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Sequence-Dependent Peptide Surface Functionalization of Metal Organic Frameworks

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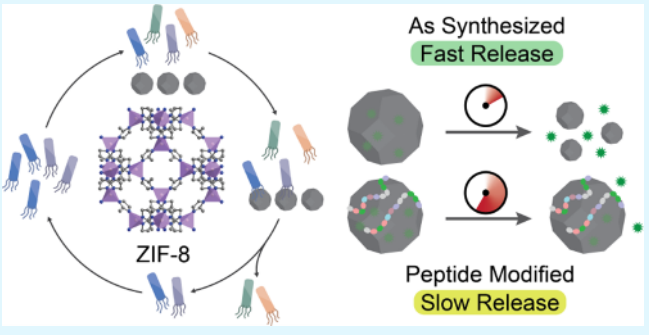
Supporting nformation

ABSTRACT: We report a noncovalent surface functionalization technique for water-stable metal organic frameworks using short peptide sequences identi ed via phage display. Speci c frameworks-binding peptides were identi ed for crystalline $Zn(MeIM)_2$ (MeIM: 2-methylimidazole, ZIF-8), semiamorphous Fe-BTC (BTC: 1,3,5-benzene-tricarboxylate), and $Al(OH)(C_4H_2O_4)$ (MIL-53(Al) FA, FA: fumaric acid), and their thermodynamic binding affinities and speci cities were measured. Electron microscopy, powder X-ray diffraction, and gas adsorption analysis con rmed that the peptide-functionalized frameworks retained similar characteristics compared to their as-synthesized counterparts. Confocal laser-scanning microscopy demonstrated that peptide was localized on the surface of the frameworks, whereas surface area measurements showed no evidence of pore blockage. Finally, we measured the pH-dependent release of fluorescein from peptide-functionalized frameworks and discovered that peptide binding can attenuate fluorescein release by improving framework stability under low pH conditions. Our results demonstrate that phage display can be used as a general method to identify speci c peptide sequences with strong binding affinity to water-stable metal organic frameworks and that these peptides can alter drug release kinetics by affecting framework stability in aqueous environments.



KEYWORDS: *peptides metal organic frameworks surface functionalization phage display and drug delivery*

INTRODUCTION

Metal organic frameworks (MOFs) are two- or three-dimensional arrays of organic ligands linked together through inorganic nodes that have shown promise in a variety of applications, including gas separation,[1] gas storage,[2 4] catalysis,[5 7] sensing,[8,9] and drug delivery.[10] These materials are particularly promising for biological applications due to their high surface areas, which allow for record loadings of diagnostic and therapeutic agents, including methotrexate,[11,12] doxorubicin,[13] and fluorouracil.[14] For biomedical applications, functionalization of the framework surface is extremely important, because this interface controls the stability of the framework, the rate of drug release, cell uptake, and the overall biological response.[10] However, in contrast to mesoporous silicas and metal nanoparticles,[15 19] there are few general techniques for surface functionalization of metal organic frameworks,[20] which result in part from a fundamental lack of knowledge on the surface chemistry and interfacial interactions of these materials.

Several covalent methods for metal organic framework surface modi cation have been reported. For example, postsynthetic exchange of surface-exposed ligands with functionalized alternatives enabled surface modi cation via standard coupling chemistry.[21 26] Core shell materials containing a metal organic framework core and a grown shell of silica or polymer are another popular surface functionalization strategy that takes advantage of well-developed chemistries for the shell materials.[27 29] In conjunction with these covalent strategies,[30] milder, noncovalent methods for functionalizing framework surfaces using polymers[31 33] or lipid bilayers[12,30] have recently been reported. These approaches are applicable to a wide range of frameworks, and their mild nature limits the formation of undesirable structural features, such as defects, that negatively may affect material performance. Nevertheless, further development of noncovalent surface functionalization techniques for metal organic frameworks is warranted to prevent pore blockage and to accentuate desirable framework properties.[32]

One promising class of molecules for the functionalization of metal organic framework surfaces is short peptides,[34 38] which are a popular class of ligands for binding to metals, metal oxides, and other inorganic materials. Peptide sequences that bind to a speci c material can be identi ed through phage display, which relies on a large library of random peptide

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sequences that are down selected to consensus sequences with strong binding affinity to the material of interest (Figure 1).[42]

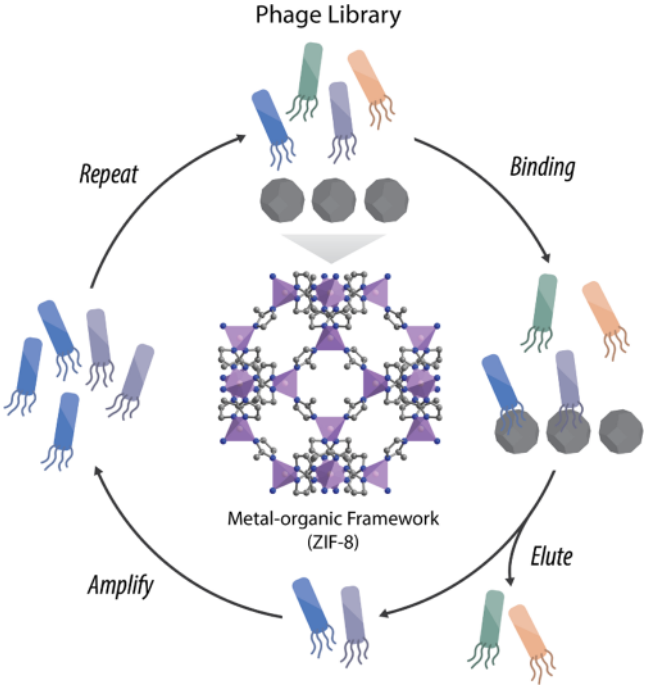

Figure 1 Phage display for identi cation of MOF-binding short peptide sequences.

Using this technique, peptide sequences that bind to speci c crystal facets of palladium, gold, and many other materials have been identi ed.[43 45] These peptides were subsequently leveraged to functionalize material surfaces,[46] control crystal growth and orientation,[47 50] and direct material formation in photovoltaic and electrochemical devices.[51 53]

In the case of metal organic frameworks, dipeptides have been used as ligands in framework synthesis, whereas longer peptides have been covalently attached to the interior and exterior of frameworks via postsynthetic modi cation.[39,40] Larger biomolecules, including proteins and nucleic acids, have also been incorporated into the pores of metal organic frameworks.[41] Finally, larger proteins, such as the tobacco mosaic virus coat protein, have been used to direct framework synthesis.[54] Despite these advances, the study of noncovalent and sequence-dependent binding of peptides to metal organic frameworks is relatively unexplored.

Here, we demonstrate that phage display can be used to identify peptide sequences with strong binding affinity to the water-stable metal organic frameworks, $Zn(MeIM)_2$ (MeIM: 2-methylimidazole, ZIF-8), semiamorphous Fe-BTC (BTC: 1,3,5-benzene-tricarboxylate), also known as Basolite F300, and $Al(OH)(C_4H_2O_4)$ (MIL-53(Al) FA, FA: fumaric acid). Consensus peptide sequences with strong binding affinity to each framework were obtained, and their thermodynamic binding affinities and speci cities were characterized. We also investigated the localization of adherent peptides and determined that their presence does not adversely affect framework properties. Finally, we demonstrate that peptide functionalization augments ZIF-8 performance in controlled release of a model small molecule, fluorescein (FITC), by improving metal organic framework stability under acidic conditions. Overall, our results demonstrate that speci c peptide sequences can exhibit strong and selective binding to metal organic frameworks and suggest that these sequences can be leveraged to modify framework surfaces or control framework nucleation.

METHODS

Chemicals and Reagents. All chemicals were analytical grade and used without further puri cation unless otherwise stated. Zinc nitrate hexahydrate ($Zn(NO_3)_2{\cdot}6H_2O$, 98), 2-methylimidazole (99), copper(II) nitrate hemi(pentahydrate) ($Cu(NO_3)_2{\cdot}2.5H_2O$, 98), and trimesic acid were purchased from Sigma-Aldrich. Sodium formate (98), fumaric acid (99), and fluorescein were purchased from Alfa Aesar. Ferric chloride hexahydrate ($FeCl_3{\cdot}6H_2O$) and methanol were purchased from Fisher Scienti c. Aluminum sulfate octadecahydrate ($Al_2(SO_4)_3{\cdot}18H_2O$, ACS grade) and urea were purchased from VWR International. Ultrapure water was generated from a Milli-Q Integral Water Puri cation System. Sodium hydroxide was purchased from EMD Millipore Corporation (Germany). *N*-hydroxysuccinimide (NHS)-fluorescein (5/6-carboxyfluorescein succinimidyl ester) was purchased from ThermoFisher Scienti c. The framework-binding peptides were synthesized using solid-phase peptide synthesis technique and purchased from Bio-Synthesis Inc. The purity of peptide is higher than 95 according to high-performance liquid chromatography analysis (Onyx Monolithic C18, flow rate: 1.0 mL min ^{1}) and matrix-assisted laser desorption/ionization time-of-flight test (Applied Biosystems Voyager System 1099, calibration matrix: -cyano-4-hydroxycinnamic acid).

Thermogravimetric Analyzer (TGA). Thermogravimetric analysis (TGA) was performed using a PerkinElmer TGA 7 with a nitrogen atmosphere and a flow rate of 30 mL min ^{1}. The temperature was ramped from 25 to 800 °C at 5 °C min ^{1}.

X-ray Di raction (XRD). X-ray diffraction (XRD) was performed on a Rigaku R-Axis Spider diffractometer with an image plate detector using Cu K radiation (λ = 1.54 Å) and a graphite monochromator. XRD samples were prepared by mixing a small amount of dried framework with a droplet of mineral oil followed by mounting on a cryoloop.

Transmission Electron Microscopy (TEM). Low-resolution transmission electron microscopy (TEM) images were acquired on an FEI Tecnai Spirit Bio Twin operated at 80 kV. High-resolution transmission electron microscopy images were acquired on a eld emission JEOL 2010F TEM operated at 200 kV. TEM samples were prepared by dropcasting 5 μL of dilute framework dispersion in water onto a 200 mesh carbon-coated copper TEM grid (Electron Microscopy Science).

Dynamic Light Scattering (DLS). DLS measurements were performed at 25 °C on a Zetasizer Nano ZS, Malvern, using a 25 mW helium neon laser (632.8 nm).

Low-Pressure Gas Adsorption. Gas adsorption isotherms in the range of 0.00 1.01 bar were measured volumetrically using a Micromeritics ASAP2020 instrument. All gases were 99.998 purity or higher. Isotherms at 77 K were measured using liquid nitrogen baths. Langmuir and Brunauer Emmett Teller surface areas of ZIF-8, Fe-BTC, and MIL-53(Al) FA were consistent with literature reports.[55 57]

Metal Organic Framework Synthesis. *ZIF-8 was Synthesized in Water According to a Published Procedure.*[55] $Zn(NO_3)_2{\cdot}6H_2O$ (744 mg, 2.50 mmol) was dissolved in 10 mL of deionized water and added to a solution consisting of 2-methylimidazole (2-MeIM) (8.2 g, 0.10 mol) in 90 mL of deionized water. The nal molar composition of the synthesis solution was Zn^{2+}/2-MeIM/water = 1:40:2228. The mixture was stirred at room temperature and quickly became cloudy. After 24 h, the suspension was centrifuged at 8000 × *g* for 10 min and washed with methanol three times. The products were then dried for 24 h under reduced pressure at room temperature.

Fe-BTC was Synthesized in Water According to a Published Procedure.[56] Two solutions were prepared: Solution 1 was prepared by dissolving H_3BTC (0.263 g, 1.25 mmol) and NaOH (0.150 g, 3.75 mmol) in H_2O (10 mL). Solution 2 was prepared by dissolving $FeCl_3{\cdot}$

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