REPORT
CH-4160

11-16 December 2014 @ BM25A
8-10 February 2015 @ BM01A

Main Proposer:
M. Teresa Duarte

Other team members:
Vânia André
Sílvia Quaresma

Centro de Química Estrutural, Instituto Superior Técnico, Universidade de Lisboa
Portugal

Contact persons at ESRF:
Eduardo Salas Colera – BM25A
Philip Pattison – BM01A

Abstract

Bioinspired metal organic frameworks (BioMOFs), using active pharmaceutical ingredients (API) and non-toxic metals have been developed within our group for applications 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 in 2014. We were allocated time on BM25A for powder diffraction experiments and BM01A for single crystal data.

A total of 12 samples were analyzed during our stay in BM25A, from 11to16 December 2014. Collected data is under analysis and progress has been done, but it is still an on-going work. We believe that the data obtained will result in two publications.

A total of 5 samples were successfully analyzed in BM01A from 8 to 11 February 2015. Structures of these 5 samples have already been determined and the final refinements are being carried out. We expect to publish two papers including the data obtained at this beamline.

The results obtained form high-resolution data collected at the BM25A and BM01A, 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 while expanding our studies to include ZIFs, MZIfs and other compounds based on pharmaceutical molecules.

Scientific background

The synthesis of BioMOFs, "bioinspired" MOFs, using active pharmaceutical ingredients (API) and mainly safe metals, such as Mg, Zn, and Cu, applies the underlying concepts of crystal engineering and supramolecular chemistry. 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. Some results have been obtained with flufenamic acid, and carnosine. Nevertheless, the use of generally regarded as safe linkers to build porous BioMOFs for the incorporation of APIs, allowing a controlled drug transport and release is also a very interesting approach that we have explored, being the most relevant results obtained so far the ones with adenine and muconic acid.

We are exploiting a new pathway to build BioMOFs, using co-crystals as starting materials, expecting the simultaneous integration of both co-formers into the BioMOFs framework. For this alternative, the APIs that are being studied are pirlindole, carnosine, sulfanilamide and flufenamic acid.

The products are obtained *via* conventional solvothermal synthesis or by mechanosynthesis and thus are obtained mainly as microcrystalline powders from which structural solution using conventional powder X-ray diffraction proved to be unsuccessful. Recrystallization attempts were unsuccessful to grow suitable single crystals for "in-house" equipments. Data collected at ESRF for both powder and single crystal data was of upmost importance for our work. The complementarity of the data is fundamental for developing our research, single crystal results will be helpful in solving powder diffraction data.

Results at BM25A and their significance in the respective field of research

Twelve samples were collected in capillaries, using λ= 0.826Å (Table I). Data was collected from –5 to 30° for most samples and 2 to 52° for the samples that revealed to be most promising for structural solution; longer data acquisition time was carried out for higher angles. Data collection was carried out at 100K.

Table I - List of samples collected at BM25A, at 100K, using 0.826Å radiation

Sample Code	*Comments*
Ad_Zn	Indexing and space group determination on going
AdCu1:1_inicial	The sample revealed to contain multiple phases. Full identification of phases is complete. Indexing for the new phases is being attempted.
AdCu1:1_final	Indexing and space group determination ✓
AdCu1:2_inicial	The sample revealed to contain multiple phases. Full identification of phases is complete. Indexing for the new phases is being attempted.
AdCu1:2_final	The sample revealed to contain multiple phases. Full identification of phases is complete. Indexing for the new phases is being attempted.
AFlufCuAcet	Indexing and space group determination on going
CarnFum	Indexing and space group determination ✓
CarnMaleic	The sample revealed some amorphous content. Full identification of phases is complete. Indexing for the new phases is being attempted.
CarnAzelaic	The sample revealed some amorphous content. Full identification of phases is complete. Indexing for the new phases is being attempted.
CarnPimelic	The sample revealed some amorphous content. Full identification of phases is complete. Indexing for the new phases is being attempted.
AflufDABCO	Indexing and space group determination on going
PerlMandel	Indexing and space group determination on going
PerlToluen	Indexing and space group determination on going Data being combined with data acquired by SCXRD

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. Unfortunately, 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 seven samples we have succeeded in the early steps and we hope to be able to go further in the structural characterization.

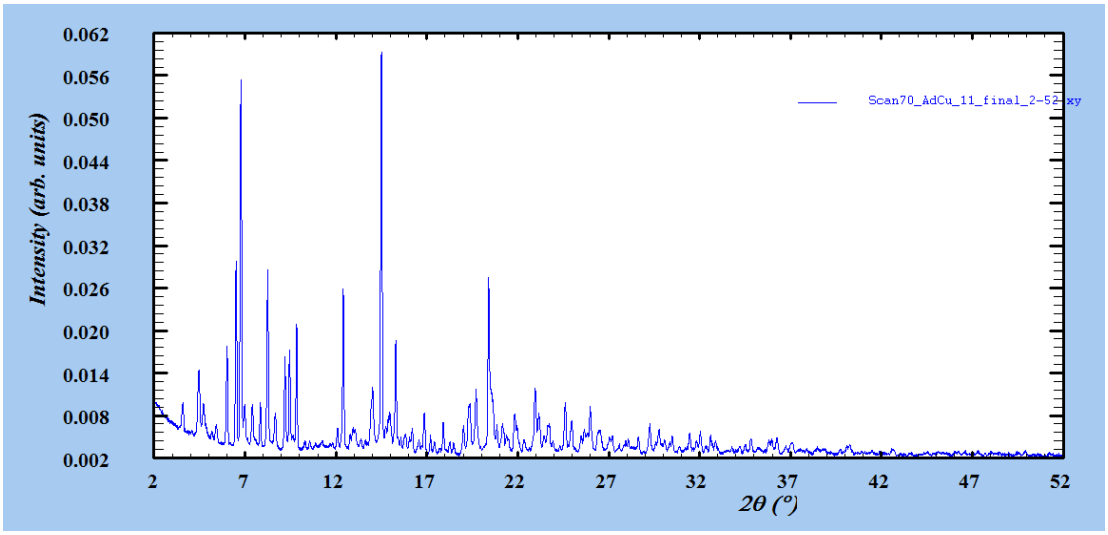

Figure 1 – Powder diffraction pattern for the stable form of the 1:1 Adenine:Cu MOF (a=17.08249 Å, b=13.37835 Å, c=12.91116 Å, α=91.76604°, β=106.02671°, γ=86.45451 °, triclinic space group *P*-1)

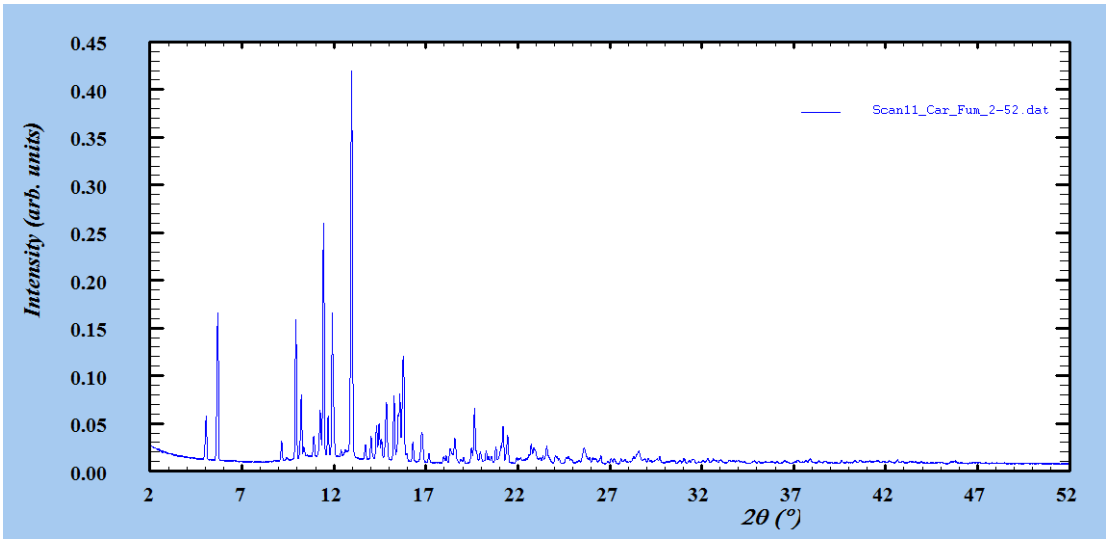

Figure 2 - Powder diffraction pattern for the Carnosine.fumaric acid cocrystal (a=17.54192 Å, b=34.66696 Å, c=9.33674 Å, β=100.37997°, monoclinic space group $P2_1/n$)

Results at BM01A and their significance in the respective field of research

Five new samples were successfully analyzed at BM01 (Table II). Several other samples were tested, but the size and/or quality of the crystals precluded any meaningful data collection.

Table II - List of samples collected at BM01A, at100K, using 0.69563Å radiation

Sample Code	*Comments*
Carnosine_Zn	Structure solved but similar to a previously reported one ✓
Flufenamic_Cu	Structure solved, but possible twinning problems still must be solved
Muconic_Mg	Structure solved ✓
Pirlindole	Structure solved ✓
Sulfanilanide_DABCO	Structure solved ✓

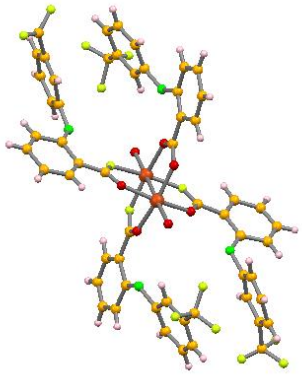

Figure 3 – Crystal structure for the Cu:Flufenamic acid coordination compound

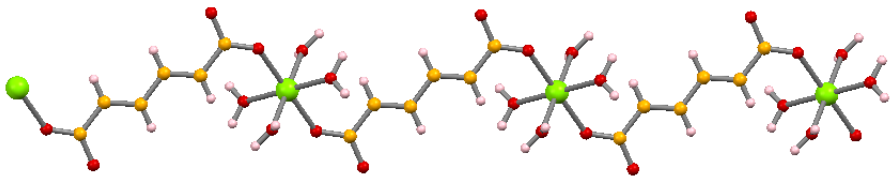

Figure 4 - Mg:Muconic acid 1D chain

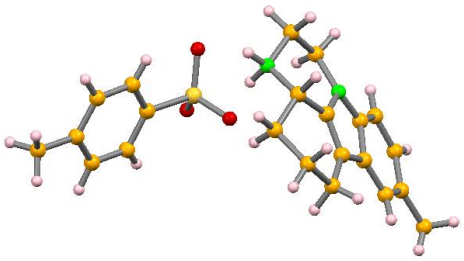

Figure 5 - Crystal structure for the Pirlindole:toluenosulfate cocrystal

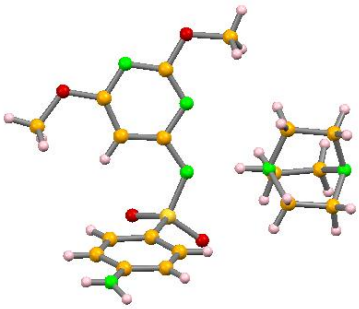

Figure 6 - Crystal structure for the Sulfanilamide:DABCO cocrystal

The determination of these structures is very important to assure the type of coordination obtained in the BioMOFs attempts. In the case of cocrystals it is equally important because very important structure-property relationships can be withdrawn from these results.

Conclusions

As stated before, the results obtained form high-resolution data collected at the ESRF BM25A beam line revealed to be most promising and this is indeed the best/only way for accurate structural elucidation of our compounds,

Also the results obtained at BM01A are of upmost importance for our studies and the structures determined are crucial for the development of our project and allow the establishment of relevant structure-property relationships.

Data collection was done very recently in both BM25A and BM01A and yet there are no publications or communications regarding these results. However we are expecting to publish at least four publications with these results in a near future.

All this prompts us to apply for a continuation proposal of this project.