Olsalazine-Based Metal–Organic Frameworks as Biocompatible Platforms for H₂ Adsorption and Drug Delivery

Dana J. Levine, † Tomče Runčevski, † Matthew T. Kapelewski, † Benjamin K. Keitz, † Julia Oktawiec, † Douglas A. Reed, † Jarad A. Mason, †§ Henry Z. H. Jiang, †§ Kristen A. Colwell, †§ Christina M. Legendre, † Stephen A. FitzGerald, †∥ and Jeffrey R. Long*†§

ABSTRACT: The drug olsalazine (H₄olz) was employed as a ligand to synthesize a new series of mesoporous metal–organic frameworks that are expanded analogues of the well-known M₂(dobdc) materials (dobdc⁴⁻ = 2,5-dioxido-1,4-benzenedicarboxylate; M-MOF-74). The Mₓ(olz) frameworks (M = Mg, Fe, Co, Ni, and Zn) exhibit high surface areas with large hexagonal pore apertures that are approximately 27 Å in diameter. Variable temperature H₂ adsorption isotherms revealed strong adsorption at the open metal sites, and in situ infrared spectroscopy experiments on Mg₂(olz) and Ni₂(olz) were used to determine site-specific H₂ binding enthalpies. In addition to its capabilities for gas sorption, the highly biocompatible Mg₂(olz) framework was also evaluated as a platform for the delivery of olsalazine and other encapsulated therapeutics. The Mg₂(olz) material (86 wt % olsalazine) was shown to release the therapeutic linker through dissolution of the framework under simulated physiological conditions. Furthermore, Mg₂(olz) was used to encapsulate phenethylamine (PEA), a model drug for a broad class of bioactive compounds. Under simulated physiological conditions, Mg₂(olz)(PEA)₂ disassembled to release PEA from the pores and olsalazine from the framework itself, demonstrating that multiple therapeutic components can be delivered together at different rates. The low toxicity, high surface areas, and coordinatively unsaturated metal sites make these Mₓ(olz) materials promising for a range of potential applications, including drug delivery in the treatment of gastrointestinal diseases.

INTRODUCTION

Metal–organic frameworks (MOFs) are an important class of materials with high internal surface areas and tunable pore environments that make them of interest for a wide variety of potential applications, including gas sorption,¹⁻⁴ catalysis,⁵,⁶ conductivity,⁷ and drug delivery.⁸⁻¹⁰ One of the most ubiquitous materials in the literature is a series of isoreticular frameworks of the type Mₓ(dobdc) (2,5-dioxido-1,4-benzenedicarboxylate), sometimes referred to as M-MOF-74 or CPO-27. These frameworks are composed of dicationic metals and the tetraanionic linker dobdc⁴⁻ and feature one-dimensional hexagonal pores with open metal sites at the vertices.¹¹⁻¹⁵ The pores of these frameworks can be expanded while preserving the parent framework structure by using ligands such as 4,4'-dioxido-3,3'-biphenylidicarboxylate (dobpdc⁴⁻)¹⁶ and other analogues with multiple phenylene groups.¹⁷ Further variation can be introduced by using a structural isomer such as m-dobdc⁴⁻ (4,6-dioxido-1,3-benzenedicarboxylate), which alters the pore environment and enhances the positive charge densities of the open metal sites.¹⁸ Notably, the Niₓ(m-dobdc) variant exhibits an H₂ binding enthalpy of −13.7 kJ/mol, which is the largest of any framework and −1.4 kJ/mol larger than the parent Ni₂(dobdc). With an interest in exploring new ligands for expanded MOF-74 architectures, we sought to use the anti-inflammatory compound olsalazine, which exhibits the same coordinating functionality as dobpdc⁴⁻ while potentially having altered electronics.¹⁹ Olsalazine is also slightly longer than dobpdc⁴⁻, allowing it to accommodate larger guest molecules in the expanded pore of the corresponding framework. Olsalazine itself is a produg of the anti-inflammatory 5-aminosalicylic acid, and it is widely used in the treatment of ulcerative colitis and other gastrointestinal diseases.²⁰ Olsalazine has been shown to inhibit the development of colorectal cancer in patients,²¹⁻²³ and it has also been proposed as a broad spectrum anticancer agent.²⁴ Olsalazine is often taken daily in multigram doses,²⁵⁻²⁷ making it an effectively nontoxic ligand that can be useful in the...
design of new materials. Indeed, there has been an increased focus on the development of low-toxicity metal–organic frameworks due to the necessary safety and environmental considerations of their potential industrial applications.

Low-toxicity frameworks have also been explored as porous platforms for drug storage and release, and a broad spectrum of materials has been investigated for this purpose, including Cr-MIL-101, Fe-MIL series, Zn-ZIF-8, Zr UiO derivatives, and Fe$_2$(dobdc). However, there are only a handful of metal–organic frameworks where a bioactive molecule serves as the sole bridging ligand. These materials include frameworks with iron and nicotinic acid (vitamin B$_3$) zinc and the antibacterial azelaic acid, hafnium and a photosensitizing porphyrin ligand for cancer therapy magnesium and the antioxidant gallic acid, and zinc and the anti-inflammatory curcumin, which active organic component represents 99–79 wt % of the total framework. Of these, only a few materials have sufficiently large pores to encapsulate additional therapeutics. While several three-dimensional structures have also been reported with olsalazine as a bridging ligand, they require ancillary or pillaring ligands that are not biocompatible, making them unsuitable materials for drug delivery applications.

In this study, a new family of expanded MOF-74 materials was synthesized using the anti-inflammatory olsalazine acid (H$_4$olz) as a ligand to form M$_2$(olz)$_2$, where M = Mg, Fe, Co, Ni, and Zn. Upon activation, these materials exhibit the highest Langmuir surface areas among bioactive frameworks. The M$_2$(olz)$_2$ frameworks contain pore apertures of approximately 27 Å, corresponding to the mesoporous range (≥20 Å). Strong H$_2$ adsorption was observed by gas adsorption studies and in situ infrared spectroscopy, confirming the presence of open metal sites for all but the Zn analogue. The Mg$_2$(olz)$_2$ framework, which disassembles under physiological conditions to release olsalazine, represents an unprecedented level of loading in a bioactive metal–organic framework of 86 wt % drug. In addition to delivery of olsalazine, the large pores of Mg$_2$(olz)$_2$ were used to encapsulate a second drug, illustrating the potential of this platform to deliver multiple therapeutic components. To this end, we demonstrated that the model drug phenethyamine (PEA) can be loaded into the pores of Mg$_2$(olz)$_2$ to generate Mg$_2$(olz)$_2$(PEA)$_2$, and both PEA and olsalazine can be subsequently released under physiological conditions.

**Experimental Section**

All reagents and solvents were obtained from commercial sources at reagent-grade purity or higher. Synthesis of olsalazine (H$_4$olz) is described in the Supporting Information. Laboratory powder X-ray diffraction patterns were collected using Cu Kα radiation (λ = 1.5418 Å) on a Bruker AXS D8 Advance diffractometer equipped with a Göbel mirror and a Lynxeye linear position-sensitive detector and mounted with the following optics: a fixed divergence slt (0.6 mm), receiving slt (3 mm), and secondary-beam Soller slits (2.5°). The generator was set at 40 kV and 40 mA. Thermogravimetric analyses were carried out at a ramp rate of 2 °C/min under nitrogen flow with a TA Instruments Q5000 instrument. 1H NMR experiments were carried out on a Bruker Avance III NMR spectrometer equipped with a BBO broadband probe operating at 600.13 MHz. Elemental analyses for C, H, and N were performed at the Microanalytical Laboratory of the University of California, Berkeley.

**Synthesis of Mg$_2$(olz)$_2$**. The metal salt Mg(NO$_3$)$_2$·6H$_2$O (242 mg, 0.945 mmol) was dissolved in 12 mL of ethanol, and H$_4$olz (136 mg, 0.450 mmol) was dissolved separately in 18 mL of N,N-dimethylformamide (DMF). These solutions were combined in a 50 mL Pyrex glass jar, sealed, and heated in an isothermal oven at 120 °C for 1 day. The reaction mixture was subsequently decanted, and the dark yellow solid was washed with successive aliquots of DMF (3 × 30 mL) at 80 °C followed by aliquots of methanol (3 × 30 mL) at 60 °C. The slurry was then transferred to a tared analysis tube, and excess solvent was removed via cannula. The framework was activated for 12 h at 180 °C under a flow of argon and then placed under vacuum on an ASAP 2420 instrument at the same temperature. Activated yield: 125 mg (80% based on ligand). EA: calcd C 48.5%, H 1.70%, N 8.10%; found C 48.4%, H 1.55%, N 7.94%.

**Synthesis of Fe$_2$(olz)$_2$**. In a nitrogen-filled glovebox, a 20 mL vial was charged with H$_4$olz (30 mg, 0.10 mmol) and FeCl$_3$ (30 mg, 0.24 mmol). Methanol (5 mL) and DMF (5 mL) were added, and the vial was sealed with a PTFE-lined cap and shaken until a homogenous solution formed. The vial was placed on a dry bath preheated to 100 °C and left at this temperature, without stirring, for 16 h. The dark red/brown precipitate that had formed after this time was collected by filtration and washed with a small amount of methanol. The solid was washed with successive aliquots of DMF (3 × 15 mL) at 100 °C followed by aliquots of methanol (5 × 15 mL) at 60 °C. After the final wash, the dark red/brown solid was collected by filtration and dried under reduced pressure. In a glovebox, the methanol-solvated Fe$_2$(olz)$_2$ was placed in a tared glass ASAP tube equipped with a Transel. The tube was removed from the box and heated under vacuum to 120 °C at a rate of 0.2 °C/min to give Fe$_2$(olz)$_2$. Activated yield: 26 mg (54% based on ligand). EA: calcd C 41.00%, H 1.50%, N 6.80%; found C 40.70%, H 1.18%, N 6.53%.

**Synthesis of Co$_2$(olz)$_2$**. The metal salt Co(NO$_3$)$_2$·6H$_2$O (72.8 mg, 0.250 mmol) was dissolved in 3.3 mL of ethanol and 3.3 mL of water, and H$_4$olz (302 mg, 0.100 mmol) was dissolved separately in 3.3 mL of N,N-dimethylacetamide (DMA). The solutions were combined in a 10 mL Pyrex glass jar, sealed, and heated in an isothermal oven at 100 °C for 1 day. The reaction mixture was decanted, and the orange powder was washed with successive aliquots of DMF (3 × 10 mL) at 80 °C and methanol (3 × 10 mL) at 60 °C. The slurry was then transferred to a tared analysis tube where excess solvent was removed via cannula. The framework was activated for 12 h at 180 °C under an argon flow and then placed under vacuum at the same temperature on an ASAP 2420 instrument. Activated yield: 25.8 mg (62% based on ligand). EA: calcd C 40.40%, H 1.50%, N 6.70%; found C 40.13%, H 1.32%, N 6.84%.

**Synthesis of Ni$_2$(olz)$_2$**. The metal salt Ni(NO$_3$)$_2$·6H$_2$O (218 mg, 0.750 mmol) was dissolved in 10 mL of ethanol and 10 mL of H$_2$O, and H$_4$olz (90.7 mg, 0.300 mmol) was dissolved separately in 10 mL of N,N-diethylformamide (DEF). These solutions were combined and then distributed into three 20 mL glass scintillation vials, sealed with a PTFE-lined cap, and heated in a dry bath at 100 °C for 1 day. The reaction mixtures were then combined, and the solvent was decanted. The resulting orange solid was washed with successive aliquots of DMF (3 × 20 mL) at 80 °C followed by aliquots of methanol (3 × 20 mL) at 60 °C. The slurry was then transferred to a tared analysis tube where excess solvent was removed via cannula. The framework was activated for 12 h at 180 °C under a flow of argon and then placed under vacuum at the same temperature on an ASAP 2420 instrument. Activated yield: 59.6 mg (62% based on ligand). EA: calcd C 40.50%, H 1.50%, N 6.70%; found C 40.35%, H 1.32%, N 6.84%.

**Synthesis of Zn$_2$(olz)$_2$**. The metal salt Zn(NO$_3$)$_2$·6H$_2$O (298 mg, 1.00 mmol) was dissolved in 20 mL of ethanol, and H$_4$olz (121 mg, 0.400 mmol) was dissolved separately in 20 mL of DMA. These solutions were combined and then distributed into four 20 mL glass scintillation vials, sealed with a PTFE-lined cap, and heated in dry bath at 100 °C for 1 day. The reaction mixtures were then combined, and the solvent was decanted. The resulting yellow solid was washed with successive aliquots of DMF (3 × 20 mL) at 80 °C followed by aliquots of methanol (3 × 20 mL) at 60 °C. The resulting methanol slurry was then transferred to a tared analysis tube where excess solvent was removed. The framework was activated under argon flow at 100 °C for 12 h and then under vacuum at the same temperature on an ASAP 2420 instrument. Activated yield: 90.0 mg (52% based on ligand). EA:
calcd C 39.20%, H 1.40%, N 6.50%; found C 38.15%, H 1.34%, N 6.82%.

Preparation of Mg\(_2\)(olz)(PEA). A 20% solution of phenethylamine in CH\(_2\)Cl\(_2\) (500 \(\mu\)L) was sparged under N\(_2\) and added to 6.5 mg of activated Mg\(_2\)(olz) in a vial under a nitrogen atmosphere, and the mixture was left undisturbed for 24 h. The product was then washed copiously with fresh CH\(_2\)Cl\(_2\) and dried to obtain Mg\(_2\)(olz)(PEA), an orange-yellow solid (yield: 10.7 mg, 97%). Stoichiometry was determined by \(^1\)H NMR spectroscopy upon digestion of the material in a 4% DCl solution in DMSO-\(_d6\). An analogous procedure was also used to load N-methylphenethylamine into Mg\(_2\)(olz).

Gas Adsorption Measurements. Gas adsorption isotherms with pressures in the range 0–12 bar were measured using a volumetric method on either a Micromeritics ASAP 2020 or ASAP 2420 instrument. Samples were transferred under a N\(_2\) or Ar atmosphere to tared analysis tubes and then capped with a Transeal. The samples were evacuated at the original activation temperature until the outgas rate was <1 \(\mu\)bar/min, at which point the tube was weighed to determine the mass of the activated sample. The tube was transferred to the analysis port of the instrument, and the outgas rate was again checked to ensure that it was below 1 \(\mu\)bar/min. UHP-grade (99.999% purity) N\(_2\), H\(_2\), and He were used for all adsorption measurements. For all isotherms, warm and cold free spaces were measured using He. N\(_2\) and H\(_2\) isotherms at 77 and 87 K were measured in liquid nitrogen and liquid argon baths, respectively. Oil-free vacuum pumps and oil-free pressure regulators were used for all measurements. Brunauer–Emmett–Teller (BET) surface areas were calculated from the linear region of the N\(_2\) isotherms at 77 K prior to the step at 0.1 bar, and Langmuir surface areas were determined using Micromeritics software.

Powder X-ray Diffraction. Powder X-ray diffraction patterns of the samples were collected at the 17-BM beamline at the Advanced Photon Source (Argonne National Laboratory) with a wavelength of 0.72768 Å. Scattered intensity was recorded by PerkinElmer a-Si flat panel detector at room temperature. Prior to measurement, the samples were sealed under N\(_2\) in borosilicate glass capillaries of 1 mm diameter. Powder diffraction data analyses (pattern indexing, profile fitting, Pawley refinement, and crystal structure model) were performed with the program TOPAS-Academic V4.125. Specifically, a standard peak search followed by indexing via the single value historically. A restrained Rietveld refinement was performed where the positions of the linker were frozen at the predicted fractional coordinates. The unit cell and profile parameters were then refined using the program TOPAS \(^{58}\) and used to generate a structural model (Figure S4).

Accordingly, we found that the M\(_2\)(olz) materials are isoreticular to the M\(_2\)(dobpdc) frameworks and crystallize in the space group P3\(_2\)1, exhibiting large pores that are approximately 27 Å wide. Unit cell parameters for each framework are given in Table S1, and their corresponding Pawley fits are shown in Figures S5–S9.

The as-synthesized M\(_2\)(olz) can be activated by performing successive solvent exchanges with DMF and methanol, followed by heating under argon and vacuum to remove residual or coordinated solvent. Surface areas of the desolvated M\(_2\)(olz) frameworks were then determined from N\(_2\) adsorption measurements performed at 77 K (Figure S10). With the exception of Zn\(_2\)(olz), which loses crystallinity upon activation, the M\(_2\)(olz) frameworks exhibit high surface areas that are consistent with the expanded linker size (Table S1). The Langmuir surface areas are indeed the highest reported for any framework with a bioactive molecule as the sole linker.\(^{59}\) In the

![Figure 1. Powder X-ray diffraction patterns of activated M\(_2\)(olz) frameworks (M = Mg, Fe, Co, Ni) and ethanol-solvated Zn\(_2\)(olz); \(\lambda = 0.72768 \) Å. The diffraction patterns are offset for clarity.](image-url)
case of Mg$_2$(olz), Fe$_2$(olz), Co$_2$(olz), and Ni$_2$(olz), the N$_2$
adsorption isotherms exhibit a step at approximately 0.1 bar
pressure. Similar behavior has been observed in the Ar
adsorption isotherms of other frameworks in the expanded
M$_2$(dobdc) series and is ascribed to the occupation of
secondary adsorption sites.\textsuperscript{17}

**H$_2$ Adsorption in M$_2$(olz) Frameworks.** In the
isoreticular M$_2$(dobdc) series, the removal of axial metal-
bound solvent molecules results in coordinatively unsaturated
metal centers that are poised to interact with guest molecules
such as CO$_2$,\textsuperscript{59,60} NO,\textsuperscript{50,61} and O$_2$.\textsuperscript{15} These open metal sites are
also particularly selective for H$_2$ adsorption,\textsuperscript{62–64} and slight
electronic changes afforded by replacing dobdc$^{4-}$ with m-
dobdc$^{4-}$ further result in substantial enhancement of the H$_2$
binding enthalpies.\textsuperscript{16} We therefore sought to confirm the
presence of open metal sites within the structurally similar
M$_2$(olz) frameworks and examine their potential as H$_2$ storage
materials. Hydrogen adsorption isotherms were collected at 77
and 87 K for all activated M$_2$(olz) frameworks (Figure 2), and
fits to the data were obtained employing the Langmuir–
Freundlich equations for dual-site and trisite models (fit
parameters are given in Table S2). Isosteric heats of adsorption
(Q$_s$) were calculated using the Clausius–Clapeyron relation,
which revealed strong H$_2$ binding at low coverage for the Mg,
Fe, Co, and Ni frameworks, with Q$_s$ values ranging from −10.8
to −12.1 kJ/mol (Figure 2 and Table 2). These values are
comparable to those obtained for M$_2$(m-dobdc)$^{18}$ and
M$_2$(dobpdc).\textsuperscript{65}

**Table 1. Surface Areas of the M$_2$(olz) Frameworks**

<table>
<thead>
<tr>
<th>M</th>
<th>BET surface area (m$^2$/g)</th>
<th>Langmuir surface area (m$^2$/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mg</td>
<td>2545</td>
<td>4593</td>
</tr>
<tr>
<td>Fe</td>
<td>1485</td>
<td>2618</td>
</tr>
<tr>
<td>Co</td>
<td>2060</td>
<td>3838</td>
</tr>
<tr>
<td>Ni</td>
<td>2067</td>
<td>3813</td>
</tr>
<tr>
<td>Zn</td>
<td>636</td>
<td>770</td>
</tr>
</tbody>
</table>

**Table 2. Isosteric Heats of Adsorption of H$_2$ in M$_2$(olz)**

<table>
<thead>
<tr>
<th>M</th>
<th>Mg</th>
<th>Fe</th>
<th>Co</th>
<th>Ni</th>
<th>Zn</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q$_s$ (kJ/mol)</td>
<td>−10.8</td>
<td>−10.9</td>
<td>−11.4</td>
<td>−12.1</td>
<td>−7.3</td>
</tr>
</tbody>
</table>

As judged from the position of the inflection points in the
isosteric heat plot of Figure 2 (upper), the performance of
Co$_2$(olz) is notable because it shows near complete saturation
of the metal centers. This high accessibility of the open metal
sites is not observed in the smaller M$_2$(dobdc) or M$_2$(m-dobdc)
materials, likely due to partially blocked pores. The Ni$_2$(olz)
and Mg$_2$(olz) materials also exhibit reasonably good coverage at
about 85% and 70% saturation, respectively. About 55% saturation is observed for Fe$_2$(olz), which may be due to the
milder activation conditions employed for this material. In the
case of Zn$_2$(olz), the isosteric heat of adsorption is significantly
lower in magnitude than the other frameworks in the series.
This material also does not exhibit a steep rise in H$_2$ adsorption
at low pressures (Figure 2, lower), which suggests that open
metal sites may not be present in the activated Zn$_2$(olz)
material. This behavior is also consistent with the comparatively
low surface area and loss in crystallinity observed upon
activation.

**Characterization of H$_2$–M$_2$(olz) Interactions by Infra-
red Spectroscopy.** In situ infrared (IR) spectroscopy was
used to further characterize the nature of the M$_2$(olz)
interaction with H$_2$ for two of the highest performing materials,
Mg$_2$(olz) and Ni$_2$(olz). Although H$_2$ is IR-inactive in the gas
phase, its adsorption at surfaces breaks the vibrational
symmetry, rendering the molecule IR-active (a schematic
energy diagram is given in Figure S23). In particular, the
binding of H$_2$ at open metal coordination sites with positive
charge densities can be measured by a characteristic red-shift of
the H–H stretching frequency. Importantly, recent studies have
also shown that the magnitude of this frequency shift can be
correlated to the strength of the binding energy at a particular
site in the framework.\textsuperscript{66} We examined the H$_2$
vibrational frequencies for Mg$_2$(olz) at several different loadings of H$_2$, as
shown in Figure 3 (extended spectral ranges are given in Figure
S24). At a loading of one H$_2$ per metal, a doublet is observed in
the spectrum (maxima at 4097 and 4091 cm$^{-1}$) that
corresponds to the pure vibrational modes of ortho-H$_2$ and
para-H$_2$ bound to the open metal site. The spectrum of one H$_2$
bound to Ni$_2$(olz) exhibits a greater red-shift than that of H$_2$
bound to Mg$_2$(olz), which is consistent with stronger binding
of H$_2$ to Ni$^{2+}$ compared to Mg$^{2+}$ in M$_2$(dobdc) (Figure S26).
For both metals, the spectra indicate that the strength of H$_2$
binding is only slightly higher in the M$_2$(dobdc) than in
M$_2$(olz) frameworks. Increasing the H$_2$ loading beyond 1 equiv
per metal results in binding at secondary sites, as evidenced by
the appearance of multiple peaks (from 4150 to 4100 cm$^{-1}$) in
the IR spectra. Similar spectral features were observed for the
secondary adsorption sites of M$_2$(dobdc) and M$_2$(m-dobdc)
frameworks.\textsuperscript{18} Additional increases in loading result in further

**Figure 2.** Top: isosteric heats of adsorption plotted as a function of the
amount of H$_2$ adsorbed for M$_2$(olz). Bottom: equilibrium H$_2$
adsorption isotherms for M$_2$(olz) at 77 K, where the amount adsorbed
is plotted in terms of H$_2$ molecules per metal atom.
filling of the channels, giving rise to more complicated spectral features, indicating the presence of multiple binding sites within M2(olz).

Variable-temperature IR spectra were also collected for Mg2(olz) and Ni2(olz) to extract the enthalpy of H2 adsorption at the open metal sites (Figure 4).67,68 The initial H2 loading was set such that only the open metal sites were occupied during the measurements. The fractional occupancy was then determined as the ratio of the area under the resulting IR band to the area observed at complete saturation. The enthalpy and entropy changes were extracted from van’t Hoff plots, which are shown as insets in Figure 4. We note that the slopes extracted from these plots are very sensitive to variation in the maximum saturation area, and an error of 1 kJ/mol can be estimated for the corresponding enthalpy values. For Ni2(olz) the enthalpy of H2 adsorption was found to be $\Delta H^\circ = -13(1)$ kJ/mol, which is higher than the $\Delta H^\circ = -10(1)$ kJ/mol of Mg2(olz). Fairly large values of entropy changes were also measured for both frameworks ($\Delta S^\circ = -150(10)$ and $-130(10)$ J/K for Ni2(olz) and Mg2(olz), respectively), which is consistent with previous studies that revealed a positive correlation between the entropy and enthalpy change of bound H2 in Mg2(dobdc) and Co2(dobdc).68

**Mg2(olz) as a Drug Delivery Platform.** The high biocompatibility and large pore dimensions of the M2(olz) frameworks make them promising candidates for drug delivery applications. Given the low atomic weight of Mg and its role as an essential metal in the human diet,69 Mg2(olz) was selected for the initial drug release studies. Notably, the desolvated material is composed of 86 wt % olsalazine, which represents one of the highest loadings for a therapeutic molecule in any reported metal-organic framework.36,70 We prepared pellets of Mg2(olz) framework and exposed them to simulated physiological conditions (37 °C PBS solution at pH 7.4 with bidimensional stirring at 60 rpm) to evaluate framework disassembly and olsalazine release. Aliquots were collected from the buffered solution at different time points, and the appearance of olsalazine was tracked by measuring its characteristic absorbance at 360 nm. The resulting degradation profile of Mg2(olz) shows gradual release of olsalazine as the framework disassembles into its constituent parts (Figure S27). This release behavior, coupled with the high olsalazine composition, makes Mg2(olz) a potential candidate for delivery of the anti-inflammatory therapeutic.

We further sought to utilize the high surface area and porosity of the Mg2(olz) framework to codeliver a second drug with olsalazine. Phenethylamine (PEA) was selected as a model drug for loading because derivatives of this molecule form a large class of bioactive compounds with diverse pharmacological properties (e.g., stimulants, appetite suppressants, antidepressants, and anti-Parkinsonian agents; see Figure S28). Because of the extensive metabolism and addictive nature of some of these compounds, there is a need for controlled release formulations that reduce dramatic fluctuations in drug concentrations while maintaining adequate therapeutic levels over time. In this way, a controlled release dosage form may improve performance of the drug while reducing the likelihood of side effects and abuse.

Many approaches have been employed to load drugs into porous metal-organic frameworks including noncovalent drug encapsulation,36,40,45,71,72 postsynthetic modification of the linker or framework surface,47 framework amorphization after loading,59,60 “ship in a bottle,”73 and “bottle around ship”43 strategies. An alternative approach is to use the drug as a ligand to bind to open metal sites within a framework, as has been
shown for anionic ibuprofen\textsuperscript{49} and nitric oxide\textsuperscript{50} in Fe\textsubscript{2}(dobdc). Taking advantage of the coordinatively unsaturated metal sites and large pore apertures of the M\textsubscript{2}(olz) frameworks, we sought to graft drugs containing a Lewis-basic functional group directly to the metal ions of the framework. Indeed, previous studies have demonstrated grafting of various functional groups, including amines,\textsuperscript{16,74,75} alkoxides,\textsuperscript{76} phenoxides,\textsuperscript{77} and other anions\textsuperscript{78} onto the open metal sites of M\textsubscript{2}(dobdc), M\textsubscript{2}(dobpdc), and MIL-101 frameworks. We therefore wanted to explore whether biologically active molecules possessing these functional groups could be similarly coordinated to the open metal sites of Mg\textsubscript{2}(olz).

To this end, PEA was incorporated into Mg\textsubscript{2}(olz) by soaking the framework in a 20\% solution of the drug in CH\textsubscript{2}Cl\textsubscript{2}. After 24 h, the resulting material was washed and dried, and the stoichiometry was confirmed by \textsuperscript{1}H NMR spectroscopy as two PEA per olsalazine, or one PEA per Mg\textsuperscript{2+} ion (Figure S29). A proposed structural model for Mg\textsubscript{2}(olz)(PEA)\textsubscript{2} is depicted in Figure 5, where the amine of PEA is coordinated to the Mg\textsuperscript{2+} ions in the observed 1:1 stoichiometry. The secondary amine N-methylphenethylamine was also shown to bind to Mg\textsubscript{2}(olz) in the expected stoichiometry of one amine per metal (Figure S30), suggesting that Mg\textsubscript{2}(olz) is a versatile platform that could accommodate a variety of phenethylamine derivatives or other small-molecule therapeutics.

In order to simulate physiological conditions for drug release, the Mg\textsubscript{2}(olz)(PEA)\textsubscript{2} material was pressed into 4 mm pellets, which were immersed in PBS with shaking at 37 °C. Aliquots were taken at regular time points until the framework was fully dissolved, and release of both PEA and olsalazine was quantified by reversed-phase HPLC (Figure S5, right). Based on the observed cumulative release, the PEA is released more rapidly than the olsalazine linker. For example, approximately 95\% of PEA was released compared to 50\% of the olsalazine after 3 h. This result suggests that PEA may be displaced as water diffuses into the one-dimensional channels prior to the dissolution of the framework itself, resulting in multirate drug release.

In Mg\textsubscript{2}(olz)(PEA)\textsubscript{2}, over 90 wt \% of the material consists of a therapeutic organic molecule, with PEA and olsalazine accounting for 41 and 51 wt \%, respectively. Such high concentrations of active pharmaceutical ingredients are desirable as they can reduce the size of the administered dose and minimize the need for other components that may produce side effects in some patients. The disassembly of the loaded framework into components that have well-established pharmacological and safety profiles in humans is also a beneficial feature that may greatly expedite the translation of any promising M\textsubscript{2}(olz) materials into a clinical setting.

\section*{CONCLUSIONS}

We have synthesized and characterized a new family of M\textsubscript{2}(olz) (M = Mg, Fe, Co, Ni, and Zn) metal–organic frameworks that utilize the anti-inflammatory drug olsalazine as the sole bridging ligand. The M\textsubscript{2}(olz) materials are the first series of isostructural bioactive frameworks exhibiting mesoporosity and can be made with a variety of metals. They contain 27 Å pores and have the highest Langmuir surface areas for metal–organic frameworks with a therapeutic linker. This level of mesoporosity can be useful in accommodating large guest molecules in the hexagonal channels. The M\textsubscript{2}(olz) materials are also the first bioactive metal–organic frameworks containing open metal sites, which may enhance interactions of encapsulated guest molecules within the pore. Indeed, these open metal sites have a strong affinity for binding H\textsubscript{2}, as demonstrated by H\textsubscript{2} adsorption studies and in situ IR spectroscopy. While the volumetric capacity of M\textsubscript{2}(olz) frameworks may not be optimal for H\textsubscript{2} storage,\textsuperscript{65} their high gravimetric capacity could be useful for other gas capture strategies that may benefit from an expanded pore size.

Notably, the M\textsubscript{2}(olz) frameworks have intrinsic therapeutic properties since they contain high quantities of the anti-inflammatory olsalazine, which can be released under simulated physiological conditions. This is especially true of Mg\textsubscript{2}(olz), the least dense M\textsubscript{2}(olz) framework, which represents the highest drug loading within any bioactive metal–organic framework to date. These mesoporous materials may also serve as platforms for the simultaneous delivery of multiple therapeutic compounds. This concept was demonstrated through the encapsulation of phenethylamine in Mg\textsubscript{2}(olz) and the successful release of both drugs under physiological conditions. The observed disassembly of the drug-loaded frameworks into
their original components is also advantageous for translation to clinical studies, since the safety and performance profiles will have been established previously for the constituent approved drugs.

Through judicious choice of metal, one can further envision tailoring the interaction between framework and drug to alter the strength of binding at the open metal site and tune the rate of release. For instance, the Mg$_2$(olz) and Co$_2$(olz) frameworks would be well suited for strong interactions with hard nitrogen and oxygen donors, while the Zn$_2$(olz) framework would be well matched for softer sulfur-based drugs loaded in solution.

Additionally, the Fe$_2$(olz) framework could be oxidized to [Fe$_2$(olz)]$^{2+}$ as has been done for Fe$_2$(dobdc) and Fe$_2$(dobpdc), thereby producing a cationic framework capable of strong binding to anionic drugs. In some cases, it may also be beneficial to administer a precise ratio of metals in a drug formulation to serve as nutritional supplements or to address metal deficiencies in patients. Derivatives of M$_2$(dobdc) have been made with combinations of up to ten metals distributed throughout the framework in precise ratios, and a similar strategy could be pursued with M$_2$(olz).

 ASSOCIATED CONTENT

Supporting Information
The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b03523.

Synthesis of olsalazine, scanning electron microscopy, comparison of M$_2$(olz) to M$_2$(dobdc) and M$_2$(dobpdc), structural model of M$_2$(olz), Rietveld refinement, unit cell parameters and Pawley fits, 77 K N$_2$ adsorption isotherms, linear BET plots, thermogravimetric analysis, and oxygen donors, while the Zn$_2$(olz) framework would be well matched for softer sulfur-based drugs loaded in solution. Additionally, the Fe$_2$(olz) framework could be oxidized to [Fe$_2$(olz)]$^{2+}$ as has been done for Fe$_2$(dobdc) and Fe$_2$(dobpdc), thereby producing a cationic framework capable of strong binding to anionic drugs. In some cases, it may also be beneficial to administer a precise ratio of metals in a drug formulation to serve as nutritional supplements or to address metal deficiencies in patients. Derivatives of M$_2$(dobdc) have been made with combinations of up to ten metals distributed throughout the framework in precise ratios, and a similar strategy could be pursued with M$_2$(olz).

AUTHOR INFORMATION

Corresponding Author
*E-mail: jlong@berkeley.edu (J.R.L.).

Present Addresses
D.J.L.: Department of Chemical Engineering, California Institute of Technology, Pasadena, CA 91125.
B.K.K.: Department of Chemical Engineering, University of Texas at Austin, Austin, TX 78712.
J.A.M.: Department of Chemistry, Northwestern University, Evanston, IL 60208.
C.M.L.: Département de Chimie, École Normale Supérieure de Paris et Département de Chimie, Université Pierre et Marie Curie, 75005 Paris, France.

Notes
The authors declare no competing financial interest.

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