Highly defective ultra-small M(IV)-MOF nanocrystals

Shan Dai,^{1,4} Charlotte Simms,² Gilles Patriarche,³ Marco Daturi,⁴ Antoine Tissot,^{1*} Tatjana N. Parac-Vogt,^{2*} Christian Serre^{1*}

¹ Institut des Matériaux Poreux de Paris, Ecole Normale Supérieure, ESPCI Paris, CNRS, PSL University, 75005 Paris, France; Email: antoine.tissot@ens.psl.eu; christian.serre@ens.psl.eu

² Laboratory of Bioinorganic Chemistry, Department of Chemistry, KU Leuven, Celestijnenlaan 200F, 3001 Leuven,

Belgium; Email: tatjana.vogt@kuleuven.be

³ Université Paris-Saclay, CNRS, Centre de Nanosciences et de Nanotechnologies, 91120 Palaiseau, France

⁴ Normandie Univ., ENSICAEN, UNICAEN, CNRS, Laboratoire Catalyse et Spectrochimie, 14000 Caen, France

Abstract

A precise and concomitant control of both the size and defects in inorganic materials is of importance in many applications, particularly catalysis, as it often results in enhanced properties or emerging new features. So far, applying the strategy of modulation chemistry has been unable to afford high-quality functional Metal-Organic Frameworks (MOFs) nanocrystals with minimized size while exhibiting maximized defects. We report here a general sustainable strategy for the design of highly defective and ultra-small M(IV)-MOFs crystals (*ca.* 35% missing linker, 4-6 nm). Advanced characterizations have been performed to shed light on the main factors governing the crystallization mechanism and to identify the nature of the defects. The ultra-small Zr-MOFs showed excellent performance in peptide hydrolysis reaction, including high reactivity, selectivity, diffusion, stability, and show emerging tailorable reactivity and selectivity towards peptide bond formation simply by changing the reaction solvent. Therefore, these highly defective ultra-small tetravalent MOFs particles open new perspectives for the development of heterogeneous MOF catalysts with dual functions.

Introduction

Over the past few decades, the development of colloidal nanocrystals has led to a revolution in material science due to their very appealing properties in heterogeneous catalysis, optics, biology, and engineering.^{1, 2} Indeed, most nanomaterials undergo dramatic changes in their properties when their particle size lies in the ultra-small scale (e.g. below 5-10 nm) such as the quantum size effect in semiconductor materials,³ catalytic properties for inert noble metals,⁴ or electrical conductivity for insulators.⁵ Metal-organic frameworks nanocrystals (nanoMOFs) are porous solids assembled from metal ions/oxoclusters and organic linkers.^{6, 7} The reduction of the MOFs size to the nanoscale has imparted nanoMOFs with various enhanced properties (i.e., catalysis, sensing, biomedicine...)^{8, 9, 10, 11} and novel features,^{8, 12, 13} but despite advances, the design of ultra-small MOF nanoparticles still faces severe difficulties.¹⁴ This can be due either to the much larger unit-cell parameters of MOFs. However, at this ultra-small size, the majority of the

atoms of MOFs lie close to the external surface, which maximizes the interface for substrate interaction alongside largely decreases diffusion/desorption path length,⁴ naturally resulting in enhanced catalytic properties.

Defect engineering is a long term interest in crystalline nanomaterials, particularly due to the influence of vacant sites on catalysis.^{15, 16} Interestingly, structural defects in MOFs have shown similar optimizations towards catalytic properties and/or gas separation.¹⁷ However, this is in most cases associated with a lower chemical stability due to the reduction of metal-ligand connectivity and/or the presence of additional accessible metal sites.¹⁸ UiO-66(Zr) or $Zr_6O_4(OH)_4(BDC)_6$ (BDC= Benzene-1,4-dicarboxylic acid) is a prototypical zirconium-based MOF with a very high thermal and chemical stability due to its high connectivity (12-connected mode) and robust Zr-carboxylate bonds.¹⁹ Consequently, defect engineering in MOFs has been to date mainly focused on UiO-66(Zr) and its derivatives.¹⁸ The most typical method for the defect engineering in Zr-MOFs is the modulator-induced-defect approach (MIDA), where a monocarboxylate modulator (formate, acetate...) is added, binding preferentially with metal centers in place of the linker, leading to the missing ligand vacancy defects. As such, the defect content can be controlled by the amount of the modulator used.^{20, 21, 22, 23}



Figure 1. Scheme of a) the conventional modulator-induced-defect approach (MIDA) for the size-defect tuning of MOFs, b) the new approach that produces ultra-small and highly defective Zr-MOFs nanoparticles.

During the MOF synthesis, the modulator binds to the Zr_6 nodes to produce crystals with lower connectivity, and consequently with larger size due to slower nucleation and crystal growth kinetics. Although this is a reliable way to produce MOF particles with tunable particle sizes,^{24, 25} it is at the expense of control over the number of defects (**Figure 1a**).^{26, 27, 28, 29} The MIDA strategy therefore prevents the synthesis of highly defective and ultra-small nanoMOFs which are optimal candidates for catalysis. Notably, numerous reports have pointed out the importance of overcoming diffusion barriers, with MOF catalysed reactions mainly taking place on the outer surface of the particles.^{30, 31, 32} This is the case particularly when the size of the substrate is comparable to the aperture size of the MOF's pores. Although the substrates may diffuse inside the MOF framework, the desorption of the resulting products can be hampered by kinetic limitations. Relying on exfoliated high aspect ratio 2D porous nanosheets is an appealing alternative strategy to overcome these limitations.³³ However, these nanomaterials are usually more challenging to prepare (or

exfoliate) and/or exhibit usually a reduced stability compared with their related 3D counterparts. Therefore, developing new routes to both downsize robust nanoMOFs whilst ensuring a high defect content to address challenging catalytic reactions is a hot topic. The MIDA approach, which is usually carried out in DMF at high temperature and pressure, has mainly been explored with UiO-66 with missing linker defect content of ca. 10-20%. However, it has not been extended to the functionalized derivatives and thus, the full potential of this defective nanoMOFs family has not been exploited so far. It is therefore required to develop new synthetic versatile strategies to maximize these defects while maintaining reasonable thermal/chemical stability of the nanoMOFs to meet the demands of applications.

We report here a new and sustainable route to produce a series of ultra-small UiO-type MOFs (4-6 nm) with exceptionally high defect content. A set of advanced characterization techniques revealed that the large defect content on such small UiO-66 nanoparticles is attributed to the presence of missing linker defects and that the crystallization is growth-dominated. Noteworthy, this strategy is versatile and can be applied to many UiO-66(Zr)-X derivatives (X = NH₂, NO₂, (OH)₂, Br), to the Hf counterpart UiO-66(Hf) and finally to other Zr-MOFs structures like the Zr fumarate MOF-801(Zr), resulting in ultra-small nanoMOFs with very high defect content. Additionally, our mild green synthetic conditions are far more sustainable than the traditional solvothermal routes, which is of interest to save energy and/or strongly reduce the quantity of hazardous wastes. Moreover, the nanoMOFs synthesized here present excellent catalytic performance in peptide bond hydrolysis showing much better reactivity, chemicals diffusion, selectivity and stability than benchmark catalysts. Significantly, these nanoMOFs show bifunctionality as by simply changing the reaction solvent, the hydrolysis of peptide bonds can be replaced by the opposite condensation reaction, resulting in amide bond formation. Additionally, these nanoMOFs also show novel tailorable selectivity due to the molecular-sieving effect.

Results

To prepare highly crystalline ultra-small nanoparticles of UiO-66(Zr) with maximal defect content, we first considered carefully the main relevant state-of-the-art strategies. For instance, the acidity of the solution was shown to significantly influence the kinetics of crystallization due to the changes in protonation state of the carboxylic acids that lead to faster kinetics at higher pH.^{24, 34, 35} In addition, the presence of water in the reaction mixture appeared to be a critical factor in determining the defects resulting from the formation of Zr-OH or Zr-OH₂ bonds rather than Zr-ligand connections.³⁶ Using a low synthesis temperature was also shown to be beneficial towards both the defect engineering³⁷ and downsizing due to the inhibited formation of coordination bonds and to limited Ostwald ripening (illustrated in Figure 1b).³⁸ Thus, to achieve our ambitious goal to prepare ultra-small nanoMOFs with a high defect content, we developed a new simple green strategy that : (i) avoids the use of very acidic Zr salts (e.g., ZrCl₄, ZrOCl₂.xH₂O) and slightly acidic modulators (e.g. formic acid) by using pre-synthesized Zr₆ acetate oxoclusters (Figure S1); (ii) discards dimethylformamide (DMF) and replaces it by water and ethanol to avoid the release of formates upon DMF degradation (and enables a sustainable approach); (iii) ensures dissolution of the organic linker by diluting the reaction media in ethanol, subsequently fastening the synthesis kinetics; and (iv) is operated at room temperature.

The initial synthesis of UiO-66(Zr) was performed by first mixing Zr_6 oxoclusters with acetic acid. Water, ethanol, and benzene-1,4-dicarboxylic acid (BDC) were subsequently introduced in the oxocluster solution. After 2 h at room temperature under stirring, the resulting solid showed a PXRD pattern (see Figure S2) in agreement with the theoretical diffraction pattern of UiO-66. Transmission Electron Microscope (TEM) indicated a particle size of 40 nm (\pm 7) (Figure S3). This value is close to the particle size (44 nm) calculated

from Scherrer equation, indicating that the particles are well-crystalline. The 77K N₂ adsorption (Figure S4) showed a type I isotherm with extremely high N₂ capacity (404 cm³/g) and a calculated Brunauer–Emmett–Teller (BET) surface area (1617 (±5) m²/g) larger than the BET surface area of defect-free UiO-66(Zr) (1000 m²/g). Such a huge expansion in the surface area is indicative of the formation of a large amount of defects.²⁰ No symmetry-forbidden peak at low angle (under 20<7°) was observed in the PXRD pattern of the sample, suggesting the absence of missing cluster defects that would lead to an ordered structure with *reo* topology (Figure S2).²² Thus, we hypothesized the presence of missing linkers in our material. Fourier transform infrared spectroscopy (FTIR) demonstrated the absence of linker defects (Figure S5). Thermogravimetric analysis (TGA) under oxygen atmosphere evidenced that the 40 nm UiO-66 nanoMOF exhibited a very low ligand-to-metal ratio (linker:Zr₆ = 3.96:1, Figure S6), in agreement with a high missing linker content. The number of missing ligands in our sample corresponds to one of the most defective UiO-66 reported so far and concomitantly, to the best of our knowledge, the surface area of 40 nm UiO-66 represents the highest value reported compared to the state-of-the-art.^{23, 37, 39, 40}



Figure 2. a) Schematic diagram of our strategy, b) powder X-ray diffraction (PXRD) ($\lambda_{Cu} = 1.5406$ Å) patterns of UiO-66 synthesized with different volumes of EtOH, c) statistical mean size of the synthesized UiO-66, d) TEM image of the 5 nm UiO-66 (obtained with 80 mL EtOH), i) enlarged selected zone, ii) structure of UiO-66 viewed from (101) axis direction, e) SAED pattern of the 5 nm UiO-66, f) High-resolution Transmission Electron Microscope (HRTEM) images of HD-US-UiO-66 and their contrast intensity profiles, viewed along (i) (220) and (ii) (011) directions, scale bar= 5 nm, g) TGA of the UiO-66 with different sizes, adsorption and desorption are represented by filled spheres, and open spheres, respectively, i) pore size distribution for different sizes of UiO-66 (same color label as in h).

The general method we developed to control the particle size is illustrated in Figure 2a. As our first attempt led to highly defective 40 nm UiO-66 while using only 10 mL EtOH with 50 mg of BDC, the reaction media was further diluted stepwise with EtOH (20, 40, 80 mL, respectively) enabling a better dissolution

of the BDC ligand. Interestingly, this led to a dramatic reduction of nanoparticle size, as evidenced by the PXRD patterns in Figure 2b. Notably, when the volume of ethanol reached 80 mL, only a broad envelop of the main characteristic diffraction peaks of UiO-66 could be observed due to the considerable loss of longrange order, which is consistent with Scherrer equation. The TEM images (Figure S3, S7, S8, and Figure 2c-2d) evidenced the precise control of downsizing down to between 4 nm and 6 nm. Nevertheless, the crystal lattice planes can still be observed by TEM (Figure 2d), confirming the crystallinity of the nanoparticles. The selected area electron diffraction (SAED) pattern only showed the characteristic rings (no diffraction spots) of the UiO-66 nanoparticles with different crystal orientations (Figure 2e), further proving the crystallinity of these nanoMOFs, as well as homogeneous size distribution. Further enlargement of Figure 2d(i) clearly shows the pores and crystallinity of a 4.4 nm nanoparticle, in good accordance with the structural model from Figure 2d(ii). From the profile analysis on HRTEM images along (220) and (011) directions (Figure 2f), the distances between two adjacent Zr_6 oxoclusters are highly homogeneous with an average value of 1.1 nm that is close to the theoretical one (1.2 nm), suggesting that the defects are missing linkers in our HD-US-UiO-66(Zr). To be noted, such a small particle corresponds to only ca. 2 unit-cell dimensions, i.e. 8 unit-cells or 13 octahedral-cages per nanoparticle. This system therefore lies at the frontier between nanocrystals and discrete metal-organic polyhedra. However, to be noted, although Metal-Organic Cages/Polyhedra (MOCs/ MOPs) have intrinsically discrete supramolecular architectures, they often strongly suffer from poor chemical/hydrolytic stabilities and structural collapse upon activation, preventing their applications.⁴¹

According to TGA, all the different as-prepared nanoparticles exhibited very similar linker content, with close to 2 missing linkers per formula (Figure 2g). This, once combined with nuclear magnetic resonance (NMR) analysis (Figure S9) and Energy Dispersive X-ray spectroscopy (EDX) (Figure S10), leads to a general formula of $Zr_6O_4(OH)_4(BDC)_{3,9}(C_2H_3O_2)_{0.8}(H_2O)_{2,9}Cl_{0.5}$. Note that the connection of crystal size to defectiveness in our syntheses is the first of its kind and allows for achieving <5 nm MOF nanoparticles with defectiveness up to 4.2 missing linkers per oxocluster, by far exceeding the commonly reported values (Figure S11).¹⁸ Nitrogen porosimetry at 77K on the activated highly defective UiO-66 particles (HD-US-UiO-66) evidenced in all cases a high sorption capacity (from 404 cm³/g to 260 cm³/g, Figure 2h) associated with a hysteresis. A decrease of N₂ adsorption capacity occurred upon downsizing, in line with a progressive increase of the external to internal surface ratio. Pore size distribution analyses (DFT model) indicated overall a preserved pore size (Figure 2i), which is once again in line with the constant missing linker content. For the sake of comparison, we followed the conventional MIDA, as well as the synthetic parameters of 40 nm UiO-66 and carried out a set of synthetic experiments by reducing the amount of acetic acid. Noteworthy, the preparation of smaller particles, down to 5 nm, denoted as MI-US-UiO-66 (modulator-induced ultrasmall UiO-66), is associated with lower number of defects (2.6 missing linkers per Zr₆ oxoclusters) in good accordance with the previous findings where the missing linker defect content strongly depended on the modulator quantity (see SI for details).

To further investigate the nature of the missing linker defects at atomic level, *in situ* FTIR spectroscopy in presence of acetonitrile-d₃ (CD₃CN) vapors was performed. The acidity of pristine UiO-66(Zr) is mostly assigned to its intrinsic Brønsted acid sites (four μ_3 -OH), while, upon high temperature activation, additional Lewis acid sites associated to the defects (missing linker) are present. When introducing CD₃CN aliquots to 10 torr equilibrium pressure, three vibrational bands could be observed at 2306, 2301, and 2276 cm⁻¹, associated with the chemisorption of CD₃CN on different Lewis and Brønsted acid sites (Figure 3). The *v*(CN) bands at 2306 and 2301 cm⁻¹ mostly dominate the spectra in the first three doses, indicating a strong interaction between the Lewis acid sites (Zr⁴⁺) of the MOF and CD₃CN. Interestingly, these Zr-CD₃CN bands showed a slight blue shift, from 2296 cm⁻¹ to 2306 and 2301 cm⁻¹, in comparison to the constant peak position of the physisorbed CD₃CN (2261 cm⁻¹) in other reported works.^{42, 43} This clearly

indicates a higher acidic strength of the sites, likely promoted by the large concentration of defects. Their concentration could be calculated by integrating the corresponding bands vs. the molar amount of CD₃CN introduced. The obtained value of 1.19 mmol/g corresponded to a much larger number of Lewis acid sites than commonly reported defective UiO-66, e.g. typically around 300 μ mol/g⁴², which further demonstrates that our ultra-small UiO-66 nanoparticles exhibit a much higher degree of defects, being therefore particularly interesting for Lewis acid based catalysis.



Figure 3. *In situ* FTIR spectra at 298 K of CD₃CN (red to grey, probe small doses to up to 10 torr equilibrium pressure) adsorbed on HD-US-UiO-66 (5 nm).

Several hypotheses can be proposed to understand the formation of HD-US-UiO-66. First, the pre-formed Zr₆ acetate oxoclusters establish the pH of the solution near 4 which favors ligand deprotonation of the carboxylic groups of the ligand and thus leads to a faster nucleation upon substitution of the terminal acetates from the oxoclusters in the presence of the dicarboxylate moieties. Then, the dilution upon addition of ethanol impairs the effective collision rate, and once combined with the high modulator content, might limit the crystal growth as well as Ostwald ripening. However, upon downsizing, the reaction kinetics becomes faster, from 3h for the largest particles to less than 1h for the 4-6 nm particles. Thus, other parameters are likely in play. For instance, the solubility of the ligand is limited at RT in ethanol and therefore, the proportion of ligand that is solubilized increases with the ethanol dilution, which favors a faster kinetics for the smallest particles. To validate this hypothesis, considering the much better solubility of BDC in DMF, we replaced 50% of EtOH by DMF whilst keeping all other synthetic parameters constant. The resulting nanoparticles were found to be only ca. 8 nm instead of 40 nm in comparison with the use of EtOH (Figure S18), which corroborates the influence of the linker solubility on the kinetics. Such a bottleneck was observed previously by some of us when increasing the size of the dicarboxylic acid organic spacer over the crystallization under solvothermal conditions of UiO-66(Zr) and its extended analogues.⁴⁴



Figure 4. a) Hydrodynamic size of HD-US-UiO-66 colloids (T= 25 °C) determined by in situ timedependent DLS (time resolution $t_R=120$ s), and the b) ex situ HAADF-STEM (0=i, 1 min=ii) and HRTEM (120 min=iii, 180 min=iv) images of HD-US-UiO-66 at different times, scale bar= 5 nm.

To gain further understanding about the formation mechanism of the HD-US-UiO-66, in situ timedependent dynamic light scattering experiments (TD-DLS) were conducted. Figure 4a showed the evolution of particle size as a function of crystallization time of HD-US-UiO-66. The fast size increase process in the first 15 min was attributed to the formation of MOF nuclei. The MOF's growth was observed in the range between 15 min and 130 min and reached saturation after 130 min with a hydrodynamic size at ca. 18 nm. The clear slope revealed that the crystallization of HD-US-UiO-66 follows a growth-dominated process, in good agreement with the role of linker dissolution. The very low polydispersity index (Pdi) (Figure S19) implied a homogeneous nucleation followed by crystal growth of UiO-66 in solution. To confirm the growth kinetics of HD-US-UiO-66, an ex situ HRTEM/STEM study was carried out after 0, 1, 120, and 180 min. Figure 4b shows that only Zr_6 oxoclusters (ca. 0.6 nm) were observed before the introduction of BDC. Larger nanoparticles (around 1.3 nm) very quickly formed as soon as the ligand was added (1 min), which indicates the very fast nucleation of UiO-66 nanoparticles in solution, in agreement with the stage (i) in Figure 4a. The TEM images at 120 and 180 min demonstrated the growth of the small MOF nuclei and the saturation of nanoparticles growth. These results are fully consistent with TD-DLS, confirming the ligand dissolution acts as the bottleneck in controlling the MOF growth. Notably, the *in-situ* TD-DLS not only shed light on the crystallization process but also strongly highlighted the excellent colloidal stability of the HD-US-UiO-66. This effect, correlated to the highly positive charge evaluated by Zeta potential analysis, was observed whatever the nanocrystal size (Figures S20, S21) and is a strong asset for their solution processability in a view of applications such as ultrathin film fabrication, drug delivery, sensing and electronics, among others.45

One very appealing feature of MOFs is their ligand functionalization to achieve desired properties. Thus, we extended the new synthetic strategy to produce other functional HD-US-UiO-66-X derivatives, including $X = NH_2$, NO_2 , $(OH)_2$, Br, as well as replacing Zr₆ by Hf₆ oxocluster and BDC-based planar linkers by fumarate. Remarkably, all these MOFs exhibited 2-3 unit-cell sizes and very similar connectivity (*ca.* 3.3-4 linkers per formula) as the pristine HD-US-UiO-66 (see detailed analysis in SI).

In light of the properties of our HD-US-UiO-66-X, we decided to explore their use in heterogeneous catalysis.^{6, 18} The challenging hydrolysis of peptide bond in glycylglycine (GG) was selected as the model reaction to investigate the significance of downsizing/defect formation of MOF nanoparticles on the overall catalytic performance (Figure 5a). HD-US-UiO-66-NH₂ nanoMOF was subsequently selected for catalysis

due to the potential H-bonding that could occur between the peptide substrate and the $-NH_2$ group on the ligand, of $-NH_2$ between H_2O and substrate for the hydrolysis to occur, which could contribute to the overall catalysis.

As anticipated, the use of HD-US-UiO-66-NH₂ led to *ca*. 3 times higher reactivity compared to conventional UiO-66-NH₂ particles (*ca*. 200 nm) reported previously (Figure 5b). ⁴⁶ Such an enhancement might be due to the significantly expanded external surface area and/or the large defect content. Thus, we have compared the performance of HD-US-UiO-66-NH₂ and MI-US-UiO-66-NH₂ nanoMOFs with the previous study. Noteworthy, although MI-US-UiO-66-NH₂ showed better reactivity compared to the previous study, it performed worse (ca. 2 times) than HD-US-UiO-66-NH₂, despite their very similar particle size. This suggests that maximizing the amount of missing linker defects is critical to enhance the reactivity of UiO-66 derivatives towards peptide bond hydrolysis, in combination with decreasing the particle size. Notably, the reactivity here is comparable to benchmarks materials such as "superactive" MOF-808 (35 nm), which exhibited a GG hydrolysis rate of 2.69 x10⁻⁴ s^{-1.47}



Figure 5. a) Illustration of peptide hydrolysis using HD-US-UiO-66, b) Pseudo first order hydrolysis rate of glycylglycine (GG) to glycine (G) using HD-US-UiO-66-NH₂ and MI-US-UiO-66-NH₂ nanoMOFs, reference refers to the value reported in the previous studies under the same conditions,⁴⁶ c) Selectivity of hydrolysis by HD-US-UiO-66-NH₂ and HD-200-UiO-66-NH₂ in producing the desired product G, as the starting concentration of GG increases from 2 mM to 500 mM, d) Recyclability of HD-US-UiO-66-NH₂ over 5 reaction cycles in comparison to best-performing MOFs to date, percentage compared to yield of cycle 1, e) illustration of amide bond condensation using HD-US-UiO-66, in MeOH, f) Amide bond formation yield with HD-US-UiO-66 and HD-US-UiO-66-NH₂ starting from G, GG and AG.

The recyclability of HD-US-UiO-66-NH₂ nanoMOF was tested over five subsequent reaction cycles (Figure S35), with the slight loss of reactivity being only recorded after the 4th cycle, where the reactivity dropped to 80% of the reactivity observed in cycle 1. This is however still an excellent recyclability, especially when compared to benchmark materials, such as MIP-201 and MOF-808,^{47, 48} which suffered

from lower recyclability (55% and 80% activity reduction after up to 5 cycles, respectively, Figure 5d), and highlights the water stability of these ultra-small highly defective nanoMOFs,

The specificity of the catalyst was further studied, as GG may be hydrolyzed to G, or may undergo cyclisation (amide bond formation), forming cyclic GG (cGG) (Figure S32). By using HD-UiO-66-NH₂ nanoMOFs of two different sizes (4 nm vs 200 nm), the influence on particle size and external vs internal surface area on the reaction specificity was examined. The 200 nm UiO-66-NH₂ is labeled as HD-200-UiO-66-NH₂, and was fully characterized prior to catalytic reaction (Figure S36-38). Interestingly, the HD-US-UiO-66-NH₂ was found to be more selective, consistently giving a greater proportion of hydrolysis product G, rather than cGG, regardless of the starting concentration of GG substrate (Figure 5c). The HD-200-UiO-66-NH₂ produced considerably more cGG (40 - 50% of product), likely due to the increased internal surface area compared to HD-US-UiO-66-NH₂, which promotes amide bond condensation in the absence of water in the more hydrophobic pores, rather than hydrolysis reaction at the water exposed external surface of the nanoMOF.

As cGG was found to be a side product of hydrolysis with HD-200-UiO-66-NH₂, the nanoMOFs were further examined for their ability to catalyse the peptide bond formation between amino acids and small peptides. The condensation reaction can be promoted over hydrolysis simply by changing the solvent from water to methanol.⁴⁹ Both HD-US-UiO-66-NH₂ and HD-US-UiO-66 nanoMOFs showed the ability to promote amide bond formation in MeOH (Figure 5e,f), but the HD-US-UiO-66 exhibited much higher reactivity than the functionalized HD-US-UiO-66-NH₂. Similar to the previous report,⁴⁹ for both MOFs the intramolecular peptide bond formation was favored over intermolecular one between individual glycine molecules (Reaction 3, Figure 5f). Interestingly, the functionalized HD-US-UiO-66-NH₂ was ineffective in forming cGG when starting from GG (Reaction 2), but the fact that cGG was observed in other two reactions shown in Figure 5f, suggests that the efficiency of intramolecular bond formation is influenced by substrate interaction with the MOF, rather than a reduced catalytic activity. These differences in the interactions could be in influenced by the presence of the electron donating -NH₂ on the MOF, as well as by the MOF pore sizes, as the functionalized MOF exhibits slightly smaller pores due to the steric hindrance of the -NH₂, which increases the diffusion barrier of the substrate into and out of the pores of the MOF.

Outlook

In this work, we have reported a new general strategy for the preparation of a series of highly defective (35%-45% missing linker) and ultra-small (4-6 nm) UiO-66-based nanocrystals under fully sustainable conditions, suggesting feasibility towards upscaling. Crystal growth acts as a bottleneck in crystallization as evidenced by in situ TD-DLS with ex situ HRTEM/STEM and can be manipulated by simply using additional solvent. Missing linker defects have been assessed by multiple advanced techniques, including PXRD, FTIR, TGA, HRTEM and in situ FTIR spectroscopy coupled with CD₃CN probe, which revealed the importance of Lewis-acidity of the HD-US-UiO-66. The resulting HD-US-UiO-66-X showed excellent catalytic performance in both peptide bond hydrolysis and formation with very remarkable catalytic reactivity, selectivity, product recovery efficiency, and recyclability compared to other reported materials. Detailed investigation of the influence of defects, particle size and functionalization on the catalytic activity of the nanoMOFs provided unique insights into the key parameters that influence the reactivity, and as such demonstrate how nanoMOFs can be tuned to show specific and selective reactivity through precise control of catalysts' properties. Therefore, the discoveries reported here might further promote the development of nanoMOFs as heterogeneous catalysts having dual functions and performance enhancements in varying aspects. Furthermore, the novel materials presented here may be also used for the development of sensing/optical devices (preliminary results in SI, Figure S24), membranes, nanomedicine formulations and to explore other fundamental size-dependent properties.

Acknowledgements

SD, C. Serre and MD acknowledge the European Union's Horizon 2020 research and innovation program under grant agreement No. 831975 (MOF4AIR project) for providing financial support. C. Simms thanks the Research Foundation-Flanders (FWO) for the fellowship grant (68090/11C9320N). The authors appreciate the help of Dr. X. Xu for TEM measurements. SD, AT, GP and C. Serre acknowledged the Paris region, through the DIM Respore priority project, for the access to HRTEM.

Method

Synthesis of HD-US-UiO-X (X=H, NH, NO₂, (OH)₂, Br). In a typical synthesis, $M(IV)_6$ oxoclusters (0.06 mmol, 75 mg) were dispersed in acetic acid (0.5 mL) under stirring at 600 rpm. H₂O (1.25 mL) was subsequently added, and the reaction mixture was stirred until it became completely colorless. Ethanol was introduced into the solution followed by the immediate addition of 1.2 mmol BDC-X, and the reaction was stirred for 2h at room temperature. The resulting solution was evaporated by rotary evaporation at room temperature until approximately 10 mL volume was left. The colloidal suspension was centrifuged at 14,500 rpm for 60 min and then washed twice with the mixture of 20 mL of acetone and 20 mL of ethanol (14,500 rpm, 1.5h). The collected solid was dried under vacuum for 3 h for characterizations and applications. The particle size can be controlled simply by using different amounts of ethanol in the synthesis batch.

Data availability

All data supporting the finding of this study are available from the corresponding authors upon request. Source data are provided with this paper.

Author contributions

S.D., A.T., and C. Serre conceived the research. S.D., C. Simms and T.V. designed the experiments and analyzed the data. G.P. conducted the STEM/HRTEM analysis. M.D. supervised the *in situ* FTIR experiments. S.D. wrote the original draft with the help of C. Simms. All authors contributed in the paper discussion and revision. C. Serre supervised the project.

Competing interests

The authors declare no competing interests.

References

- 1. Roduner E. Size matters: why nanomaterials are different. *Chemical Society Reviews* 2006, **35**(7): 583-592.
- 2. Chen Y, Lai Z, Zhang X, Fan Z, He Q, Tan C, *et al.* Phase engineering of nanomaterials. *Nature Reviews Chemistry* 2020, **4**(5): 243-256.
- 3. Wang Y, Herron N. Nanometer-sized semiconductor clusters materials synthesis, quantum size effects, and photophysical properties. *Journal of Physical Chemistry* 1991, **95**(2): 525-532.

- 4. Valden M, Lai X, Goodman DW. Onset of catalytic activity of gold clusters on titania with the appearance of nonmetallic properties. *Science* 1998, **281**(5383): 1647-1650.
- 5. Zhang P, Tevaarwerk E, Park B-N, Savage DE, Celler GK, Knezevic I, *et al.* Electronic transport in nanometre-scale silicon-on-insulator membranes. *Nature* 2006, **439**(7077): 703-706.
- 6. Cai XC, Xie ZX, Li DD, Kassymova M, Zang SQ, Jiang HL. Nano-sized metal-organic frameworks: Synthesis and applications. *Coordination Chemistry Reviews* 2020, **417**.
- 7. Protesescu L, Calbo J, Williams K, Tisdale W, Walsh A, Dincă M. Colloidal nano-MOFs nucleate and stabilize ultra-small quantum dots of lead bromide perovskites. *Chemical Science* 2021, **12**(17): 6129-6135.
- 8. Sakata Y, Furukawa S, Kondo M, Hirai K, Horike N, Takashima Y, *et al.* Shape-memory nanopores induced in coordination frameworks by crystal downsizing. *Science* 2013, **339**(6116): 193-196.
- 9. Krause S, Bon V, Senkovska I, Többens DM, Wallacher D, Pillai RS, *et al.* The effect of crystallite size on pressure amplification in switchable porous solids. *Nature communications* 2018, **9**(1): 1-8.
- 10. Horcajada P, Chalati T, Serre C, Gillet B, Sebrie C, Baati T, *et al.* Porous metal–organic-framework nanoscale carriers as a potential platform for drug delivery and imaging. *Nature materials* 2010, **9**(2): 172-178.
- 11. Marshall CR, Dvorak JP, Twight LP, Chen L, Kadota K, Andreeva AB, *et al.* Size-Dependent Properties of Solution-Processable Conductive MOF Nanocrystals. *Journal of the American Chemical Society* 2022, **144**(13): 5784-5794.
- 12. Fabrizio K, Brozek CK. Size-Dependent Thermal Shifts to MOF Nanocrystal Optical Gaps Induced by Dynamic Bonding. *Nano Letters* 2023, **23**(3): 925-930.
- 13. Xia H-L, Zhang J, Si J, Wang H, Zhou K, Wang L, *et al.* Size- and Emission-Controlled Synthesis of Full-Color Luminescent Metal-Organic Frameworks for Tryptophan Detection. *Angewandte Chemie International Edition*, **n**/**a**(n/a): e202308506.
- 14. Zhao M, Wang Y, Ma Q, Huang Y, Zhang X, Ping J, *et al.* Ultrathin 2D metal–organic framework nanosheets. *Advanced Materials* 2015, **27**(45): 7372-7378.
- 15. Nowotny MK, Sheppard LR, Bak T, Nowotny J. Defect chemistry of titanium dioxide. Application of defect engineering in processing of TiO2-based photocatalysts. *The Journal of Physical Chemistry C* 2008, **112**(14): 5275-5300.

- 16. Busch G. Early history of the physics and chemistry of semiconductors-from doubts to fact in a hundred years. *European Journal of Physics* 1989, **10**(4): 254.
- 17. Furukawa H, Müller U, Yaghi OM. "Heterogeneity within order" in metal–organic frameworks. *Angewandte Chemie International Edition* 2015, **54**(11): 3417-3430.
- 18. Dissegna S, Epp K, Heinz WR, Kieslich G, Fischer RA. Defective metal-organic frameworks. *Advanced Materials* 2018, **30**(37): 1704501.
- 19. Cavka JH, Jakobsen S, Olsbye U, Guillou N, Lamberti C, Bordiga S, *et al.* A new zirconium inorganic building brick forming metal organic frameworks with exceptional stability. *Journal of the American Chemical Society* 2008, **130**(42): 13850-13851.
- 20. Wu H, Chua YS, Krungleviciute V, Tyagi M, Chen P, Yildirim T, *et al.* Unusual and highly tunable missing-linker defects in zirconium metal–organic framework UiO-66 and their important effects on gas adsorption. *Journal of the American Chemical Society* 2013, **135**(28): 10525-10532.
- 21. Vermoortele F, Bueken B, Le Bars G, Van de Voorde B, Vandichel M, Houthoofd K, *et al.* Synthesis modulation as a tool to increase the catalytic activity of metal–organic frameworks: the unique case of UiO-66 (Zr). *Journal of the American Chemical Society* 2013, **135**(31): 11465-11468.
- 22. Shearer GC, Chavan S, Bordiga S, Svelle S, Olsbye U, Lillerud KP. Defect engineering: tuning the porosity and composition of the metal–organic framework UiO-66 via modulated synthesis. *Chemistry of Materials* 2016, **28**(11): 3749-3761.
- 23. Liang W, Coghlan CJ, Ragon F, Rubio-Martinez M, D'Alessandro DM, Babarao R. Defect engineering of UiO-66 for CO2 and H2O uptake–a combined experimental and simulation study. *Dalton Transactions* 2016, **45**(11): 4496-4500.
- Schaate A, Roy P, Godt A, Lippke J, Waltz F, Wiebcke M, *et al.* Modulated synthesis of Zr-based metal–organic frameworks: from nano to single crystals. *Chemistry–A European Journal* 2011, 17(24): 6643-6651.
- 25. Forgan RS. Modulated self-assembly of metal–organic frameworks. *Chemical science* 2020, **11**(18): 4546-4562.
- 26. Fang Z, Dürholt JP, Kauer M, Zhang W, Lochenie C, Jee B, *et al.* Structural complexity in metal– organic frameworks: Simultaneous modification of open metal sites and hierarchical porosity by systematic doping with defective linkers. *Journal of the American Chemical Society* 2014, **136**(27): 9627-9636.

- 27. Taylor JM, Dekura S, Ikeda R, Kitagawa H. Defect control to enhance proton conductivity in a metal–organic framework. *Chemistry of Materials* 2015, **27**(7): 2286-2289.
- Abánades Lázaro I, Wells CJ, Forgan RS. Multivariate modulation of the Zr MOF UiO-66 for defect-controlled combination anticancer drug delivery. *Angewandte Chemie* 2020, **132**(13): 5249-5255.
- 29. Wei R, Gaggioli CA, Li G, Islamoglu T, Zhang Z, Yu P, *et al.* Tuning the Properties of Zr6O8 Nodes in the Metal Organic Framework UiO-66 by Selection of Node-Bound Ligands and Linkers. *Chemistry of Materials* 2019, **31**(5): 1655-1663.
- 30. Dang S, Zhu Q-L, Xu Q. Nanomaterials derived from metal–organic frameworks. *Nature Reviews Materials* 2017, **3**(1): 1-14.
- 31. Gao WY, Cardenal AD, Wang CH, Powers DC. In Operando Analysis of Diffusion in Porous Metal-Organic Framework Catalysts. *Chemistry–A European Journal* 2019, **25**(14): 3465-3476.
- 32. Sharp CH, Bukowski BC, Li H, Johnson EM, Ilic S, Morris AJ, *et al.* Nanoconfinement and mass transport in metal–organic frameworks. *Chemical Society Reviews* 2021, **50**(20): 11530-11558.
- Wang M, Dong R, Feng X. Two-dimensional conjugated metal-organic frameworks (2D c-MOFs): chemistry and function for MOFtronics. *Chemical Society Reviews* 2021, **50**(4): 2764-2793.
- 34. Dai S, Nouar F, Zhang S, Tissot A, Serre C. One-Step Room-Temperature Synthesis of Metal (IV) Carboxylate Metal—Organic Frameworks. *Angewandte Chemie* 2021, **133**(8): 4328-4334.
- 35. Dai S, Simms C, Dovgaliuk I, Patriarche G, Tissot A, Parac-Vogt TN, *et al.* Monodispersed MOF-808 Nanocrystals Synthesized via a Scalable Room-Temperature Approach for Efficient Heterogeneous Peptide Bond Hydrolysis. *Chemistry of Materials* 2021, **33**(17): 7057-7066.
- 36. Firth FC, Cliffe MJ, Vulpe D, Aragones-Anglada M, Moghadam PZ, Fairen-Jimenez D, *et al.* Engineering new defective phases of UiO family metal–organic frameworks with water. *Journal of Materials Chemistry A* 2019, **7**(13): 7459-7469.
- DeStefano MR, Islamoglu T, Garibay SJ, Hupp JT, Farha OK. Room-temperature synthesis of UiO-66 and thermal modulation of densities of defect sites. *Chemistry of Materials* 2017, 29(3): 1357-1361.
- 38. Liu L, Chen Z, Wang J, Zhang D, Zhu Y, Ling S, *et al.* Imaging defects and their evolution in a metal–organic framework at sub-unit-cell resolution. *Nature chemistry* 2019, **11**(7): 622-628.

- 39. Decker GE, Stillman Z, Attia L, Fromen CA, Bloch ED. Controlling size, defectiveness, and fluorescence in nanoparticle uio-66 through water and ligand modulation. *Chemistry of Materials* 2019, **31**(13): 4831-4839.
- 40. Wang X, Lyu Q, Tong T, Sun K, Lin L-C, Tang CY, *et al.* Robust ultrathin nanoporous MOF membrane with intra-crystalline defects for fast water transport. *Nature Communications* 2022, **13**(1): 1-11.
- 41. Sánchez-González E, Tsang MY, Troyano J, Craig GA, Furukawa S. Assembling metal–organic cages as porous materials. *Chemical Society Reviews* 2022.
- 42. Ragon F, Campo B, Yang Q, Martineau C, Wiersum AD, Lago A, *et al.* Acid-functionalized UiO-66 (Zr) MOFs and their evolution after intra-framework cross-linking: structural features and sorption properties. *Journal of Materials Chemistry A* 2015, **3**(7): 3294-3309.
- 43. Chakarova K, Strauss I, Mihaylov M, Drenchev N, Hadjiivanov K. Evolution of acid and basic sites in UiO-66 and UiO-66-NH2 metal-organic frameworks: FTIR study by probe molecules. *Microporous and Mesoporous Materials* 2019, **281:** 110-122.
- 44. Ragon F, Chevreau H, Devic T, Serre C, Horcajada P. Impact of the Nature of the Organic Spacer on the Crystallization Kinetics of UiO-66(Zr)-Type MOFs. *Chemistry A European Journal* 2015, **21**(19): 7135-7143.
- 45. Sindoro M, Yanai N, Jee A-Y, Granick S. Colloidal-sized metal–organic frameworks: synthesis and applications. *Accounts of chemical research* 2014, **47**(2): 459-469.
- 46. Ly HGT, Fu G, de Azambuja F, De Vos D, Parac-Vogt TN. Nanozymatic Activity of UiO-66 Metal–Organic Frameworks: Tuning the Nanopore Environment Enhances Hydrolytic Activity toward Peptide Bonds. *ACS Applied Nano Materials* 2020, **3**(9): 8931-8938.
- 47. Ly HGT, Fu G, Kondinski A, Bueken B, De Vos D, Parac-Vogt TN. Superactivity of MOF-808 toward peptide bond hydrolysis. *Journal of the American Chemical Society* 2018, **140**(20): 6325-6335.
- 48. Wang S, Ly HGT, Wahiduzzaman M, Simms C, Dovgaliuk I, Tissot A, *et al.* A zirconium metalorganic framework with SOC topological net for catalytic peptide bond hydrolysis. *Nature communications* 2022, **13**(1): 1-8.
- 49. de Azambuja F, Loosen A, Conic D, van den Besselaar M, Harvey JN, Parac-Vogt TN. En Route to a Heterogeneous Catalytic Direct Peptide Bond Formation by Zr-Based Metal–Organic Framework Catalysts. *ACS Catalysis* 2021, **11**(13): 7647-7658.