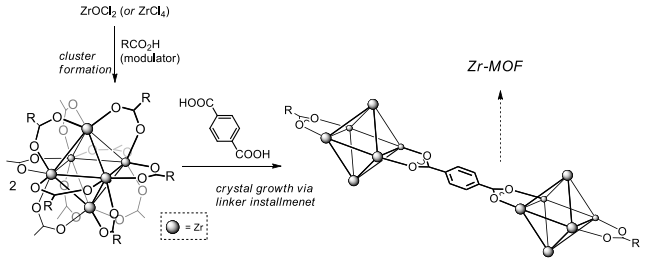
Modulation by amino acids: towards superior control in Zr-MOFs synthesis

Oleksii V. Gutov,[a]* Sonia Molina[a], Eduardo C. Escudero-Adán,[a] Alexandr Shafir*[a]

Abstract: Zr-MOF synthesis modulated by various amino acids, including *L*-proline, glycine and *L*-phenylalanine is shown as a straightforward approach towards functional group incorporation and particle size control. High yields in Zr-MOF are achieved employing 5 equiv of the modulator at 120 ºC; at lower temperatures, the method provides a series of Zr-MOFs with increased particle size, including many suitable for single crystal X-Ray diffraction. Furthermore, amino acid modulators can be incorporated at defect sites of Zr-MOFs with up to 1:1 amino acid-to-strut ratio, depending on the ligand structure and reaction conditions. The MOFs obtained through amino acid modulation exhibit improved CO_2 capture capacity when compared to non-functionalized material.

Introduction

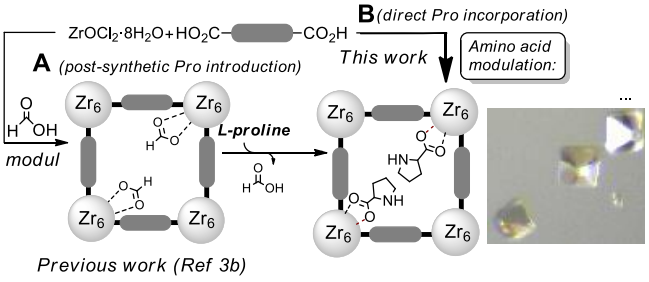
The Metal-Organic Frameworks (MOFs) assembled from the Zr_6-oxo cluster nodes and a polytopic carboxylate linker, pioneered by Lillerud *et al*.,[1] have emerged as promising porous materials for applications ranging from gas storage and separations to catalysis and sensing. In addition to the chemical versatility offered by the organic linker, these Zr-based MOFs show a remarkable stability, partly attributed to the high degree of connectivity, up to 12 carboxylates/cluster, associated with the Zr_6 node.[1,2] Interestingly, the synthesis of such materials, exemplified by the UiO-family[1] of MOFs, is commonly accomplished in the presence of a modulating agent, often a mono-carboxylic acid, *e.g.* benzoic or formic acids.[3] It is likely that the modulator, used in excess, leads to a more controlled network growth through the initial formation of soluble monomeric $Zr_6(OH)_4(O)_4(RCOO)_{12}$ clusters which then assemble through a slower dynamic exchange between the modulator and the linker units (Scheme 1). Indeed, assembly of discrete isolated Zr_6 carboxylate clusters has been established as a valid route towards UiO-type MOFs.[4]



Scheme 1. The modulation phenomenon illustrated for the formation of UiO-66 MOF.

Thus, modulation is now commonly used to induce higher levels of crystallinity and larger particle size often desired in several applications, including the possibility of a high-yield generation[3] of MOF particles of >1 μm size desirable in chromatography and continuous flow chemistry. Acid modulation has also been the key to achieve single crystals of Zr-MOF suitable for X-Ray analysis, aiding in the rational design of new materials and their detailed structural characterization.[3,5] Despite these advances, the generation of X-Ray quality single crystals in Zr-MOFs remains largely a trial-and-error enterprise. Interestingly, acid modulation in Zr-MOF synthesis has been recently shown to play a key role in the nature and quantity of defects present in the Zr MOF network. These defects, in turn, have come under an intense spotlight as potential sites for MOF functionalization,[3b,6] complementing the covalent linker modification approach.[7]

During the course of our own work on defect control and chemical modification in the UiO-family of MOFs, we reported that *L*-Proline (*L*-Pro) could be incorporated at missing linker formate-capped defects sites by treating samples of UiO-67 (Scheme 2A) with *L*-Proline hydrochloride.[3b,8] This led us to ponder the possibility of achieving Zr-MOFs containing *L*-Pro (or other amino acids) directly through modulation with the corresponding amino acid (Scheme 2B). Independently, since 2015, the Forgan laboratory has exploited the excellent modulating abilities of *L*-Pro and studied the phenomenon of amino acid modulation.[9] It should also be mentioned that applications of *L*-Proline in MOF design include the induction of supramolecular chirality in Zn-based MOF-5 crystals.[10]



Scheme 2. A) Anchoring of L-Pro onto Zr-MOF (ref. 3b); B) amino-acid modulated MOF synthesis.

Here, we wish to report our full study on the amino acid effect in the growth of Zr-MOF, including the exceptional modulating ability of *L*-Proline. Through a series of optimization experiments, two protocols have been identified for the use of *L*-Proline·HCl modulator in an exceptionally efficient generation of X-Ray quality single crystals. In addition, it was also found that amino acids can be incorporated at Zr MOF defects sites opening the door to new functional materials.

[a] Dr. O.V. Gutov, S. Molina, Dr. E.C. Escudero-Adán, Dr. A. Shafir
Institute of Chemical Research of Catalonia (ICIQ), Barcelona Institute of Science and Technology, Avda. Països Catalans 16, 43007, Tarragona, Spain
E-mail: ashafir@iciq.es; avgutov@gmail.com.

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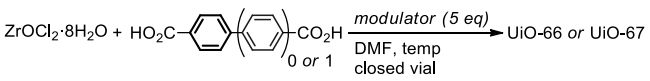
Results and Discussion

For the modulated synthesis of metal-organic framework, the solubility of the modulator acid in the reaction medium is likely a key factor for efficient growth of the 3D network. For several amino acids, including *L*-proline, the free base form proved largely insoluble in DMF, and showed poor modulating ability in the preparation of Zr-MOFs. Experimentally, converting the amino acids into the corresponding hydrochlorides proved crucial to ensure their solubility in DMF, enabling their use as modulators in the syntheses of Zr-MOF. Initial tests were conducted by exploring the growth of the isoreticular UiO-66 and UiO-67 pair in the presence of glycine (Gly), *L*-proline (*L*-Pro) and L-phenylalanine (*L*-Phe). Thus, in a sealable vial a mixture of $ZrOCl_2{\cdot}8H_2O$ and the aminoacid (5 equiv with respect to the linker) was dissolved in a mixture of DMF and HCl_{aq}; the linker diacid (*p*-terephthalic or biphenyl dicarboxylic) was then added and the vial was stored at 120 °C. Both UiO-66 or UiO-67 were readily obtained under these conditions (as per powder X-Ray diffraction, pXRD) with particle sizes <1 μm for L-Phe, and >1 μm for Gly and L-Pro (Figures S1, S2). ^{1}H NMR analyses of the acid-digested samples (see ESI) showed substantial level of amino acid incorporation into UiO-66 and moderate into UiO-67 (Table 1). *L*-Proline was particularly efficient, affording a high yield (≥90%) of the MOF in both cases. Importantly, the 5 equiv of proline loading employed here was a fraction of the commonly used modulator amounts (≥ 30 equiv), as has also been observed by Forgan *et al.*[9] The nitrogen sorption on amino acid modulated MOFs demonstrate high porosity of the samples (Figure S3, BET SAs: 1270, 1220, 1030 m^2/g for UiO-66Pro, UiO-66Gly and UiO-66Phe correspondingly) despite the high amino acid loadings. We take this data as evidence that amino acids are not simply "stuck" inside the pores, but are likely present as a defect-capping structural elements. Moreover TGA (Figure S4) show substantial linker deficiency in the studied samples. As a key observation, proline modulation at 70 °C, although much less efficient in terms of yield, led to the formation of X-Ray quality crystals of UiO-67 (Scheme 3a) on the walls of the reaction vial.

Table 1. Performance of three model amino acids as modulators for Zr-MOF syntheses.

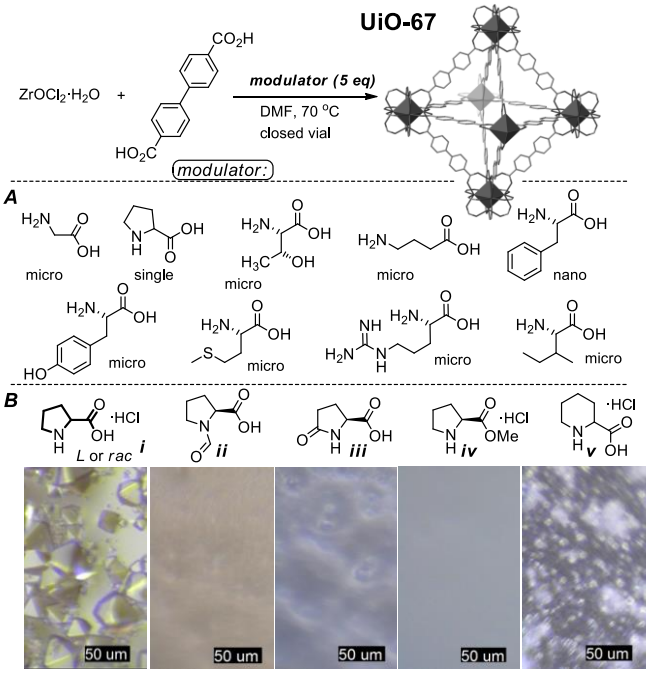


Temp, °C	*Mod* acid	UiO-66		UiO-67	
		Mod/L[a]	Range[b]	Mod/L[a]	Range[b]
120	*L*-Pro	0.5	Micro[c]	0.12	Micro[d]
	Gly	1.0	Micro	0.11	Micro
	L-Phe	0.8	Nano	0.14	Nano
70	*L*-Pro	0.9	Micro	<0.01	Single

[a] Defined as mmol (amino acid)/mmol HO_2C-R-CO_2H;

[b] Micro: (1-10 μm), Nano: (40-300 nm); [c] Yield: 95%; [d]: 90%

Intrigued by this ability to induce the growth of larger crystals at lower modulator loading, we tested a wider range of amino acids (Scheme 3A) as modulators of the formation of UiO-67 at 70 °C. This screen revealed that while several amino acids do provide the desired MOF (see pXRD in Figure S5), only proline (*L* or *rac*) appears to have the capacity to generate the material in a single crystalline form. It would appear, thus, that the steric/electronic properties balance in proline provides the right conditions for slower growth of high quality crystals. Addition experiments were carried out in order to pinpoint the structural parameters responsible for proline's unique modulation capacity. The use of *N*-formyl proline, detected during the proline-modulated Zr-MOF synthesis (see below), did not offer single crystals (Scheme 3B, compare ***i*** and ***ii***). Similarly, very small particles were observed using the pyroglutamic acid or the proline methyl ester (structures ***iii*** and ***iv***), indicating the participation of both the NH_2^+ and the CO_2H moieties in the modulation phenomenon. The poorer crystallinity registered for proline's next higher homologue, pipecolinic acid (entry ***vi***) was more surprising, and suggests even more subtle conformational effects on modulating ability. On the other hand, switching from the hydrochloride to the trifluoroacetic acid salt of *L*-proline led to an equally effective modulation (Figure S6).



Scheme 3. A) Amino acid screen in UiO-67 synthesis; B). Proline *vs* analogues in modulated synthesis.

As mentioned in the introduction, the generation of X-Ray quality crystals in Zr-MOF is far from trivial, and proline modulation appears to constitute a promising "point of attack" in this endeavor. Thus, proline modulation was applied to a range of potential linker structures (Figure 1) applying a set of conditions involving the use of $ZrOCl_2{\cdot}8H_2O$ and the in situ generated *L*-

proline hydrochloride (using HCl_{aq}, Method A). We were pleased to find that while MOF formation was observed in most cases tested, several of these were obtained in the form of X-ray quality single crystal (Figure S7). As a proof of concept, in addition to re-determining the single crystal structures of UiO-67 (reported recently, including by our group[11,3b,5b,9e]) and of a methylated UiO-68 derivative (also known as PCN-56),[12] we now prepared and solved the single crystal structure of the previously unknown UiO-67Cl, and of the NU-801, synthesized from the 1,4-benzenediacrylic acid (Figure 1, Method A). The structure of the latter had previously been determined from powder X-Ray analysis, and the new determination corroborates the previous structure.[2e]

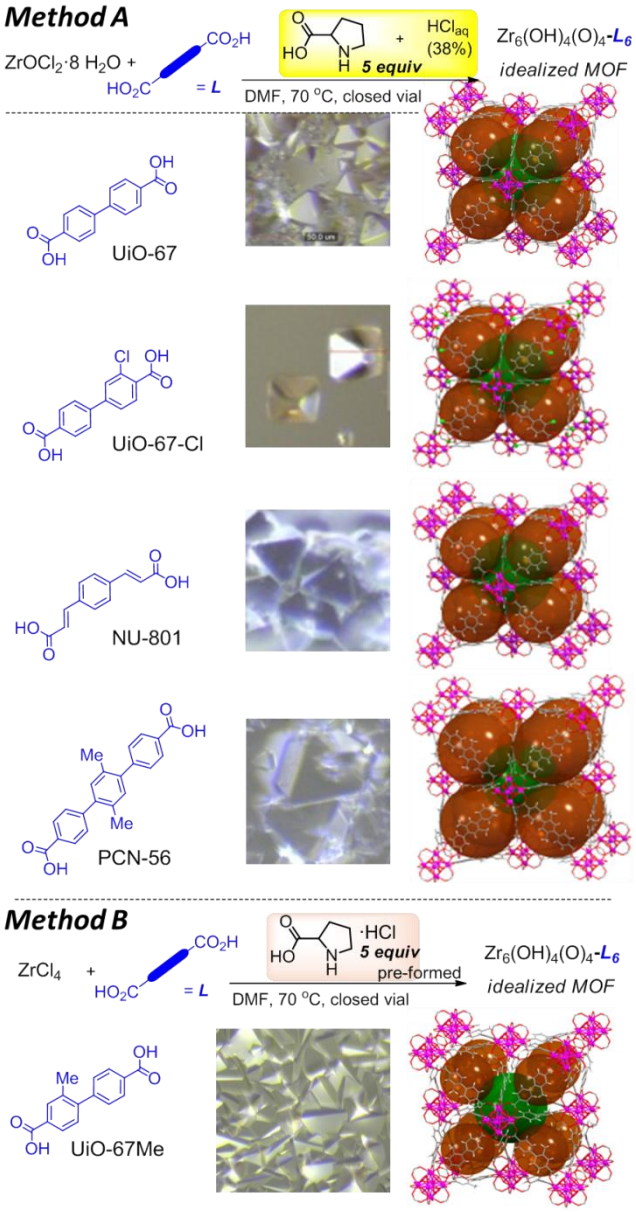


Figure 1. Ligands space explored in the current work for single crystal growth under 5 eq. L-Pro modulation.

While a 5-fold excess of *L*-proline was used to ensure optimal performance, single crystals could be achieved even with the stoichiometric quantity of *L*-Pro (Table S3), once again in sharp contrast to the classical protocols typically based on a large (≥30 equiv) modulator excess. However, when using the 5 equiv of *L*-Pro, diluting the reaction mixture led to smaller particles (Table S4). For certain linkers, it was observed that conditions employed in Method A were still insufficient to provide crystals large enough for conventional structure determination. We speculated that minimizing the reaction water content (present through the Zr(IV) hydrate source and also as HCl co-solvent) might further slow down the reaction, thus aiding in the formation of larger crystals. Indeed, using the pre-formed isolated *L*-Pro·HCl and the anhydrous $ZrCl_4$, large single crystals of UiO-67Me and Zr-muc were obtained, allowing in both cases for structure determination through single crystal X-Ray analysis (Figure 1, Method B; also Figure 2). In the context of the formation of a UiO-type network using the 2-Me-biphenylcarboxylic acid, it is interesting to mention the possibility of an alternative kinetically controlled ligand-deficient structure, PCN-700, reported recently by Zhou *et al* for a closely related 2,2'-dimethyl ligand.[13] As we see here (and as one might expect), it appears that having just one 2-Me substituent is insufficient override the thermodynamic preference for a cubic UiO-67 structure.[13b] Interestingly, the muconate-derived framework presents a structure different from that previously determined from pXRD for the material synthesized by ligand exchange from pre-formed Zr_6 methacrylate clusters.[4] While the reported structure featured the muconic acid in the *s*-cis conformation with a framework essentially identical (through disorder) to UiO-66 (Figure 2-B'), the single crystal structure of the material obtained here *via* proline modulation (Method B) is constructed with linkers in the extended *s*-trans conformation. The loss of co-linearity between the two RCO_2 coordination vectors is reflected in the lowering of the space group symmetry to $Pn\bar{3}$, down from the $Fm\bar{3}m$ ubiquitous for this type of networks. Specifically, the Zr_6 cluster now resides on a $\bar{3}$ site, which only imposes a crystallographic D_{3d} symmetry of a trigonal antiprism. The strut occupancy was refined to 0.82, meaning that roughly 1 out of 6 muconates is missing, in perfect agreement with proline levels obtained *via* digestion NMR of these crystals (0.4 L-Pro / 1 ligand, Table S2).

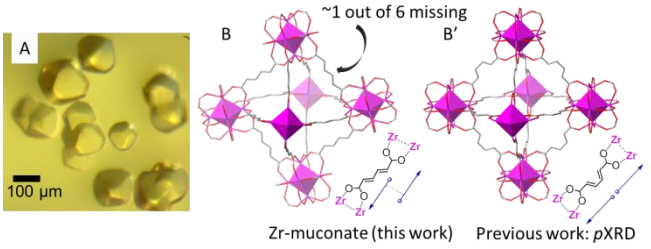


Figure 2. A) Crystal of the Zr muconate obtained by Method B, and B) the material's single crystal X-ray structure. For comparison, the pXRD structure for the material synthesized from Zr_6 methacrylate (ref 4) is shown as B'.

A second corollary of using amino acid modulators is the potential entry into amino acid-containing MOF structures. We found a roughly inverse correlation between amino acid incorporation and crystal size/quality (Tables 1, S2). This meant respectable levels (up to 1:1 *L-Pro* : ligand) of proline incorporation for the less crystalline UiO-66, for Zr-muc synthesized at low temperature, and for the high temperature batches of UiO-67, opening a way to control the amino acid loading. The amino acid binding is assumed to be the normal carboxylate bidentate coordination, as seen in the crystal structure of the related discreet Zr_6 glycinate.[14]

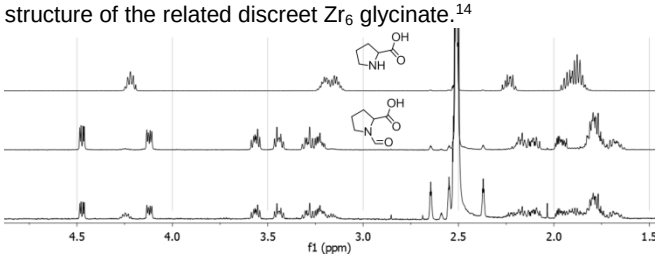
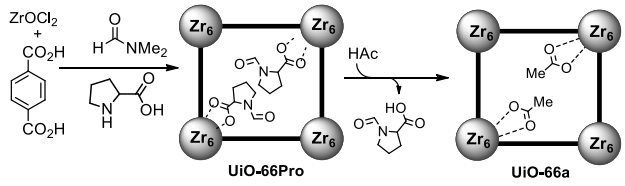


Figure 3. Fragment of NMR spectra of proline (top), *N*-formyl proline (middle) and proline-modulated UiO-66 (bottom).

The digestion NMR analysis in several of our UiO-66 and UiO-67 samples revealed that amino acid is included in the form of the *N*-formate, presumably through the reaction with DMF (Figure 3, Schemes 4 and S1), a process that we determined for various amines to be assisted by the presence of Zr(IV). For instance, heating a DMF solution of benzyl amine at at 100°C in the presence of either UiO-66 or $ZrOCl_2{\cdot}8H_2O$ for 20h led to the full conversion into N-formyl benzyl amine.

To confirm that the amino acid is chemically bound to the MOF (rather than being present as insoluble amorphous admixture), the recent technique of quantitative defects capping exchange[3b] for a new anion was applied (Scheme 4). Thus, a sample of UiO-66Pro, for which a close to 1:2 proline-to-terephthalic acid ratio had been determined by NMR, was immersed into a 4% AcOH solution in DMF for 20h, and then thoroughly washed with DMF and acetone. pXRD of the resulting material showed retention of crystallinity (Figure S12) and nitrogen sorption demonstrated increased porosity (BET SA 1550 m^2/g, Figure S13) consistent with substitution of formylprolinate with lighter acetate anion. Indeed, the digestion NMR of the resulting material showed a close to 1:2 acetic acid to framework ligand ratio, demonstrating quantitative substitution of the modulator capping defects with the new acid and lending further evidence for its position at defect sites.



Scheme 4. UiO-66Pro formation with simultaneous L-Pro formylation followed by its substitution with acetate for defects content confirmation.

As a final note, we briefly tested the effect that the effect of the modulator would have on the MOF's carbon capture capacity (an aspect that has been gained attention from the MOF community[15]). Here, we employed samples of UiO-66 prepared on a multi-gram scale using proline and benzoic acid modulation. The former (prepared at 120 °C), UiO-66Pro, was found to contain 0.5:1 *N*-formyl-L-Pro:ligand); the latter, UiO-66b,[3b] contained 0.8:1 benzoate:ligand. Measurements showed (Figure 4) that even though UiO-66Pro is less porous than UiO-66b (BET SAs 1270 versus 1520 m^2/g accordingly), the CO_2 uptake of the latter is 30% higher than that of the former. We tensatively attribute this increase to a stronger interaction of CO_2 with polar groups introduced via amino acid modulation. The CO_2 sorption capacity of UiO-66Pro is completely recovered after evacuation at room temperature.

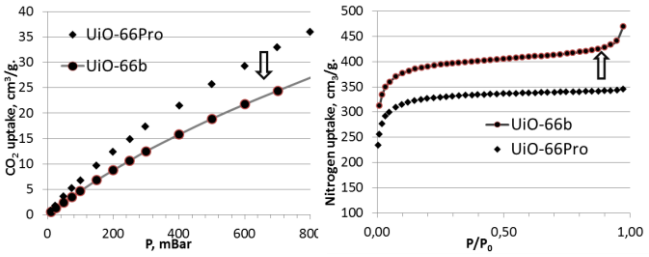


Figure 4. Nitrogen at 77K (left) and CO_2 at 300 K (right) sorption for UiO-66Pro in comparison to related UiO-66b.

Seeking to suppress proline formylation, modulated growth of Zr MOFs was also tested in other solvents. For environmental reasons, we are particularly interested in water, which was already demonstrated to work well for Zr-MOF syntheses.[16] We were pleased to find that water (and also DMSO, Figure S15, S16) is compatible with amino acid modulation and provides highly crystalline UiO-66 grafted with non-formylated proline.

Conclusions

Amino acid modulation for Zr-MOF synthesis was developed as a straightforward way for functionality incorporation and particle size control. This method (especially with proline) provides Zr-MOFs with increased particle size (μm to single crystals) important for chromatographic/flow chemistry applications and X-Ray characterization. New Zr-MOF single-crystal structures were studied as a result. On the other hand amino acid modulators can be incorporated into Zr-MOFs on defect sites in 0 to 1 ratio to the framework ligand which is controlled by ligands structure and reaction conditions. With the possibility of bigger biomolecules (peptides etc.) installation it opens straightforward opportunities for the design of new hybrid materials for separations and catalysis. Our amino acid modulated Zr-MOFs demonstrated improved CO_2 capture capacity comparing to non-functionalized material.

Experimental Section

General experimental information and additional procedures are provided in the Supporting information.

Method A for amino acid modulated Zr-MOF synthesis. The solid $ZrOCl_2 \cdot 8H_2O$ (485 mg, 1.51 mmol) and the amino acid modulator (7.53 mmol) were dissolved in a mixture of DMF (20 mL) and hydrochloric acid 37 % (0.625 mL, to convert amino acid to a soluble salt) in a vial (choose the size in terms of total volume, so that it is as full as possible under a 5 min sonication. The dicarboxylic acid ligand (1.51 mmol) was added and the mixture was further sonicated for an additional 5 min. The vial was sealed with a screw cap and was then stored undisturbed in a temperature-controlled oven preheated to the target temperature (120 ºC or 70 ºC, depending on the application requirements, such as yield/crystallinity/amino acid loading vs. single crystals, according to Table 1 in the main text) for 4 days. At this point, a part of the supernatant solution was decanted (the biggest single crystals were found on the walls of the reaction vessel), and the remaining resulting precipitate was separated by filtration or centrifugation (for nano-crystals) and washed with DMF (5 x 20 mL). For UiO-66Gly synthesis DMF-water (3:2 ratio) was used for washings instead of DMF to remove Gly byproducts. Each washing cycle consisted in adding the DMF, stirring the sample with spatula to achieve a homogeneous suspension, allowing the mixture to repose for 30 min, and then isolating the precipitate. The same procedure was then repeated with THF washes (5 x 20 mL). To remove the solvents from the pores (activate), the material was evacuated 5 h at room temp., and then for 15 h at 120 ^{0}C at a ramp of 1 ^{0}C/min.

X-Ray structure determination. All the structures determined by X-ray diffraction during this work have been deposited in the Cambridge Structural database.[17]

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Keywords: Zr-MOF -· Amino acids • proline • modulation • Zr MOF defect• functional MOFs

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[17] All the structures determined by X-ray diffraction during this work have been deposited in the Cambridge Structural database under CCDC numbers 1453411- 1453416.

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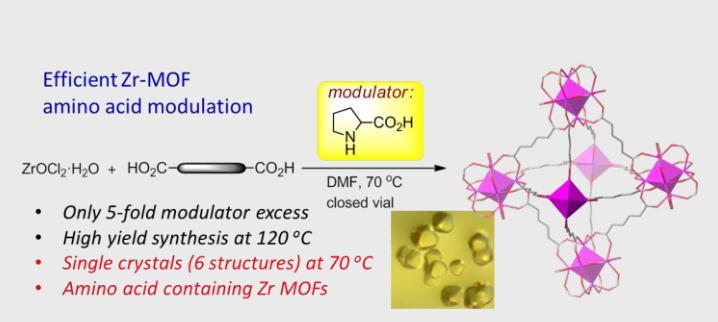

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