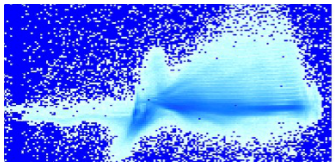

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Organic Crystals –TEM Imaging and Techniques Developed for Elucidating Polymorphism and Crystallization

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Crystallization is a well-established topic. It covers many life science fields, and its importance varies from understanding nanoparticle arrays to protein formations and drug engineering through molecular design. One of the most popular methods for direct imaging of crystal formation, defects, etc., is transmission electron microscopy (TEM), mainly used for inorganic materials since the electron dose is not as limiting as it is for the imaging of organic materials. While challenging, high-resolution electron microscopy of organic material is possible due to the recent revolutions of stable and sensitive detectors and microscopes. Real-space images of organic crystals and their aperiodic features obtained by a modern cryo-electron microscope potentially show the detailed structure. However, high-resolution details remain hidden because strong defocus conditions must be applied to produce contrast at a low electron dose. We used phase retrieval by focal series reconstruction (FSR) developed originally for inorganic samples. We have adapted the method for fast series recording of hundreds of frames within a few seconds on a direct-electron detector, all at low dose conditions (at the order of 101-102 e-/Å2 per acquisition) in cryogenic temperatures. After the reconstruction of the exit-plane wavefunction, we could eventually retrieve focus and two-fold astigmatism aberration-fixed phase images of small organic crystals with a resolution up to the information limit of the microscope. Implying further techniques, such as density functional theory (DFT), ultimately allows for solving a crystal structure with high confidence based on the image in real-space.

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