

applications and scientific insights [1]. It is also closely related to carbon nanotubes, fullerenes or graphite, which can be described as rolled-up or stacked graphene sheets [2]. Hence, the graphene structure and its defects are of outstanding interest for the science and applications of all these new materials. Static deformations, topological defects, various vacancy configurations or the two-dimensional equivalent of dislocations can be studied by aberration-corrected transmission electron microscopy (TEM) [2-5]. Existing defects in as-synthesized graphene, CVD synthesized graphene, and reduced graphene oxide are analyzed [6-7]. The formation and evolution of defects under electron irradiation is observed in real time with atomic resolution. High-energy electron irradiation provides a “randomization” of some atoms, which then allows new insights into the complicated bonding behaviour in carbon materials [5]. Further, we show that the charge distribution in graphene defects or other 2-D materials can be analyzed on the basis of high-resolution TEM images [8]. I will also discuss important aspects of radiation damage and instrumental performance in the context of radiation sensitive nano-carbon materials.

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Keywords: HREM, graphite, nanotechnology

MS.52.4

Acta Cryst. (2011) **A67**, C123

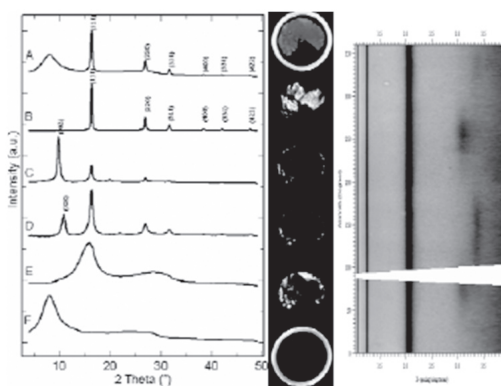
Carbon polyamorphs in pressure-crushed C60 analyzed by scattering tomography

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Laboratory carbon samples can be heterogeneous. Among them, the high-pressure polymorphs of C60 are of particular interest for the study of their complex phase diagram and structural properties. We have used scattering resolved tomography (or XRD-CT) as a non-destructive local probe, with depth resolution and structural selectivity [1], to investigate this multi-phased carbon system.

Under hydrostatic pressures C60 molecules are stable up to 20 GPa, but at higher non-hydrostatic compression at room temperature they collapse into polycrystalline cubic diamond and insulating sp³ amorphous phase. Quasi-hydrostatic loading at high temperature produce a conductive graphitic amorphous sp² structure. Furthermore, HP-HT experiments on C60 allow synthesis of several polymeric and disordered allotropes with a wide range of physical properties [2].

Scattering resolved tomography uses micro-focused synchrotron radiation, allows to extract the spatial distribution of four carbon phases in this system and to recover selectively their scattering diagram (Fig. BCDE). First tomography image corresponds to a full phase reconstruction (all Bragg peaks of the phase were taken into account for the reconstruction). Using selective scattering signal, this probe reveals concentric spatial distribution of cubic diamond, sp³-amorphous diamond, sp² graphite-like carbon phase and a new ill-ordered carbon phase having an unexpected short interlayer distance of 3.11 Å (Fig. D + unrolled pattern) [3].



Usually in “sp²-graphitic” phases, interlayer distance is found larger than 3.34Å, however it should be noted that in shocked meteorites it was reported a compressed “graphite-like phase” with an 3.19Å interlayer distance and a similar spatial concentric relationship between different carbon polymorphs [4]. Additionally, lattice d-spacing maps on the low compressible diamond phase reveal different strained diamond crystallites in the core of the sample.

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Keywords: diamond, graphite, diffraction-tomography

MS.52.5

Acta Cryst. (2011) **A67**, C123-C124

In-situ characterization of the carbon nanotube growth process by X-ray diffraction

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In the last few years carbon nanotubes (CNT) attract more and more attention due to their interesting physical properties especially in the field of micro electronics. Synthesis of CNTs with tailored properties is still a critical point, especially for their applications as interconnects. The growth of CNT by chemical vapor deposition (CVD) is an established synthesis route and it was used in this study.

In-situ X-ray diffraction experiments during growth conditions are performed at the beamline BM20 at the ESRF operated by the Helmholtz-Zentrum Dresden-Rossendorf using a high temperature annealing chamber suitable for reactive gases. Acetylene was used as carbon precursor for the CVD of CNT. Different catalyst systems were studied. For iron nano-particles acting as CNT catalyst, there is still a debate which species can be catalytically active: metallic iron and/or iron carbide. The formation of the metal nano-particles by dewetting and respective crystallisation of the initial thin film was followed by X-Ray reflectivity (XRR) and diffraction (XRD) measurements. We proved that CNT growth can occur without the presence of Fe₃C. In general two reaction pathways denoted by a high and low (or zero) iron carbide concentration were observed. Which route the growth follows depends in a statistical way on the ratio of different iron phases (α - and γ -Fe) present in the nano-particles. This can be influenced also by the reaction conditions like temperature and kind of the buffer

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layer supporting the catalyst film. One challenge is to grow CNT on a conducting support without scarifying the CNT yield and structural quality of the grown CNTs.

Using a Co-buffer layer in-between Si-support and Fe-catalyst leads to the formation of conductive CoSi_2 via CoSi by subsequent silicidation during the growth process. Herby a high yield of CNT was obtained.

CoSi_2 support is more promising than Ta support, but we used Ta as model system to explain all possible interactions, all occurring phases during processing by side reactions were recorded. Notable CNT yield triggered by high catalytic activity of iron at low temperatures $\sim 550^\circ\text{C}$ was observed.

This study shows that in-situ diffraction experiments are a powerful tool to investigate catalytic reactions. The understandings of these processes are the basis of tailoring future materials.

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Keywords: carbon nanotubes, in-situ diffraction, synchrotron radiation

MS.53.1

Acta Cryst. (2011) **A67**, C124

High-throughput crystallization as a part of streamlined drug development

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The pharmaceutical industry is in a challenging situation - decreasing number of new molecules reaching the market and simultaneous generic competition creates a need to identify, utilize and protect the full potential of both the new and existing active molecules. One efficient strategy is to explore the physical properties of active compound and to use the identified solid forms (salt, polymorphic, solvate, co-crystal, and amorphous) as a central part of product development. This decision-making point is extremely crucial - the best solid form candidate with optimal bioavailability needs to be identified; still keeping in mind that solid matter with ideal particulate properties ensuring robust processability and stability is needed.

Screening of pharmaceuticals early in the drug development to identify all possible solid state forms has significant impact. This aids in choosing the 'best solid form' for further development and reduces emergence of unexpected forms later on in the drug development process. A startling example of appearing new polymorphic form is the case ritonavir, a peptidomimetic drug used to treat HIV-1 infection and introduced in 1996 (Norvir). Two years after entry into the market, several lots of Norvir capsules began failing dissolution specifications. Evaluation of the failed drug products revealed that a second crystal form of ritonavir (form II) had precipitated from the formulation. At some considerable cost a new formulation of Norvir was eventually developed and launched.

Current polymorph screening practice is aiming at maximizing the number of solid forms identified as early as possible in the drug development phase. Each new solid form can be patented and by this means, the lifetime of a possible "blockbuster" drug can be optimized. There is not always enough fundamental knowledge available on crystallization and nucleation of pharmaceuticals, which underlines the need for experimental approaches in this field. Current state of art

in the field of solid form screening involves techniques and solutions originating from the field of synthetic chemistry. Labor intensive crystallizations are performed in vessels of varying size (from well plates with few microliters to bigger scale) and the resulting solid product is analyzed using suitable methods. These approaches are having one major drawback in connection to the final dosage form - they do not include the evaluation of the role of formulation and secondary manufacturing (with small molecules granulation, tableting, coating, and with protein/peptide systems freeze drying) on the solid state stability of matter. This type of processing typically involves the use of heat, pressure, and solvents, which again may affect the solid state stability of the drug product, and even introduce a new, previously unidentified polymorphic form. Performing solid form screening by combining the small scale crystallizations and the evaluation of processing induced solid state changes in miniaturized scale will provide remarkable improvement to the current practice of polymorph screening. Well-plate based approach can be used to mimic conditions during secondary manufacturing and further, role of the excipients can be investigated using both small molecule as well as protein/peptide based formulation strategies.

Keywords: polymorph screening, pharmaceutical, high throughput screening

MS.53.2

Acta Cryst. (2011) **A67**, C124-C125

PROTEUS – a fully automated crystallization screening equipment at AstraZeneca

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During a period from 2002 to 2003 a team at AstraZeneca set up plans to develop a fully automated system, which could handle all sorts of small scale crystallization experiments, including polymorph-, salt- and co-crystal screening. During 2004, an agreement was made with TTP LabTech, a global developer and manufacturer of automated laboratory equipment based in the UK, to form a team with the task to develop and build such a system. In late 2008 the first of two benches was accepted and put into service and in early 2010 the system was upgraded with a second bench. The system, which is today running on a routine basis, is a medium throughput system, which can accommodate approximately 200 experiments running in parallel. It is fully automated with regard to sample preparation, crystallization, sampling and analysis. Crystallization can be performed using evaporation, cooling and anti-solvent additions and re-crystallization can be performed by means of slurry experiments. The working scale is 0.3 – 10 mL and the temperature range is -15 to 100°C . On each bench a large number of reagents can be accessed at a given time. The analytical resources include light microscopy, Raman spectroscopy and powder X-ray diffraction-analysis.

The design of the system has been based on trying to access as much of the available design space as possible, from both a thermodynamic and a kinetic perspective. For this reason the system was designed as a highly flexible, medium throughput system, instead of as a high throughput one, with little versatility. As a result the system can work dry as well as wet, in a broad temperature range, using different compositions of binary, as well as ternary, mixtures of solvents and API, and using different rates of crystallization. The system is also designed to maintain strict control over all experimental parameters as well as recording them for later use during evaluation of the screen. All different types of experiment can run in parallel.

So far we have performed some 40 screens, identifying new salts,