrogen bond is observed. The acid is completely ionized, the proton is transferred across the hydrogen bond and one obtains a salt rather than a co-crystal. As is usual, the expected amide homosynthon I is obtained ($D = 2.937$, $d = 1.847\, \text{Å}$).

When the co-crystallization of equimolar amounts of IN and DNBA is attempted in tetrahydrofuran (THF), however, an unusual 2:1 co-crystal is obtained in space group $P\bar{1}$ ($Z' = 1$, $Z'' = 3$). The asymmetric unit consists of two molecules of IN and one molecule of DNBA. The structure is shown in figure 2. The expected acid···pyridine hydrogen bond is found and there is partial proton transfer across the hydrogen bond. However, rather than form synthon II directly, the NH$_2$ group of the amide forms an unusual N–H···N hydrogen bond to the heterocyclic N-atom of another IN molecule giving rise to synthon IV. The basic motif (growth unit) is therefore a hexamer: an N–H···O ($D$, $d$; 2.941, 1.930Å) amide···amide dimer is flanked by amide molecules attached to it with N–H···N bonds (2.958, 1.962Å), which in turn are N···H–O.
Figure 2. Unusual structure of the 2:1 IN–3,5-DNBA co-crystal. Notice the N–H···N interaction, and the finite hexamer of hydrogen-bonded molecules, which is the building block of the structure. (Online version in colour.)

hydrogen bonded (2.564, 1.333 Å) to DNBA acid molecules. The finite hexamers are two-dimensionally cross-linked to one another with additional N–H···O bonds (2.985, 2.025 Å) to form sheets that are π···π stacked. The structure therefore contains strong (Nδ−···Hδ+−O), moderate (N–H···O) and variable (N–H···N) hydrogen bonding. A weak C–H···O bond (d = 2.717), perhaps facilitated by the partial proton transfer across the N···H−O hydrogen bond in the acid···pyridine synthon I, is also seen.

N−H···N hydrogen bonding is not a preferred mode of binding in systems that are also capable of N–H···O and O–H···N bonding. The interaction is seen rarely in IN systems, and also only when an acid is not involved. For example, it occurs in one of the polymorphs of pure IN (figure 3) [11]. Our example is certainly the first time it is seen in an IN:acid co-crystal. Curiously, another polymorph of pure IN has amide dimers linked with single N–H···O hydrogen bonds (not pairs of hydrogen bonds as in the 5 Å amide tape that is favoured by many primary amides) [11], and this pattern too is seen in the IN:DNBA 2:1 co-crystal. Other polymorphs have been reported recently, and one of them contains the N−H···N interaction [14].

The formation of this unusual structure of the IN:DNBA 2:1 co-crystal can be accounted for on the basis of various supramolecular entities that are present in solution. Some of these species are shown in figure 4. It is reasonable to assume that the acid···pyridine dimer and the amide···amide dimer are present in solution because they are the top two structures predicted with the hierarchical model. The usual outcome of hierarchic crystallization is that
the acid···pyridine synthon I (dimer) hydrogen bonds to an IN molecule via the amide···amide synthon II to give a trimer. This is seen very often in IN co-crystals. Alternatively, two acid···pyridine dimers could well associate via amide···amide hydrogen bonds to give a symmetrical tetramer. In the present instance, the acid···pyridine dimer is hydrogen bonded to an amide···amide dimer via the rare (for this family) N−H···N hydrogen bond to give an unsymmetrical tetramer, which then extends to a symmetrical hexamer. The fact that this unusual structure also contains supramolecular strands that are seen in the IN polymorphs is surely not a coincidence. Several of these species probably exist in solution, and high-throughput crystallography has revealed the existence of a form that might have passed undetected in the past. The fact that this 2:1 crystal is obtained from THF, while the ‘normal’ 1:1 co-crystal is obtained from MeOH is rationalized by stating that the more strongly hydrogen-bonding solvent MeOH is perhaps able to break up many of the supramolecular aggregates that are made up of weaker hydrogen bonds (like the N−H···N). This is why the 2:1 crystal contains a large variety of strong and weak hydrogen bonds.

Interestingly, none of the three IN crystal structures reported here are solvated. However, it may be noted that the solvent interactions in the supramolecular species shown in figure 4 could be important. These polar solutes can have strong interactions with the solvent that have to be broken during the crystallization process. However, and as mentioned earlier in this paper, many organic crystals are non-solvated even though the molecules are highly polar. The reason for this could be entropic: the solvent–solute interactions are broken easily during crystallization because of the entropic gain that takes place when the interacting solvent molecule enters the bulk solvent [27].

*Phil. Trans. R. Soc. A* (2012)
That the formation of this unusual 2:1 co-crystal is a one-off observation is shown by the fact that IN forms a 2:1 co-crystal with DNSA (\(P^1, Z'' = 3\)) wherein \(N-H \cdots N\) hydrogen bonds are not seen. There is one DNSA molecule and two IN molecules in the asymmetric unit. In the DNSA molecule, the carboxyl OH group has an unusual \textit{anti} conformation and is intramolecularly hydrogen bonded to the (ionized) phenolic group. The IN molecule is protonated at the pyridyl-N atom. Effectively, we are speaking about a genuine salt. Complete proton transfer has occurred perhaps because DNSA is a stronger acid than DNBA, but unusually, it is the phenolic group that is ionized rather than the carboxyl group. A normal amide \cdots amide dimer completes the symmetrical tetramer that is common in IN–acid co-crystals. The second IN molecule acts as a bridge between amide dimers to form a ribbon (figure 5).

\textit{Phil. Trans. R. Soc. A} (2012)
3. Review

The crystallization of an organic molecule is a complex and yet efficient process in which a number of functional groups compete with each other as recognition sites. Elucidating the mechanism of crystallization is important for the systematic development of the subject of crystal engineering, but it is not a simple phenomenon and still far too difficult to study exhaustively, either with experiment or computation. One may consider crystallization to be a supramolecular reaction in which one moves from the entropy-dominated solution to the largely enthalpically determined crystal. Between these must lie the crystal nucleus, the highest energy point in the reaction coordinate. Very little is known about the actual course of events during crystallization but a scenario may be sketched by assuming that the nucleus lies somewhere along a smooth pathway from solution to crystal. Near nucleation, the solution ‘rigidifies’ as a solute–solvent cluster. The nucleation point may be likened to the transition state in a covalent-bond-making process; it is followed by the exit of solvent into the bulk with the simultaneous formation of a (kinetic or metastable) crystal that then transforms to another, according to Ostwald’s Rule of Stages until the final global minimum (thermodynamic crystal) is achieved.

X-ray crystallography can, in principle, access all crystals that are formed after the point of nucleation. In former times, small molecule crystallographers were content to obtain a single crystal of a compound and determine its (molecular and crystal) structure. Today, with the heightened interest in crystal engineering, polymorphism and co-crystallization, high-throughput methods have become a reality. Also popular are the methods that employ unusual crystallization conditions (low temperatures, high pressures, rapid cooling, hydrothermal) for sample isolation and analysis. This has inevitably led to the examination of many interesting crystals. The crystal structures so obtained can offer a glimpse into some of the events that accompany the later stages of crystallization—in other words, the transformations of solvated crystals to non-solvated ones and the transformations of higher energy metastable crystals to more stable ones, and eventually the thermodynamic crystal. The following is a brief review of some selected examples of unusual crystal structures. The list is neither
exhaustive nor representative—it consists generally of examples from our own research but these structures offer a glimpse of how a structural landscape may be envisaged.

(a) Solvated crystals as crystallization intermediates

Most crystals of non-ionic organic compounds do not contain solvent. Accordingly, a characteristic occurrence during or just after nucleation would be the expulsion of solvent from the nucleus to the bulk solvent; this removal of solvent from the crystal is entropically advantageous [27]. Conversely, the retention of solvent in a crystal is evidence of enthalpic factors, notably the formation of strong hydrogen bonds between solute and solvent. The presence of solvent in a crystal could be taken as evidence of interrupted crystallization. If solvent expulsion is characteristic of completed crystallization, solvent retention is evidence of incomplete or interrupted crystallization.

In the geminal diol mentioned earlier, crystals were obtained both for the unsolvated diol and for the cyclooctylamine solvate [28]. The asymmetric unit of the solvate comprises two half molecules of the diol, each sitting on distinct inversion centres, together with one amine molecule (figure 5). The interaction hierarchies of the two diol molecules are distinctly different; while one of them is involved in forming an O−H⋯O and C−H⋯O based tetramer synthon, the hydroxyl group of the other forms a strong O−H⋯N hydrogen bond with the amine. In doing so, it comes between two ethynyl groups and intervenes in the formation of another C−H⋯O based synthon that is characteristic of solvent-free crystals in this family. The solvent hinders the formation of a representative synthon.

(b) Cryocrystallography and the formation of high $Z'$ forms

Recent advances have made it possible to grow single crystals in situ, at low temperatures, of organic compounds that are liquids at room temperature. Two polymorphs of phenylacetylene, α and β, with $Z'$ values of 2.5 and 3, respectively (both in space group $P\overline{1}$), have been characterized previously [29,30]. Using vigorous cooling conditions (quenching with liquid N$_2$), we were able to isolate a third γ polymorph of phenylacetylene ($Z' = 6$). The third form shows some similarities to the two earlier known forms in that it contains fragments of the structures of the α and β forms. The γ form appears to be a metastable kinetic phase. The molecule does not possess any strong hydrogen-bonding functionality and thus the overall crystal packing in all the polymorphs relies substantially on weak interactions of the C−H⋯π and π⋯π type. Compared to the γ form, there is an increased importance of the $\equiv$C−H⋯π (ethynyl) hydrogen bonds in the α and β forms. In short, the α and β forms are more ‘rigid’ while the γ form is more ‘liquid like’. We suggest that the crystal structures of polymorphs with higher values of $Z'$ occur earlier in the crystallization reaction coordinate and provide clues as to how the lower $Z'$ forms evolve during crystallization (figure 6).

Crystal engineers continue to discuss the formation of high $Z'$ crystals. In the context of crystallization pathways, a crystal with $Z' > 1$ could be a kinetic form that has been trapped before the molecules have adjusted themselves in their final orientations, which might be seen in a more stable form with $Z' = 1$.
S. Tothadi and G. R. Desiraju

Figure 6. Evolution of synthons in the polymorphs of phenylacetylene. (Online version in colour.)

(or some value lesser than in the kinetic form). Steed has referred to high-$Z'$ structures as fossil relics of more stable crystals [31] while Nangia has termed them as snapshots of the crystallization reaction [32]. Three situations could be postulated and debated: (i) the underlying cause of the formation of all $Z' > 1$ structures is the same; (ii) all high $Z'$ structures arise because of some underlying cause but these causes may be different in different situations; and (iii) there is no particular reason for the formation of some or even all high $Z'$ structures. The three polymorphs of phenylacetylene constitute an interesting landscape and offer hints about the evolution of supramolecular synthons in crystals [33].

(c) Conformational space and the structural landscape

Orcinol (5-methyl-1,3-dihydroxybenzene) exists in three conformations: syn–syn, anti–anti and syn–anti. We have studied the crystal structures of a large number of co-crystals and polymorphs of this compound in order to sample the conformational variations. The relative stabilities of the three conformers are 0.6, 0.1 and 0 kcal mol$^{-1}$, respectively [10]. The low energy rotational barrier hints at the nearly equal probabilities for the three conformations. Hence, any preference for a particular conformation or mixture of conformations could possibly be assumed from the solvent- or co-former-driven conformation selection. The orcinol molecule will selectively adopt any of these three conformations as per the requirement of the growing nuclei such that the intermolecular interactions are well optimized to suit the supramolecular environment. This can lead to numerous packing possibilities during the crystallization event. Exploring each of these possibilities for a particular orcinol co-former system is a difficult task. However, some information about these motifs can be indirectly sampled by performing
co-crystallization experiments with a large number of similar co-formers. One attempts to perturb the system chemically in order that the structural landscape is more easily accessed (figure 7).

Shown here is anhydrous orcinol (P2$_1$2$_1$2$_1$, Z' = 8) obtained from nitromethane. Of the eight symmetry independent molecules, four adopt the stable syn–anti conformation and there are two molecules each with syn–syn and anti–anti conformations. This structure is characterized by a one-dimensional chain of O−H···O hydrogen bonds consisting of a sequence of four symmetry-independent molecules in the order syn–syn, anti–anti, syn–anti and syn–anti. In contrast, a second polymorph that is obtained from CHCl$_3$ takes the tetragonal space group I4 with Z' = 2 but both symmetry independent molecules adopt the syn–anti conformation. Many orcinol co-crystals also illustrate the earlier mentioned concepts but, for reasons of brevity, we are unable to describe them here. Typical co-formers include urea, quinoxaline, IN and urotropin.

(d) Sampling the landscape with chemical variety

6-Amino-2-phenylsulphonyliminio-1,2-dihydropyridine is a compound that exhibits polymorphism [34,35]. This molecule was supplied as one of the blind test molecules for crystal structure prediction in 2001. There are three crystal forms. Twelve phenyl-substituted derivatives were examined for polymorphism [36] (figure 8). The parent compound contains hydrogen bond donor (D) and acceptor sites (A) located in an AADD juxtapositioning. Two structural families that differ in their use of the AADD hydrogen bond functionality can be identified. Methyl- and chloro-substitution in the ortho position or fluoro-substitution in the para position leads to a catemer motif. Substitution in either the meta or para positions by methyl and larger substituents blocks this structural option and a dimer is obtained. It is notable that none of the 12 derivatives examined show polymorphism as is seen in the parent derivative. However, there is another way of considering these results. The landscapes for all the 12 derivatives may be said to be broadly similar, and we may consider an ‘average’ landscape for the entire family. This landscape is populated with all the catemers and dimers that are experimentally observed. A particular experimental structure, say the catemer of the ortho-methyl derivative, may also be taken as a high-energy structure of the meta-methyl derivative, which has so far not been isolated; we note that the meta-methyl derivative has so far only been obtained as a dimer. Variation of experimental conditions of crystallization is one way of sampling a particular
landscape, and each new polymorph corresponds to a local minimum. Variation of functional groups is a chemical probe of the landscape. Structural variations that are found for differently substituted derivatives represent putative polymorphic structures that might still be found for any one particular compound if the experimental conditions are further varied, or these new polymorphs may be identified computationally.

4. Experimental section

(a) Co-crystallization experiments

IN–3,5-DNBA, 1 : 1 salt. 61 mg of IN and 106 mg of DNBA were ground together with two to three drops of EtOH (solvent drop grinding). 20 mg of the ground sample was dissolved in 5 ml of MeOH and crystals of the 1 : 1 complex (m.p. 179°C; IR 3470, 3382, 3313 cm\(^{-1}\)), suitable for X-ray diffraction, were obtained after 4 days. The choice of crystallization solvent was made after a number of experiments with EtOH, MeOH, MeCN, THF, 2-PrOH and dioxane. All crystals were colourless and block shaped.

IN–3,5-DNBA, 2 : 1 co-crystal. When the earlier mentioned procedure was repeated with THF as the crystallizing solvent, the 2 : 1 amide–acid co-crystal was obtained (m.p. 181°C; IR 3314, 3160, 3109 cm\(^{-1}\)).

IN–3,5-DNSA, 2 : 1 salt. 61 mg of IN and 114 mg of DNSA were ground with two to three drops of EtOH. 20 mg of the ground material was crystallized from 5 ml of warm dimethylsulphoxide. Crystals of the 2 : 1 complex suitable for X-ray diffraction experiments were obtained after a week.

(b) Powder X-ray diffraction

Powder X-ray diffraction (PXRD) data were collected on a Philips X’pert Pro X-ray powder diffractometer equipped with X’cellerator detector. The scan range,
step size and time per step were \( \theta = 5.00 \) to 40°, 0.028° and 30 s, respectively. The PXRD for the MeOH and THF batches are distinct. However, we cannot rule out other crystal forms. The forms determined by the single crystal method occur in the bulk recrystallizes.

(c) Single-crystal X-ray diffraction

Single-crystal X-ray diffraction data were collected for the co-crystals on a Rigaku Mercury375/M CCD (XtaLAB mini) diffractometer using graphite monochromated Mo-K\( \alpha \) radiation equipped with a Rigaku low temperature gas spray cooler. In all cases, data were processed with the Rigaku CRYSTAL CLEAR software. Structure solution and refinement were performed with SHELX-97 [37] using the WinGX [38] suite. All structures were solved by direct methods and refined by full-matrix least-squares on \( F^2 \) with anisotropic displacement parameters for all non-hydrogen atoms. Details of the crystal structure determinations may be obtained from the Cambridge Crystallographic Data Centre with the following reference numbers: 833664 IN–3,5-DNBA 1 : 1 co-crystal; 833665 IN–3,5-DNBA 2 : 1 co-crystal; 833666 IN–3,5-DNSA 2 : 1 co-crystal.

5. Conclusions

The concept of a structural landscape is strengthened by the isolation and characterization of a large number of crystal structures for a given chemical system. Increasingly, one gets the feeling that what the experimentalist observes is merely a crystal structure of a compound rather than the crystal structure. Each observed crystal structure is just that, a data point in a landscape of nearly equienergetic crystals. Such crystals will, in all likelihood, be observed in increasing numbers because crystal engineers and structural chemists are employing diverse methods of crystal growth; they are using computation to obtain new structures in silico, and chemical probing of the landscape through the study of solvated forms and substitutional variation further expands the structural panorama. Crystal engineering is now moving beyond the crystal to a study of mechanisms of crystallization.

S.T. thanks the UGC for the award of a Junior Research Fellowship. G.R.D. thanks DST for the award of a J. C. Bose fellowship. We thank the Rigaku Corporation, Tokyo, for their support through a generous loan of a Rigaku Mercury-375R/M CCD (XtaLAB mini) table-top diffractometer. This paper is dedicated to Alan L. Mackay, who has addressed difficult issues pertaining to structural complexity, on the occasion of his 85th birthday.

References

23 Thompson, L. J., Voguri, R. S., Male, L. & Tremayne, M. 2011 The crystal structures and melting point properties of isonicotinamide cocrystals with alkanedicarboxylic acids HO2C(CH2)n−2CO2H where n = 7–9. CystEngComm 13, 4188–4195. (doi:10.1039/C1CE05160A)

25 Nichol, G. S. & Clegg, W. 2006 The importance of weak C–H⋯O bonds and \( \pi \cdots \pi \) stacking interactions in the formation of organic 1,8-bis(dimethylamino)naphthalene complexes with \( Z' > 1 \). *Cryst. Growth Des.* **6**, 451–460. (doi:10.1021/cg0503806)


30 Dziubek, K., Podsiadio, M. & Katrusiak, A. 2007 Nearly isostructural polymorphs of ethynylbenzene: resolution of \( \equiv \text{CH} \cdots \pi \) (arene) and cooperative \( \equiv \text{CH} \cdots \pi \text{C} \equiv \text{C} \) interactions by pressure freezing. *J. Am. Chem. Soc.* **129**, 12620–12621. (doi:10.1021/ja074885r)


