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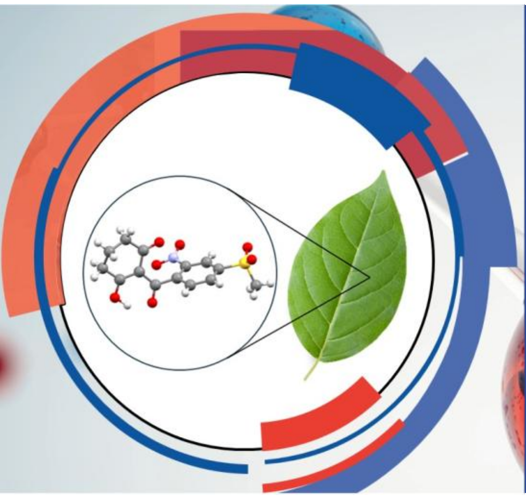


3D ED Analysis of Agrochemical Nanocrystals from Spray Droplet Crystallisation

Spray Droplet Crystallisation of Agrochemicals

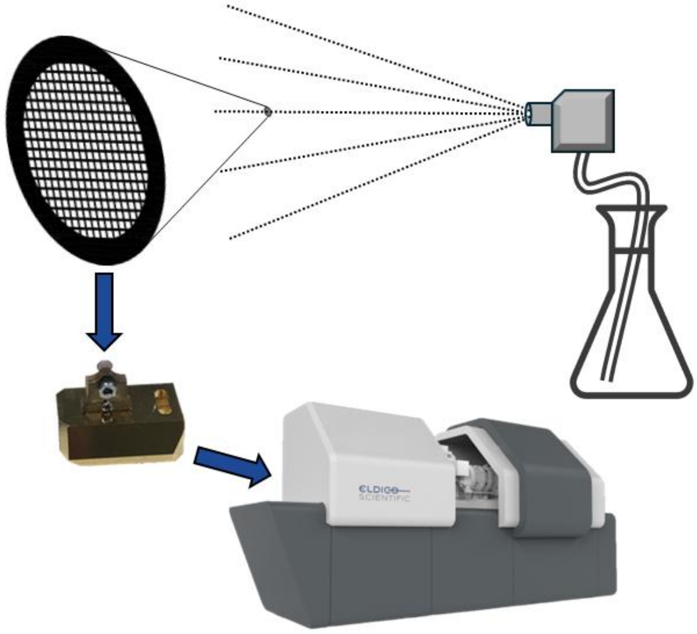
A typical way of deploying agrochemicals is spraying crops with diluted formulations of the active ingredient. Analysis of the solid form obtained upon evaporation of spray droplets is crucial for understanding bioefficacy, but also challenging because the crystallisation conditions usually produce nanocrystalline material that is mixed with other components of the formulation. Electron diffraction crystal mapping is the perfect tool to analyse such samples and study the solid form of active ingredients under these conditions.

Introduction

The solid form of agrochemical active ingredients (AIs) is very important for product stability and controlling uptake, just like for active pharmaceutical ingredients (APIs). For instance, if a product contains a metastable polymorph, over time there will be crystal growth causing blockages in nozzles and changes to bioefficacy. To know if the AI can change to a different solid form when it is deployed on the crops, is important for formulation design to control uptake because the process of spraying a diluted formulation leads to very different crystallisation conditions than in standard laboratory protocols. Even when the AI is a suspension on dilution, mechanical stress (spraying through a nozzle) and changes in humidity can still lead to a change in solid form. Unlike controlled conditions in a laboratory, the evaporation of spray droplets cannot be precisely controlled in a real life environment. The analysis of the obtained residue is challenging for multiple reasons: First, the fast crystallisation produces nanocrystals which are too small for single-crystal X-ray diffraction (SC-XRD). Second, the low levels of AI and other components of the formulation lead to multi-phase mixtures that make getting sufficient quality powder XRD (PXRD) for phase matching very challenging. Third, sampling from the plant leaves will introduce additional complications like the epicuticular wax of the leaf and environmental material.

Simulating Spraying on Leaves

In a cooperation between Syngenta and ELDICO we simulated the spraying of an AI formulation on leaf surfaces by directly spraying on the grid (continuous carbon film on copper grid), which is used as sample support for electron diffraction (ED) measurements. The crystallites can then be analysed directly as they formed upon evaporation of the droplets. A commercial formulation was prepared and diluted with water to the correct application rate that would be used by farmers. This diluted formulation was sprayed using a handheld atomiser to replicate a typical spray droplet size (nanolitre) from a large boom sprayer.



Schematic of the experimental procedure

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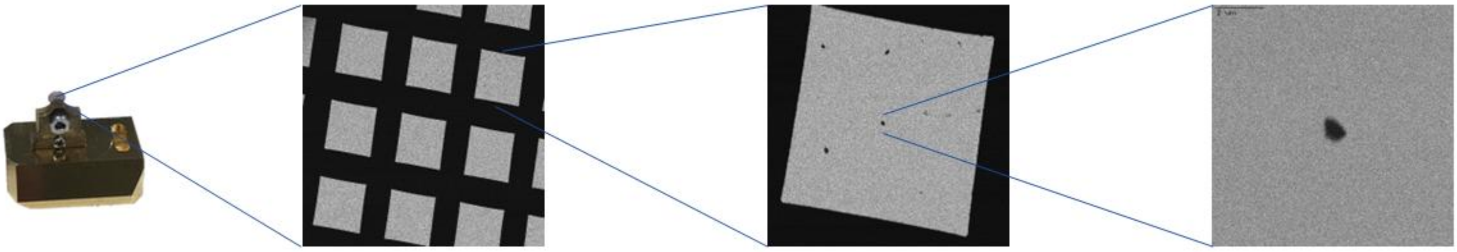
Case Study: Mesotrione



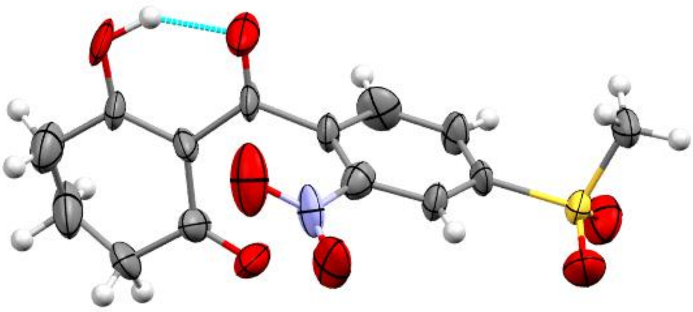
Sample holder with the prepared grid and STEM (scanning transmission electron microscopy) images at different fields of view: 400x400 µm^2, 100x100 µm^2, and 10x10 µm^2 (left to right)

Electron Diffraction Crystal Mapping

Mesotrione is a broad-spectrum HPPD (4-Hydroxyphenyl-pyruvate dioxygenase) inhibitor that is used to control pre- and post-emergence broadleaf weeds and some grasses to protect corn and other crops such as sugarcane.

A sample of mesotrione was prepared as described before and measured on an ELDICO *ED-1* electron diffractometer. Out of 38 particles, the unit cell of anhydrous mesotrione form 1 was identified in 36 crystallites and no other polymorphs were found. In the other particles the data quality was not sufficient for unit cell determination. Form 1 is indeed the technical product used in the formulation and the results confirm that the same form is also obtained after spraying and evaporation on air.

Although a unit cell is already sufficient for identification via matching with literature data, the collected data were of high quality and the structure could easily be solved ab initio. Refinement required no restraints and allowed the location of hydrogen atoms and therefore the determination of the tautomeric form of the mesotrione molecule. Even though no unknown polymorphs were present, the data quality shows that the method would also be capable of solving the crystal structures of new polymorphs that could form during spray droplet crystallisation.



Molecular structure of mesotrione form 1 from ED data

Crystallographic data for mesotrione form 1 (4 merged datasets)

a, *b*, *c* (Å)	10.41(10), 11.52(11), 12.31(11)
α, β, γ (°)	90, 94.965(19), 90
space group	$P2_1/c$
formula	$C_{14}H_{13}NO_7S$
independent reflections	2233
parameters	211
restraints	0
resolution (Å)	0.80
completeness (%)	88.8
R_{int} (%)	16.96
R_1 [$I > 2\sigma(I)$] (%)	17.20
wR_2 [all data] (%)	45.84
goodness of fit	1.06

Conclusion

ED crystal mapping is a powerful tool to analyse phase mixtures as it can collect data from individual nanocrystals, which can not only be used to identify known forms, but also to determine crystal structures of minor species, like other polymorphs, contaminants or decomposition products. In this case study we were able to solve the crystal structure of mesotrione form 1 from a nanolitre spray droplet crystallisation experiment of a diluted formulation. This experimental setup simulates the crystallisation of agrochemical active ingredients for foliar application and can thus help in formulation development.

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