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Adventures in crystal engineering

Prof Delia Haynes
Department of Chemistry and Polymer Science
Faculty of Science

2021

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Biography of author

Delia Haynes was born in Durban, and spent most of her school years in Pretoria. She completed her BSc in Chemistry and Genetics and her BSc Honours in Molecular Genetics at the University of Natal, Pietermaritzburg. She then saw the light and switched back to Chemistry, completing an MPhil and a PhD in Inorganic Chemistry at the University of Cambridge in the UK, under the supervision of Jeremy Rawson. On completion of her PhD in 2002, Delia remained at Cambridge as a postdoctoral associate with the Pfizer Institute for Pharmaceutical Materials Science, where she worked with Bill Jones and Sam Motherwell. In 2006, she returned to South Africa as a lecturer at the University of KwaZulu-Natal in Durban. In 2007 she joined the Department of Chemistry and Polymer Science at Stellenbosch University, and has discovered that her current head of department is correct: the problem with working in Stellenbosch is that it is such a lovely place you never want to leave! Delia was a Fulbright scholar at the University of California, Berkeley in 2010, and a visiting professor at the University of Lorraine in 2013 and the University of Warsaw CNBCh in 2019. She was the 2015 recipient of the Jan Boeyens medal, which is "awarded to a young South African researcher (under the age of 40 years) who has made a distinguished contribution to the utilization of crystallography and other structural methods in a holistic manner to investigate fundamental problems in nature". She is a member of the European Crystallographic Association's Executive Committee, chair of the Steering Committee for the African Crystallographic Association and a member of the *CrystEngComm* Advisory Board. Her research focuses on crystal engineering with multi-component crystals.

ADVENTURES IN CRYSTAL ENGINEERING

Prof Delia Haynes

ABSTRACT

Crystal engineering is about making crystals that have interesting properties on purpose; that is, it involves the intentional design of functional crystals from molecular building blocks. This is done using supramolecular synthons, which are robust and predictable interactions that form between molecules. These interactions have known geometries and are used to arrange molecules in a desired pattern in a crystal in order to yield specific properties. In this presentation, crystals and crystal engineering will be introduced and explained, with a focus on the particular chemical systems that my group is interested in. Our efforts to understand and control the crystal structures of dithiadiazolyl radicals will be discussed, as well as the nature of pancake bonding and the construction of functional materials from radical building blocks. Our work on organic salts and co-crystals, with a specific focus on porous salts, will be described. Our results using mechanochemistry as a method for preparing organic materials will be considered, alongside our latest surprising work on the sublimation of salts and co-crystals. I will discuss why understanding and controlling the way molecules arrange themselves in crystals is important, and hopefully show you why I consider research in this area to be an adventure.

Adventures in crystal engineering

Dedicated to my parents:

My mother, Dawn, who never tired of explaining why, and my father,
Robert, who did so much to allow me to do what makes me happy

As I child, I spent an inordinate amount of time mixing things together to see what would happen: paint colours (you get brown), mud (not much changes but it is fun), all sort of things in the kitchen (I have a very patient mother). On one memorable occasion a concoction of mint leaves and other garden paraphernalia fermented on the top of my grandmother's fridge. This should probably have been a warning to my nearest and dearest (and quite possibly was). Much later in my life, I was asked in an interview why I changed from an Honours in Genetics to Chemistry, to which I truthfully replied that in chemistry, 'things change colour'. This is all by way of explaining why I enjoy chemistry so much. In chemistry, you get to mix things together and see what happens. I was specifically drawn to inorganic chemistry: that's where you get the colours!

I have also always been fascinated by patterns and symmetry, and spent many hours as a child finding the patterns in bedroom curtains. I wanted to know how things worked, and I wanted to know *why*. When I discovered real chemistry at university, it was a perfect fit, in a Goldilocks sense. Plants and animals are just too big, and quarks are way too small. But atoms and molecules? Now those are just right.

All of this came together in a quite marvellous way when I started my PhD with Jeremy Rawson, which happened completely by chance. I got to mix things together to make new molecules, with all sorts of colour changes along the way. I got to crystallise these molecules and look at the patterns in how they fitted together, and I was doing all this because we were trying to understand why the molecules behaved as they did, in order to control this behaviour in the future. It was during my PhD that I read Desiraju's monograph,[1] *Crystal engineering: The design of organic solids*, as well as *Molecular crystals* by J.D. Wright.[2] I was completely fascinated, and completely hooked. This was my introduction to crystal engineering – at the time a quite new and emerging field.

WHAT IS CRYSTAL ENGINEERING?

To understand crystal engineering, we must first be clear on exactly what a crystal is. Crystals are solid materials, and many crystals are considered to be attractive objects due to their symmetric shapes. The precise definition of what a crystal is changed relatively recently due to the discovery of quasicrystals. The International Union of Crystallography gives two alternative but equivalent definitions of a crystal: "A solid is a crystal if its atoms, ions and/or molecules form, on average, a long-range ordered arrangement" and "A material is a crystal if it has essentially a sharp diffraction pattern".[3]

There are two key points here. The first is long-range order. The molecules in crystals are arranged in an ordered pattern that usually repeats itself throughout the crystal. The second important thing about crystals is that they diffract light. Specifically, crystals diffract X-rays. This is how we are able to find out how the molecules are arranged inside a crystal: using the technique of X-ray diffraction.

Why are we interested in the way molecules are arranged in crystals? The arrangement of the molecules in a crystal determines many of the properties of that crystal: what temperature it melts at, how easily it dissolves, whether it absorbs gases or whether it behaves as a magnet. These properties are important for many reasons, but I will give just one example: chocolate. One of the molecules in cocoa butter has six different crystal forms; that is, there are six different ways in which the molecules can arrange themselves in a crystal.[4] These different forms are called *polymorphs* (Figure 1).

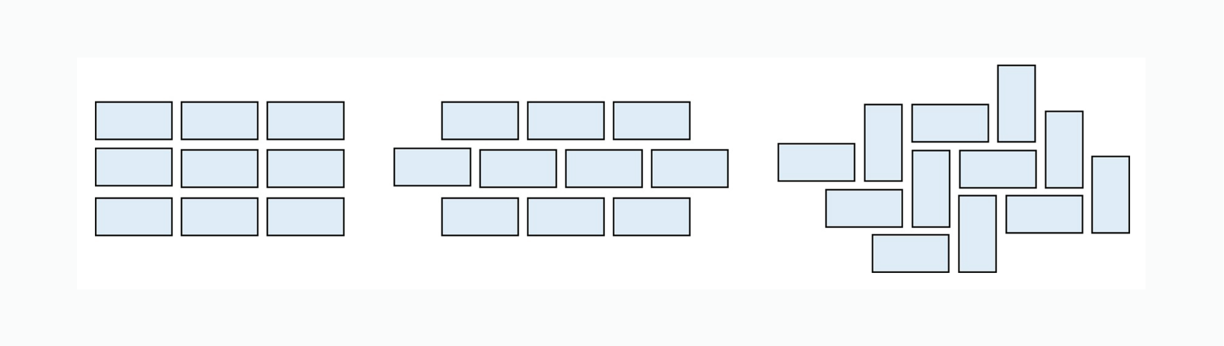


Figure 1: A schematic representation of polymorphism. The rectangle represents a molecule, which can be arranged in several different ways. All of the arrangements have long-range order (a repeating pattern). When a molecule crystallises in different arrangements like this, the different crystal forms are called *polymorphs*.

Polymorphs are crystals of the same molecule, but they are not the same thing. Because the molecules are arranged in a different pattern in the crystal, polymorphs of a molecule do not all have the same physical properties. The six different polymorphs of the molecule in cocoa butter do not all behave in the same way. Most importantly, only one of the forms melts in the mouth, so of course that is the desirable form. This is why chocolate is tempered – the chocolate has to be heated to melt the undesirable polymorphic forms, and then cooled at the right rate to crystallise the desirable, melt-in-the-mouth form. This is also why chocolate gets a white bloom if it is kept in the fridge – this is a different, less melt-in-the-mouth, form of the cocoa butter molecules.

A crystal is an ordered arrangement of molecules, and the arrangement of the molecules in the crystal has a significant effect on the properties of the crystal. In order to result in desirable properties, the molecules in a crystal should be arranged in an appropriate way. But how is this done? How is the arrangement of the molecules in a crystal controlled? Molecules are held together in a crystal by intermolecular interactions – the interactions between the molecules. It is by controlling these interactions that the arrangement of the molecules within a crystal can be controlled. There are several classes of intermolecular interactions, including hydrogen bonding, halogen bonding and coulombic (electrostatic) interactions.

This control of molecular architecture in the solid state is *crystal engineering*: "the understanding of intermolecular interactions in the context of crystal packing and the utilization of such understanding in the design of new solids with desired physical and chemical properties."[1] Alternatively, and much more simply, crystal engineering is "making crystals by design".[5] The crystal engineer aims to construct functional crystalline materials through the directed assembly of molecules or ions.[6] In the past, attempts to develop functional materials have often focused on *molecular engineering*, which entails tailoring the molecule and its substituents in order to influence the properties of the molecule. In *crystal engineering*, the interactions *between* molecules are used in order to influence the arrangement of molecules in the solid state, thereby controlling the properties and allowing the design of novel molecule-based functional materials.

To effectively use intermolecular interactions to construct crystals, an in-depth understanding of how the interactions work is required. There are a number of ways to approach this problem. One method that has been successful is to use data from large numbers of published crystal structures. Crystal engineers are very lucky to have the Cambridge Structural Database (CSD),[7] a database of all published small-molecule organic and organometallic crystal structures. These data can be analysed to identify trends in the behaviour of molecules in crystals. This approach has led to the identification of *supramolecular*[8] *synthons*,[9] which are interactions between functional groups on molecules that are known to occur with a high degree of predictability (Figure 2). Because the geometry of these interactions is predictable, and it is known that the interactions are likely to occur between molecules containing these functional groups, supramolecular synthons can be used to direct the arrangement of molecules in crystals.

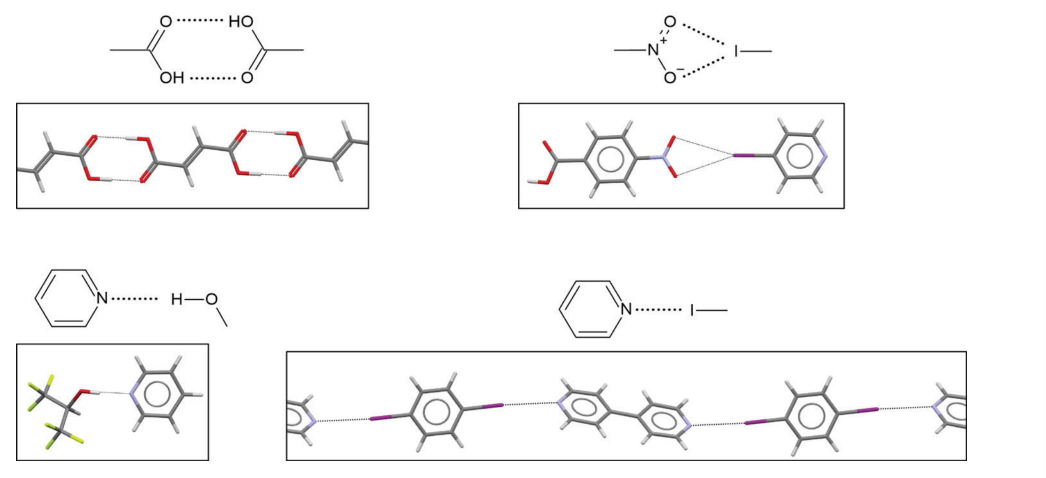


Figure 2: Selected supramolecular synthons. A sketch of each synthon is given, along with a known example.[10] Clockwise from top left are the hydrogen-bonded carboxylic acid dimer, the nitro-iodo synthon, the iodo-pyridine halogen bond and the pyridine-hydroxy hydrogen bond. Dotted lines indicate the interactions between molecules.

Another way to develop an understanding of intermolecular interactions in crystals is to carry out systematic experimental studies. The crystal structures of a series of related molecules are determined, making only small changes to each molecule in the series. The way in which the crystal structure changes with small changes in the molecule is then analysed. In this way, the links between molecular structure and crystal structure become clear. The nature of intermolecular interactions themselves can also be investigated, either experimentally or through the use of computational tools. Finally, the way in which the crystals of interest are grown can be changed, which can have a profound effect on how the molecules arrange. In my research group, we have used all of these approaches to probe the link between structure and properties for several groups of molecular materials.

MULTI-COMPONENT CRYSTALS

One promising approach for crystal engineering of molecular materials is to introduce the atoms that will form strong and predictable intermolecular interactions (supramolecular synthons) on two or more different molecules, resulting in a multi-component crystal. Multi-component crystals contain more than one molecule or ion in a defined (stoichiometric) ratio (Figure 3). If the molecules used are neutral molecules, the material is called a co-crystal. If they are charged, the material is a salt. Combinations of these also exist: if a salt crystallises together with a neutral molecule, this would be a co-crystal of a salt (or an ionic co-crystal). If one of the molecules that make up a multi-component crystal is a solvent, the crystal is known as a solvate.

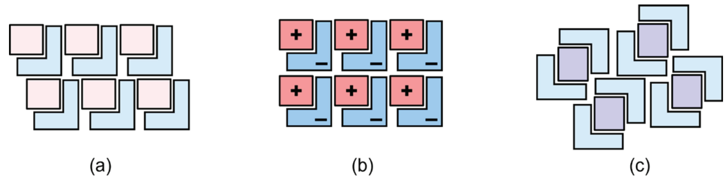


Figure 3: A schematic representation of multi-component crystals. If the molecules making up the crystal are neutral, the material is called a co-crystal. A 1:1 co-crystal is depicted in (a), while (b) represents a 1:1 salt, where the two components of the crystal are charged. In (c), the co-crystal has 2:1 stoichiometry (blue:purple). This also represents a host-guest system, where the purple guest is included between molecules of the blue host. If the guest is a solvent, this type of crystal is called a solvate.

THE ADVENTURE BEGINS

As mentioned above, my interest in crystal engineering started during my PhD with Jeremy Rawson, which focused on 1,2,3,5-dithiadiazolyl (DTDA) radicals (Figure 4). Often, radicals are considered to be unstable transient species involved fleetingly in reactions. However, several families of stable neutral organic radicals are known.[11] One class of stable radicals is based on thiazyl rings (rings containing sulfur and nitrogen atoms), and the 1,2,3,5-dithiadiazolyl radical is a particularly well-studied member of this class.[12] These neutral radicals are thermally and kinetically stable, and can be stored in the absence of oxygen or moisture for indefinite periods. This means that they can be made, crystallised and stored in the laboratory. In fact, DTDAs are sufficiently stable that they are usually crystallised by sublimation, which involves heating the solid material under vacuum (*vide infra*).

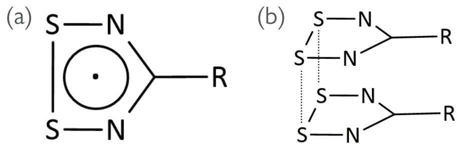


Figure 4: (a) The 1,2,3,5-dithiadiazolyl radical; (b) a diamagnetic DTDA dimer.

Stable radicals are of interest for their potential use in applications such as design of organic magnets and conductors.[12] Magnetic ordering (the alignment of electrons leading to magnetic behaviour) arises from the existence of unpaired electrons in the molecule. If molecules containing unpaired electrons could be arranged appropriately in a crystal, this would generate a magnet that does not contain any metals. Such organic magnets would be lightweight, and potentially bendable or transparent, or have other properties conventionally associated with organic materials.

DTDAs have been investigated for their potential as building blocks for molecular magnetic or conducting materials for some time. Radicals with a variety of different chemical substituents bonded to the carbon of the heterocycle can be synthesised using established literature procedures, often in a one-pot synthesis.[13] This makes DTDAs ideal candidates for crystal engineering: one end of the molecule can be changed in order to control the intermolecular interactions it forms, thereby changing the way the radicals crystallise. With careful consideration, a molecular magnet or a conductor could be designed.

This sounds quite straightforward. But of course, there is a catch: DTDAs tend to dimerise in the solid state (Figure 4b) via an interaction known as *pancake bonding* (*vide infra*).[14] When this happens, the electrons on each radical pair with each other, and the resulting dimer is diamagnetic. In this state, the molecules are no longer able to form magnets, because there are no unpaired electrons. Overcoming this dimerisation interaction has therefore been the focus of much research.

Several DTDAs have been shown to crystallise as monomers, retaining their unpaired electron and therefore their paramagnetic nature in the solid state. Some of these derivatives do show magnetic ordering, although at very low temperatures.[15] The DTDA molecules that crystallise as monomers all have something in common: they all contain perfluoroaryl rings; that is, they have several fluorine atoms on the molecule. As part of my PhD research, we therefore set out to understand the effect that fluorine atoms have on the crystal structures of DTDAs. We approached this by carrying out a systematic study of a series of DTDAs where we changed the position of the fluorine atoms in the molecule and looked at how this changed the crystal structure.[16] We focused on the molecular electrostatic potential (MEP) of these molecules (which parts of the molecule are slightly negatively charged and which are slightly positively charged). We clearly showed that the position of the fluorine atoms relative to one another strongly affected the electrostatic potential of the whole molecule, and this relates directly to how these molecules arrange in a crystal (Figure 5). This was quite an early example of the use of MEP in understanding crystal structures, and was important because it focused on the whole molecule, not just on interactions between specific atoms.

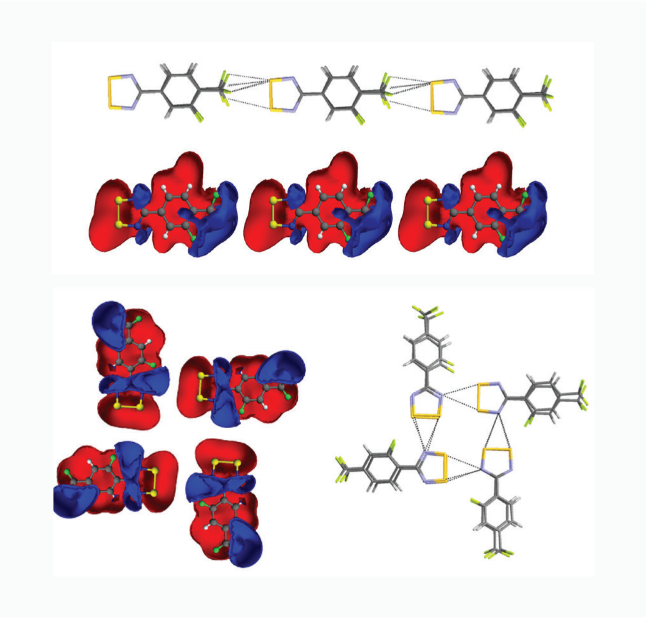


Figure 5: Molecular electrostatic potential (MEP) as a tool for rationalising the crystal structures of DTDAs; 3′-fluoro-4′-(trifluoromethyl)phenyl-1,2,3,5-dithiadiazolyl (above) and 2′-fluoro-4′-(trifluoromethyl)phenyl-1,2,3,5-dithiadiazolyl (below). MEP maps are depicted alongside portions of the crystal structure. Red represents electropositive areas and blue represents electronegative areas. It is clear that in the crystal structures of these materials, electrostatic interactions are structure-directing.

Upon completion of my PhD, I wanted to continue working in crystal engineering, and I was lucky that an ideal position opened up at just the right time. My postdoctoral research was carried out with Bill Jones and Sam Motherwell at the Pfizer Institute for Pharmaceutical Materials Science, based in the Department of Chemistry at Cambridge University. My particular project involved understanding pharmaceutically relevant salts in the solid state, with a specific focus on hydrates. We wanted to know whether some groups of salts were more likely to form hydrates than others. This project was my first experience with thinking about multi-component crystals, and it introduced me to a number of methodologies that form a key part of my research today. This is where I first used the CSD,[7] described by Sam as a "treasure trove of answers looking for a question". We used the data in the CSD to study hydrate formation in structures containing pharmaceutically acceptable anions[17], and to catalogue the occurrence of pharmaceutically relevant ions in the CSD.[18] I was also involved in a study showing that mechanochemistry is a useful method to screen for new salt forms of a drug.[19] Mechanochemistry involves using mechanical energy, in my research usually grinding in a mortar and pestle or a ball mill, to induce a chemical reaction.

My research career has continued to combine aspects from the work I did during both my PhD and my postdoctoral fellowship. My group now studies the construction of functional materials from multi-component crystals. We work on DTDA radicals, as well as on organic carboxylate salts and co-crystals. We are particularly interested in understanding the intermolecular interactions in these materials. We also systematically investigate both mechanochemistry and sublimation as routes to new crystal forms. Each of these aspects of the ongoing adventure that is a career in research is described in more detail below.

DITHIADIAZOLYLS: THE RADICAL PART OF THE STORY

Understanding pancake bonding

As mentioned, DTDAs often form pancake-bonded[14] dimers in crystals. What exactly is a pancake bond? Pancake bonding occurs between π-radicals in general (radicals where the unpaired electron is on a flat part of the molecule, like DTDAs), and results in diamagnetic dimers of molecules. In DTDAs, the pancake-bonded dimers can have several different geometries (Figure 6). Each observed geometry corresponds to an arrangement of molecules where there is favourable overlap between the orbitals containing the unpaired electron. Intermediate geometries are never observed, clearly indicating that there is a bonding aspect to this interaction. The distances between the molecules involved in a pancake bond are too long to be considered normal covalent bonds, but they are also shorter than what is usually observed for intermolecular interactions. In addition, an equilibrium between pancake-bonded monomers and dimers is observed in solution, indicating that pancake bonds are also much weaker than covalent bonds. Pancake bonds are an interesting and unusual class of interaction, and we want to understand them better – both from the perspective of improving our fundamental understanding of bonding, and also because we want to be able to overcome this interaction to generate magnetic materials.

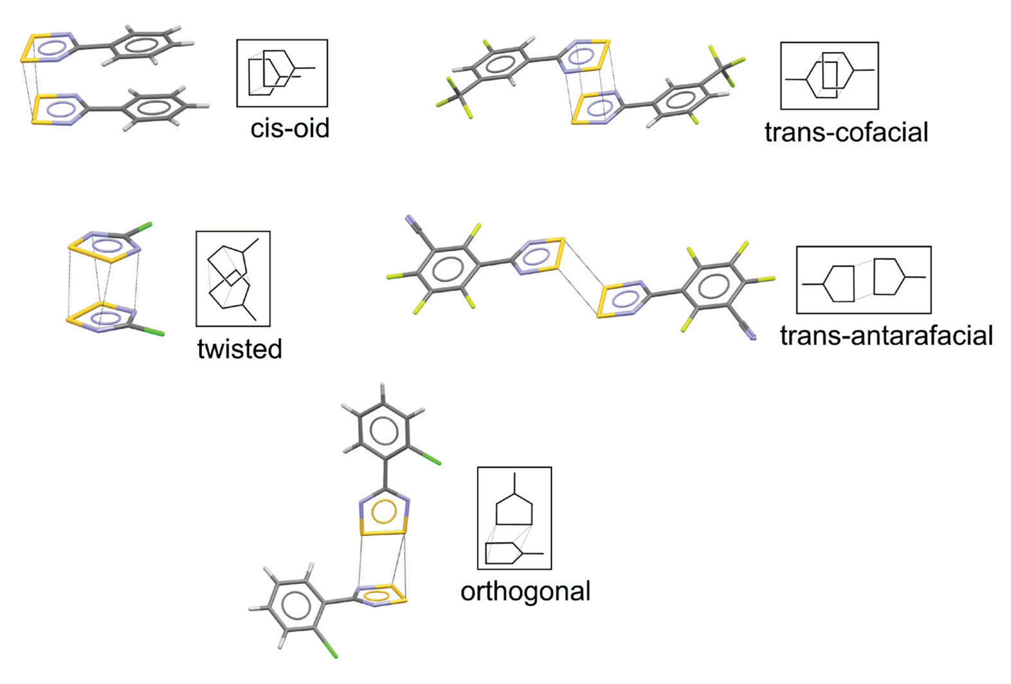


Figure 6: Pancake-bonded dimers of 1,2,3,5-dithiadiazolyls. The five known dimer geometries are illustrated with examples from the literature[16,20] as well as schematically.

Together with researchers in Poland and France, we have used experimental charge density analysis to probe the nature of the pancake bonding interaction.[21] These experiments involve collecting very high-resolution X-ray diffraction data, giving a detailed picture of the electron density distribution in the molecule. Because bonds involve electrons, having a detailed picture of the distribution of the electrons in a molecule gives insight into the bonding in that molecule. The high-resolution data are analysed using a theory called *Atoms in Molecules*,[22] focusing on the topology of the electron density. Local maxima in the electron density, called critical points, can be identified. These critical points tell us something about the nature of the bonding interactions between atoms. We can identify critical points on the covalent bonds in DTDAs, and also between the atoms involved in intermolecular interactions, as well as between the sulfur atoms in the pancake-bonded dimers. However, the properties of these bond critical points are not the same (Figure 7). For pancake bonds, the values of the electron density at the bond critical points, as well as the values of the Laplacian at the bond critical points, fall between the values observed for covalent bonds and intermolecular interactions. In terms of the topology of their charge density, pancake bonds are distinct from both covalent bonds and intermolecular interactions.

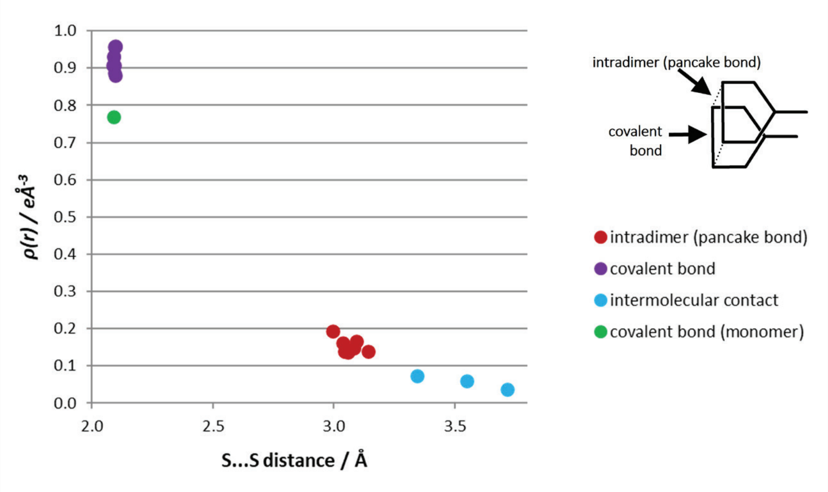


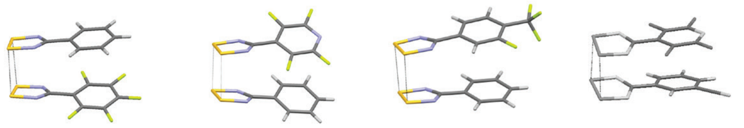
Figure 7: Values of the electron density at bond critical points plotted against S…S distances for covalent bonds, pancake bonds and intermolecular interactions in a series of DTDAs.

These results give us a picture of how pancake bonding differs from both covalent bonding and intermolecular interactions. Currently, we are studying pancake bonds in DTDAs under very high pressure, using a diamond anvil cell to put crystals under pressure during X-ray diffraction experiments. We hope to learn more about this unusual interaction by studying how it changes in extreme conditions.

Dithiadiazolyl co-crystals

Pancake bonding leads to DTDA dimers in the solid state, resulting in diamagnetic materials. One possible route to overcoming the problem of dimerisation in DTDAs is to ensure that there is an interaction in the crystal that is stronger than the dimerisation interaction that could effectively compete with it; in other words, to introduce a strong competing supramolecular synthon. One way to do this is to introduce a second molecule and form a co-crystal. As discussed above, co-crystals are crystals containing more than one neutral molecule in a stoichiometric ratio. Our previous work has shown that electrostatic potential is important in the crystal structures of DTDAs. If the electrostatic potential difference between a DTDA radical and the chosen co-former is sufficiently large, the electrostatic interaction may be able to compete with the dimerisation interaction.

We therefore set out to make some DTDA co-crystals. We wanted to co-crystallise two DTDAs that would have a strong intermolecular interaction between them – strong enough to ensure that this interaction happens instead of the dimerisation interaction. We decided to co-crystallise aryl-substituted DTDAs with perfluoroaryl-substututed DTDAs, taking advantage of the known aryl-perfluoroaryl supramolecular synthon. The first two DTDA combinations we tried gave co-crystals, although in both cases, the DTDAs were dimerised.[23] We have been trying to make more DTDA co-crystals for over 10 years, and in all this time we have only succeeded in making two more co-crystals, giving a total of four known DTDA-DTDA co-crystals (Figure 8). The Rawson group has also reported several co-crystals between DTDAs and other radicals, where they have used MEP to design the co-crystals.[24]



$E_{\text{heterodimer}}$ / kJ mol^{-1}	-31.506	-33.179	-31.631	-41.162
ΔE_{rxn} / kJ mol^{-1}	-16.987	-24.184	-12.929	-12.418

Figure 8: Heterodimers from three of the known DTDA co-crystals. The fourth dimer, shown in grey, is hypothetical. The values for the energy of each heterodimer, as well as for the dimer formation reaction, are given below each dimer (in kJ mol^{-1}).

When we can successfully make a DTDA co-crystal, it is the only product of the reaction, but it has proven difficult to find a combination of molecules that will result in co-crystal formation. We wanted to understand why this is, so we turned to computational methods. We calculated the energy of the dimerisation interaction in the gas phase for three of the known DTDA co-crystal dimers (Figure 8). All three co-crystal heterodimers have more favourable energies than the homodimers from which they are formed. We then calculated the energies for potential DTDA co-crystal dimers that we have tried to make, but never observed. We still found that these heterodimers have favourable energies – in some cases even more favourable than the heterodimers we have observed experimentally. The most relevant energy to understand whether a co-crystal will form is actually the energy for the co-crystal formation reaction, ΔE_{rxn}, where $\Delta E_{\text{rxn}} = 2(E_{\text{heterodimer}}) – (E_{\text{homo1}} + E_{\text{homo2}})$. We calculated these energies as well, and found that in many cases, the reaction energy for co-crystal formation is very favourable. It seems that we should be able to form many DTDA co-crystal dimers, we have just not yet managed to access the right reaction conditions in order to observe them.

Ultimately, we would like to produce co-crystals that contain monomeric DTDAs. We therefore tried to co-crystallise two DTDAs that are known to exist as monomers in the crystalline state. We did not get a co-crystal, but we did get an unexpected and interesting result. Many DTDAs are polymorphic; that is, they have more than one crystal form of the same molecule. It can sometimes be quite difficult to grow crystals of a particular desirable polymorph. One example of this is 4′-cyano-perfluorophenyl-1,2,3,5-dithiadiazolyl. This radical crystallises as a monomer in two polymorphic forms. The ß-polymorph crystallises as long needle-shaped crystals and orders as a ferromagnet below 36 K. The α-polymorph, on the other hand, is notoriously difficult to crystallise. Beljoudi *et al.* reported that this form could only reproducibly be obtained by subliming on to a cold finger kept at -10 °C.[25] While trying to make a new co-crystal, we crystallised this DTDA with 2′,6′-difluorophenyl-1,2,3,5-dithiadiazolyl. Keen observation revealed that when co-subliming these two radicals, crystals of the elusive α-polymorph of 4′-cyano-perfluorophenyl-1,2,3,5-dithiadiazolyl were readily obtained. Careful systematic investigation has shown that not only must the two radicals be co-sublimed to yield the -polymorph, they must also be mixed in ether beforehand. Slurrying with ether without the second radical present does not yield crystals of the elusive polymorph.

Towards functional materials from dithiadiazolyls

One of the ways in which molecules can be arranged in a particular way in the solid state is to attach them to a scaffold or a framework. We wanted to investigate the coordination of DTDAs to frameworks containing porphyrins, so, together with Orde Munro, we started looking at the coordination of DTDAs to metalloporphyrins.[26] One of our first reactions was between 4'-pyridyl-1,2,3,5-dithiadiazolyl and cobalt(II) tetraphenylporphyrin (CoTPP). Some very small crystals were isolated from the reaction, revealing a very interesting product (Figure 9).

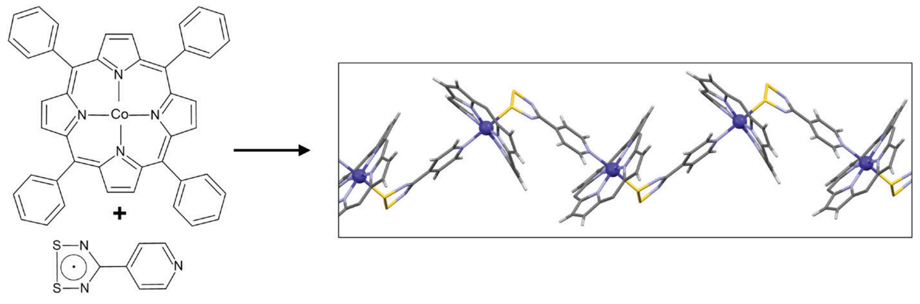


Figure 9: A coordination polymer (right) formed from the reaction between cobalt (II) tetraphenylporpyrin and pyridyl-dithiadiazolyl (left). The image of the coordination polymer is taken from the crystal structure. The cobalt ion is shown in ball-and-stick mode, and the phenyl groups have been deleted for clarity.

The material we isolated is a coordination polymer, and the DTDA connects to the metal centre in a way that had not previously been observed for DTDAs. What is particularly interesting is the length of the S-S bond in the DTDA in this material: it is significantly longer than observed in neutral DTDA radicals. This gave us an indication that perhaps there was some electron transfer between the DTDA and the cobalt, resulting in a partially anionic DTDA. We investigated the formation of the porphyrin-radical complex using electron paramagnetic resonance (EPR) spectroscopy, a technique that allows us to study molecules containing unpaired electrons. We found that when CoTPP is added to a solution of the DTDA radical, the EPR signal is quenched, meaning there are no longer any unpaired electrons. But is this because the electrons have paired up (like in a DTDA dimer), or because an electron from the metal has been completely transferred to the DTDA, yielding Co(III) and the DTDA anion? Another type of spectroscopy, nuclear magnetic resonance spectroscopy, confirmed that the latter is the case on dissolution of the coordination polymer.

Calculations on this coordination polymer also indicate that this material has the potential to act as a molecular wire, a chain of molecules that could conduct electric current, and thereby form part of a molecular electronic device. This DTDA-metalloporphyrin complex also acts as an oxidation catalyst in solution. Our further studies indicate that a variety of DTDAs complex to a variety of metalloporphyrins in solution, but we have not yet managed to identify the right conditions to grow crystals of these materials. Our work in this area is ongoing.

We have also investigated the inclusion of thiazyl radicals into porous materials, work carried out in collaboration with Jeremy Rawson and Len Barbour.[27] One of the systems we have investigated involves a seemingly non-porous material – that is, it does not have obvious channels going through the crystal, such that you might expect it to be porous to other molecules. This particular material contains a Cu^{2+} metallocycle, and crystallises as its MeOH solvate. On removal of the solvent, the material retains discrete empty pores. However, it has been shown that it is porous to gases, and to a number of solvents and volatile molecules. We decided to see whether it would be porous to a DTDA, and exposed it to the vapour of a DTDA radical. On exposure to the radical, there was a distinct colour change in the material, but the crystals remained as single crystals. Determining the crystal structure of the resulting material showed that the radical had indeed been included in the metallocycle (Figure 10). The radicals included in this porous material are not dimerised, and so we did some experiments to see whether this material had any interesting magnetic behaviour. We found that the electrons on the DTDA communicate with the electrons on the metallocycle at low temperatures. While this material is not a magnet, it does indicate that this approach to constructing magnetic materials with DTDAs shows promise.

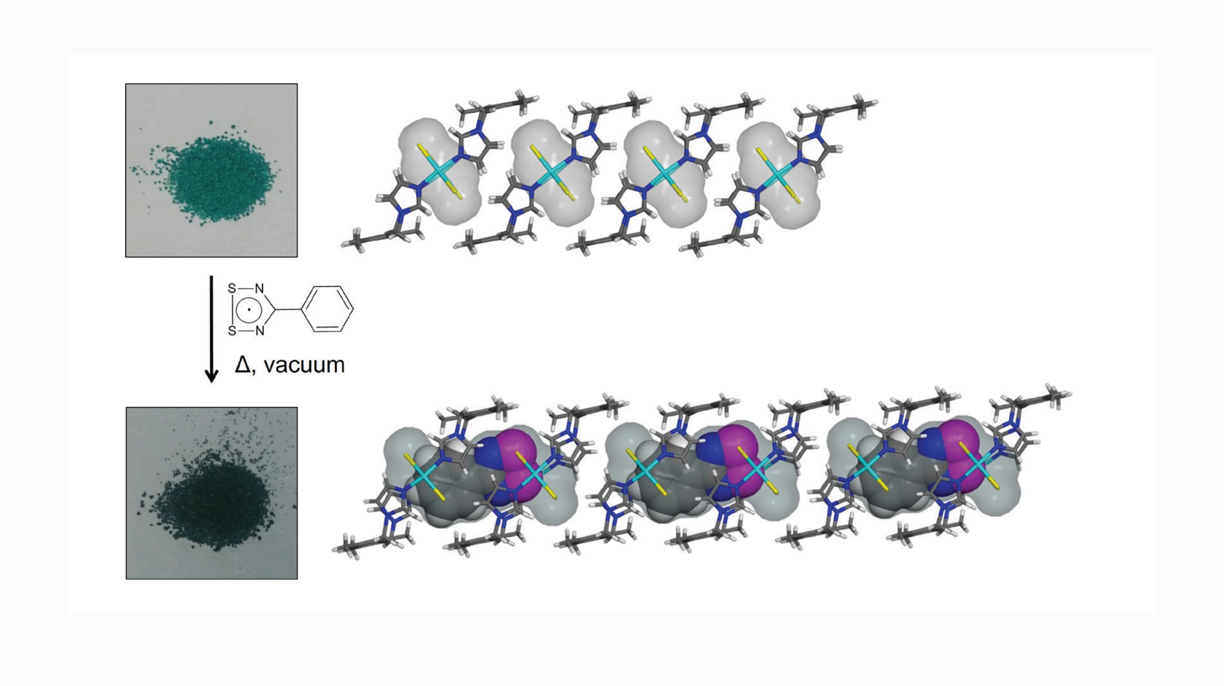


Figure 10: Exposure of a material containing discrete pores (above) to vapours of phenyl-1,2,3,5-dithiadiazolyl results in inclusion of the radical into the pores of the crystal (below).

Our most recent work on DTDAs, carried out in collaboration with Panče Naumov's group, investigated the magnetic behaviour of a mechanically flexible DTDA radical.[28] This radical grows long needle-like crystals that bend quite remarkably (Figure 11). We wanted to investigate whether the magnetic properties of this radical would change on bending. The polymorph we studied (the ß-polymorph of 4'-cyano-perfluorophenyl-1,2,3,5-dithiadiazolyl mentioned before) crystallises as a monomer. The unpaired electrons in the DTDA molecules in the crystal communicate with one another in such a way that the electrons are arranged in an antiparallel fashion in the crystal (antiferromagnetic coupling). At room temperature, this only happens to a small extent, and most of the electrons remain uncoupled and randomly oriented. The amount of spin in a sample (that is, the number of unpaired electrons) can be measured using EPR spectroscopy. Specialised EPR-imaging measurements showed that the number of unpaired electrons in our crystals changed on bending (and grinding), but not in the way we were expecting. We thought that bending might force the radicals to dimerise, and that the number of spins in the crystal would drop. However, we observed the opposite – on bending or grinding, the total number of spins in the sample *increased*. We explained this based on the intermolecular interactions. There are four interactions between the DTDA rings that allow the unpaired electrons on different molecules to communicate with one another. When these contacts get shorter, the communication gets better, and more of the electrons line up in an antiparallel manner (the antiferromagnetic coupling is strengthened).

But when these contacts get longer, the communication between unpaired electrons is weakened. This means the electrons remain randomly oriented, and overall, the spin count of the sample increases. When the crystal is bent, some of these contacts are lengthened or broken, and this explains the overall increase in spin that we observed on bending.

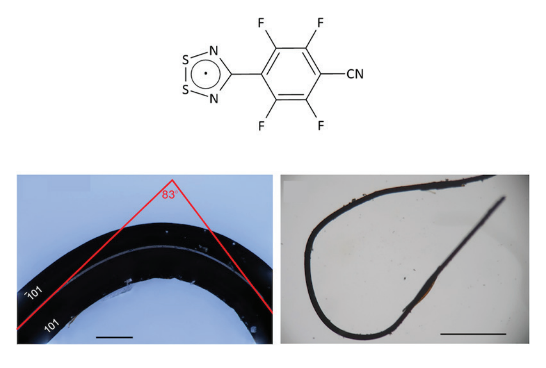


Figure 11: Crystals of the ß-polymorph of 4ꞌ-cyano-perfluorophenyl-1,2,3,5-dithiadiazolyl (above) bend plastically up to almost 360° (below).

What have we learned about DTDAs through our research? Our work has clearly shown that the crystal structures of DTDAs are strongly driven by electrostatic interactions between the molecules involved, and that this can be profoundly influenced by the substituent on the DTDA molecule. Understanding these electrostatic interactions can aid in the design of DTDAs where dimerisation does not occur in the crystal. Our charge density experiments have confirmed that the pancake-bonding dimerisation interaction is a unique interaction somewhere between a covalent bond and an intermolecular interaction – an 'incipient bonding' interaction. It is apparent that overcoming dimerisation is quite complex – a combination of approaches is required. We have also shown that DTDAs are useful building blocks for functional materials, and our work in this area is ongoing.

SALTS AND CO-CRYSTALS: THE CHARGED CHAPTER

The other important aspect of the research carried out in my group is the systematic study of organic multi-component crystals, which include both salts and co-crystals.

Systematic studies

We have approached the question of why salts and co-crystals crystallise the way they do by carrying out a number of systematic studies. One aspect of this work considered the importance of cation-anion interactions in the crystal structures of organic carboxylate salts. Previous work by Bond[29] had shown that the crystal structures of a group of organic salts (ammonium halides) could be rationalised according to the ring-stacking and laddering principle. In purely ionic structures, the electrostatic interactions are maximised by maximising the contact between cations and anions, forming a three-dimensional arrangement of ions. The rings, ladders and stacks observed in the crystal structures of materials containing organic substituents can be viewed as fragments of an ionic lattice, cut off from other cations and anions by the organic parts of the molecule. We showed through an extensive CSD study, coupled with an experimental study, that these principles also apply to the structures of ammonium carboxylate salts.[30] The size of the ionic fragment decreases with increasing substitution of the ammonium cation. The more organic substituents there are, the fewer cation-anion contacts can be made. This work shows that hydrogen bonding is not the only important factor in the crystal structures of these organic salts; it may not even be the dominant factor. Analysing the crystal structures of organic salts in terms of electrostatic interactions in this way has also given some insight into the properties of the salts – for example there is a relationship between the cation-anion motif observed in some salts and whether or not they are gelators. This relationship would not have been clear from considering hydrogen bonding alone. Analysis of the crystals of organic salts in this way gives new insight into structure-property relationships.

We have also carried out several systematic studies on hydrate formation in organic carboxylate salts. One of these studies led to the preparation of a particularly interesting material: the hemihydrate of 3,4-lutidinium pamoate.[31] Pamoic acid (Figure 12) is a pharmaceutically acceptable salt-former, which is why we were studying this molecule in the first place. It also has a quite awkward shape, and when it crystallises together with 3,4-lutidinium and some water, the resulting crystal has channels containing solvent molecules. Why is this interesting? Crystals with channels like this have the potential to act as porous materials – analogous to sponges with holes that are able to take up other substances (usually water in the case of a sponge). We were not able to remove the solvent from the channels in this crystal without the crystal collapsing, but we were able to exchange the solvent for a variety of other small molecules.[32] This could be done both by putting the crystals in liquid solvent, or by exposing the crystals to vapours of volatile molecules. Complete exchange was observed with 20 different molecules, including with volatile solids such as iodine (Figure 12). This occurred without the crystal losing its structure (single-crystal to single-crystal transformation), which allowed us to confirm that exchange had taken place using X-ray diffraction. For several of the solvents we studied, the exchange is reversible. For example, we can replace tetrahydrofuran (THF) in the crystal with chloroform, and then replace all the chloroform with THF to go back to the original state. In one experiment, we carried out five consecutive exchanges for different solvents before the crystals started to degrade. This is clearly an extremely robust host material.

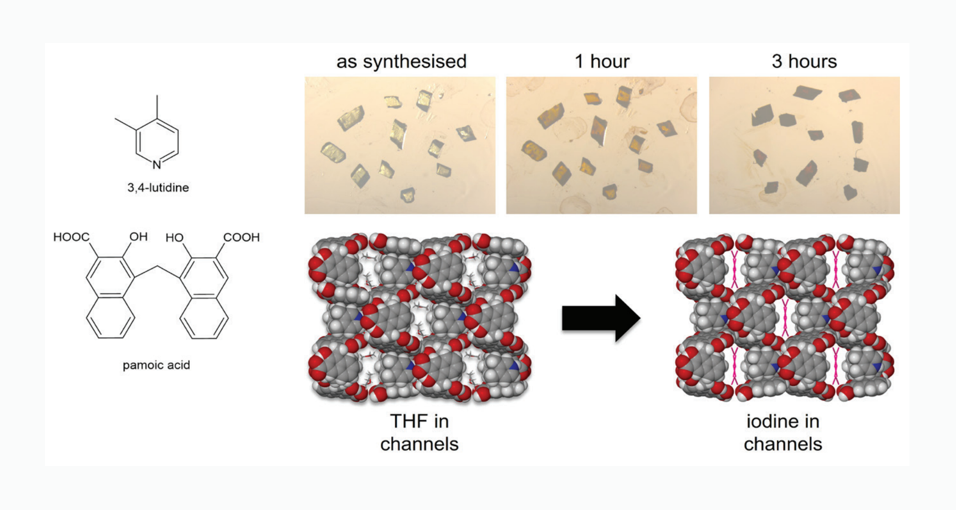


Figure 12: Single-crystal to single-crystal exchange of THF for iodine in a porous organic salt. The molecules making up the salt are shown on the left. The colour change of the crystals as the iodine enters the pores is shown above on the right. The crystal structures are shown below.

This material also takes up some solvents preferentially over others, in other words it is a selective host.[33] During experiments to study this selectivity behaviour, we made the interesting observation that when the pamoate framework is exposed to the vapours of solvents, these are included in the same ratios as if the crystals were immersed in liquid solvent. This happens despite the significant differences in mole ratios of solvents between the liquid and vapour phases due to the different vapour pressures of the solvents investigated. This may indicate that solvents in the gas phase are sorbed into the framework by the mechanism of first liquefying on the surface of the crystals in small amounts.

We think that one of the most important factors in crystallising a framework such as this is the awkward shape of the molecular building blocks involved. This had led us to look for other organic salts based on awkwardly-shaped ions that may be useful as porous materials. We have identified several other host materials, some of which also show selectivity for some guests over others on crystallisation.[34]

Non-solution-based methods of crystallisation: Mechanochemistry and sublimation

Mechanochemistry has been an important tool in our studies of organic salts and co-crystals. As mentioned above, mechanochemistry involves using mechanical energy to carry out chemical reactions. In our laboratory, we do these reactions either in a mortar and pestle or in a ball mill.

We have investigated a number of multi-component crystal systems using mechanochemistry. One of these is another system involving pamoic acid, which forms two different salts with a base called 1,4-diazabicyclo[2.2.2] octane (DABCO) (Figure 13). One of these salts has one anion (-1), one cation and two water molecules. The other has one anion (-2), two cations and three water molecules. It is possible to repeatedly convert between these two forms by adding the appropriate quantity of either DABCO or pamoic acid and water and grinding (Figure 13).[35] Facile conversion between stoichiomorphs in this way was considered quite rare, but we have since found it to occur when using mechanochemistry in several systems we have studied.

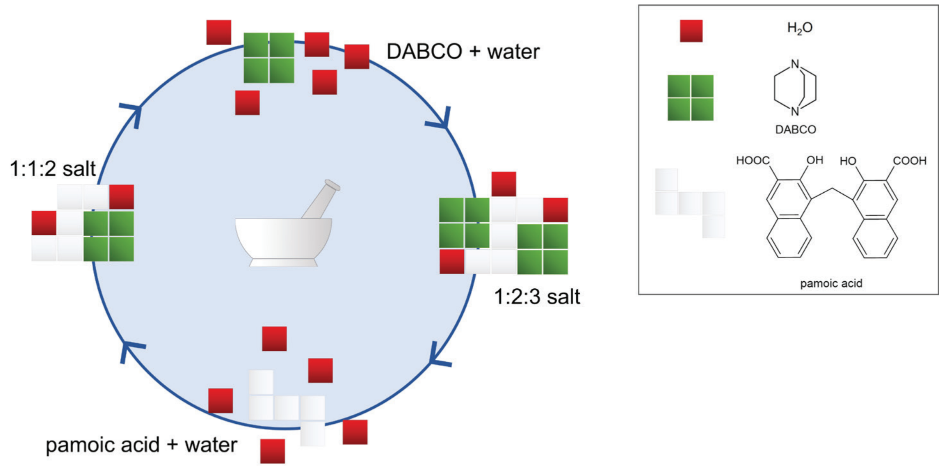


Figure 13: Schematic representing the mechanochemical conversion between the 1:1:2 and 1:2:3 stoichiomorphs of a salt hydrate by addition of the relevant component, followed by grinding in a mortar and pestle.

Recently, we have started investigating sublimation as a crystallisation method for multi-component crystals.[36] Sublimation is the process of going from a solid to a gas, or from a gas to a solid. We have used this method to grow crystals of DTDAs for many years, but only recently have we applied it to the other systems studied in our laboratory. Our experiments have shown that sublimation can sometimes give different forms of a crystal than those obtained from solution.

We have studied the competition between hydrogen and halogen bonding using both mechanochemistry and sublimation.[37] Halogen bonding is a strong intermolecular interaction, as strong as hydrogen bonding. It has been shown[38] that in experiments where there is competition between halogen bonding and hydrogen bonding, the solvent in which the experiment is carried out plays an important role. In these experiments, there is one molecule that could form an interaction with two different co-former molecules: with one it could form a hydrogen bond, with the other it could form a halogen bond. In polar solvents, the halogen bonding wins. This is because the solvent interacts with the hydrogen-bonding molecule, thereby blocking it from forming an interaction with another molecule. In non-polar solvents, hydrogen bonding is preferred. We thought that in the gas phase, which is essentially a completely non-polar environment, we would see hydrogen bonding in preference to halogen bonding. But when we actually did these experiments, we found that we saw both hydrogen- and halogen-bonded crystals. We then carried out a series of mechanochemical experiments to investigate the effect of solvent volume on the product obtained from these crystallisations. When there is a large amount of solvent, for example in a slurry, we see the same result as reported previously: polar solvents promote halogen bonding, while non-polar solvents promote hydrogen bonding. However, when the experiments are carried out with a reduced amount of solvent, by grinding in a ball mill with very small solvent volumes, the selectivity is far less pronounced. When all solvent is removed, in other words when the crystals are grown by sublimation, the preference for one interaction over another also disappears. This work highlights the key role that solvent plays in the outcome of a crystallisation experiment – a role that is often neglected.

We have also shown that crystals of organic salts can be grown by sublimation.[39] We have demonstrated this for several different salts. This is a surprising result, because it is generally believed that the interactions holding salts together in a crystal are too strong to allow them to sublime at the relatively low temperatures we can access in the laboratory. In all of these systems, we start with a neutral acid and a neutral base, and the salt is formed when a hydrogen ion (a proton) transfers from the acid to the base (Figure 14).

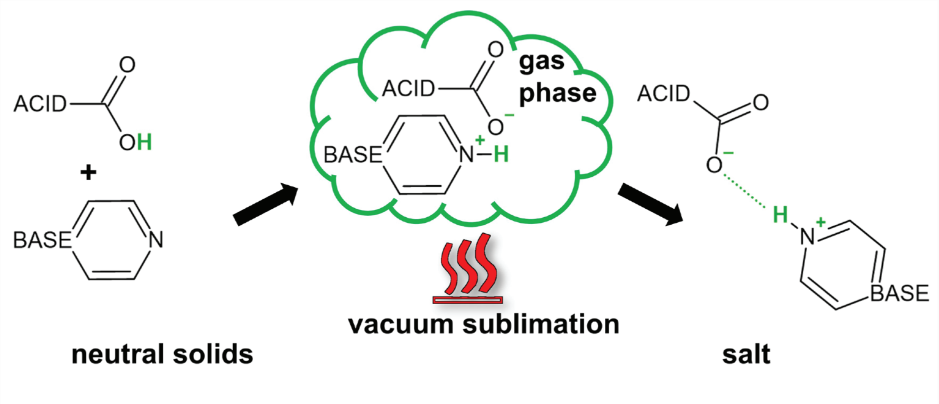


Figure 14: Transfer of a hydrogen ion, H^+, from a neutral acid to a neutral base results in two charged species (a salt). Our work has shown that this may be occurring in clusters of molecules in the gas phase during sublimation.

We believe that in these systems, the transfer of the proton from the acid to the base to form the salt is happening in the gas phase. This is considered to be energetically unfavourable, but we have done several key experiments that support our conclusion that it is occurring. The first was to show that we get crystals of the salt through sublimation even when the solid acid and base are physically separated from each other. In these experiments, the acid and the base molecules will only encounter one another in the gas phase. This means that either proton transfer happens in the gas phase, or the molecules deposit into a crystal as neutral acid-base pairs, after which proton transfer occurs. The second key experiment showed that we can re-sublime the salt, and that we get crystals of both the salt and the co-crystal from this experiment. This result also has several implications. It could be that cation-anion pairs sublime, and proton transfer within these ion pairs occurs in the gas phase to go back to the neutral molecules, which is why we see deposition of some co-crystal. Or, it may be that proton transfer happens before sublimation, and the neutral acid and base components sublime. If this was happening, we might expect to see a neutral form of the material with the same crystal structure of the salt, and this form should exist just before the crystals sublime. We carried out experiments in the environmental gas cell designed and constructed by Len Barbour, and showed that up to the temperature at which it sublimes, the crystals of the material under investigation are still a salt. We concluded that proton transfer does occur in the gas phase, but that this happens in clusters of molecules, which stabilise the ions.

This work has some important implications for how we think about the behaviour of organic salts. Usually, the cation and the anion are considered as separate units. But there is increasing evidence, from our work on sublimation and also from our other studies on organic salts, that in many cases the interaction between the cation and anion is sufficiently strong that the cation-anion unit behaves as a discrete supramolecule. It is this unit that sublimes, and this unit that crystallises.

Our most recent research supports this conclusion. We have been using both experimental and computational methods to probe what properties of molecules are important in growing good-quality crystals. We hypothesised that salts would grow better crystals than co-crystals, due to the favourable electrostatic interactions in the crystal. However, our results show very clearly that this is not the case. In fact, we are best able to explain our observations if we consider the crystal to be made up of supramolecular constructs containing two molecules (or ions) strongly hydrogen-bonded together. It is most useful to think of the supramolecule as being the building block of the crystal. The importance of considering the molecule as a whole, and in some cases even the supramolecule, has been a theme running throughout our work in crystal engineering.

CONCLUSION

My crystal engineering journey has been quite an adventure. It began because I liked using a Schlenk line, and enjoyed the challenge of solving and refining a crystal structure. Along the way I have encountered several heroes and a few dragons. I have become excited by problems as profound as the true nature of the chemical bond, and frustrated by issues as bizarre as why we cannot make radicals as easily in the winter. We have added some small pieces to the grand puzzle that is organic solid-state chemistry. And the best part of all is that I still feel like this is just the beginning.

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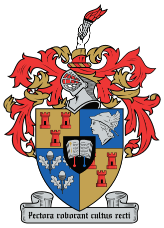

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