REPORT
CH-3876

5-10 September 2013

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Abstract

We have been synthesizing bioinspired metal organic frameworks (BioMOFs), using active pharmaceutical ingredients (API) and non-toxic metals for application into biological and medicinal chemistry. Recrystallization in order to obtain single crystals suitable for structure determination using lab standard diffractometers, has been an impossible task and we were/are strongly relying in powder diffraction to proceed with the structural characterization. This was the reason for requesting time at the ESRF ID31 beam line in 2013.

A total of 14 samples were analyzed during our stay, from 5-10 September 2013 at ESRF by M. Teresa Duarte, Vânia André and Sílvia Quaresma at ID31, having Dr. Christina Drathen as a contact person at ESRF. Collected data is under analysis and progress has been done, but it is still an on-going work. Partial results have already been presented in two oral presentations ([1] Vânia André, *XRD – a fundamental tool in the world of pharmaceutical crystal forms*, Methods of Structure Elucidation – 2013, Instituto Superior Técnico, Lisbon, Portugal ,14 November 2013; [2] Vânia André, M. Teresa Duarte, *Bio-MOFs as potential drug delivery materials: a new approach to traditional MOFs*, 1st Cluster Workshop in Materials and Nanotechnology, Instituto Superior Técnico, Lisbon, Portugal, 6 December 2013) and will be presented at 3rd ENURS and ESRF-Day to be held in April at Marinha Grande, Portugal. We believe that the data obtained will result in at least one publication.

The results obtained form high-resolution data collected at the ESRF ID31 beam line, revealed to be most promising and this is indeed the best/only way for accurate structural elucidation of our compounds, we intend to apply for a continuation proposal of this project at the new beam line ID22.

Scientific background

The project that led us to ESRF applies the underlying concepts of metal organic frameworks (MOFs) in biological and medicinal chemistry for the synthesis of BioMOFs, "bioinspired" MOFs, using active pharmaceutical ingredients (API) and mainly safe metals, such as Fe, Mg, Zn, Mn and Bi, for potential use in the transport and release of APIs. One approach that is undoubtedly promising is to use the API as the organic fragment – linker, turning BioMOFs into one of the best possible nanocarriers. Early steps are being taken using nalidixic acid (system A), dapsone (system B), norfloxacin (system C) and pipemidic acid (system D) as linkers. Details on

the function, preparation and characterization of these samples can be found in APPENDIX 1 at the end of this report. The products are obtained *via* conventional solvothermal synthesis or by mechanosynthesis and thus are mainly microcrystalline powders from which structural solution using conventional powder X-ray diffraction proved to be unsuccessful. Data collected at ESRF was of upmost importance for our work.

Results and their significance in the respective field of research

Fourteen samples were collected in capillaries, using a 31 keV (0.39985067 Å) radiation at ID31 (Table I). Data was collected from –5 to 30° for most samples and –5 to 45° for the samples that revealed to be most promising for structural solution; longer data acquisition was carried out for higher angles. Room temperature data collection revealed to be inappropriate for our samples due to very fast radiation damage. Therefore data collection was carried out at 100K.

Table I - List of samples collected at 100K, using 31 keV radiation

Sample Code	*Comments*
GBP_Nd	Very fast radiation damage was observed at RT
NORFL_BiCl3_LAG_BM	The sample revealed to contain multiple phases. Full identification of phases is complete. Indexing for the new phases is being attempted.
NORFL_BIP_BiCl3_1:1:1_LAG_BM	The sample revealed to contain multiple phases. Full identification of phases is complete. Indexing for the new phases is being attempted.
NORFBispBi	The sample revealed to contain multiple phases. Full identification of phases is almost complete and indexing for the new phases will be attempted.
NALIDIX45	Indexing and space group determination ✓
DAPNi	Indexing and space group determination ✓
APBi	The sample revealed to contain multiple phases. Full identification of phases is complete. Indexing for the new phases is being attempted.
PABipBip	The sample revealed to contain multiple phases. Full identification of phases is almost complete and indexing for the new phases will be attempted.
APC62_2	Very fast radiation damage was observed even at 100K
APC62_3	Very fast radiation damage was observed even at 100K
APC38	Indexing and space group determination ✓ Data being combined with (bad) data acquired by SCXRD
SR35	Too many few peaks for indexing
Tb37	Indexing and space group determination ✓
Tb37C	Indexing and space group determination ✓

The optimization of the structure-properties relationship for any chemical system can only be fully achieved once the structural details are known and this is our main aim. From the data collected at ESRF we are expecting to be able to obtain full

structural characterization on the novel compounds: (a) index powder pattern and determine lattice; (b) check data bases for related structures; (c) determine space group; (d) gather as much supporting information as possible (chemical composition, density, solid state NMR), (e) extract integrated intensities / structure factors; (f) and ultimately solve structure and refine the model. For some of the samples we unfortunately concluded that this was not possible either due to their sensitivity to radiation damage or to their very low crystallinity. Unfortunately, also a few samples revealed to be a mixture of phases what has been delaying the process and structure solution is most likely unviable for these cases. With five samples we have succeeded in the early steps and we hope to be able to go further in the structural characterization.

From all the samples the DAPNi is the most promising for a full structure characterization, due the quality of the diffraction pattern. With this experiment we are expecting to fully elucidate the fine structural details of the DAPNi systems to explain its behaviour under physiological environment.

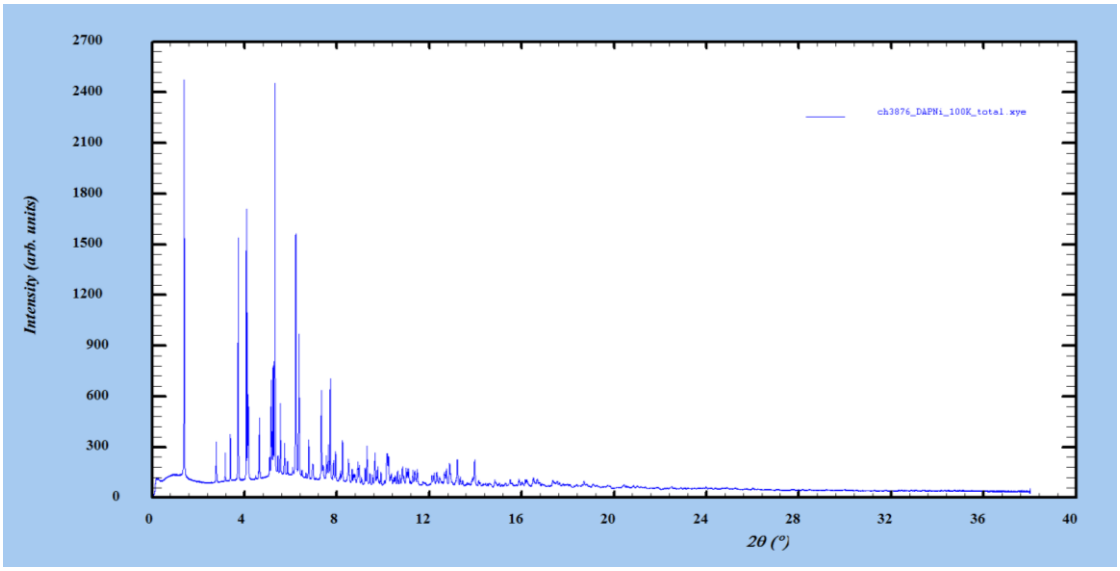

Figure 1 – Diffraction pattern of the DAPNi sample, indexed with the following unit cell: a=33.685Å, b=7.417Å, c=5.673Å, α=90°, β=101.63°, γ=90° (space group $P2_1$)

Conclusions

As stated before, the results obtained form high-resolution data collected at the ESRF ID31 beam line revealed to be most promising and this is indeed the best/only way for accurate structural elucidation of our compounds, prompting us to apply for a continuation proposal of this project at the new beam line ID22.

Appendix 1

(A) ***Dapsone-based BioMOFs:*** Dapsone is a medication used in the multidrug therapy for the treatment of leprosy and malaria; it is also a second-line treatment for prophylaxis against *Pneumocystis pneumonia* in HIV patients and it is used for the treatment of acne and other rashes like *dermatitis herpetiformis*. PXRD data collected in our lab equipments clearly showed the formation of new compounds with Zn, Fe and Ni, but no further structural characterization was possible. These compounds have shown to have good thermal and on-shelf stabilities. The compound with Ni is indeed the most crystalline and pure sample, having been the only of these samples tested at ESRF.

(B) ***Nalidixic acid-based BioMOFs:*** Nalidixic acid is the first of the synthetic quinolone antibiotics and it is especially used for the treatment of urinary tract infections. Reactions with Zn, Cu, Fe, Mn and Mg were confirmed by PXRD data. Despite all the efforts, no single crystals suitable for structural characterization were obtained and all the attempts to attain structural characterization from our in-house PXRD data were unsuccessful. The new compound obtained with Zn was the most promising for data collection at ESRF.

(C) ***Norflocaxin-based BioMOFs:*** Norfloxacin is a synthetic chemotherapeutic antibacterial agent occasionally used to treat common as well as complicated urinary tract infections. Its combination with metals that also display antibacterial effects may be of potential interest, exploring the synergetic effect.

(D) ***Pipemidic acid-based BioMOFs:*** Pipemidic acid is a member of the pyridopyrimidine class of antibacterials, which display some overlap in mechanism of action with analogous pyridone-containing quinolones. Also its combination with metals that also display antibacterial effects may be of potential interest, exploring the synergetic effect.