INVESTIGATION OF POLYMORPHISM AND STABILITY IN THE ARTEMISININ FAMILY OF ANTI-MALARIALS BY SOLVOTHERMAL CRYSTALLIZATION

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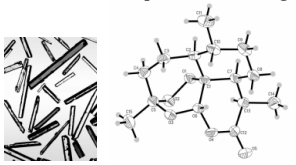
The crystal growth and structure analysis of the anti-malarial compound artemisinin (right) and its derivatives has been examined using hydrothermal, sub-hydrothermal and solvothermal methods. These strategies are useful for growing large crystals, high recovery of materials, identification of new polymorphic forms and monitoring of hydrolytic stability. Despite low aqueous solubility artemisinin itself can be grown hydrothermally as long bars up to 4mm dimension, as shown in the polarized micrograph figure on left.



Two commercial anti-malarial drugs have also been investigated with a new stable high temperature polymorph found for artemether and a first reported structure for arteether. (see Table) The hydrolytic stability of these drugs can be monitored over time by analysis of the product solids by powder X-ray diffraction. Both show a decomposition pathway to dihydroartemisinin and deoxyartemisinin (also found in a new polymorphic form).

Compound	Space Group and Unit Cell Constants (150K)
Arteether	$P3_221$ a = 10.011(1), c = 28.588(2)Å, V = 2481Å^3
Artemether-II	C2 a=18.158(5) b=10.070(3) c=19.360(5)Å β=112.51(1)^o, V = 3270Å^3
Deoxyartemesinin-II	$P2_1$ a =5.444(1) b=15.172(1) c=17.206(2)Å β=95.69(1)^o, V = 1418Å^3

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Keywords: HYDROTHERMAL CRYSTALLIZATION

WHICH IS THE REAL CELL? - LOCATING THE CORRECT INDEXING SOLUTION FROM MERIT-MAP TOPOGRAPHY WITH MMAP

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Before a powder structure can be solved, or a polymorph characterized, first its pattern must be indexed. The MMAP facility within the Crysfire 2001 powder-indexing suite makes exhaustive step-searches across high-probability α*/β* sections of indexing parameter space, selected via the SIW (Shirley-Ishida-Watanabe) dominant-zone heuristic. This allows *ab initio* indexing of general powder diffraction patterns, though less efficiently than comparable dichotomy-based programs such as LZON. But that is not the end of the story. Like most indexing programs, MMAP yields a list of possible indexing solutions, ranked by figure of merit. However, MMAP provides further information: because an entire section of parameter space has been mapped, the topography around each peak in the merit surface is also available. This extra information supplements the peak figure of merit in two important ways. Firstly, the topography around each peak provides a criterion for distinguishing correct indexing solutions from pseudo-solutions. Correct solutions usually appear as well-formed, approximately circular peaks, while pseudo-solutions, despite high merit values, are often ill-formed local maxima on shoulders or ridges. Secondly, much time and effort can be saved by quickly identifying pathological datasets that are a waste of resources to try to index (due to systematic errors, mixed phases, etc.) and basis sets that offer little hope of success. In both cases, the warning signs are usually visible in the general landscape of their merit surfaces, which lack distinct and well-formed peaks. Examples will be demonstrated.

Keywords: POWDER INDEXING SOFTWARE

STRUCTURAL ELUCIDATION OF TERBINAFINE HCl FROM POWDER X-RAY DIFFRACTION

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During the development of pharmaceutical compounds, a thorough investigation of properties, such as melting point, solubility, crystallinity, stability and morphology is commonly performed. Crystal structure determination is becoming a crucial step towards identification and characterization of drug substances in the solid state, especially when polymorphism or pseudo-polymorphism phenomena [1] occur. Single crystal X-ray diffraction is the choice for such investigation, but it requires crystals of suitable size and quality. If this condition is not met within a reasonable amount of time, high-resolution powder X-ray data can be exploited for structure determination [2]. We currently use the program PowderSolve [3] for such purpose, which utilizes the direct space strategy and a Simulated Annealing method. The title substance is the active ingredient of the marketed product LAMISIL. The crystal structure has been successfully solved utilizing synchrotron X-ray powder data recorded at the BM16 beamline (ESRF, Grenoble). Beside its pharmaceutical interest, this chloride salt represents a challenging case for structure solution since there are two independent fragments in the asymmetric unit, for a total of 14 degrees of freedom varied during the SA run. The crystal packing is stabilized by hydrogen bonding interactions involving the Cl^- ion. The structure determination and analysis will be thoroughly illustrated.

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THE QUASICRYSTAL-TO-CRYSTAL TRANSFORMATION – UNIT CLUSTER APPROACH FOR DECAGONAL QUASICRYSTALS

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A large volume of theoretical work on the mechanism of the quasicrystal-to-crystal transformation between the decagonal phase and its periodic approximants has already been published. However, most of these studies have concentrated on models based on the higher-dimensional quasi-crystal description and authors use the phason-strain formalism or more general shears and rotations of the hyperlattice. These approaches, however, say little about the real atomic-scale processes. In a previous study [1] we used Monte Carlo simulation to demonstrate that it is possible using phason flips to transform a Penrose rhomb tiling into an orientationally ordered crystalline nanodomain structure, using only local tile-pair energies. While this produced diffraction patterns that displayed features very similar to ones observed in studies of real transformed materials [2], the fact that the study involved tile-flips that might represent a concerted movement of a large number of atoms detracted from the model's viability. In this paper we present work based on the Gummelt 1996 concept of nonperiodic coverings [3], which use only a single 'unit-cluster'. We show that it is possible to use such a single 'unit-cluster' to describe both a decagonal quasicrystal and an approximant whose unit cell has dimensions in agreement with observed diffraction peaks. Using this new formulation it is possible to invoke a tile-flipping mechanism on the cluster scale each flip of which, however, involves only small movements (<1 Å) of a small number of atoms.

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