1. PUBLISHABLE SUMMARY

Metal-Organic Frameworks (MOFs) are a class of crystalline materials built up from the interconnection of organic linkers and metal nodes.[1] The judicious choice of these organic and inorganic synthons and the control exerted on their spatial arrangement enables fine-tuning of their intrinsic porosity and accessible surface area. This controllable structure-to-function relationship, together with their extraordinary structural and chemical versatility, have resulted in the evaluation of these porous coordination polymers in applications such as gas storage and separation,[2] heterogeneous catalysis,[3] or sensing[4] amongst others

The development of open frameworks by introduction of biologically derived molecules as organic linkers is attracting particular attention nowadays. To date, the incorporation of amino acids or nucleobases has proven a valid route towards the design of bio-analogous MOFs. These hybrid biomaterials combine the intrinsic MOF characteristics with the metal-binding versatility, structural flexibility, homochirality, stereochemical selectivity or biological compatibility provided by the bio-backbone.[5] In this context, the use of oligopeptides has recently led to unprecedented adaptable porosity of the host upon gas sorption in [Zn(Gly-Ala)$_2$].[6] The flexibility of the peptide linker plays a key role in adapting the pore conformation as the multiple torsions available to polypeptide chains results in a wide distribution of combined torsional degrees of freedom, which permit the framework to adopt a wider energy landscape of thermally accessible conformations.

In this context we have developed an exhaustive research programme by exploiting the versatility of di- and tripeptides in the synthesis of a broad range of *porous peptide-based MOFs that combine their intrinsic porosity with the chirality introduced by the peptidic backbone*. Beyond this intrinsic multifunctionality, we have demonstrated how specific sequences of amino acids enable control of the structural stability and functional behaviour in these biomimetic materials. The fellow has explored the use of three different types of peptides: a) Gly-X (X=Asp, Val, Tyr, His, Ser, Thr); b) Gly-Gly-X (X= Ala, Thr, Ser, Asp) and c) Gly-His-X (X= Gly, Lys, Ser, Thr, Ala, Asp) along with binary combinations of peptides within a single framework. See below a summarized list of the frameworks isolated briefly illustrating some of their properties and next targets that are currently being approached.

- Dipeptides (Gly-X; X= Asp, Val, Tyr, His, Ser, Thr)

By following mild synthetic conditions, including HT liquid handling and solvothermal reactions at temperatures below 100º C, we have isolated a family of Zn(II) frameworks with general formula Zn(Gly-X)$_2$ (X=Asp, Val, Tyr, His, Ser, Thr). It is worth outlining the vital role played by the nature of the C-terminus aa in driving the formation of different topologies that vary from 1D segregated chains for the valine or histidine cases, to layered 2D materials (X=Tyr, Ser, Thr) or extended 3D frameworks for aspartate. Among these, only X=Ser & Thr display intrinsic porosity and were analysed further.

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[1] a) See special issue on Metal-Organic Frameworks,*Chem Rev.*, **2012**, *112*, 673-1268

[2] J. R. Li, R. J. Kuppler, H. C. Zhou, *Chem. Soc. Rev.* **2009**, *38*, 1477.

[3] J.-Y. Lee, O. K. Farha, J. Roberts, K. A. Scheidt, S. B. T. Nguyen, J. T. Hupp, *Chem. Soc. Rev.* **2009**, *38*, 1450.

[4] C. A. Bauer, T. V. Timofeeva, T. B. Settersten, B. D. Patterson, V. H. Liu, B. A. Simmons, M. D. Allendorf, *J. Am. Chem. Soc.* **2007**, *129*, 7136.

[5] I. Imaz, M. Rubio-Martínez, J. An, I. Solé-Font, N. L. Rosi, D. Maspoch, *Chem. Commun.* **2011**, 1.

[6] J. Rabone, Y. F. Yue, S. Chong, K. Stylianou, J. Bacsa, D. Bradshaw, G. Darling, N. Berry, Y. Khimyak, A. Ganin, P. Wiper, J. B. Claridge, M. J. Rosseinsky, *Science* **2010**, *329*, 1053.

[Zn(Gly-Thr)$_2$]•CH$_3$OH can be assembled by reaction of Zn^{2+} ions and the dipeptide glycilthreonine (Gly-Thr) in basic methanolic solutions. Besides exhibiting selective adsorption of CO2 over CH4, this 2D layered framework with 1D porosity remains crystalline upon solvent removal as confirmed by the single-crystal structural studies of the material before and after evacuation. Whilst the dipeptide Gly-Ala behaves as a flexible peptidic unit in the related Zn(Gly-Ala)$_2$,[6] Gly-Thr behaves here as a rigid connector and locks the conformational flexibility of the peptide by forming a chelate with the Zn^{2+} ion and establishing additional H-bonding interactions in the solid-state as result of its specific sequence of amino-acids. This scenario contrasts with the poor structural stability generally attributed to peptide-based materials and demonstrates how precise control of the coordination modes and supramolecular interactions via suitable choice of the peptide linker might enable to access combination of both, rigid and flexible connectors, to reach fine compromise between flexibility and structural stability to pave the way for the design of a next generation of robust adaptable porous materials.

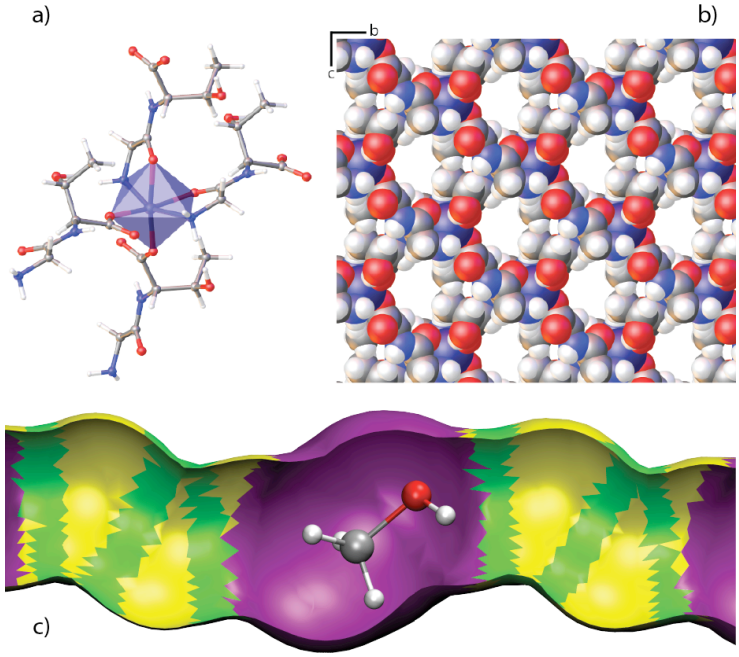

Figure 1. Secondary building (a) unit and perspective showing the intrinsic porosity of [Zn(Gly-Thr)$_2$] (b). Morphology of the 1D pores in the structure illustrating how the pockets are filled with methanol molecules in the solvated structure (c).

[Zn(Gly-Ser)$_2$]•CH$_3$OH is a 2D layered material built-up from the packing of grid-like sheets. These are formed from tetrahedrally coordinated Zn^{2+} ions that are connected to four peptides acting as μ-2 bridges. The as-made material is isostructural with [Zn(Gly-Ala)$_2$]•CH$_3$OH, so it can be considered a chemically modified analogue of this framework that introduces –OH groups in the α-carbon position of the C-terminus residue. Like Gly-Thr, Gly-Ser also leads to structurally-stable frameworks that retain crystallinity upon solvent removal but, in contrast with the rigidity displayed by the former, it is flexible enough to enable reversible single-crystal-to-single-crystal (SCTSC) transformations between two distinct structural configurations. These changes can be correlated with switchable porosity as the "open" solvated structure leads to a "closed" topology when the gest molecule is removed in vacuum. Next, exposure to polar guest like methanol drives the re-opening of the pores and recovers the original "open" structure.

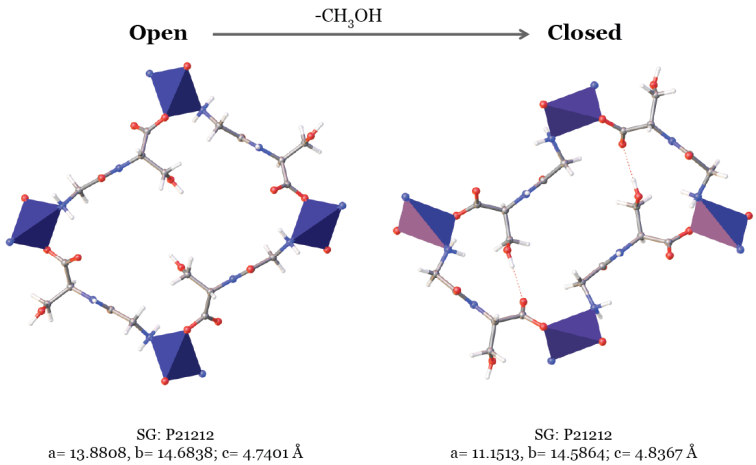

Figure 2. Reversible SCTSC transformation displayed by [Zn(Gly-Ser)2] upon de- and resolvation.

We have confirmed this experimental behavior by theoretically modeling this dynamic transformation and our results indicate that this reversible SCTSC change is

controlled by the presence of –OH groups introduced by the serine aa. These enable formation of intralayer H-bonds between the –OH and terminal –CO2 groups belonging to the C-term residues of neighboring peptides thus driving the folding of the peptide and leading to a controlled structural re-arrangement. This is consistent with the multiple relaxation pathways available for the desolvation Gly-Ala. Here, the presence of –CH3 groups do not allow for the appearance of an energetically favorable intermediate therefore leading to a disordered desolvated phase that will irreversibly decompose in air. The presence of a desolvated state stabilized by intralayer H-bonds also controls the porosity of the solid as our sorption experiments reflect that the framework remains closed upon CO2 sorption up to 15bar.

In summary, introduction of Ser and Thr in the peptidic sequence are determinant for controlling the structural stability of the frameworks. Whilst the use of GlyThr drives the formation of a rigid structure from the formation of a metal-to-peptide chelate and the presence of extra H-bond in the structure, GlySer acts as a flexible linker but introduces intralayer H-bonds that controls the folding of the peptide and controls the structural re-arrangement of the framework. The introduction of –OH containing aa's (or introduction of –OH functional groups in the synthetic equivalents of the peptides) appears very promising as a chemical route to control the structural stability of future flexible frameworks.

Controling the structural stability and porosity of peptide-based porous materials by combination of multiple peptides. Our results on single-peptide frameworks indicate that there is an intimate relationship between the aa sequence of the dipeptide connecting the metal nodes and the intrinsic features of the framework. Hence, Gly-Ala, Gly-Ser and Gly-Thr behave as loose, flexible and rigid connectors, respectively and this has a drastic effect not only in their structural stability upon desolvation: uncontrolled collapse, reversible SCTSC open-to-close transformation and unchanged structure; but also in their porous behaviour upon CO2 sorption: adaptable porosity, non-porous up to 15bar, classic type-I porosity (no gate opening, the structure remains open after evacuation). These observations together with the equivalent synthetic conditions used for the isolation of these family of [Zn(Gly-X)$_2$], encouraged us to study how these features could be effectively modulated by the combination of different Gly-X linkers within a single framework.

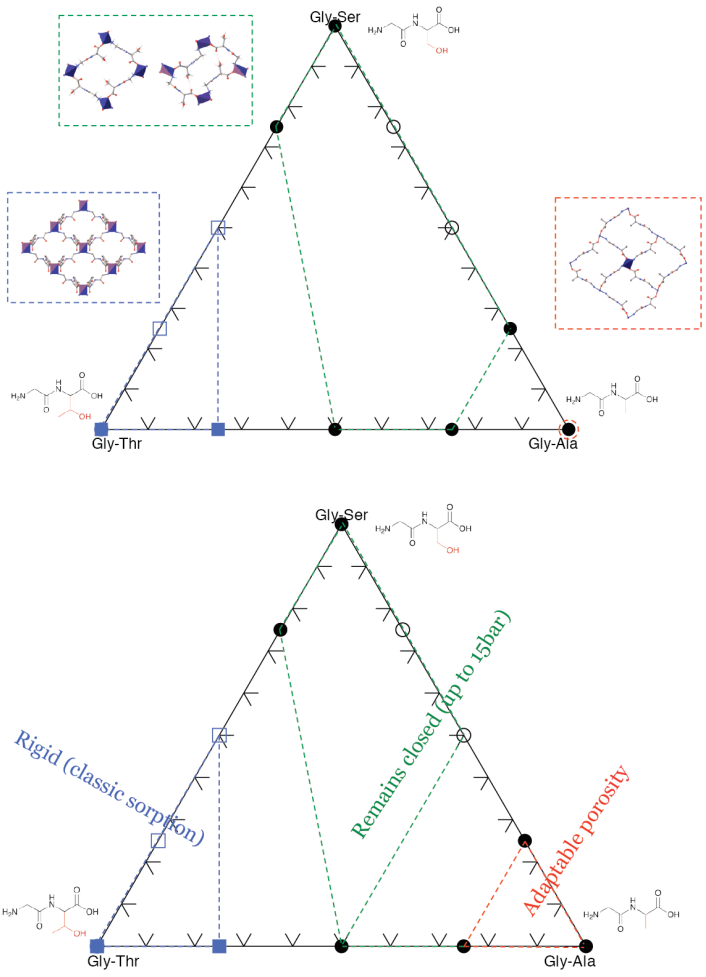

Figure 3. Ternary compositional diagrams summarising: the structural topologies (*top*) and porous behaviours (*bottom)* encountered for the different relative dipeptide-to-dipeptide ratios explored in the Zn(GlySer$_x$GlyAla$_{1-x}$)$_2$, Zn(GlySer$_x$GlyThr$_{1-x}$)$_2$ and Zn(GlyAla$_x$GlyThr$_{1-x}$)$_2$ (x=0.25, 0.50, 0.75) families.

By introducing slight changes to the original route, we have synthesised the families

$Zn(GlySer_xGlyAla_{1-x})_2$, $Zn(GlySer_xGlyThr_{1-x})_2$, $Zn(GlyAla_xGlyThr_{1-x})_2$ (x=0.25, 0.50, 0.75). Single crystal analysis has been performed for all binary combinations confirming that combination of both peptides in the frameworks results in structures with partial disorder in the α-carbon position of the C-term aa as expected from the distinct side-chains introduced by each peptide. NMR studies have been used to quantify this combination from digestion of as-made crystals in D_2O and our results confirm that the peptide-to-peptide ratios are in excellent agreement with the experimental values.

Our structural studies also reveal that the framework topology is fixed by the different Gly-Thr:Gly-Ser/Gly-Ala peptide combinations and varies from the Gly-Thr structure to the isostructural Gly-Ser/Gly-Ala topologies, except for binary Gly-Ser:Gly-Ala combinations, as summarized in the ternary composition diagram (see Fig.3; top). It is worth outlining that except for the 100% Gly-Ala material, all compounds remain crystalline upon desolvation and display reversible open-to-close crystalline transformations (Gly-Ser topology) or remain structurally unchanged (Gly-Thr topology) for given ratios. Given the loose nature of Gly-Ala as a linker (see above), this confirms that doping with other peptides appears as an effective route to enhance the structural stability of this framework and prevent uncontrolled collapse upon desolvation.

As for the porous behavior of these binary combinations (see Fig.3; bottom) it is clearly distinct for the two different topologies present. Whilst, Gly-Thr-like frameworks display almost identical, classic CO2 sorption regardless the relative peptide ratio, this variable clearly defines two different types of porosity for Gly-Ser-like materials depending on the amount of –OH containing peptides in the framework. Hence, materials containing 50% or more of Gly-Ser/Gly-Thr do not display CO2 loading up to 15bar due to the stabilization of the closed configuration via H-bond formation enabled by the presence of -OH groups. On the other hand, reduction of this percentage to 25% allows for the appearance of adaptable-porosity and sorption is observed above a gate-opening pressure (P_{GO}). Preliminary studies indicate that these gate-opening pressure values are strongly dependent on the relative amount of Gly-Ala:Gly-Ser/Gly-Thr peptides, and the gate-opening requires higher CO2 pressures as the amount of –OH groups increases. We are currently studying a narrower compositional interval to define more precisely the P_{GO} f([H-bonds]) relationship and the boundaries of adaptable porosity/non-porous regions, respectively.

In our opinion these preliminary results confirm that the functionality –structural stability and porosity- of peptide-based porous materials can be effectively controlled by combination of different type of connectors, whose ability to acts as loose, flexible or rigid connectors is fixed by specific aa's in the C-terminus position. The combination of two types of peptides within a single framework represents a remarkable advance in comparison with the use of single-peptides since the controlled introduction of specific aa's permits reaching not only the fine compromise between robustness and flexibility encountered in proteins, but also affect their porous behavior just like they control the biological function of proteins.

- Tripeptides Gly-Gly-X (X= Ala, Thr, Ser, Asp) and Gly-His-X (X= Gly, Lys, Ser, Thr, Ala, Asp)

$[Zn(Gly\text{-}Gly\text{-}X)_2]$•S (X=Ala, Thr) Equivalent synthetic conditions to those described for the ZnGly-X family drive the formation of $Zn(Gly\text{-}Gly\text{-}Ala)_2$ and $Zn(Gly\text{-}Gly\text{-}Thr)_2$ from the combination of Zn^{2+} ions and the tripeptides. These layered 2D frameworks exhibit open porous structures where the additional degrees of freedom introduce by the extra aa result in a broader range of accessible conformational configurations. As result of this extreme flexibility, the use of these tripeptides result in denser structures with reduced solvent accessible volumes if compared with those encountered in the Gly-X family. In the light of

our recent findings that reveal the role played by metal-chelation and supramolecular H-bonds in determining the structural stability and porosity of dipeptide-based porous materials (see above), we are currently exploring suitable modifications in the peptide sequence that will enable accessing increased porosities by locking its conformational flexibility.

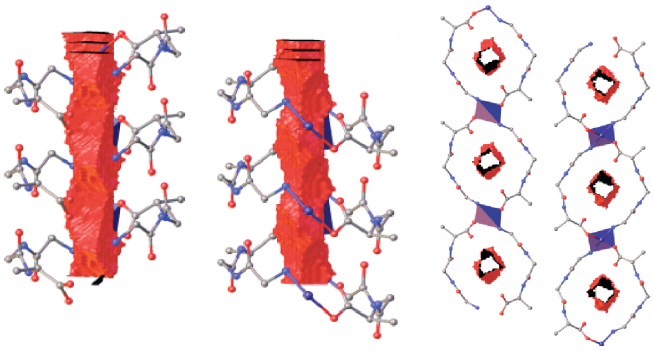

Figure 4. Perspective showing the layered structure and intrinsic porosity of [Zn(Gly-Gly-Ala)$_2$] along the 100 (*left*) and 001 (*right*) crystallographic directions.

[Cu(Gly-His-X)]•S (X=Gly, Lys, Ser) The addition of the tripeptides Gly-L-His-Gly and Gly-L-His-L-Lys to an ethanolic solution containing copper(II) ions leads to the formation of two isoreticular 3D peptide-based porous frameworks. They are built-up from the coordination of two tripeptides to the central Cu^{2+} atom via the C-terminus carboxylate. These materials are distinct from the compounds described above in several aspects – they are based on a dimeric unit, the peptide is deprotonated at the histidyl amide to form a characteristic triaza coordination at Cu and the resulting network is helical and three- rather than two-dimensional. These solids display sponge-like behaviour as they undergo reversible structural collapse upon evacuation that can be reverted by exposure to water vapours. This amorphous-to-crystalline transformation is favoured by the presence of H-bond interactions between the polar guest and the variety of accessible functional organic sites that decorate the surface of the pores, which permit recovering the open channel structure. This has been additionally confirmed by our sorption studies that reveal that both solids exhibit selective sorption of H_2O over CO_2. For the Gly-His-Lys case, it contains 12-14 guest water molecules per formula unit and displays 58.9% of solvent accessible volume (*cf* 28% Zn(GlyAla)$_2$),[6] demonstrating that large open frameworks are potentially accessible in the metal peptide family.

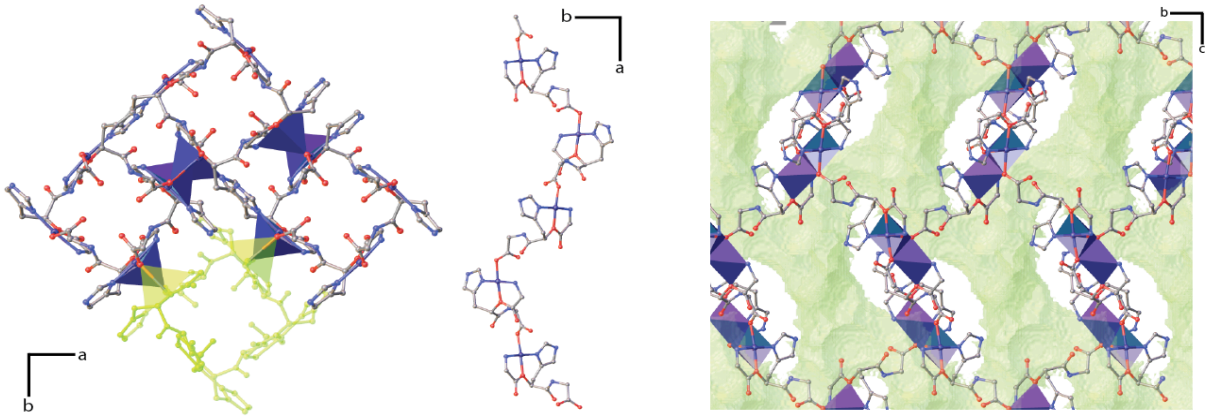

Figure 5. *Left:* Perspective showing how the sequence Cu-peptide-Cu defines 4-fold helicoidal chains (highlighted in pale green) that are bridged into a three-dimensional framework by the formation of μ_2-carboxylate bridges in the family [Cu(Gly-His-X)]. *Right*: Connolly surface representation of the 3D porosity (pale green, probe radius 1.2Å) that results from the interconnection of 1D pores in the open structure of [Cu(Gly-His-Gly)].

Finally, we have also shown how these biologically inspired materials can be also post-synthetically modified (PSM) by following standard methodologies generally used for classical frameworks built from more rigid "classical" linkers.[7] In this way, the pendant aliphatic amine chains present in the Lys C-term aa in [Cu(Gly-His-Lys)] have been reacted

[7] E. Dugan, Z. Wang, M. Okamura, A. Medina, S. M. Cohen, *Chem. Commun.*, **2008**, 3366

with ethyl isocyanate modified to produce an urea-functionalised framework that without significant loss of crystallinity. Given the catalytic activity of urea groups as hydrogen bond donors in aldol condensation reactions, this modification paves the way to study the potential interest of these materials as individual catalysts (100% urea sites) or in tandem catalytic processes by dual nucleophilic-electrophilic activation when both, unmodified amine and PSM-introduced urea groups, are present in the framework.

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