Experimental report

20/03/2016

Proposal: 7-01-416 **Council:** 10/2014

Title: Lattice dynamics of polymorphic pyrazinamide drug crystals from inelastic neutron scattering measurements

Research area: Chemistry

This proposal is a new proposal

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Samples: Pyrazinamide (pyrazine-2-carboxamide) gamma polymorph
Pyrazinamide (pyrazine-2-carboxamide) delta polymorph
Pyrazinamide (pyrazine-2-carboxamide) alpha polymorph
Pyrazinamide (pyrazine-2-carboxamide) beta polymorph

Instrument	Requested days	Allocated days	From	To
IN6	4	4	17/04/2015	21/04/2015
IN5	4	0		

Abstract:

Lattice-dynamical models of the polymorphic crystal forms of the anti-tuberculosis drug pyrazinamide will help us to obtain a better understanding of the contribution of vibrational entropy and enthalpy to the free energy, and thus relative stability of these crystalline systems. To develop these models it is necessary to obtain accurate information on the low-energy phonon spectra using inelastic neutron scattering measurements. The pyrazinamide system serves as a model system for development of new approaches to structure and properties prediction of molecular crystals.

Latttice-dynamics of polymorphic pyrazinamide drug crystals using inelastic neutron scattering measurements

The fact that many molecular crystalline compounds display crystal polymorphism has become a major concern for the pharmaceutical industry in the formulation of new drug products. Here it is essential to gain a rigorous understanding of the solid-state behaviour in order to market the right system and avoid disastrous situations for the patients as well as for the companies that are required to make a market withdrawal and reformulation of the drug product. However, understanding the stability relationship between structurally different crystalline phases to the degree where structural phase transitions can be predicted and designed is desired in all types of molecular materials design.

In order to obtain the stability relation between different crystal structures it is necessary to calculate Gibb's free energy accurately - including the contribution from vibrational entropy which requires the frequencies of the normal modes of vibration (phonon modes) of the full Brillouin zone and knowledge about their temperature dependence. Although quantum chemical codes provide the phonon modes - and in some cases for any point in momentum space - they do not acces their temperature evolution.

To obtain this information we take advantage of incoherent inelastic neutron scattering (time-of-flight) technique on powder samples that allows us to probe the generalised phonon density of states, $G(\omega)$, directly. We measure the inelastic spectrum from powder samples of all four known polymorphs (denoted α, β, γ and δ) of pyrazinamide [1, 2] on the IN6 spectrometer in the temperature range between 50-300 K. The α, γ and δ polymorphic samples were of excellent quality and with a sample mass of 1 g allowing for data collection at six different temperatures. The β crystals of pyrazinamide are, on the other hand, rather difficult to produce since they are obtained through phase transformation from the γ phase, limiting the sample mass and allowing for three temperature points (100 K, 200 K, 300 K) in the available experimental time. Moreover, the risk of phase change during pressure application prohibited us in grinding the

β sample to powder, and we note that the sample is subject to preferred orientation.

The obtained GDOS for the different phases are shown in figure $1x$ with $x = \alpha, \beta, \gamma, \delta$ denoting the depicted polymorphic phase. The data shows significant differences between the different polymorphic phases. The γ phase, which is the high-temperature stable phase, displays broad peaks below 25 meV whereas the α and δ phases that are thermodynamically stable at low temperatures show several well separate peaks in this range. Furthermore, it is possible to trace clear features of crystal anharmonicity evident from peak shifts that reduce in energy transfer with increasing temperature.

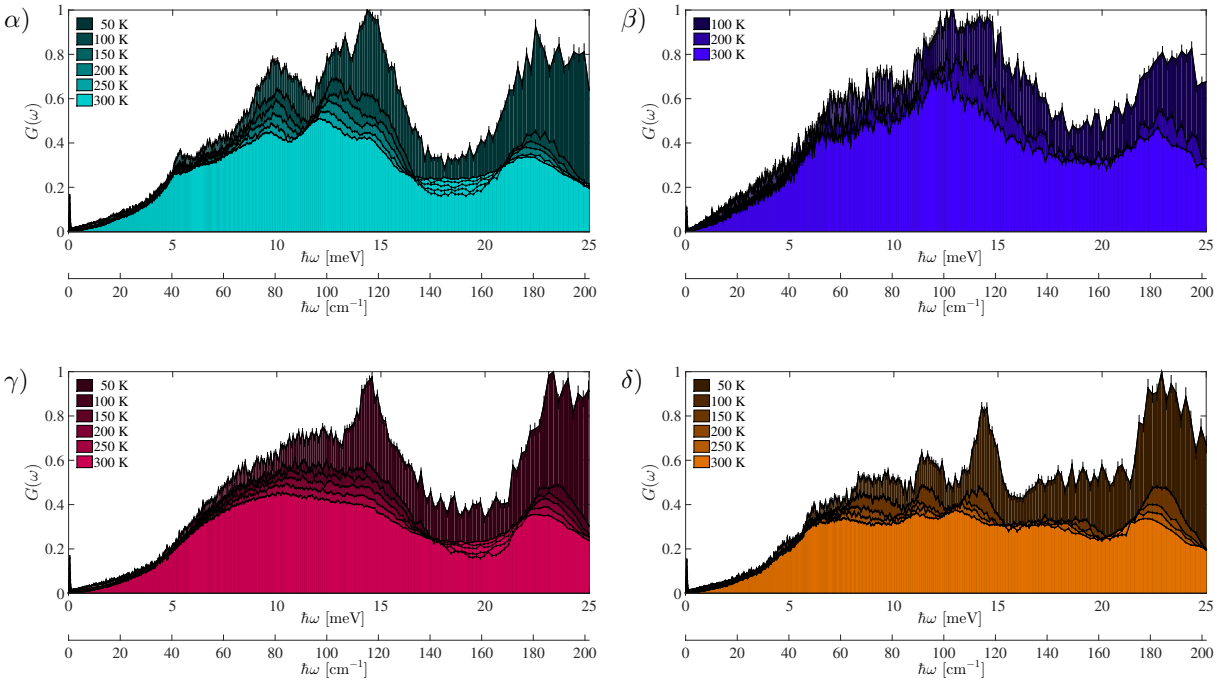

Figure 1: Panels show the GDOS, in arbitrary units, from incoherent neutron scattering at multiple temperatures for the polymorphic phase of pyrazinamide indicated by the label.

We are currently in the process of modelling the anharmonic behaviour by making use of the observed anisotropic expansion of the unit cell with increasing temperature. In order to do this, we perform periodic DFT calculations using the CRYSTAL code that allows us to compute the frequencies of the normal modes of vibration at the Γ-point given the crystal-

lographic information. Here we employ the PBE exchange and correlation functionals with a 6-31G split-valence basis set. Moreover, we include the empirical Grimme dispersion correction. Preliminary results are shown in figure 2 for the polymorphic δ phase to visualise that some frequencies indeed become redshifted with increasing temperature in agreement with the experimental trends.

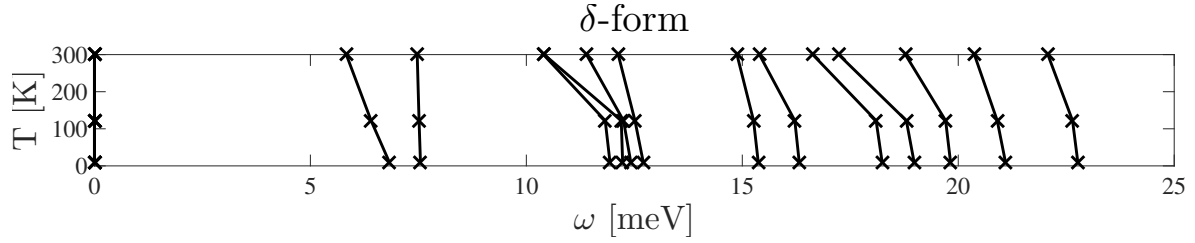

Figure 2: Roughly illustrating that the computed *ab intio* frequencies of the phonon modes, ω, at the Γ-point depend on the geometry of the unit cell, which changes with temperature T resulting in redshifted frequencies with increasing temperature.

In conclusion, the GDOS data obtained demonstrates that inelastic neutron scattering provides an excellent and accessible experimental probe of the lattice dynamics for (polymorphic) molecular crystals that together with phonon dispersion measurements on single crystals can supplies a reliable validation of theoretical models. Especially, the quick acces to the temperature dependence of phonon modes is an advantage of INS on powder samples that gives information, which cannot be obtained through present lattice dynamical models but necessary to unravel the driving mechanism of temperature-driven phase transitions in molecular systems.

[1] R. A. Castro et al., *Crystal Growth Design*, **2009**, 10, 274-282.

[2] S. Cherukuvada et al., *Crystal Growth Design*, **2010**, 10, 3931-3941.

[3] N. Wahlberg, A. Ø. Madsen et al., *Crystal Growth Design*, **2014**, 10, 381-388.