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**Supplementary Material**

Solid state NMR is important for organic molecular solids as it offers structural information complementary to that derived from X-ray diffraction and computational modelling methods, especially in cases of structurally and dynamically heterogeneous materials. In his talk, Yaroslav Khimyak, of the University of East Anglia, Norwich, UK (“Understanding structure of molecular organic solids: combining crystallography with insights from NMR”) opened the **NMR Crystallography** session, describing two such examples of this combined approach. Orotic acid exists in anhydrous and monohydrated forms. In the monohydrate, the orotic acid and water molecules are linked by strong hydrogen bonds in nearly perfect planar stacked layers. The layers are spaced by 3.1Å and are not linked by hydrogen bonds. Upon dehydration the XRPD and solid state NMR peaks become broader, indicating some disorder in the anhydrous form. However, the monohydrate stacking reflection (122) is maintained, suggesting that the anhydrous orotic acid structure is still arranged as stacked layers. XRPD can distinguish between three different anhydrous forms – each with different ordering.

The combination of structure prediction calculations with NMR is a powerful approach to investigate the supramolecular arrangement in gel fibres, and helps understand the relationships between molecular structure and gel formation. For example, a urea gelator such as 4-methoxyphenyl urea will form tape motifs whereas 4-nitrophenyl urea will not. This could not be ascribed solely to substituent effects on the H-bonding capabilities of the urea protons, and crystal structure prediction calculations indicated alternative low energy H-bonding between the nitro group and urea protons. This was supported by NMR spectroscopy and it was possible to relate the observed differences to interference of the head substituents with the urea tape motif, disrupting the order of supramolecular packing.

Karen Johnston, of Durham University, Durham, UK continued with a study of transition metal organometallic complexes using diffraction, 35Cl solid state NMR and first principles DFT calculations. Transition metal organometallic complexes are routinely used as homogeneous and heterogeneous catalysts in a wide range of polymerisation processes and organic reactions. The metal centre is usually the active catalytic site and probing it directly can provide important structural information. However, sometimes this is not feasible, and it can be more informative to probe the surrounding ligands, as is often done using 13C and 1H NMR. Chlorine is a commonly occurring ligand in many transition complexes and can act as a useful NMR probe. Solid state NMR spectra of nuclei such as 35Cl are highly responsive to subtle changes in molecular structure.

A series of complexes with commonly occurring metal-chlorine bonding motifs were characterised using PXRD, 35Cl solid state NMR spectroscopy, 35Cl nuclear quadrupole resonance (NQR) spectroscopy and first principles density functional theory (DFT) calculations of NMR interaction tensors. Static 35Cl ultra-wideline NMR spectra were acquired in a piecewise manner at standard (9.4T) and high (21.1T) magnetic field strengths using the WURST-QCPMG (Wideband Uniform Rate Smooth Truncation – Quadrupolar Carr-Purcell Meiboom-Gill) pulse sequence. The quadrupolar parameters are sensitive to structural differences and can easily differentiate between chlorine atoms in bridging and terminal bonding environments. 35Cl NQR spectra were acquired for many of the complexes which aided in resolving structurally similar, yet crystallographically distinct and magnetically inequivalent chlorine sites.

Ann-Christin Poeppler, of Warwick University, Coventry, UK (“Good Cop and Bad Cop – NMR, Crystallographic and Powder X-ray analysis of lithium and magnesium orotate hydrates.”) concluded, from her talk, that small molecules, particularly hydrated ones can present unexpected difficulties. For example, lithium orotate monohydrate may be used as a mood-stabilizing drug, while the corresponding magnesium salt (octahydrate) has shown potential in the treatment of cardiovascular diseases. In order to obtain more information on the close interplay between structure, interactions and reactivity, both compounds were synthesised from orotic acid and analysed by solid state NMR together with GIPAW (Gauge Including Projector Augmented Waves) calculations using software package CASTEP, powder diffraction (PXRD), Hirshfeld Surface Analysis (HSA) and infrared spectroscopy (IR). In the case of lithium orotate, data from all techniques are in good agreement, but magnesium orotate has proved difficult to study. Upon magic angle spinning (MAS) in the NMR spectrometer, changes in the sample were observed. PXRD under vacuum showed pattern changes over a ten hour period.

Phosphorus, in several allotropic forms, is emerging as a high capacity anode candidate for lithium and sodium batteries. To date, some composites of carbon with red or black phosphorus, or phosphorene have been investigated; however, the amorphous or poorly crystalline nature of these composites has hindered the understanding of phosphide intermediates and reaction mechanisms. Andrew Morris, of Cambridge University, Cambridge, UK presented his work on “High throughput crystal structure prediction: using NMR and DFT to design phosphorus electrodes for Li and Na-ion batteries.”

High-throughput computation and the *ab initio* random structure searching method (AIRSS) has been used to predict the structure of lithium and sodium phosphides, followed by calculation of the NMR chemical shielding using DFT. Specific ranges in the calculated shielding can be associated with specific ionic arrangements, results which play an important role in the interpretation of NMR spectroscopy experiments. The Inorganic Crystal Structure Database (ICSD) has been used as a source of suitable structures. Sets of atoms placed at random positions within a unit cell have been subjected to energy calculations and then their positions allowed to move (relaxation) in order to minimise the energy, and the process repeated. Suitable structures include Na5P4, Li4P3, NaP5 and Na4P3.

In a **Chemical Crystallography Group** session entitled “Tips, tricks and trials”, four speakers provided talks on diverse topics. First, David Allan of the Diamond Light Source, Chilton, UK spoke on growing crystals at high pressure.

Variation of the fundamental thermodynamic variables of temperature and pressure can reveal a variety of physical phenomena in materials, such as the alteration of thermal conductivity, changes in optical, electrical and magnetic properties, and can lead to profound structural change via phase transitions. The parameter of temperature can be used to alter the thermal energy of the atoms within a material and is routinely applied in many experimental studies over the range of several orders of magnitude both above and below ambient temperature. Hydrostatic pressure, however, tends to be underutilised as a thermodynamic parameter although it enables the variation of atomic distances and atomic potentials at constant thermal energy and, in this sense, it can be considered to be an extremely “clean” probe of the crystalline state. In combination, temperature and pressure allows the phase mapping of a material to be conducted and in the Earth and Planetary Sciences, for example, it is essential for research on minerals at depth to be conducted at simultaneously high pressure and temperature.

Ice, it has been found, has no fewer than 16 different structural phases, and the structure determination of some of these phases is amenable to single crystal diffraction techniques, as single crystals can be grown directly from the melt at high pressure. These methods can be easily translated to the study of the phase behaviour of other small molecules that are either liquids at room temperature or have a sufficiently low melting point. The application of pressure can also cause small molecule systems to precipitate from solution. This is particularly useful for the formation of otherwise inaccessible polymorphs, when the material will dissociate before the melting point is reached.

High pressure diffraction experiments have been undertaken using a modified Merrill-Bassett miniature diamond anvil cell, with the inclusion of tungsten carbide backing seats with Boehler-Almax cut diamonds. These have replaced the previously used beryllium seats and modified brilliant-cut anvils. This has removed troublesome beryllium powder lines from diffraction images, whilst maintaining the pressure range and opening angle of the original design. One hydrostatic medium used was methanol: ethanol (4:1) which is still liquid at 100kBar, and the medium contains the crystal under study and a ruby chip. Under illumination with green laser light, a change in pressure causes a shift in the ruby fluorescence which is monitored by a ruby fluorescence spectrometer. The temperature is first raised to dissolve the material and then lowered to allow it to crystallise. After a few cycles this results in acceptable crystals, and the difficulty then is in centring the crystal for the X-ray beam.

Patrick Shaw Stewart of Douglas Instruments, Hungerford, UK spoke on Microseed matrix-screening (rMMS): introduction, theory, practice and a new technique for membrane protein crystallization in Lipidic Cubic Phase (LCP).

Crystallization of macromolecules uses a set of experimental techniques aimed at producing crystals suitable for structure determination. Advances in molecular biology and X-ray data collection methods have simplified the task by providing pure proteins in large quantities and by utilizing smaller crystals, respectively. Crystallization methods have also improved over the years through the introduction of standard screens and the use of robotics which allows the screening of a large number of crystallization conditions in a miniaturized format, reducing the amount of protein needed. Another major development has been the application of various microseeding techniques. Seeding exploits the hypothesis that the optimal conditions needed for crystal nucleation and for crystal growth can be quite different. The seeding technique has been extended by the microseed matrix screening approach (MMS) in which seeds are systematically transferred into new conditions to promote crystal growth, and the screening process has been revolutionised by combining MMS with automation.

The random microseed matrix-screening (rMMS) approach to protein crystallization involves adding seed stocks containing crushed crystals to random crystallization screens. The method has three important advantages: (i) it picks up additional crystallization conditions that would not be found by conventional screening, including conditions that are chemically unrelated to the conditions in which the seed crystals were obtained, (ii) it reduces the need for optimization, with diffracting crystals being more likely to appear spontaneously than in conventional screening, and (iii) by diluting the seed stock, the number of crystals per drop can usually be controlled. These three advantages are the result of increasing the chance that crystals will grow in the metastable zone of the phase diagram. Since the method requires little preparation or planning, is simple and can be automated, it dramatically increases the productivity of a typical structural biology laboratory.

Seed crystals were grown directly in LCP and, as with conventional rMMS, a seeding experiment was combined with an additive experiment. The new method was used with the bacterial integral membrane protein OmpF, and it was found that it increased the number of crystallization hits by almost an order of magnitude; without microseeding one new hit was found, whereas with LCP-rMMS eight new hits were found.

Natalie Johnson, of Newcastle University, UK provided the final talk of the session entitled “The integration game: data processing for small crystallography.” There are many reasons for inadequate structure solutions from single crystals, including poor crystal quality, unoptimised experimental setup, and insufficient data collection. However, there are circumstances where data that could be expected to be of high quality give unacceptable structure refinements. This can still hold where data sets were collected with small beams from high quality crystals and produce optically good diffraction. One example of these problematic data sets is prevalent when reflections are present that have small point spread functions with respect to the pixel size of the detector. While there has been much research into optimal data collection strategies, the effect of the processing strategy on the final structure refinement appears to have been less investigated. Several different data processing programs, both commercial and not-for-profit, have been investigated for data integration. Inside each program, both profile fitting (PF) and simple summation (SS) integration algorithms were utilised. Data sets analysed were collected on a pixel hybrid detector using synchrotron radiation at Beamline I19 at Diamond Light Source. The reduced data were then refined using SHELX suite, applying the same methods to each data set.

It was found that all individual packages gave reasonable results if interpreted separately, as well as giving good agreement of unit cell parameters between different methods within each package. However, there was disparity between different software suites, including statistical differences between reported unit cell sizes. SS integration algorithms tended to yield better results than PF methods, and auto-processing, whilst often successful could be problematic. Default settings in software packages may not be the best way to process data, and in many cases the settings chosen by an experienced user will prove to be more effective.

The late afternoon session of the **Physical Crystallography Group** entitled “Modelling crystals and crystallographic data” was opened by Carole Morrison, of the University of Edinburgh, UK with a talk entitled “Frustrated MOFs: insight from modelling when crystallography is stumped.”

Metal-organic frameworks (MOFs) continue to attract high interest from the scientific community due to their promise in fields of guest-specific gas sorption, separation, drug delivery and catalysis. However, these structurally versatile materials often have soft mechanical properties that distort or even collapse upon application of temperature, shear stress or hydrostatic pressure. This poses problems for the sintering and pelletizing steps required to shape MOF powders into industrially useful morphologies.

Zr-UiO-type MOFs with unsaturated linker units (e.g. biphenyl-4,4’-dicarboxylic acid, UiO-67 and 4,4’-diazene-1,2-diyldibenzoic acid, UiO-abdc) yield unexpected benefits. The linker units were chosen to study the effects of post-synthetic modification of an MOF material, but the resulting unmodified framework displayed an unprecedented response to the effects of high pressure, with the unit cell (for UiO-abdc MOF) compressing by less than 1.2% at pressures of up to 5 GPa in the presence of a methanol pressure-transmitting medium. While high pressure diffraction data could be collected, interpretation proved difficult. The structure is dominated by the heavy atom core Zr6O4(OH)4 and the diffraction pattern conforms to the cubic space group *Fm*3*m*. Forcing these space group constraints throughout the unit cell results in structural oddities. The linkers are made to bisect mirror planes, inducing occupational disorder. In order to understand the local structure, *ab initio* molecular dynamics calculations were applied to the crystallographic model which revealed why the material was so good at withstanding high pressures.

Young’s Modulus and hardness measurements were made on evacuated crystals of both Zr-UiO-67 and Zr-UiO-abdc MOFs, confirming that the latter structure is more flexible and the former more rigid. It is clear that the bowed ligand (UiO-abdc) offers greater resilience to external pressures, and that to make and characterize frustrated MOFs requires combined studies of structure, dynamics and mechanical properties.

Matt Cliffe, of the University of Cambridge, UK (one of two ICDD Bursary recipients (see picture) continued MOF chemistry with his talk “Correlated defects in Hafnium and Zirconium MOFs”.

Defects are crucial to the chemistry of metal-organic frameworks (MOFs) with recent studies demonstrating the prevalence of defects, especially ligand vacancies (missing linkers), in MOF chemistry. These defects may improve sorption properties, catalytic activity and ionic conductivity. In many functional materials, it is not just the presence of defects but their interactions and correlations that determine their properties. Correlated defects can be accommodated in an MOF, by including “modulators” (ligands such as trifluoroacetic acid (TFA) able to bind to clusters but not form part of the network structure). Using a combination of anomalous Hf-K edge X-ray diffraction, total scattering and electron diffraction measurements, it is clear that these defects are not just of ligand vacancies, but also include Hf cluster absences.

Just as in oxide frameworks, the presence of defects leads to a huge variety in the range of structures formed. The formation of these new phases depends not only upon the concentration of defect-promoting modulators, but also upon the reaction temperature, and it evolves over time. Control over the defects allows us to, in turn, tune the unusual thermomechanical properties of UiO-66(Hf), in particular allowing control over its very large isotropic negative thermal expansion.

Paul Saines, of the University of Kent, UK concluded the session with his talk “Probing the local magnetic structure of a magnetocaloric framework, Tb(formate)3.”

Exploring local magnetic order is crucial to understanding the interaction between topology, electronic structure and magnetic coupling. The magnetic structure and properties of Tb(formate)3 have been studied in both its antiferromagnetic and paramagnetic states. Its local structure has been examined using new Reverse Monte Carlo techniques for analysing diffuse magnetic scattering from powder diffraction. Even in its antiferromagnetic state, below 1.7K, complete long range order is frustrated due to antiferromagnetic interactions between ferromagnetic chains on a triangular lattice. More importantly, in the paramagnetic phase there are strong 1D ferromagnetic correlations with indications that these are retained to an order of magnitude above its Néel temperature. The 1D ferromagnetic interactions in Tb(formate)3 leads to a larger magnetocaloric effect than its related antiferromagnetic Gd analogue, in the low applied magnetic fields at >4K practical for a magnetocaloric device. One outcome of these studies is that short range magnetic order may be probed when only powders are available.

Ivan Marziano of Pfizer Worldwide Research & Development, Sandwich, UK, was the opening speaker in a joint **Chemical/Industrial Crystallography Group** session entitled “From amorphous to crystalline”. His talk entitled “The pursuit of the structure-function relationship in pharmaceutical crystallisation” made reference to the “Materials Science Tetrahedron” (processing, properties, structure and performance) which provides a multidisciplinary framework within the pharmaceutical sciences and includes: the use of modelling tools to identify the “canvas” of physical properties available for a given material, and the process and product design which consider the implicit properties of the materials involved. Crystallization plays a key role in delivering materials with the desired physical properties within the range allowed for a given crystal structure.

The success of a given drug product depends upon its stability, efficacy and quality, and the drug product process has to be robust, reproducible, economic and must conform to regulatory requirements. Inconsistent dissolution of a drug may be caused partly by the milling process. Milling will alter the ratio of hydrophilic to hydrophobic crystal faces, and the extent of milling will determine just how much of the original surface chemistry is retained, and will influence the dissolution profile. Water adsorption calculations are used to quantify the affinity of the dominant crystal surfaces. Removal of impurities in the product is an essential part of the process, and decisions have to be made concerning the timing of the impurity purge. Interaction (between product and impurity) energy calculations are required in order to estimate the purge factors for process impurities and to identify alternative purge points. Where possible, however, upstream control of impurities, rather than purge, is the preferred strategy.

In his talk, Jerome Wicker (Oxford University, UK) attempted to answer the question “When will it crystallise?” The ability to predict the tendency of a particular material to crystallise is of significant use in both research and industrial processes. Knowledge of whether or not a material is likely to crystallise can help to prioritise recrystallization experiments and can be used to predict chemical modifications to increase the chances of crystals growing. The crystallinity of a pharmaceutical material can also change physical properties of the solid form, such as its solubility and hence bioavailability of the drug in the body. Therefore it is useful to be able to classify a particular substance as crystalline or non-crystalline.

A promisingly low error rate has been achieved with support vector machines (SVMs) on a drug-like set of test molecules using data extracted from the Cambridge Structural Database (600,000+ crystalline substances) and the ZINC database (a database of 21 million “purchasable” compounds, some of which are crystalline). This model revealed that size and flexibility are key factors influencing the ease of crystallisation and it has been extended to include descriptors which capture 3-dimensional information about the molecules, such as the number of rotatable bonds. The overall prediction accuracy was 92%.

Colan Hughes, of Cardiff University, UK described the use of *in-situ* NMR to inform us about amorphous intermediates in crystallization processes. Solid-state NMR spectroscopy has been used in the past to observe the appearance and polymorphic evolution of crystals forming from cooling, supersaturated solutions. A combination of liquid- and solid-state NMR spectroscopy has been used to acquire simultaneous information on the solid and liquid phases during crystallization (so-called CLASSIC NMR) as well as examining co-crystallization, systems crystallizing from the melt, and crystallization kinetics. A number of crystalline intermediates have been observed, but now an amorphous intermediate has been detected by the same solid-state NMR spectroscopy used to observe crystalline forms.

New phases have been discovered of a co-crystal of urea/1,10-dihydroxydecane, and two new polymorphs of methyldiphenylphosphine oxide. *In-situ* NMR experiments have been performed on the enantiomeric and racemic forms of menthol. With the racemic form (DL-menthol), using 13C NMR, an amorphous phase exhibiting broad peaks appears and crystallization of this phase takes approximately 15 min. to complete. During this time a mixture of the two phases is seen, the first instance of an amorphous phase being observed as an intermediate. Periodic density functional theory (DFT) can be used to calculate NMR chemical shifts from crystal structures, but no method exists as yet for amorphous materials.

The session was closed with a talk by Christopher Jones, of Durham University, UK, entitled “Lamellar urea tape networks as building blocks for crystals and gels.”

Molecules containing two or more urea (-NHCONH-) functional groups often exhibit an exceptional capacity for gel formation, due to their tendency to form highly anisotropic networks of hydrogen bonding tape motifs. Single crystal studies of one series of sterically hindered bis-ureas display seven network topologies. Two-dimensional networks are common only among the bis-ureas derived from primary amines, which account for all observed instances of gel formation. Only some 2-D networks are compatible with lamellar aggregates and form gels. Powder diffraction studies indicate that gels of these compounds lack long-range order but are not totally amorphous, in that they exhibit a locally ordered lamellar structure.

Molecular dynamics simulations confirm that such monolayers may, in isolation, afford fibrous aggregates through spontaneous scrolling about the tape axis, provided that they are facially asymmetric and exposed to a solvent environment that lowers the energy of the potential for three-dimensional growth. The simulated outcome of folding – an unbranched radially isotropic fibre with a diameter dictated by the minimum lamellar curvature – is consistent with scanning electron micrographs of the dried gels. Helically twisted lamellae may also be possible, however, if self-assembly involves tapes oriented along non-orthogonal axes.

Another joint session between the **Industrial and Chemical Crystallography Groups** carried a novel title “Would you publish this?”

Iain Oswald, of the University of Strathclyde, Glasgow, UK described the problems and frustrations encountered with attempts to solve what should be a simple crystal structure in “Pharmaceuticals…I thought they were meant to make you better!?!”

Polymorphism of pharmaceutical materials has been one of the major areas of research for structural chemists. At the heart of this research is the drive to understand, predict and control the polymorphic forms such that the physicochemical properties may be exploited to greater effect, e.g. solubility, compaction properties etc. Sometimes the unexpected occurs, and the euphoria of finding a new polymorphic form quickly dissipates, being replaced by a gritty determination to solve the most challenging of crystallographic problems.

Phenytoin is used as the sodium salt as an anticonvulsant for the treatment of epilepsy. The structural solution of the ambient temperature crystal structure was not as straightforward as one might have expected for a small molecule, and it becomes even more complex as it is cooled. At ambient temperature an orthorhombic Pna21 structure is observed with Z’=1 but below 190K a phase transition takes place to a larger cell (P212121) with a 7-fold increase in one direction (a = 13, b = 15 and c = 44Å). Closer inspection of the diffraction pattern suggests that this is an example of a modulated structure where the position of the phenyl rings varies along the 44Å axis.

Susan Lea, of the Sir William Dunn School of Pathology, Oxford University, UK in her **Biological Structures Group** plenary talk illustrated the use of hybrid structural methods to study the protein complexes required for export of proteins from bacteria.

An understanding of the way in which an invading pathogen interacts with its host at a molecular level is an essential aid to understanding the nature and extent of disease processes. Central to this approach has been the use of X-ray crystallography to determine the structures of individual host or pathogen components and of important host-pathogen complexes. Electron cryo-microscopy has been used to reveal the architecture of the major component of the type III secretion system export apparatus, a membrane embedded nanomachine designed to export specifically targeted virulence factors from the bacterial cytoplasm. Employing a combination of X-ray methods to probe detailed interaction chemistries, and electron cryo-tomography to capture dynamic multi-protein systems, the molecular basis of host pathogen interactions is revealed in ever greater detail.