

40th Anniversary Conference 2009 6-8th September Wills Hall, Bristol University

The 40th Anniversary Conference 2009 of the BACG was held in Wills Hall in the University of Bristol. Bristol was the location for the first annual conference held in 1970, and also home to Sir Charles Frank FRS, first president of the Association, who made significant advances in the theoretical treatment of crystal growth. To celebrate this momentous event, a reception was held to honour some of the key British scientists who have led the field of crystal growth and crystallisation in the UK over the last 40 years. Lifetime membership was conferred upon **Frank W Ainger, Peter Dryburgh, John Garside, Michael Hart, Donald Hurle, Bruce Joyce, Brian Mullin, and John Sherwood** in recognition of their contributions to crystal growth science both within the UK and internationally as well as their individual contribution to BACG during the last 40 years. A commemorative copy of the history of the BACG, written by Don Hurle was presented to all delegates



Some of the Honoured Members with Chairman Ivan Marziano

The conference was opened by **Prof Guy Orpen**, Pro Vice Chancellor at Bristol University and the opening presentation from **Don Hurle**, described 40 years of BACG, from its inauguration in 1969 when Charles Frank was elected as the first

president. Many famous and familiar names were included such as Bill Bardsley, Peter Bennema, and Bryan Cockayne and many anecdotes were included such as the 1986 conference dinner at York, which was held in the York National Railway Museum, with tables in between the rolling stock, and a brass band in residence on the train turntable! The influence of the cold war, and its end, on the crystal growth industry was discussed and the rejuvenation of the organisation under the chairmanship of John Sherwood in the 1990s described. The influence of the pharmaceuticals industry means that crystallisation science has diversified from purely single crystal growth and the advent of new techniques and technologies has led to expansion into other areas. This interdisciplinary field now boasts a vibrant and varied community, and continues to face new challenges.



Don Hurle, giving a lively account of BACG History over the last 40 years.

Symposium A: Nucleation Across the Disciplines

Alex Chernov delivered a talk addressing the particular areas of crystal growth, which in his experience require a better fundamental understanding. He discussed the suppression of step bunching stability through the use of turbulent flows. His example system was the (101) face of KH₂PO₄ (KDP) crystals growing from turbulent solution. He found that turbulent flow reduces step bunching stability via strong mixing within the viscous boundary layer. Eddies produced in the boundary layer as a result of the high flowrate, cause an increased diffusivity in the layer. This increased diffusivity is greater than the static molecular diffusivity, so that upstream growth is not linked to downstream growth, thus limiting the formation of bunches. He also discussed the behaviour of weakly fluctuating steps and faces in solution and whether the Gibbs-Thomas capillarity shift is applicable, using Ferritin as an example. The problem of how nanocrystallites achieve mutual orientation to form ordered conglomerates was addressed. It was suggested that the alignment could be due to anisotropic van der Waals interactions. Lastly, the formation of KDP crystals for use in laser nuclear fusion highlighted the contribution of crystal growth scientists to the goal of sustainable energy production.



Delegates at the opening of the conference

Steve Mann addressed the formation of complex organic-inorganic nanostructures due to self assembled templates and inorganic nucleation. Three basic nucleation based routes were discussed; these were supermolecular wrapping, nanoscale templating and nanoscale incarceration. The crosslinking of block copolymer micelles was given as an example of supermolecular wrapping, more specifically calcium phosphate mineralization around micelle shells. Sol-gel replication of block copolymer cylindrical micelles was given as an example of nanoscale templating. It was shown that this method could be used to control deposition so that there is different functionality along the length of a cylindrical nanocrystal. The formation of iron oxide nanoparticles contained within ferritin, was given as an example of nanoscale incarceration. Experiments using water-in-oil microemulsions as confined reaction media for nanoparticle synthesis were presented. It was found for the AOT, Ba^{2+} , SO_4^{2-} systems, that changing the ratio of $Ba^{2+}:SO_4^{2-}$ concentration gave different results. For a ratio of 5:1 particle crystallization is initially arrested, but the barium rich micelles interact resulting in mesocrystals.

Kate Nicholson presented a talk entitled "Beating Ostwald's Rule of Stages" in the 'Nucleation across the Disciplines' symposium. Kate discussed a variety of systems that do not obey Ostwald's rule of stages, highlighting the group's current research. They currently focus upon using microemulsions for the reliable production of the thermodynamically stable form of a polymorph. This process was successfully tested with the systems ROY, a highly polymorphic material and glycine, a much studied compound.

Luci De Matos showed that ultrasound sonication can be used to decrease the crystallization time of the metastable polymorph and the subsequent transformation time from a metastable polymorph to a stable polymorph. L-glutamic acid was used as an example system because it has two polymorphs (metastable α and stable β) and the α form is known to transform to the β form by a solution mediated transformation. Sonication was initiated at the nucleation stage and the polymorphic makeup of the solution was monitored using *in-situ* wise angle scattering. This system allowed the time evolution of the polymorphic mass fractions to be monitored. Regardless of whether sonication was used the following stages were identified. In the first phase the α form crystallized until the second phase was initiated by the nucleation and growth of the β form. During this second phase the α form began to dissolve at the

point where the growth of the β form caused the solution to be undersaturated with respect to the α form. The final and third phase was initiated once all the α form had dissolved. The β form then continued to crystallise until the solution had ceased to be supersaturated in respect the β form. The use of sonication was shown to reduce the time period for all three phases. Therefore, the use of sonication can be used to favour the stable β polymorph of L-glutamic acid.

Professor **Roger Davey** began his keynote lecture by citing his relationship with Bristol. He recalled his time in Bristol during his undergraduate work on spiral growth in 1969. He outlined the importance of kinetic studies during that time, its diminished interest during 1980 and 90s with the advancement in crystallographic databases and again flourishing research for kinetics of nucleation and crystallization in the present time.

He mentioned some early work on glycine and his current favour for studying this compound in order to illustrate the conversion of two polymorphs α and β glycine. The solution crystallization produces only the α form which finally converts to the stable β form. He mentioned some researchers who used tailor made auxiliaries to get the required form and this principle was utilized to produce the β form with the addition of melonic acid, however the growth of selective form cannot be explained. Roger emphasized the importance of understanding and studying the kinetics of crystallization in these circumstances.



Roger Davey talking on polymorphism

He also discussed the case of Para Amino Benzoic Acid in which two polymorphs are known: α and β . The transition temperature is $\approx 25 \text{C}^{\circ}$. The solution crystallization produces the α form and that transforms to the β form later on. In this particular case the crystallization of the α form is favoured by its carboxylic acid dimer formation in solution. He finally gave the plausible explanation of selective crystallization of an α form of glycine from solution and its conversion into the β form by growth rate versus auxiliary (melonic acid) addition profiles of different faces of these two forms. The growth rates of two axis of α glycine were higher than the axis of β glycine and with the addition of melonic acid preferential crystallization of β glycine was possible.

The **2009 Young Scientist Award** was presented to **Andrew Bond**, of the University of Southern Denmark. X-Ray crystallographer, Andrew, discussed his work inspired by a 2005 *J. Am. Chem* paper by Vishweshwar *et al.* This paper claimed to have determined the structure of the elusive aspirin form II, however the group were concerned by the very high R-factors given. The presence of another polymorphic form of aspirin had long been speculated in the literature. The group showed in their 2007 paper that aspirin crystals could contain a disordered layer packing sequence, featuring domains of both polymorphic forms plus a less ordered region. These stacking faults were determined to be the cause of the poor R-factor reported in the Vishweshwar paper. This 'intergrown' form displays a lowered melting point and bulk dissolution rate, and it is not entirely reproducible. This form only grows from synthesised, and not commercial, aspirin. This was determined to be due to the presence of aspirin anhydride in the synthesised sample.

The **2009 Annual BACG Lecture** presented by **Margaret Sax** of the British Museum was entitled *Crystal Skulls: The Growth of an Industry*. In the late 19th Century the British Museum separately acquired two crystal skulls, both of which were catalogued as originating in ancient Mexico. By the 1990's these were joined by many more in collections housed around the world. Over the years both the authenticity of the quartz sources and the tool working techniques employed was brought into question. Initial inspection of the skulls used optical microscopy to examine the surface for tool marks. Then, to enable closer inspection without causing damage to the artifact, silicon moulds were made of the skulls. These moulds were then subjected to SEM examination, allowing individual marks to be imaged. It was determined from these images that due to the shape of the incisions the skulls were carved using rotary wheels, not hand tools as were used by this ancient society. It appears the skulls were mostly made in the late 19th Century in Mexico as 'fake' Aztec artefacts, spawning the industry referred to in the title.

Symposium B: Industrial Crystallisation

Kostas Saranteas was keynote speaker in the Industrial crystallisation symposium, giving an interesting talk entitled "Industrial Crystallisation Process Development: Timelines and Drug Product constraints Impact". Kostas discussed the high probability of drugs failing before they are launched and the various reasons why they fail, for example, lack of efficacy, toxicity, adverse effects in man and the main factor, poor pharmaceutical properties. With this in mind, the process of product development is investigated at an early stage, without focusing on process optimisation, due to the high potential of drug failure. Kostas also mentioned that when a drug does develop further the drug product and substance teams need to work closely together, rather than in parallel, to manage the ever-changing purity and properties associated with the product and illustrated this with a case study. A timeline for drug development was also presented, highlighting the increasing need for process engineers to be involved at all points throughout drug development.

An excellent presentation was given by **Nick Henley** entitled "Control of Solvate Formation in API Crystallisation" which was awarded the CrystEngComm prize for best oral presentation. Nick discussed the use of ternary phase diagrams for aiding in the development and scale up of robust API crystallisation processes. It is commonly observed in the pharmaceutical industry that an API has a tendency to crystallise in a solvate form, which is an undesirable product in many cases. In order to avoid these solvates a clear understanding of the solid state behaviour of the API is required and analysis of the phase boundaries can enable the non-solvated form to crystallise. Dr. **Simon Black** from AstraZeneca, gave an inspiring keynote presentation with the title "Solubility of small organic molecules". The importance of solubility data was discussed for crystallization studies and the design of crystallisation processes. In principle, the variation of solubility with temperature determines the feasibility of cooling crystallisation and influences the accuracy of solubility measurements. The variation of solubility with temperature was measured and compared with rule of thumb – "solubility doubles every 20 °C", which was proposed last year on the basis of a set of eight pharmaceutical compounds. After comparing with two larger data sets, of eighty and fifty solute/solvent pairs respectively, a restatement of the rule is grounded in theory, more accurate and more useful. The consequences for the measurement, analysis and representation of solubility data was also shown followed by the implications for the modeling of solubility.

M. Eicke from Max Planck Institute for dynamics of complex technical systems, Germany, presented "Polythermal coupled preferential crystallisation (PCPC): An and efficient way for the resolution of conglomerates". Preferential easv Crystallisation (PC) as a process to yield pure enantiomers from a racemic solution has been shown to be an attractive method for conglomerate forming systems. When carried out in simple batch mode under isothermal conditions, it is possible to obtain highly enantiopure crystals, after a supersaturated metastable solution has been inoculated with homochiral seed crystals of the preferred species. An alternative to the simple batch is where in two tanks one of both isomers is crystallising simultaneously. By exchanging particle free solution between the two vessels, the supersaturation of the respective unseeded enantiomer is decreased, whereas the driving force for crystallisation of the seeded species is raised. This mode of operation has been investigated theoretically and experimentally, showing significant increased product yield and purity compared to simple batch. The polythermal operation was also introduced to PC to maintain a suitably high supersaturation.

Other interesting issues regarding polymorphism, sonocrystallisation, and impurity effect on crystalisation were discussed by several researchers. Woo-Sik Kim (Kyunghee University, Korea) discussed the new way of designing polymorphs of antiviral agent adefovir dipivoxil in crystallisation using ionic liquids. Different thermal conditions were applied leading to different polymorph produced. The decomposition process and the thermal stability of various polymorphs were confirmed by XRD, FT-IR and DSC. An approach for in situ monitoring and control of the polymorph purity of sulfathiazole in batch cooling crystllisation was highlighted by Mohd R. Abu Baker (Loughborough University). The application of PAT tools including FBRM, ATR-UV/Vis was corroborated for this purpose. A hypothetical operating profile of the polymorhs was shown and the solution concentration was controlled in a in a region to realize purity control. Olga Narducci (University College London) discussed the impact of ultrasound on crystal habit, particle size and supersaturation during the continuous crystallisation of Adipic Acid. Sonication results in the production of a more uniform particle size distribution, smaller mean particle and reduced agglomeration, indicating its potential in controlling crystllisation process and chemical entities. The last speaker of the symposium was Sendhil Poornachary (Institute of Chemical and Process Engineering Science, Singapore) who focused on counteracting the inhibitory effect of impurities on crystal growth of an agrochemical active ingredient. After the investigation of effect of three reaction by-products on the crystal habit modification and its mechanism, new additives were selected based on structural correlation with the controlled impurities, improved the habit of product crystallized.

Symposium C: In situ Crystal Growth

Professor **Goran Ungar** talked about the challenge of achieving perfect monodisperse polymer synthesis. So far, the only method proven to work is to add the monomers one by one by normal chemical synthesis – which is hugely tedious. From this, it is necessary to understand the structure of these long polymer chains to better the synthesis techniques.

The structure of lamellar polymer crystals was then discussed. Polymer chains fold over themselves – as was shown in a 1 μ m crystal, where the chains were arranged in 10nm folds. Melt-crystallised polymers were shown to have both crystalline and amorphous areas, arranged in stacks. The chains in the amorphous phases were twisted and tangled. This was known from SEM images taken by Grubb and Keller.

Proper analysis was carried out by synthesising the molecule $C_{390}H_{782}$ as a totally straight-chain alkane, then crystallising the alkane from solution and from the melt, and analysed by X-Ray and neutron diffraction. From solution, at a low T_c value, the chains are folded just once. But crystallisation from the melt gave many different folding patterns, as well as non-integer folding, where molecules formed amorphous-type areas in the crystal, despite the monodispersity.

A further case study was discussed using the alkane $C_{246}H_{494}$. Variation of the temperature caused many different morphologies to be found in the crystals. Growth rate minima were found when either temperature or concentration was varied. Reducing both temperature and concentration sequentially forced a two-stage crystallisation with two different crystallisation mechanisms - self-diffusion followed by a diffusion wave. One recent experiment involved the use of partially-branched alkanes. Again, minima in growth rates were found, due to the branches themselves obstructing the crystallisation of further alkanes.

Mark Holden started with a short review on zeolites and their significance to industry today. They are usually made at temperatures of between $100-250^{\circ}$ C and pressures of between 1 and 40 atmospheres. This means that analyzing the growth of zeolite crystals via AFM is not possible. However, the group of compounds known as sodalites can be made in milder conditions and are also nanoporous materials, and so were used for the experiments. Sodalites are made up of tetrahedral units of PO₄ and ZnO₄. These units then bind together to form spheres, which themselves bind to three nearest neighbours to form the overall structure.

For the actual analysis, the sodalite crystals were coated in thermoplastic for protection. Analysis of the $\{100\}$ face showed two methods of crystal growth – a double spiral growth, where the spirals overlapped, and "birth and spread", where the growth proceeded via waves emanating from a certain point. Height analysis showed that the difference in height between steps was 0.45nm, suggesting that the crystal lattice was body-centred cubic in origin. Analysis of the $\{111\}$ face gave step heights of 0.3nm. These results overall showed the first successful analysis of the growth of nanoporous materials via AFM.



Delegates assembled at the champagne reception before the Conference Dinner

Professor **Kiyotaka Sato** gave an introduction to the classification of fats and lipids, which contained ceramides, some alkanes and the acylglycerols. Lipids especially played useful roles in nutrition, a medium for oil-soluble materials and as a constituent in lipophilic materials. Lipid crystals in colloid systems (such as chocolate, margarine and cream) determine, among other factors, the firmness and texture of the food product. Taking milk chocolate as an example, it was shown that the components of chocolate all melt at certain temperatures, producing a taste release. The action of chewing was shown to cause phase conversions to the compounds.

The general polymorphism of lipids was discussed, with lipids having three general polymorphs (α , β ' and β – the first two being metastable and the third being the stable form). Each polymorph was discovered to have a specific nucleation rate. Polymorph transformation could happen via solid state techniques or melt-mediation (faster if the total energy barrier to overcome is small – this was demonstrated by the transformation of Trilaurin).

The final part of the talk dealt with the chemistry and polymorphism of cocoa butter, which was preceded by a short history of chocolate, showing how chocolate became a solid delicacy. Cocoa butter itself has six polymorphs (all with melting points between 17 and 36 degrees Centigrade), of which forms V and VI were still unknown. A slow cooling of cocoa butter melt generated form V, and the same results were achieved by seeding the melt with crystals of form V.

Prizes for the best posters and presentations were awarded, and the conference was closed by the Chairman of the Association, Ivan Marziano.