SUPPORTING INFORMATION

Which factors govern the adsorption of peptides to Zr(IV)-based metal-organic frameworks?

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Experimental

Synthesis of Zr-MOFs

MOFs were synthesized through the procedures below following literature procedures with slight modifications of the modulator and the washing method in the case of MOF-808 and UiO-66.

NU-1000[1]: A 500 mL VWR pressure plus+ bottle is charged with $ZrOCl_2.8H_2O$ (1.94 g, 6.02 mmol), benzoic acid (54 g, 442 mmol) and 120 mL of *N,N*-dimethylformamide (DMF). This mixture is sonicated until it became homogeneous, followed by heating at 100 °C for 1 h in an oven. In a second 100 mL VWR pressure plus+ bottle, H_4TBAPy (0.800 g, 1.17 mmol) and DMF (40 mL) are added and sonicated until a suspension is obtained. Next, this suspension is heated at 100 °C for 1 h in an oven, affording a clear solution. After both solutions are ready, H_4TBAPy solution is added into the 500 mL VWR pressure plus+ bottle and manually homogenized for a few minutes while the solutions are warm. The reaction mixture is placed in an oven at 120 °C for 16 h. After cooling down to room temperature, the precipitate is recovered through centrifugation and washed with DMF (3 x 45 mL, for 2 h each time). After centrifugation, the precipitate is suspended in 260 mL of DMF and 10 mL of HCl (8 M) is added dropwise while gently manually shaking. This mixture is placed in a 100 °C oven overnight. After cooling down to room temperature, the precipitate is washed with DMF (3 x 45 mL, for 2 h each time) and with acetone (3 x 45 mL, for 12 h each time). The product is dried at 80 °C under vacuum for 1 h. The structure of the NU-1000 was confirmed comparing the PXRD and SEM analysis with previous report (Figure S1-S2). At last, NU-1000 is activated at 120 °C for 20 h. The final product was obtained as a yellow solid (1.06 g, 84% yield).

MOF-808[2]: $ZrOCl_2.8H_2O$ (0.644 g, 2.00 mmol), benzene-1,3,5-tricarboxylic acid (0.140 g, 0.66 mmol), 5.0 mL H_2O and 5.0 mL formic acid are added together in a 10 mL crimp vial. After gentle manual homogenization, the reaction mixture is heated at 100 °C for 24 h. After cooling down to room temperature, the precipitate of 5 reaction vials is collected in a centrifuge tube and recovered through centrifugation and washed with water (45 mL) overnight. After centrifugation, the precipitate is washed with methanol (2 x 45 mL for 1 h and 96 h) at room temperature, followed by a wash in 30 mL methanol at 60 °C (2 x 45 mL for 20 h and 18 h). After cooling to room temperature, the solid is washed with 45 mL acetone at room temperature for 1 h. The structure of the MOF-808 was confirmed comparing the PXRD analysis with previous report (Figure S3). At last, MOF-808 is oven activated at 150 °C for 20 h. The final product was obtained as a white solid (1.67 g, 26% yield).

UiO-66[3]: A 500 mL VWR pressure plus+ bottle is charged with of $ZrCl_4$ (0.625 g, 2.68 mmol), 5 mL HCl (37%) and 25 mL of *N,N*-dimethylformamide (DMF). A second 100 mL VWR pressure plus+ bottle is charged with terephthalic acid (0.615 g, 3.70 mmol) and 50 mL of DMF. Both bottles are sonicated until a homogeneous solution is obtained. After solutions are prepared, terephthalic acid solution is added to the 500 mL VWR pressure plus+ bottle and manually homogenized. Next, the reaction mixture is heated at 80 °C overnight in an oven. After cooling down to room temperature, the precipitate is recovered through centrifugation and washed

with DMF (3 x 45 mL, for 2 h each time), followed by EtOH (2 x 45 mL for 1 h each time, and 1 x 45 mL overnight). The product is dried under air overnight. The structure of the UiO-66 was confirmed comparing the PXRD analysis with previous report (Figure S4). At last, UiO-66 is activated at 200 °C for 20 h. The final product was obtained as a white solid (0.7 g, 94% yield).

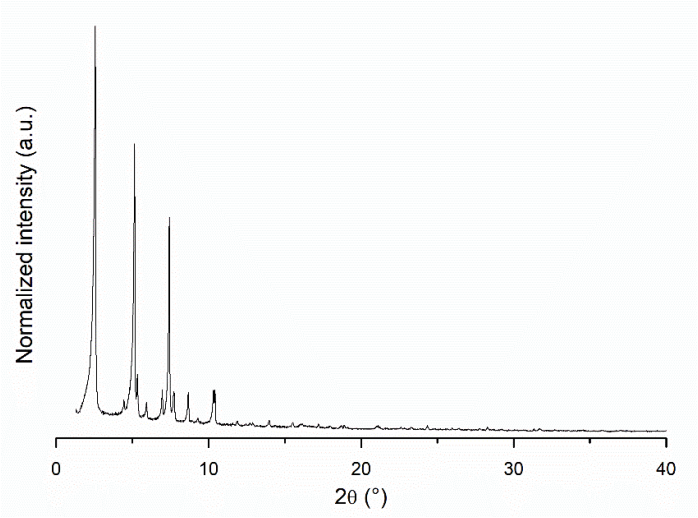


Figure S1. PXRD pattern of NU-1000 as synthesized.

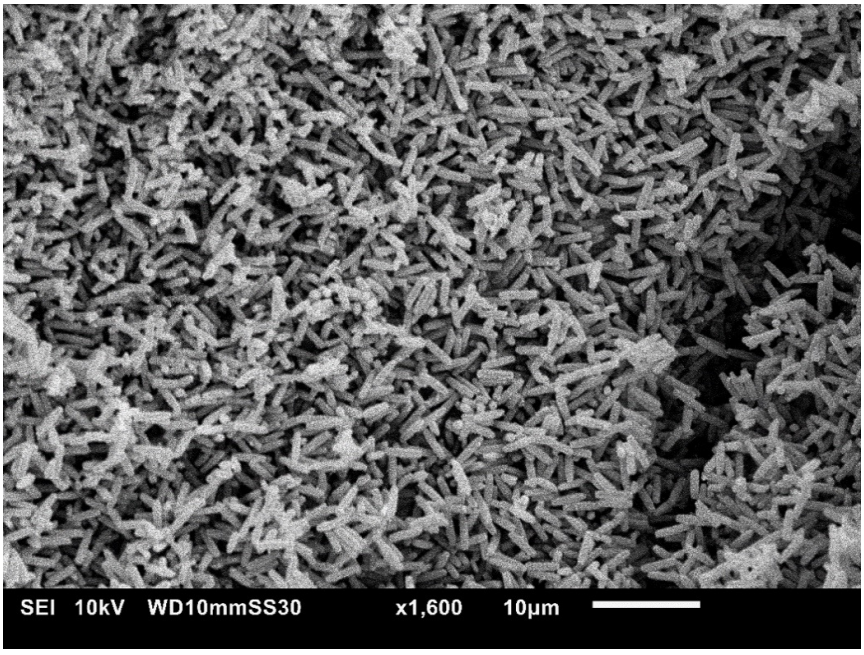
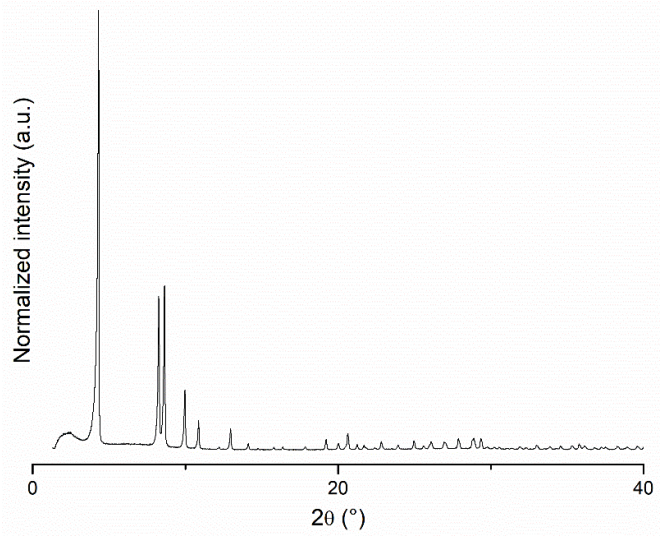
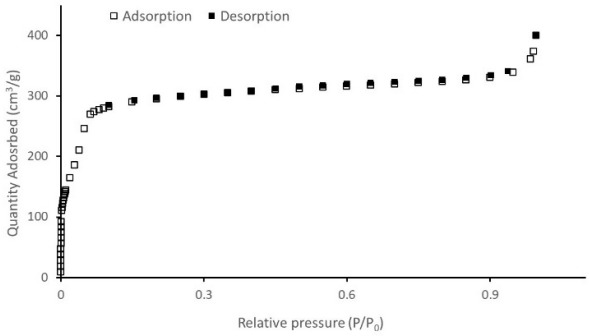


Figure S2. SEM image of NU-1000 as synthesized.

A)



B)



C)

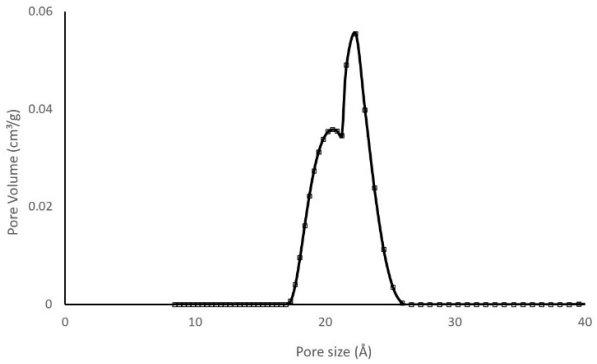
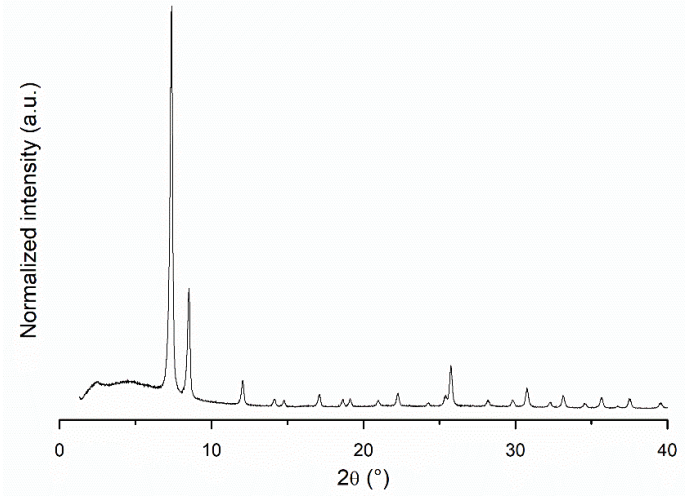


Figure S3. MOF-808 as synthesized: a) PXRD pattern of; b) Nitrogen physisorption; c) Pore size distribution.

A)



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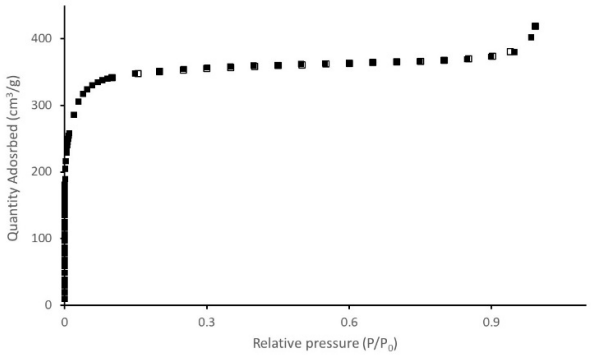

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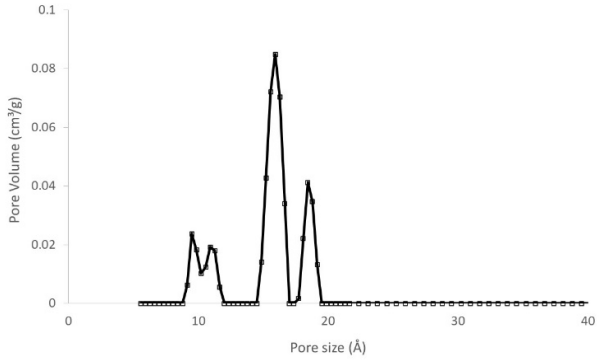

Figure S4. UiO-66 as synthesized: a) PXRD pattern of; b) Nitrogen physisorption; c) Pore size distribution.

Digestion of MOF samples

Table S1. Amount of NaOD added to MOF samples for digestion.

MOF	n (µmol)	m (mg)	NaOD (µL)
MOF-808	2	2.7	81
NU-1000	2	4.3	129
UiO-66	2	3.3	99

Results and Discussion

Analysis of different parameters affecting adsorption of dipeptides onto Zr-MOFs

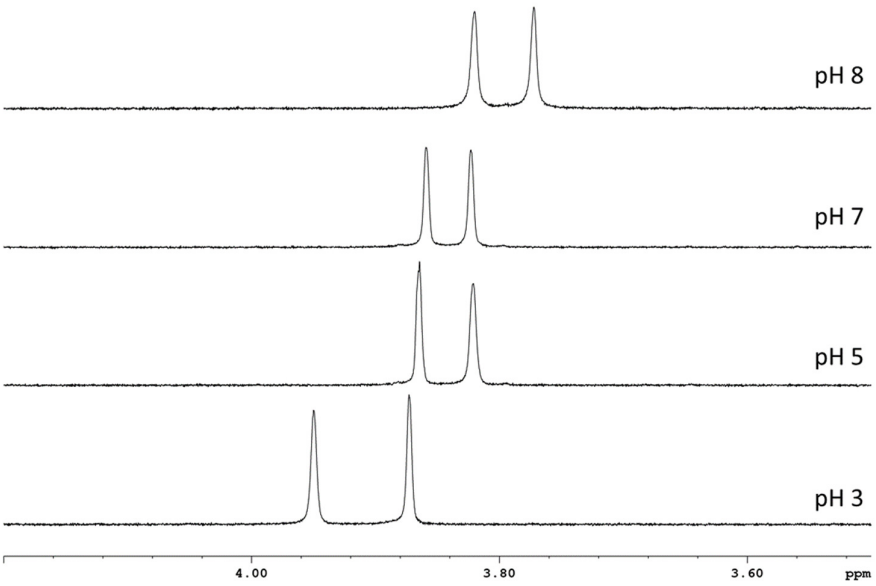

Figure S5. Peak shift of **GG** in function of pH. ^{1}H NMR spectra of adsorption of 2 mM **GG** at room temperature in the presence of 2 µmol NU-1000 after 6 h. **GG** pH 3 (3.87-3.95 ppm), **GG** pH 5 (3.82-3.86 ppm), **GG** pH 7 (3.82-3.86 ppm) and **GG** pH 8 (3.77-3.82 ppm).

Table S2. Abundance of the different forms of **GG** at different pH.

Entry	pH	$H_3N^+CH_2C(O)–NCH_2COOH$	$H_3N^+CH_2C(O)–NCH_2COO^-$	$H_2NCH_2C(O)–NCH_2COO^-$
1	3	71	29	0
2	5	2	98	0
3	7	0	95	5
4	8	0	67	33

[a] % determined via Henderson-Hasselbalch equation.[4] $pK_{a1} = 3.39$, $pK_{a2} = 8.31$.[5]

Table S3. Protonation state of different types of oxygens on Zr_6 cluster at different pH determined by potentiometric titration.[6]

Entry	pH	Cluster protons		
1	3	μ_3-OH	OH_2	OH
2	5	μ_3-O^-	OH_2	OH
3	7	μ_3-O^-	OH^-	OH
4	8	μ_3-O^-	OH^-	OH

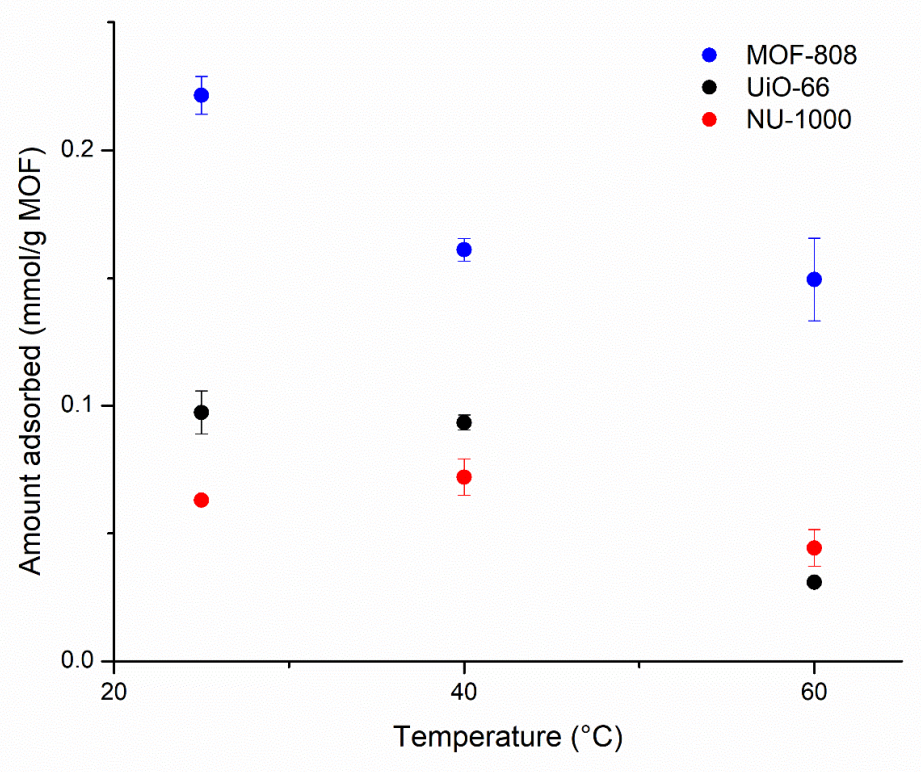

Figure S6. Effect of temperature on adsorption of **GG** onto Zr-MOFs at pH 7.0. NU-1000 (red), UiO-66 (black) and MOF-808 (blue).

Determination of amount of adsorbed substrate GG and G onto Zr-MOFs

Table S4. Adsorption values of **GG** and **G** determined via ^{1}H NMR of supernatant compared to **GG** and **G** in solution after digestion of MOF.

Entry	MOF	Substrate	%adsorption NMR[a]	%adsorption digestion
1	NU-1000	**GG**	14	19
2	NU-1000	**G**	8	8
3	UiO-66	**GG**	15	17
4	UiO-66	**G**	10	16
5	MOF-808	**GG**	28	36
6	MOF-808	**G**	26	23

[a] Adsorption value determined with ^{1}H NMR of the same supernatant as MOF sample used for digestion, not average value. *Conditions*: Zr-MOF (2 µmol), **GG** or **G** (2 mM), pH 7.0, room temperature, 6 h.

Effect of substrate structure on adsorption

Table S5. LogD of different Gly-X, X-Gly and GGG peptides reflecting their hydrophobicity and their amount of adsorption in mmol/g MOF onto NU-1000, UiO-66 and MOF-808.

Entry	-X	LogD[a]	NU-1000 (mmol/g MOF)	UiO-66 (mmol/g MOF)	MOF-808 (mmol/g MOF)
1	Gly	-4.54	0.063	0.097	0.221
2	Ala	-3.97	0.100	0.068	0.106
3	Ala-Gly	-3.96	0.078	0.064	0.169
4	Leu	-2.72	0.214	0.148	0.069
5	Ile	-2.64	0.175	/	/
6	GGG	-5.67	0.200	0.127	0.198
7	Asn	-5.42	0.145	/	/
8	Ser	-5.02	0.078	0.064	0.122
9	Thr	-4.6	0.056	/	/
10	Met	-3.32	0.296	0.228	0.117
11	Glu	-7.2	0.166	/	/
12	Asp	-6.53	0.177	0.256	0.298
13	Arg	-5.37	0.271	/	/
14	Lys	-5.24	0.137	0.178	0.085
15	His	-4.43	0.343	0.249	0.230
16	Tyr	-2.62	0.458	/	/
17	Phe	-2.32	0.452	0.153	0.059
18	Trp	-2.22	0.463	/	/
19	GGOMe	-3.27	0.067	0.014	0.004
20	*N*-acetylGG	-5.54	0.250	0.052	0.077

Conditions: Gly-X (2 µmol), MOF (2 µmol), D_2O (1 mL), room temperature, pH 7.0, 6 h. ^1H NMR yield. [a] LogD determined with ChemAxon at pH 7.[7] LogD was used for peptides as these are ionizable and logD varies at different pH while the linkers, when incorporated in the MOF, are non-ionizable and logP was used (Table 1). A higher (less negative) logD or logP corresponds to a higher hydrophobicity.

Stability of MOFs after adsorption experiments

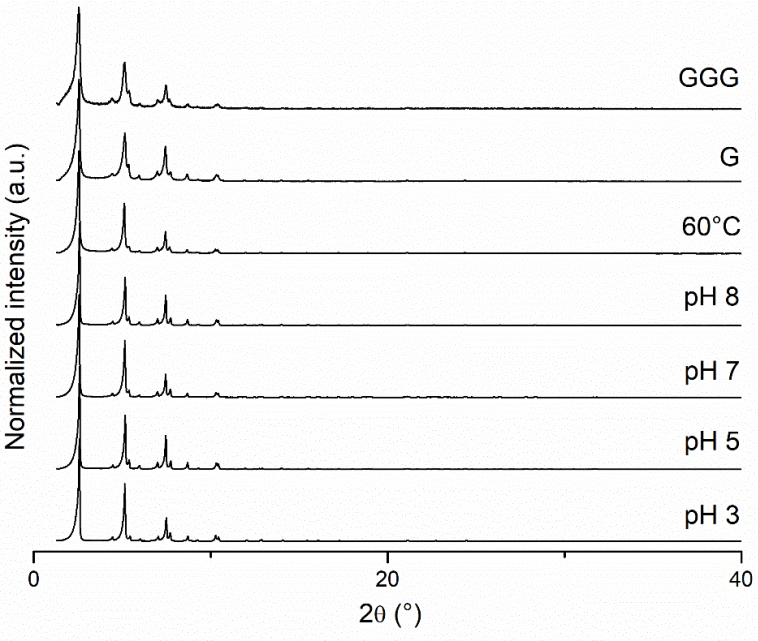

Figure S7. PXRD pattern of NU-1000 after reaction with 2 mM **GG** at different pH and temperature, and after reaction with **G** and **GGG** at pH 7.0 and room temperature, for 6 h.

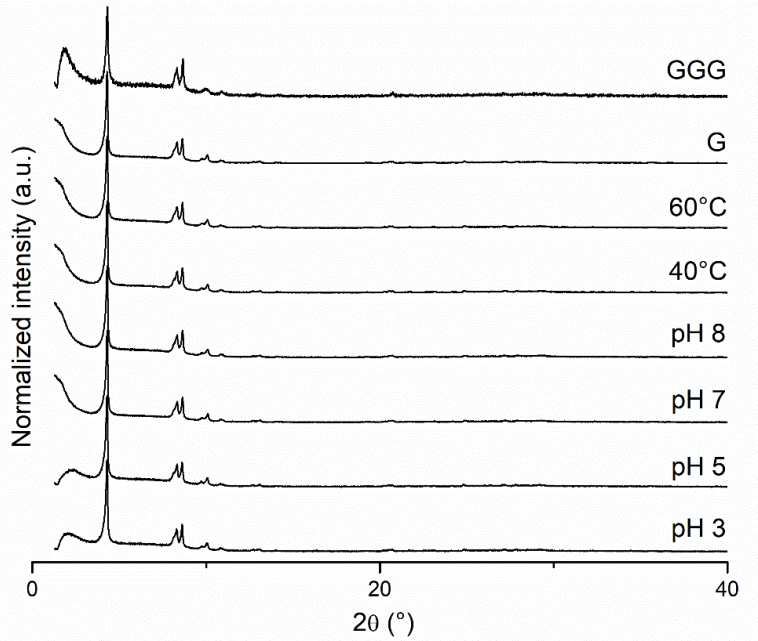

Figure S8. PXRD pattern of MOF-808 after reaction with 2 mM **GG** at different pH and temperature, and after reaction with **G** and **GGG** at pH 7.0 and room temperature, for 6 h.

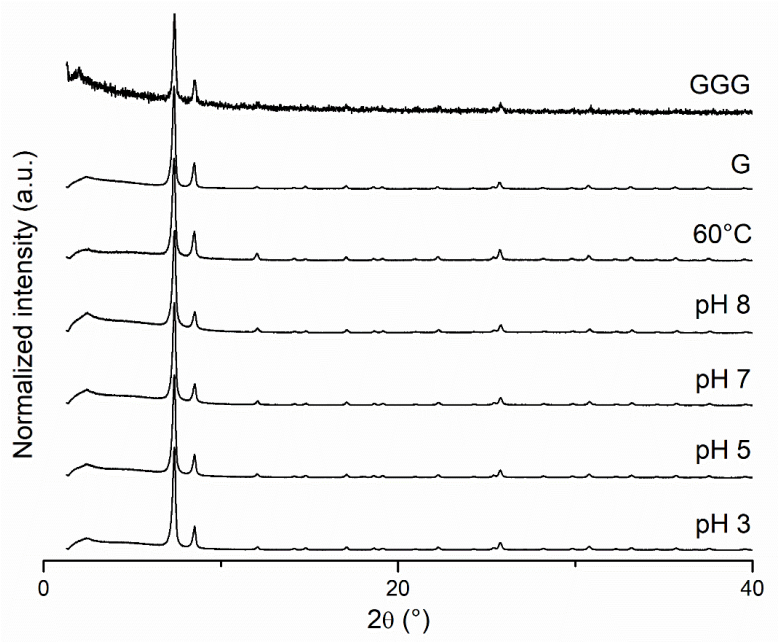

Figure S9. PXRD pattern of UiO-66 after reaction with 2 mM **GG** at different pH and temperature, and after reaction with **G** and **GGG** at pH 7.0 and room temperature, for 6 h.

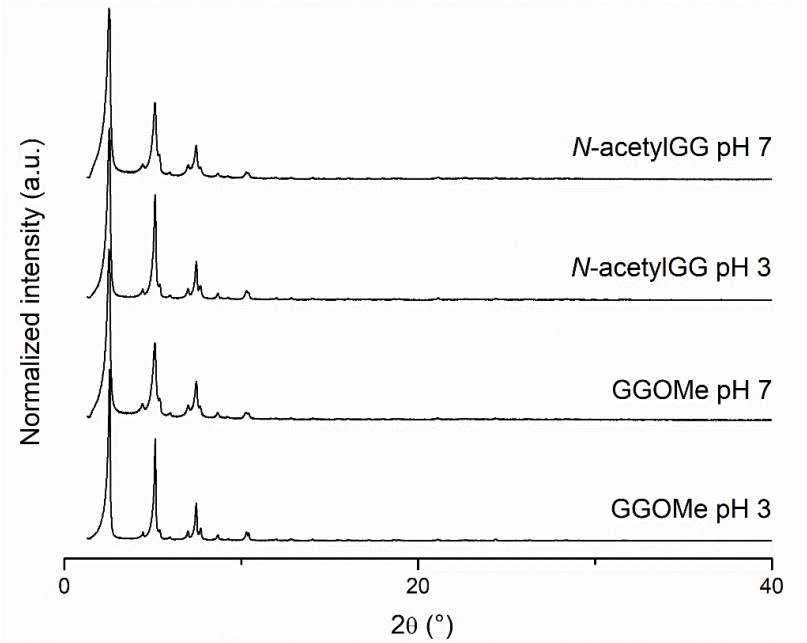

Figure S10. PXRD pattern of NU-1000 after reaction with 2 mM **GGOMe** or ***N*-acetylGG** at different pH, for 6 h at room temperature.

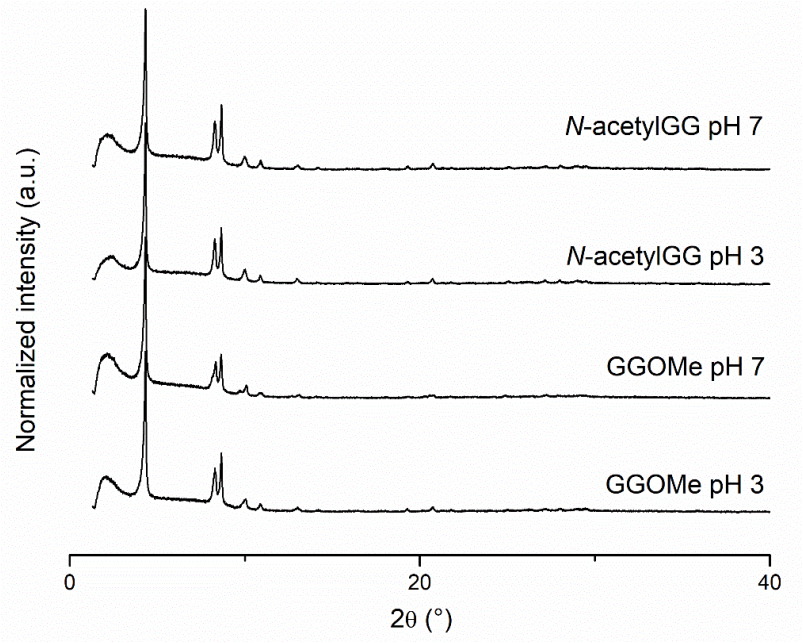

Figure S11. PXRD pattern of MOF-808 after reaction with 2 mM **GGOMe** or ***N*-acetylGG** at different pH, for 6 h at room temperature.

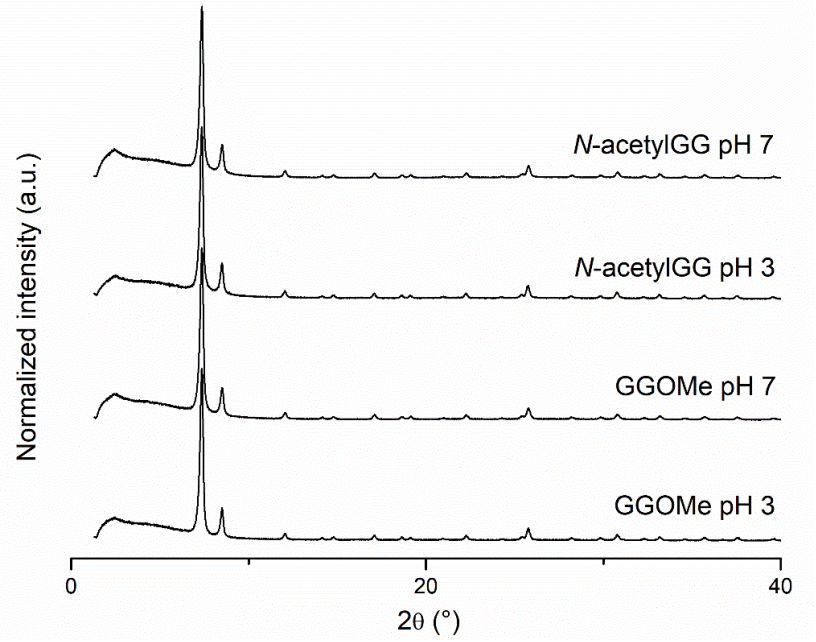

Figure S12. PXRD pattern of UiO-66 after reaction with 2 mM **GGOMe** or ***N*-acetylGG** at different pH, for 6 h at room temperature.

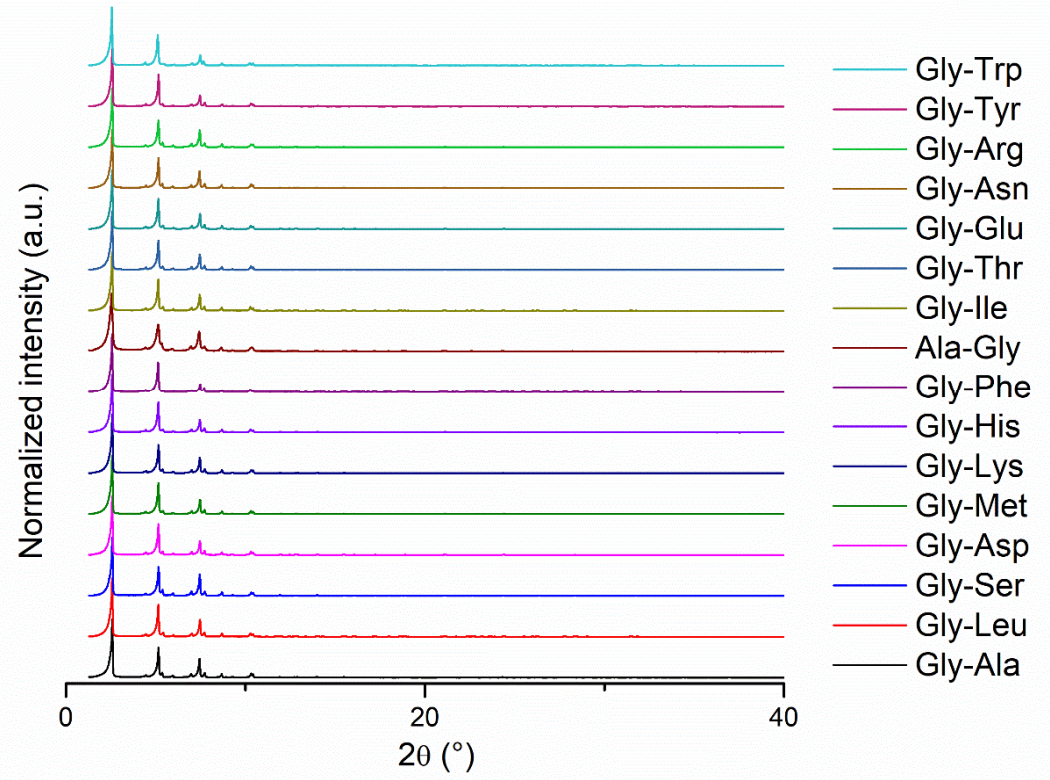

Figure S13. PXRD pattern of NU-1000 after reaction with 2 mM dipeptide at pH 7.0, for 6 h at room temperature.

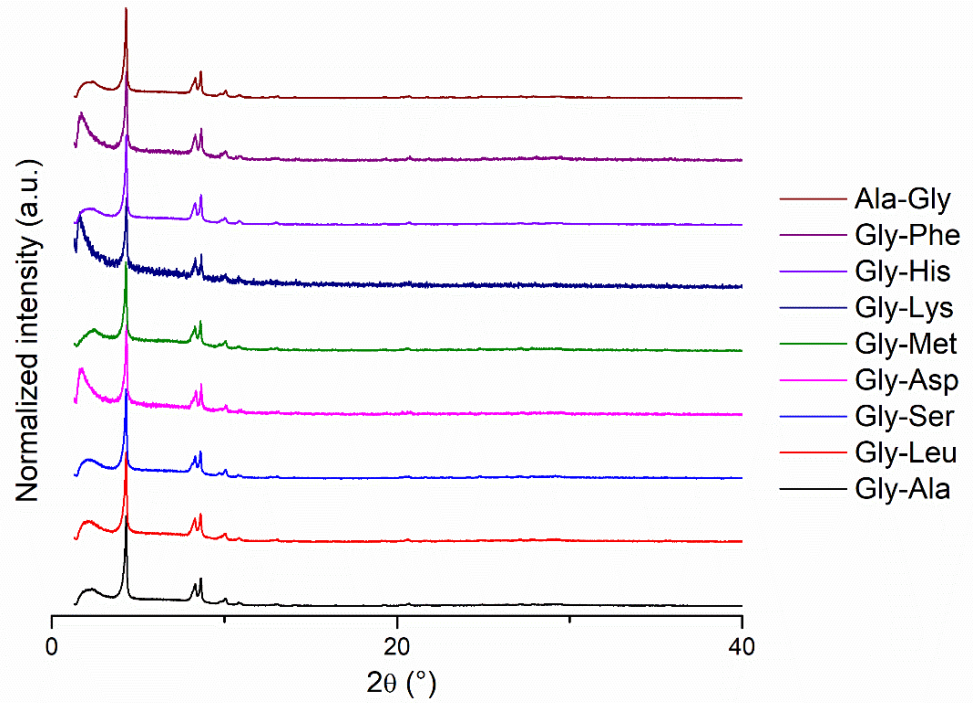

Figure S14. PXRD pattern of MOF-808 after reaction with 2 mM dipeptide at pH 7.0, for 6 h at room temperature.

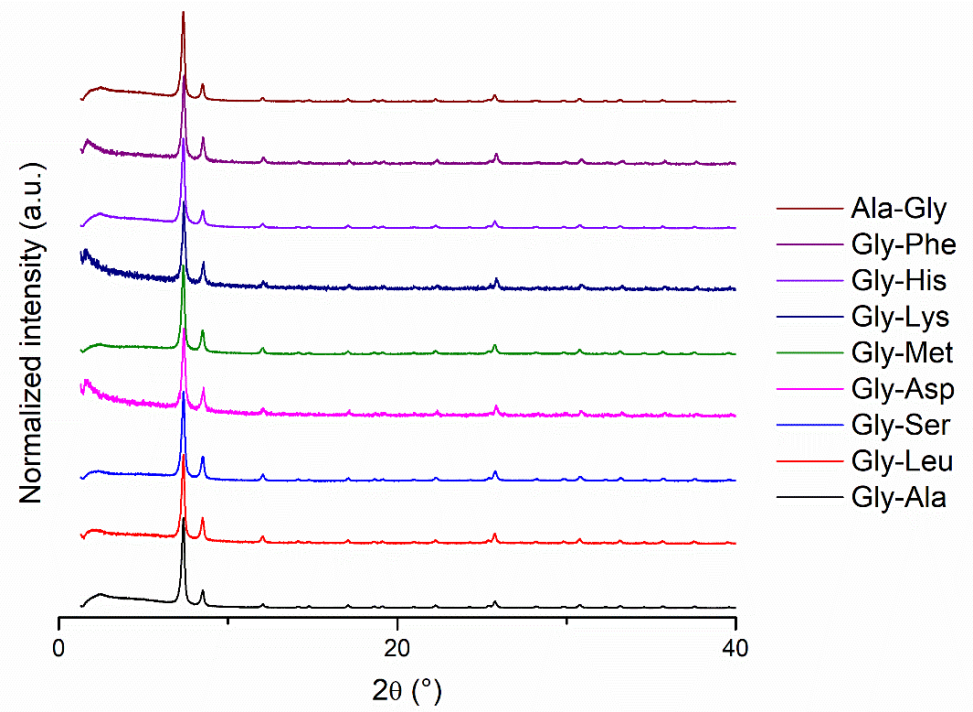

Figure S15. PXRD pattern of UiO-66 after reaction with 2 mM dipeptide at pH 7.0, for 6 h at room temperature.

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