EUROPEAN SYNCHROTRON RADIATION FACILITY

INSTALLATION EUROPEENNE DE RAYONNEMENT SYNCHROTRON

ESRF

# Experiment Report Form

**The double page inside this form is to be filled in by all users or groups of users who have had access to beam time for measurements at the ESRF**.

Once completed, the report should be submitted electronically to the User Office via the User Portal:

*https://wwws.esrf.fr/misapps/SMISWebClient/protected/welcome.do*

***Reports supporting requests for additional beam time***

Reports can be submitted independently of new proposals – it is necessary simply to indicate the number of the report(s) supporting a new proposal on the proposal form.

The Review Committees reserve the right to reject new proposals from groups who have not reported on the use of beam time allocated previously.

***Reports on experiments relating to long term projects***

Proposers awarded beam time for a long term project are required to submit an interim report at the end of each year, irrespective of the number of shifts of beam time they have used.

***Published papers***

All users must give proper credit to ESRF staff members and proper mention to ESRF facilities which were essential for the results described in any ensuing publication. Further, they are obliged to send to the Joint ESRF/ ILL library the complete reference and the abstract of all papers appearing in print, and resulting from the use of the ESRF.

Should you wish to make more general comments on the experiment, please note them on the User Evaluation Form, and send both the Report and the Evaluation Form to the User Office.

## Deadlines for submission of Experimental Reports

- 1st March for experiments carried out up until June of the previous year;
- 1st September for experiments carried out up until January of the same year.

## Instructions for preparing your Report

- fill in a separate form for each project or series of measurements.
- type your report, in English.
- include the reference number of the proposal to which the report refers.
- make sure that the text, tables and figures fit into the space available.
- if your work is published or is in press, you may prefer to paste in the abstract, and add full reference details. If the abstract is in a language other than English, please include an English translation.

| | | |
|---|---|---|
| ESRF | **Experiment title:**<br>Lattice dynamics of polymorphic molecular drug crystals from inelastic X-ray scattering | **Experiment number**:<br>HC-1928 |
| **Beamline**:<br>ID28 | **Date of experiment**:<br>from: 15-Apr-2015 to: 21-Apr-2015 | **Date of report**:<br>10-Sep-2015 |
| **Shifts:**<br>18 | **Local contact(s)**:<br>Alexei Bossak | *Received at ESRF:* |

**Names and affiliations of applicants** (* indicates experimentalists):

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**Report:**

The anti-tuberculosis drug pyrazinamide ($C_5H_5N_3O$) is a well-studied model system in the field of molecular crystals displaying polymorphism – a phenomenon that greatly troubles the pharmaceutical industry. In recent years a lot of effort has been put into improving density functional theory based computational methods that estimate the free energy of different polymorphic phases, which requires an accurate description of the lattice dynamics in the full Brillouin zone. Especially, the estimation of the low-frequency phonon modes is difficult to obtain for molecular crystals with many atoms in the unit cell. To advance, the lattice-dynamical models require experimental data that can directly compare the computed and observed phonon dispersion relations at any momentum transfer, and not exclusively indirect experiments that estimate integral properties. This is possible through inelastic X-ray and neutron scattering on single crystals, however, this is unexploited for molecular crystals.

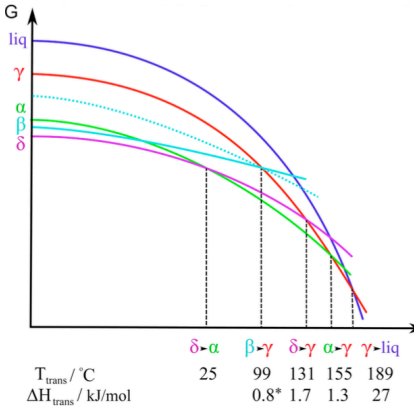


***Fig. 1:*** *A sketch of the Gibbs free energy as a function of temperature illustrating the thermodynamic stability relationship and the phase transitions present for pyrazinamide. Reprinted from [1].*

In the recent experiment (April 2015) at beamline ID28 at ESRF we aspired to attempt to measure the low-frequency phonon dispersions in different polymorphs of pyrazinamide for the first time. The aim was to demonstrate that the scattering power of millimeter-sized pyrazinamide crystals is sufficient enough to obtain a useful inelastic that can be directly compared with lattice-dynamical calculations based on density functional theory.

We were capable of producing single crystals of all four polymorphs of pyrazinamide of millimeter-size that are kinetically stable at room temperature. It was possible to record nice inelastic spectra from all four polymorphic phases without any problems. All measurements were performed as energy scans with an energy resolution of 3 meV with the sample at room temperature. We focused on energy transfers that are suitable for acoustic and the low-energy optical phonons i.e. below an energy transfer of 25 meV. The momentum transfer was chosen along high-symmetry paths between two Bragg reflections, trying to obtain information about the dispersion of both transverse and longitudinal phonon modes, and along directions significant to the stacking of molecular planes.

As an example of the data quality, we show four representative datasets in Fig. 2 α, β, γ and δ of measurements on the α, β, γ and δ polymorphs of pyrazinamide, respectively, along the path between two Bragg reflections in reciprocal space. The points of reciprocal space, which we have measured at, are given in the legend in Fig. 2. In general, it is clearly possible to observe signatures of both transverse and longitudinal acoustic phonon modes in the data. However, the data needs to be complimented by calculations of the acoustic phonon dispersions to reveal the number of modes responsible for a given peak etc. We are currently in the process of obtaining these calculations.

In summary, we have studied an interesting molecular system with inelastic X-ray scattering on single crystals to obtain information about the dispersion of the acoustic phonons, in particular, of different polymorphic phases. The experiments were highly successful and we managed to measure along several paths in reciprocal space for all four polymorphs of pyrazinamide. This resulted in benchmark data that is crucial for the validation and development of lattice-dynamical models for molecular crystals. All in all, these pilot inelastic scattering experiments on molecular single crystals of pyrazinamide are considered highly successful.

[1] N. Wahlberg, P. Ciochon, V. Petricek, A. Ø. Madsen, *Crystal Growth & Design* **2013**, *14*, 131122094750005.

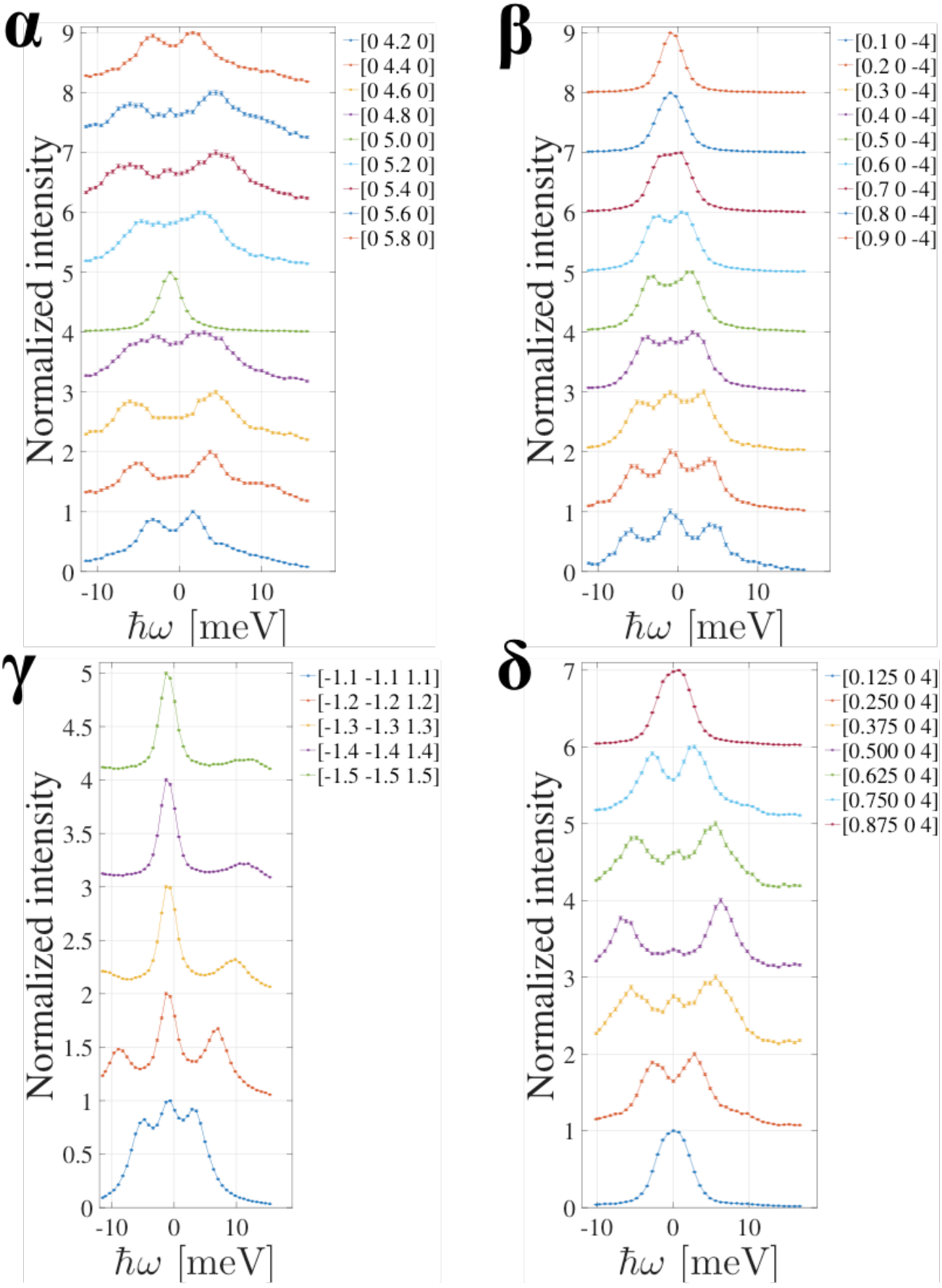


***Fig. 2:*** *Representative inelastic spectra showing energy scans with a resolution of 1.5 meV conducted at room temperature. The (α, β, γ, δ) panel shows the dispersion of acoustic phonon modes at the points in reciprocal space given in the legend for the α, β, γ and δ polymorphs, respectively.*