



Solving molecular organic crystal structures from powders

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Powder diffraction is a widespread technique found in academic, forensic, industrial research and quality-control laboratories the world over. As an analytical tool it has been extensively used as a means of qualitative and quantitative phase analysis to identify, based on their characteristic powder X-ray diffraction patterns, the components/phases present in a sample, to verify products and detect impurity phases from solid-state syntheses, and determine the amount of each phase present when possible. With the advent of the Rietveld (1969) technique, which was originally developed for refining the crystal structures of materials from their powder neutron diffraction patterns, it became possible to model complex diffraction profiles composed of multiple overlapping peaks, and the applications of powder crystallography grew rapidly, especially for inorganic materials, including those with diffraction peaks arising from magnetic ordering. Powder diffraction, because of the speed and relative simplicity of the measurement, can be especially useful for following the evolution of a known structure over time as it is heated or cooled or subjected to, for instance, changes in pressure or atmosphere. The evident next step was to attempt to solve crystal structures when there was no, or only minimal, structural information available. Although noteworthy early examples exist, *e.g.* the monoclinic structure of β -Pu at 190 °C from variable-temperature powder X-ray diffraction (Zachariasen & Ellinger, 1963), where the anisotropy of the thermal expansion allowed overlapping peaks at one temperature to be resolved at another, the solving of crystal structures from powder diffraction data poses particular difficulties, owing to the loss of the 3D information by the collapse of the diffraction pattern onto a single 2θ axis, coupled with the detrimental effects of peak overlap obscuring the individual peak intensities.

The improvements in data quality, with regard to statistical quality and angular resolution, that are possible with modern powder diffraction instruments at neutron and synchrotron radiation sources, led to a proliferation in the number of structures that could be solved from powder diffraction data. One of the early successes was of Sigma-2, a clathrasil phase, from high-resolution synchrotron data and direct methods using extracted peak intensities (McCusker, 1988, and references therein). Laboratory diffractometers have also improved in terms of their angular resolution and the quality of the data, especially those adopting capillary (Debye–Scherrer) geometry and modern position-sensitive detector systems. Whereas the data quality from a laboratory powder diffractometer may not be as high as that from a synchrotron instrument, especially for the most-crystalline of materials, it can be well adapted to a wide range of studies, and where the microstructural characteristics of the sample (crystallite-size and microstrain effects) control the effective angular resolution. Advantages of laboratory apparatus include easier access and less time pressure for carrying out crystallographic studies. In addition, samples are often more stable in the beam, especially organic and organometallic compounds that can sometimes suffer rapid degradation under the intense X-ray illumination delivered at a synchrotron source.

For organic systems, there is nearly always detailed prior knowledge of the molecular structure and this can be exploited for solving the crystal structure when no single crystal is available. This situation can arise when a particular phase or polymorph of a substance forms under conditions where single crystals do not grow, *e.g.* the low-temperature phase(s) of a material, transient phases, or polymorphs grown under particular conditions

of, for example, temperature, pH, concentration, solvent, pressure, atmosphere, *etc.* Powder diffraction also allows a bulk sample to be studied in the state under which it is exploited, such as a particular form of an active pharmaceutical ingredient, or even the whole formulation itself, in which the relevant molecule makes up only a part of the overall composition. Starting with a high-quality powder diffraction pattern, the unit cell can be determined from the positions of the low-angle Bragg peaks, and likely space groups identified. Structure solution can then be accomplished by fitting to the powder diffraction profile or extracted intensities, employing a real-space global-optimization approach that allows the crystallographically distinct molecule(s) or fragments to move within the unit cell, varying position, orientation and any free torsion angles, possibly employing constraints or stereochemical restraints, as appropriate.

Owing to the simplicity of the experiment and the seemingly intuitive approach to the structural analysis, structure solution of molecular systems *via* a real-space global-minimization approach from powder diffraction data is a popular approach and firmly established. The recent article by Kabova *et al.* (2025), ‘*A good-practice guide to solving and refining mol-*

ecular organic crystal structures from laboratory powder X-ray diffraction data’, provides exactly what its title promises, with step-by-step guidance on how to proceed and the software the authors use, from sample preparation and the powder diffraction measurement itself, to the verification of the final structure. Solving and refining crystal structures from powders almost invariably involves using the Rietveld approach, especially in the later stages as the final structural model is decided. It is therefore useful to keep in mind the guidelines of McCusker *et al.* (1999) and to understand the relevance of the various *R* factors (Toby, 2006) generated by whichever refinement program is employed.

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