Experimental Report

Proposal: **5-12-292** **Council:** 4/2012

Title: Polymorphism in the fungicide cyprodinil

This proposal is a new proposal

Researh Area: Chemistry

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Samples: 4-cyclopropyl-6-methyl-N-phenylpyrimidin-2-amine,

Instrument	Req. Days	All. Days	From	To
D19	6	4	02/05/2013	07/05/2013

Abstract:

Cyprodinil is an anilinopyrimidine folar fungicide which is believed to act by inhibiting the biosynthesis of methionine and the secretion of fungal hydrolytic enzymes. It is widely used in the EU on cereals, grapes, pome fruits, strawberries and in barley seed dressings. Two polymorphic forms are known with different melting points, A = 71°C and B = 75°C; phase transition between the two forms can occur between 15 and 40 °C with A stable at the lower temperatures. This polymorphism is related to a change in the hydrogen bonding between the molecules from a moderately strong H-bonded (N-H....N(aromatic ring)) dimeric ring (in B form) to a weaker single interaction in the A form. This behaviour is highly important to the commercial use of this material as one form undergoes a slow conversion to the other while in storage causing particle aggregation. We need to define with high accuracy the hydrogen bonds and other weaker intermolecular interactions in the two polymorphs of cyprodinil in order to understand the phase transition behaviour and use this information in modelling the formation of new polymorphs and co-crystals.

Form A of the fungicide Cyprodinil, described in proposal 5-12-292, was studied but due to problems with the instrument sample environment cooling system insufficient time was available to investigate form B during the scheduled experiment. Structural results from the SND data collected on a crystal of modification A of Cyprodinil (Figure 1) at 30K show basic agreement with the SXD measurements but reveal differences between X-rays and neutrons in the definition of the hydrogen atoms. As a result, an improvement of ten times in the precision of determination of hydrogen atom positions was obtained and accurate nuclear positional parameters were extracted allowing a much better understanding of the hydrogen bonding network. In Table 1, the cell parameters are reported.

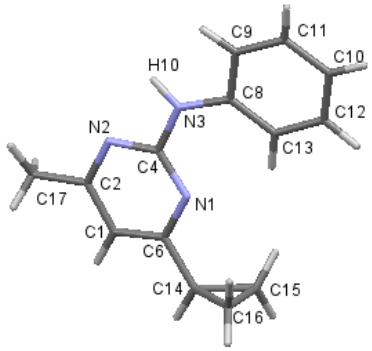

Figure 1. Molecule of Cyprodinil.

Wavelength	1.170 Å
Temperature	20 K
System	Monoclinic
Space group	$P2_1/c$
a	13.1850(2) Å
b	5.3421(1) Å
c	16.6893(3) Å
β	100.2705(11)°
Z	4
V	1156.69

Table 1. Cell parameters of form A of Cyprodinil.

The benzene and the pyrimidine rings are not co-planar: the benzene is 9.77˚ off the plane containing the pyrimidine ring. This is probably due to the presence of the cyclopropyl substituent, which points in the direction of the benzene ring, causing hindrance. The cyclopropyl is centred in respect to the pyrimidine ring, forming torsion angles up and down the ring of, respectively, 35.49˚ and -33.59˚.
Also the hydrogen atom, H10, which forms an intermolecular hydrogen bond with a neighbouring molecule of Cyprodinil, is twisted in respect to the pyrimidine ring of 7.50˚. This value of the torsion angle N2-C4-N3-H10 is due to the geometry of the intermolecular hydrogen bond: each molecule of Cyprodinil forms two hydrogen bonds with two different neighbouring molecules (Figure 2).

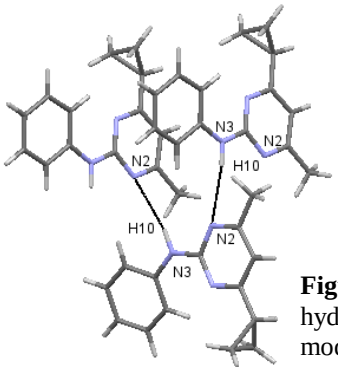

Figure 2. Intermolecular hydrogen bonds in a crystal of modification A of Cyprodinil.

	Neutrons	X-rays
N3-H10	1.015(3) Å	0.92(3) Å
H10···N2	2.533(3) Å	2.64(3) Å
N3···N2	3.513(1) Å	3.51(3) Å
N3-H10···N2	162.0(2)˚	157.97(30)˚

Table 2. Comparison between neutrons and X-rays results for form A of Cyprodinil.

The crystal packing is governed by intermolecular hydrogen bonds and by the stacking of Cyprodinil molecules in piles, held together by π-π interactions between the aromatic rings. The length of the N3-H10···N2 hydrogen bond is 2.533(3) Å, with an angle of interaction of about 162.0(2)°. The interacting molecules are placed in different planes and they are oriented so that the amino group of a molecule of Cyprodinil faces the nitrogen atom of the pyrimidine ring of another molecule, as shown in Figure 2. The cyclopropyl ring is always oriented toward the benzene ring. A comparison of the neutron results with the X-rays data is summarized in Table 2 where the main bond and interaction lengths are reported.
The refinement exhibits the following R values: R(int) = 0.0506; R(sigma) = 0.0324; R1 = 0.0508. An additional set of data at 293K was collected and analyses of these SND data are in progress, in order to investigate the role played by the temperature on the polymorphism of this compound. Further studies will involve structural refinement of the modification B of Cyprodinil and investigation in more details of the conversion between polymorphs, which occurs upon storage, leading to practical issues once the fungicide is applied on the plant (obstruction of nozzles caused by change in particle size and aggregation).