**General Chemicals and Characterization Methods**

All reagents and solvents were obtained from commercial sources at reagent-grade purity or higher. Laboratory powder X-ray diffraction patterns were collected on a Bruker AXS D8 Advance diffractometer equipped with Cu Kα radiation (λ = 1.5418 Å), a Göbel mirror, a Lynxeye linear position-sensitive detector, and mounting the following optics: fixed divergence slit (0.6 mm), receiving slit (3 mm) and secondary-beam Soller slits (2.5°). The generator was set at 40 kV and 40 mA. Thermogravimetric analysis was carried out at a ramp rate of 2 °C min^{-1} under nitrogen flow with a TA Instruments Q5000. Elemental analyses for C, H and N were performed at the Microanalytical Laboratory of the University of California, Berkeley using a PerkinElmer 2400 series II combustion analyzer.

Synthesis of Olsalazine Acid (H$_4$olz)
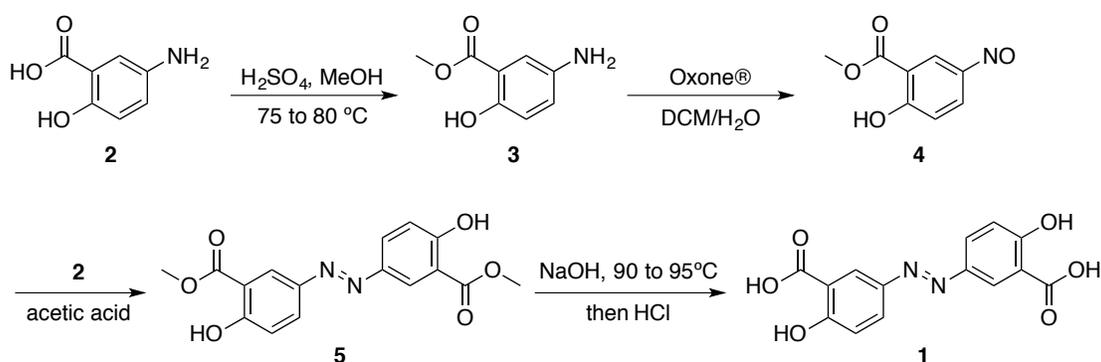
Scheme S1. Synthesis of olsalazine acid (H$_4$olz), originally reported in reference [1].

Methyl 5-aminosalicylate (2). 5-Amino salicylic acid (**1**, 20.0 g, 131 mmol) was suspended in methanol (250 mL). Concentrated sulfuric acid (10 mL) was added, and the solution was heated to reflux (75–80 °C) with stirring. The solution was kept at reflux overnight, then cooled to ambient temperature and concentrated on a rotary evaporator. The resulting pale lavender powder was treated by slow addition of saturated sodium bicarbonate (500 mL). The product was extracted with 3×200 mL portions of ethyl acetate. The organic layers were combined and dried over magnesium sulfate, filtered, then concentrated on a rotary evaporator. The residue was dried under vacuum to give the title compound as a light tan solid (10.7 g, 49.2% yield).

Methyl 5-nitrososalicylate (3). To a solution of compound **2** (3.01 g, 18.0 mmol) in CH$_2$Cl$_2$ (75 mL), a solution of Oxone (11.1 g, 18.0 mmol) in H$_2$O (75 mL) was added. The biphasic mixture was stirred vigorously at room temperature, as the CH$_2$Cl$_2$ layer developed a dark green color. The progression of the reaction was monitored by LCMS until the starting material was fully consumed (usually about two hours). The layers were separated, then the aqueous layer was washed with additional CH$_2$Cl$_2$ (2 × 75 mL). The combined organic layers were filtered through a short silica column, eluting with CH$_2$Cl$_2$. The filtrate was concentrated on a rotary evaporator and dried under vacuum to afford the title compound as a bright green solid (1.69 g). Some over-oxidation of nitroso to nitro was evident by LCMS. However, this did not interfere with the subsequent reaction, and the crude mixture was used in the next step without further purification.

Olsalazine methyl ester (4). The crude mixture obtained from the previous step was dissolved in acetic acid (35 mL). To this was added a solution of **2** (1.50 g, 9 mmol) in acetic acid (35 mL). The reaction mixture was stirred at room temperature overnight. The resulting precipitate was collected on a Buchner funnel and washed sequentially with acetic acid and water to afford **4** as a bright yellow solid (1.78 g, 29.9% yield, two steps).

Olsalazine acid (H₄olz). Compound **4** (1.75 g, 5.30 mmol) was dissolved in 50 mL aqueous NaOH (1.06 g, 26.5 mmol). The deep red solution was heated to reflux (90–95 °C) with stirring. After 2 h, the reaction mixture was allowed to cool to ambient temperature. Concentrated HCl was added dropwise with stirring until no further precipitation occurred. The precipitate was collected on a Buchner funnel, washed with water, and dried to afford H₄(olz) as an orange-yellow solid (1.492 g, 97.6%).

Preparation of Na₂(H₂olz)

Sodium olsalazine was isolated by evaporation of water and methanol during the saponification of olsalazine ester by sodium hydroxide. Sodium olsalazine may also be prepared by exposing olsalazine acid to two equivalents of sodium bicarbonate in water. Removal of water by rotary evaporation and drying under vacuum gave Na₂(H₂olz) as an orange-yellow solid. EA: calculated C 40.20%, H 3.90%, N 6.70%; found C 39.92%, H 3.67%, N 6.58%.

Synthesis of Ca(H₂olz)·4H₂O One-Dimensional Chains

The metal salt Ca(NO)₃·4H₂O (112 mg, 0.473 mmol) was dissolved in 5 mL of water and olsalazine acid (68.0 mg, 0.225 mmol) was dissolved in 10 mL water with addition of NaOH (18.0 mg, 0.450 mmol). The olsalazine solution was allowed to reach 90 °C and the metal salt solution was added under heavy stirring. The mixed solution was heated and left stirring overnight. The dark orange powder was collected on a funnel and dried to obtain the microcrystalline powder. Yield: 79.0 mg, 85.1%. EA: calculated C 40.80% H 3.90% N 6.80%; found C 40.51%, H 3.66%, N 6.68.

Alternative synthesis: Ca(OAc)₂·2H₂O (27.7 mg, 0.160 mmol) was dissolved in 1 mL of water and olsalazine acid (22.7 mg, 0.0750 mmol) was suspended in 4 mL of water with sonication. The combined solutions were then sonicated together and left to heat at 90 °C to produce yellow or red crystals depending on size. A shorter sonication time (1 min) correlated with larger crystals, while longer sonication times (> 5 min) produced a more uniform distribution of crystals by size.

Synthesis of Ca(H₂olz)·2H₂O Two-Dimensional Sheets

The metal salt Ca(NO₃)₂·4H₂O (74.4 mg, 0.315 mmol) was dissolved in 3 ml of water, and olsalazine acid (45.3 mg, 0.150 mmol) was dissolved in 1 mL of water with NaOH (12.0 mg, 0.300 mmol). The ligand solution was added to the metal solution at room temperature, producing an orange precipitate upon mixing. The vial was heated undisturbed at 90 °C for 12 h to afford the product as a microcrystalline powder (34.2 mg, 61% yield). EA: calculated C 44.70%, H 3.20%, N 7.40%; found C 44.46%; H 2.96 %; N 7.39%.

Alternative synthesis: Ca(NO₃)₂·4H₂O (18.6 mg, 0.0788 mmol, 2.1 equiv.) and Na₂(H₂olz) (13.0 mg, 0.0375 mmol) were dissolved in 0.5 mL and 2 mL of water,

respectively. The solutions were combined, producing a transient yellow precipitate that dissolved upon heating at 90 °C. The vial was left to heat undisturbed at 90 °C to produce yellow crystals. Longer reaction times can be used to produce larger crystals. Note that sonication or stirring of the reaction mixtures described may favor the one-dimensional phase, so it is important to minimize agitation to promote formation of the two-dimensional phase under these conditions.

Synthesis of Ca(H$_2$olz)·2DMF Three-Dimensional Framework
The metal salt Ca(NO$_3$)$_2$·4H$_2$O (117 mg, 0.495 mmol) was dissolved in 12 mL of EtOH and olsalazine acid (136 mg, 0.450 mmol) was dissolved in 18 mL of DMF. These solutions were combined in a jar and separated into six 10-mL aliquots in 20-mL scintillation vials. The vials were then heated in a dry bath at 120 °C for 1 d. The solvent mixture was decanted to isolate the product as dark orange needles by filtration (124 mg, 56.5% yield). Note that washing with DMF can partially dissolve the crystals and should be minimized. A bulk microcrystalline powder can also be prepared by stirring the reaction mixture described above at 120 °C. EA: calculated C 49.4%, H 4.6%, N 11.5%; found C 48.8%; H 4.7%; N 11.4%.

Conversion of Ca(H$_2$olz)·2DMF to Ca(H$_2$olz)·2MeOH·H$_2$O
Dried crystals of Ca(H$_2$olz)·2DMF (124 mg, 0.255 mmol) were immersed in 10 mL of methanol in a 20-mL scintillation vial at 65 °C and placed in a dry bath. The methanol was decanted and replaced with 10 mL fresh methanol three times every 12 h while heating at 65 °C. The product was collected and dried on a Buchner funnel (107 mg, 99.1 % yield). EA: calculated C 39.8%, H 3.8%, N 6.6%; found C 39.5%, H 4.0%, N 6.6%.

Conversion of Ca(H$_2$olz)·2DMF to Ca(H$_2$olz)
Dried crystals of Ca(H$_2$olz)·2DMF (75.0 mg, 0.154 mmol) were immersed in 3 mL of 100 mM aqueous HCl at room temperature for 24 h, converting the framework to the collapsed Ca(H$_2$olz) phase. The product was collected and dried on a Buchner funnel (52.1 mg, 98.6% yield). EA. calcd. C 39.8%, H 3.8%, N 6.6%; found C 39.5%, H 4.0%, N 6.6%. An analogous procedure can be used to convert Ca(H$_2$olz)·2MeOH·H$_2$O to Ca(H$_2$olz).

Powder X-Ray Diffraction
High-resolution X-ray powder diffraction patterns of the samples were collected at the beamline 17-BM at the Advanced Photon Source (Argonne National Laboratory) with an average wavelength of 0.72768 Å. Scattered intensity was recorded by Perkin Elmer a-Si Flat Panel detector at room temperature. Prior to measurement the samples were manually powdered in a mortar and pestle and sealed in borosilicate glass capillaries of 1 mm diameter (Hilgenberg glass No. 50). The data analysis of Ca(H$_2$olz)·2MeOH·H$_2$O (pattern indexing, profile fitting, crystal structure solution and refinement) was performed with the program TOPAS 4.1.[2] The pattern indexing was done with the singular value decomposition method,[3] resulting in monoclinic unit cell. The space group was assumed to be *Cc,* which was later confirmed by the structure solution and refinement. Precise lattice parameters were determined by a Pawley fit.[4] The crystal structure of the Ca(H$_2$olz)·2MeOH·H$_2$O was solved by the global optimization method of simulated

annealing (SA) in real space.[5] The structure solution was performed in the *Cc* space group using one rigid body for the olsalazine molecule, two methanol rigid bodies, one calcium cation and one oxygen atom representing a water molecule in the asymmetric unit. For the definition of the connectivity between the atoms within the rigid bodies, *z* matrix notation was used. During the SA runs, three rotations and three translations for each rigid body together with all possible torsion angles were set as flexible. An overall temperature factor for each atom type was included in the SA process. Once a global minimum was found, the crystal structures were subjected to Rietveld refinement,[6] in which bond lengths and angles were refined within the rigid bodies, together with free refinement of all profile and lattice parameters. The refinement converged with the following figures of merit: $R_{exp} = 0.0153$, $R_{exp}' = 0.0311$, $R_{wp} = 0.0541$, $R_{wp}' = 0.1104$, $R_p = 0.0396$, $R_p' = 0.1035$, $GOF = 3.55$ and $R_{Bragg} = 0.0205$. The final Rietveld plot is presented in Figure 3.S5. Hydrogen atoms were added at calculated positions by the program Mercury.[7] Crystallographic details are provided in the deposited CIF.

Single Crystal X-Ray Diffraction
X-ray diffraction analyses were performed on crystals of $Ca(H_2olz) \cdot 2H_2O$ and $Ca(H_2olz) \cdot 2DMF$, which were isolated from the mother liquor, coated with Paratone-N oil, and mounted on MiTeGen loops. Crystals were frozen at 100 K by an Oxford Cryosystems Cryostream 700 plus. Data for $Ca(H_2olz) \cdot 2H_2O$ and $Ca(H_2olz) \cdot 2DMF$ were collected at Beamline 11.3.1 at the Advanced Light Source, Lawrence Berkeley National Laboratory using synchrotron radiation ($\lambda = 0.7749$ Å). Raw data were integrated and corrected for Lorentz and polarization effects using Bruker AXS SAINT software.[8] Absorption corrections were applied using SADABS.[9] Space group assignments were determined by examination of systematic absences, E-statistics, and successive refinement of the structures. The structures were solved using direct methods with SHELXS[10] and refined using SHELXL[11] operated in the OLEX2[12] interface. None of the crystals showed significant decay during data collection. Thermal parameters were refined anisotropically for all non-hydrogen atoms. Hydrogen atoms were placed in ideal positions and refined using a riding model for both structures.

The crystal of $Ca(H_2olz) \cdot 2DMF$ was found to be a non-merohedral twin based on the diffraction pattern. The program CELL_NOW[13] was used to determine the orientation matrices and the domains were related by a 180° rotation around the real axis 0 1 0. The integration was performed with both matrices. TWINABS[14] was used to produce a merged HKLF4 file, for structure solution and initial refinement, and a HKLF5 file for final structure refinement. The HKLF5 file contained the merged reflection's first component and those that overlapped with the second component were split into 2 reflections. TWINABS indicated the twin faction to be 68:31. The structure was solved using the HKLF4 file, but the best refinement was given by the HKLF5 file. Treatment of each the two components as an inversion twin resulted in a better refinement. Refinement of the structure as a twin comprised of these four components, gave the following BASF values: 0.34(10), 0.07(6), 0.35(5), 0.24(6).

Olsalazine Drug Release Assay
The drug release studies were performed under conditions to simulate the passage of a solid pill through the gastrointestinal tract by placing the pellets in a solution and increasing the pH at specific time points. Pellets were prepared from all materials using a circular die with a 4-mm diameter and pressed in a vise for 15 min under a consistent pressure. All pellets had a mass of 5.0 mg (± 0.2 mg) and an approximate thickness of 0.35 mm. Dissolution was observed for pellets in 50-mL conical tubes, which were placed horizontally in a shaking incubator with bidimensional stirring at 60 rpm at 37 °C. 250-µL aliquots were collected every hour, and each material was tested in triplicate. The pellets were first exposed to 20 mL of the simulated gastric fluid solution for 2 hours. Phosphate solution (16.6 mL) was then added to produce a simulated intestinal fluid solution of pH 6.0 and left to shake for 2 hours. Then, 14.4 mL of phosphate solution was added to produce simulated colonic fluid at pH 7.3, and the samples were left to shake for 6 hours. Simulated gastric fluid was prepared as 100-mM HCl. The basic phosphate stock solution was prepared as 45-mM NaOH and 170-mM Na_2HPO_4 resulting in a pH 11.1 solution. This method was adapted from reference [15].

Quantification of Olsalazine Release
Olsalazine release was measured by absorbance in 96-well Corning Costar (Tewksbury, MA) 3915 black plates. Absorbance was measured at $\lambda = 360$ nm by a Molecular Devices SpectraMax Paradigm plate reader. For each time point, a 75-µL aliquot was plated in duplicate and measured against a calibration curve of $Na_2(olz)$ in PBS. To account for the changes in volume throughout the experiment, the following equations were used to calculate the amount of olsalazine in solution at each time point:

$$x_n = [C]_n \times V_n \qquad\qquad \text{Equation 1}$$

$$x_n = x_{n-1} + [([C]_n - [C]_{n-1})(V_{n-1} - V_A)] \qquad\qquad \text{Equation 2}$$

where:
x_n = Total mol olsalazine released at time n
x_{n-1} = Total mol olsalazine released at time $n-1$
$[C]_n$= Concentration at time n
$[C]_{n-1}$ = Concentration at time $n-1$
V_n = volume at time n
V_{n-1} = volume at time $n-1$
V_A = volume of aliquot removed
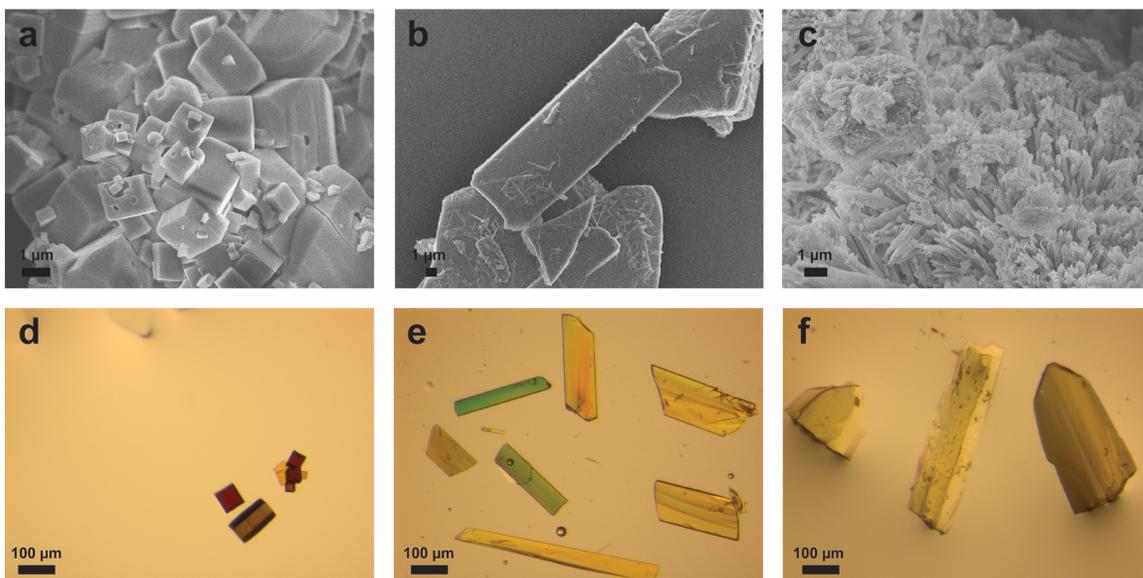
Figure S1. Scanning electron microscopy images (a–c) and optical microscopy images (d–f) of microcrystalline and single crystal materials. Images are of Ca(H$_2$olz)·4H$_2$O one-dimensional chains (a,d), Ca(H$_2$olz)·2H$_2$O two-dimensional sheets (b,e), and Ca(H$_2$olz)·2DMF three-dimensional metal-organic framework (c,f). SEM images were taken using a JEOL JSM-6340F SEM. Samples were suspended in methanol and drop cast onto a silicon chip. To dissipate charge, the samples were sputter coated with approximately 3 nm of Au (Denton Vacuum).
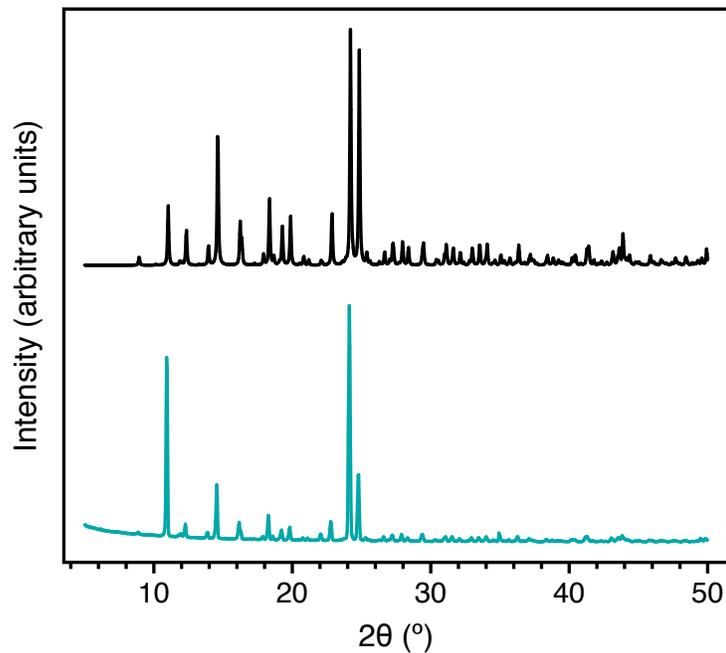
Figure S2. Comparison of the predicted (black) and experimental (teal) powder X-ray diffraction patterns for $Ca(H_2olz)\cdot 4H_2O$ (**1**) one-dimensional chains ($\lambda = 1.5418$ Å).
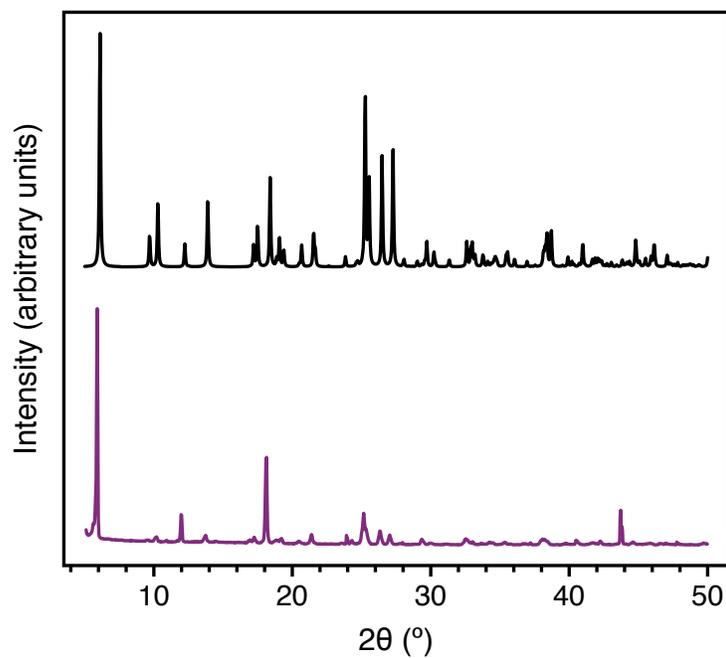
Figure S3. Comparison of the predicted (black) and experimental (purple) powder X-ray diffraction patterns for $Ca(H_2olz)\cdot 2H_2O$ (**2**) two-dimensional sheets ($\lambda = 1.5418$ Å).
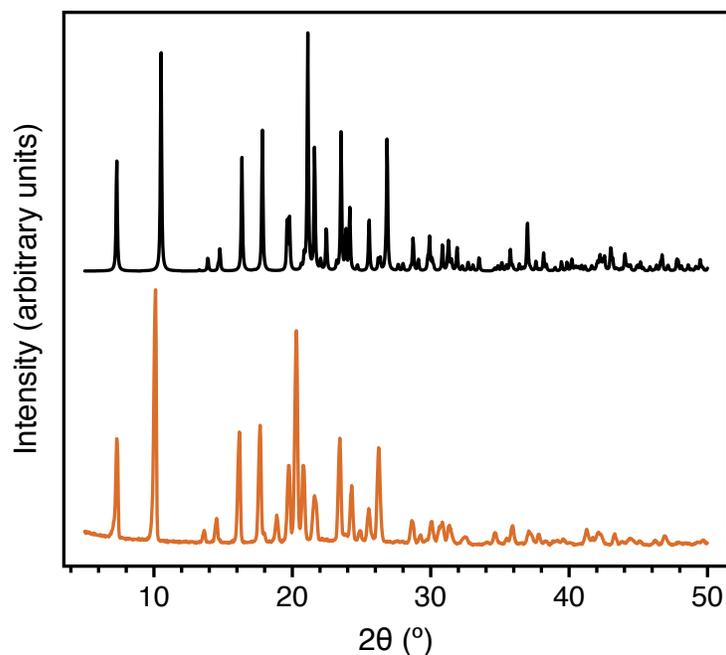
Figure S4. Comparison of the predicted (black) and experimental (orange) powder X-ray diffraction patterns for $Ca(H_2olz)\cdot2DMF$ (**3**·DMF) three-dimensional metal–organic framework ($\lambda = 1.5418$ Å).
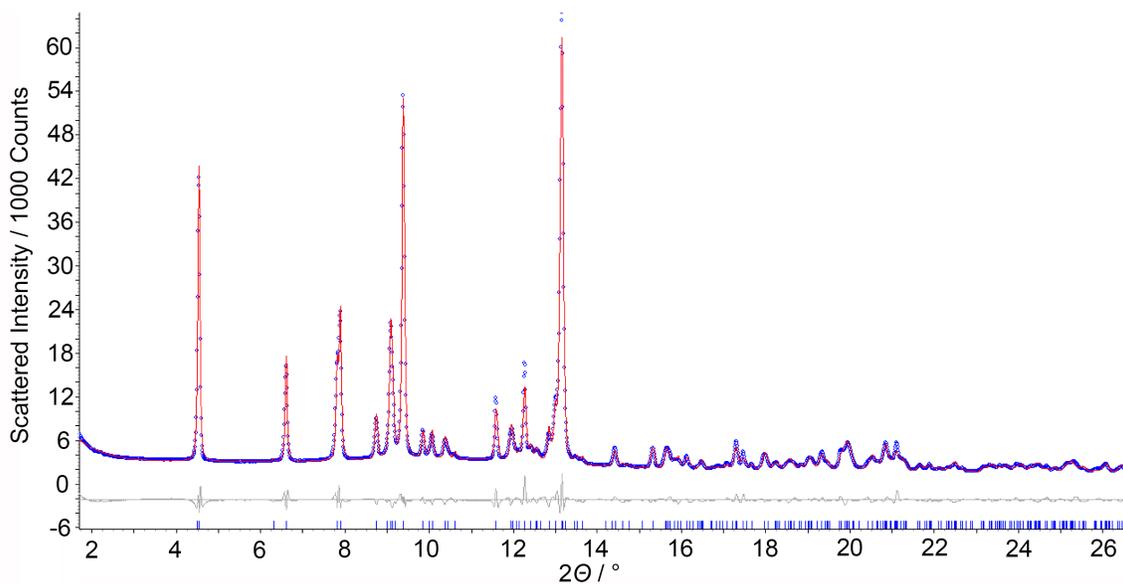
Figure S5. Rietveld refinement plot of $Ca(H_2olz)\cdot2MeOH\cdot H_2O$ ($\lambda = 0.72768$ Å). Measured scattered intensity is presented with blue dots; the best fit with red line and the corresponding difference plot with gray line. The Bragg reflections are given with blue bars.

Table S1. Crystal data and structure refinement for $Ca(H_2olz) \cdot 2H_2O$.

Empirical formula	$C_{14}H_{12}N_2O_8Ca$
Formula weight	376.34
Temperature	100(2) K
Wavelength	0.7749 Å
Crystal system	Monoclinic
Space group	$P12_11$
Unit cell dimensions	$a = 9.3413(5)$ Å $\quad \alpha = 90°$
	$b = 5.4114(3)$ Å $\quad \beta = 102.423(4)°$
	$c = 14.8190(8)$ Å $\quad \gamma = 90°$
Volume	$731.55(7)$ Å^3
Z	2
Density (calculated)	1.708 Mg/m^3
Absorption coefficient	0.609 mm^{-1}
F(000)	388
Crystal size	0.1 x 0.1 x 0.06 mm^3
Theta range for data collection	2.434 to 35.328°
Index ranges	$-13 \leqq h \leqq 13$, $-8 \leqq k \leqq 8$, $-22 \leqq l \leqq 22$
Reflections collected	13254
Independent reflections	4993 [R(int) = 0.0521]
Completeness to theta = 27.706°	99.9 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.964 and 0.860
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4993 / 5 / 240
Goodness-of-fit on F^2	1.006
Final R indices [I>2sigma(I)]	R1 = 0.0437, wR2 = 0.0792
R indices (all data)	R1 = 0.0598, wR2 = 0.0840
Absolute structure parameter	0.053(18)
Extinction coefficient	n/a
Largest diff. peak and hole	0.520 and -0.403 e.Å^{-3}

Table S2. Crystal data and structure refinement for Ca(H$_2$olz)·2DMF.

Empirical formula	C$_{20}$H$_{22}$N$_4$O$_8$ Ca
Formula weight	486.49
Temperature	100(2) K
Wavelength	0.7749 Å
Crystal system	Monoclinic
Space group	*Cc*
Unit cell dimensions	a = 24.2849(11) Å α = 90°
	b = 9.0194(5) Å β = 97.936(3)°
	c = 10.3673(5) Å γ = 90°
Volume	2249.06(19) Å^3
Z	4
Density (calculated)	1.437 Mg/m^3
Absorption coefficient	0.420 mm^{-1}
F(000)	1016
Crystal size	0.03 x 0.025 x 0.025 mm^3
Theta range for data collection	2.630 to 31.133°
Index ranges	$-32{\leqq}h{\leqq}32$, $-11{\leqq}k{\leqq}11$, $-13{\leqq}l{\leqq}13$
Reflections collected	29931
Independent reflections	5796 [R(int) = 0.0562]
Completeness to theta = 27.706°	99.9 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.990 and 0.888
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5796 / 2 / 307
Goodness-of-fit on F^2	1.048
Final R indices [I>2sigma(I)]	R1 = 0.0576, wR2 = 0.1463
R indices (all data)	R1 = 0.0783, wR2 = 0.1601
Absolute structure parameter	−0.03(2)
Extinction coefficient	n/a
Largest diff. peak and hole	0.581 and −0.450 e.Å^{-3}

Table S3. Powder data and structure refinement for $Ca(H_2olz)\cdot 2MeOH\cdot H_2O$.

Empirical formula	$C_{16}H_{16}N_2O_8Ca$	
Formula weight	422.41	
Crystal system	monoclinic	
Space group	*Cc*	
Unit cell dimensions	$a = 18.6277(3)$ Å	$\alpha = 90°$
	$b = 10.572(4)$ Å	$\beta = 84.64(1)°$
	$c = 9.1180(3)$ Å	$\gamma = 90°$
Volume	1787.8(9) Å^3	
Z	4	
Experimental crystal description	powder	
Experimental crystal color	yellow	
Experimental crystal density method	not measured	
Experimental absorptioncorrection type	none	
Refine ls hydrogen treatment	noref	
Refine ls number parameters	89	
Diffraction ambient temperature	293 K	
Cell measurement temperature	293 K	
Diffraction radiation type	synchrotron	
Diffraction radiation wavelength	0.72768 Å	
Diffraction measurement device type	synchrotron	
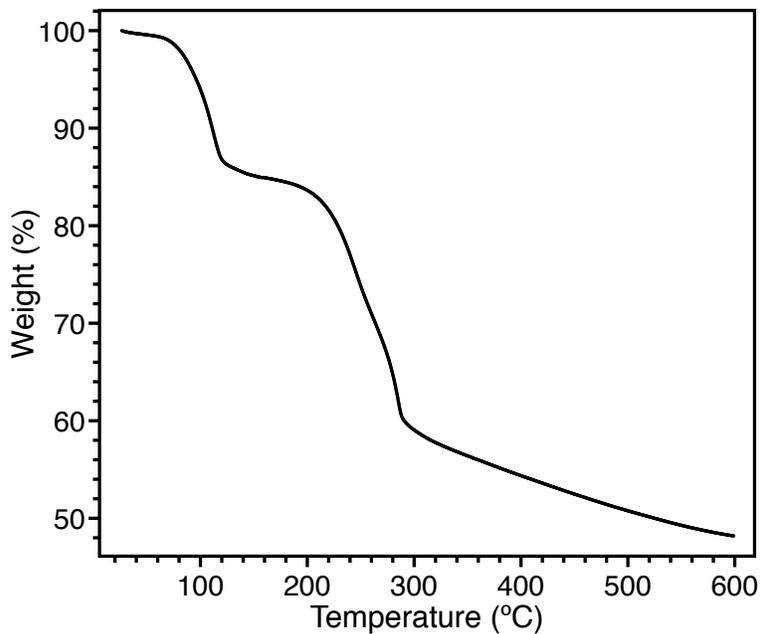
Figure S6. Thermogravimetric analysis of $Ca(H_2olz) \cdot 4H_2O$ one-dimensional chains (**1**).
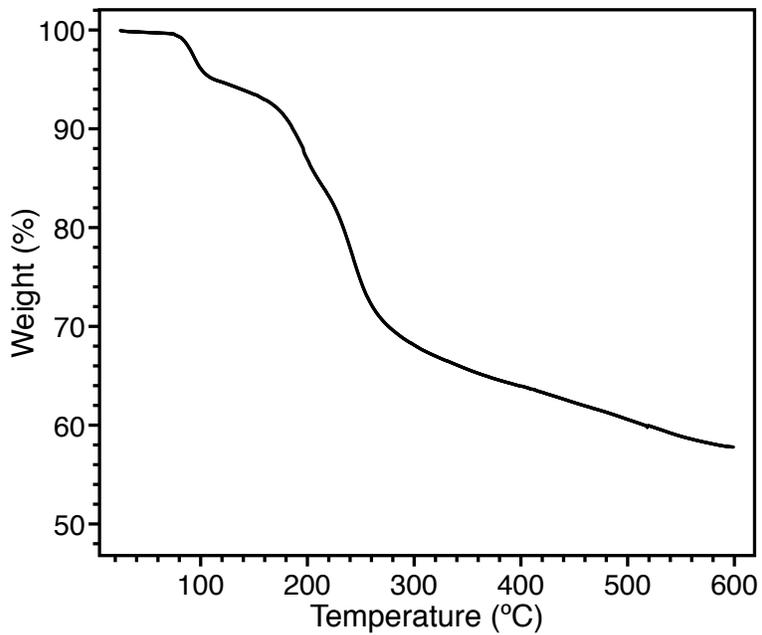
Figure S7. Thermogravimetric analysis of $Ca(H_2olz) \cdot 2H_2O$ two-dimensional sheets (**2**).
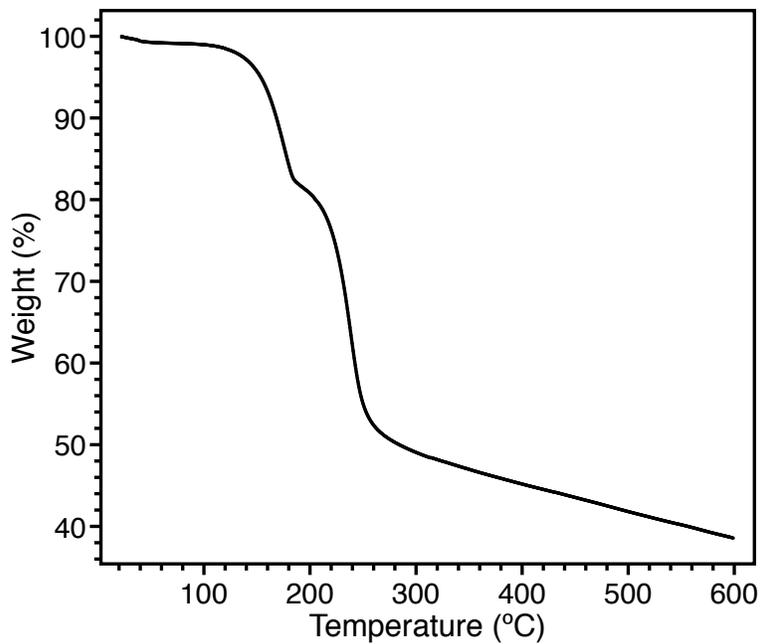
**Figure S8.** Thermogravimetric analysis of Ca(H$_2$olz)·2DMF (**3**·DMF).
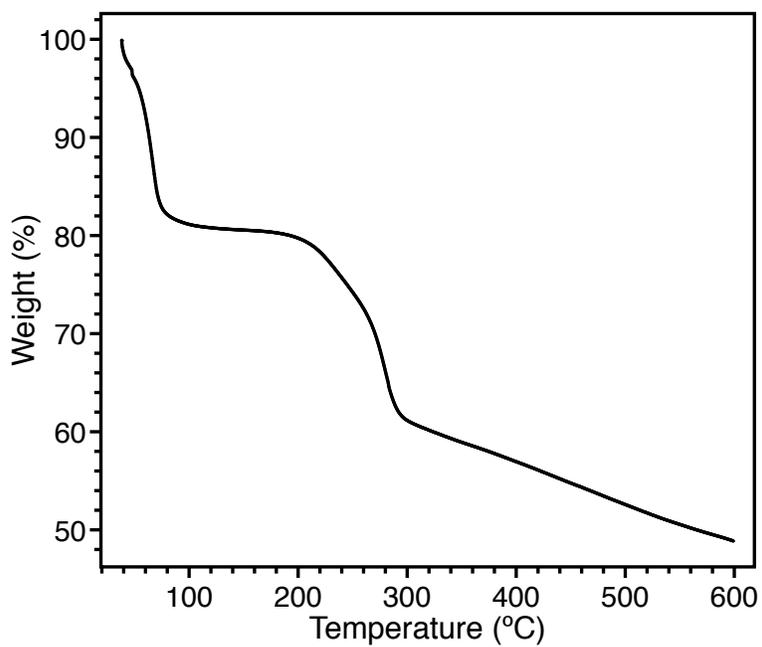
Figure S9. Thermogravimetric analysis of Ca(H$_2$olz)·2MeOH·H$_2$O (**3**·MeOH).
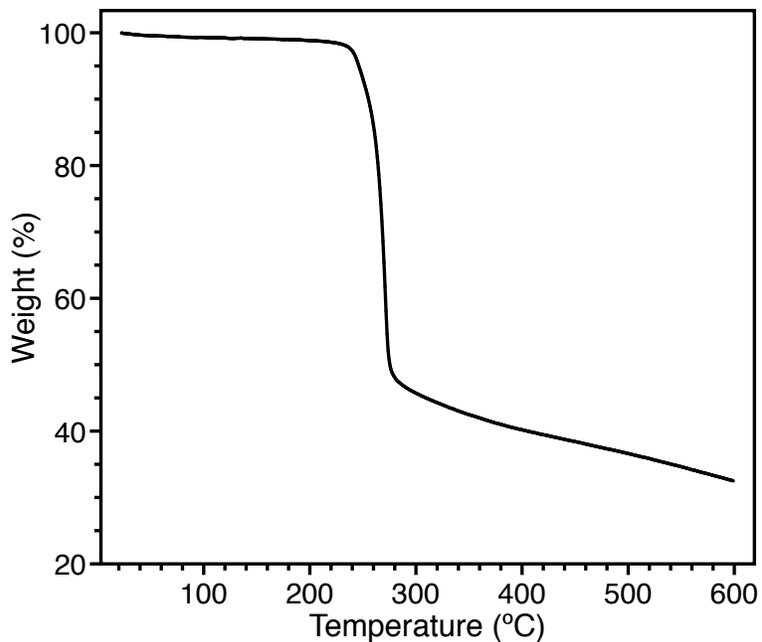
Figure S10. Thermogravimetric analysis of Ca(H$_2$olz) (**3**).
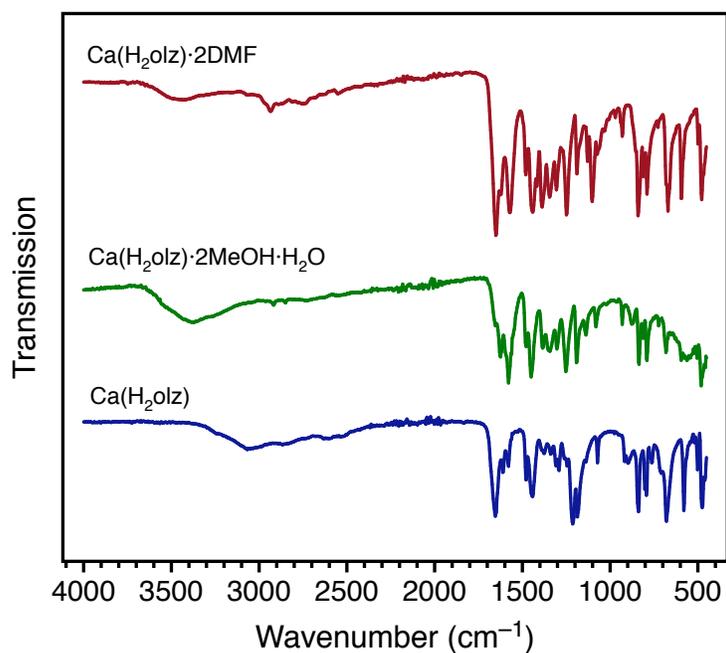
Figure S11. FTIR spectra of three-dimensional Ca(H$_2$olz) derivatives. From top: Ca(H$_2$olz)·2DMF, Ca(H$_2$olz)·2MeOH·H$_2$O, and Ca(H$_2$olz).
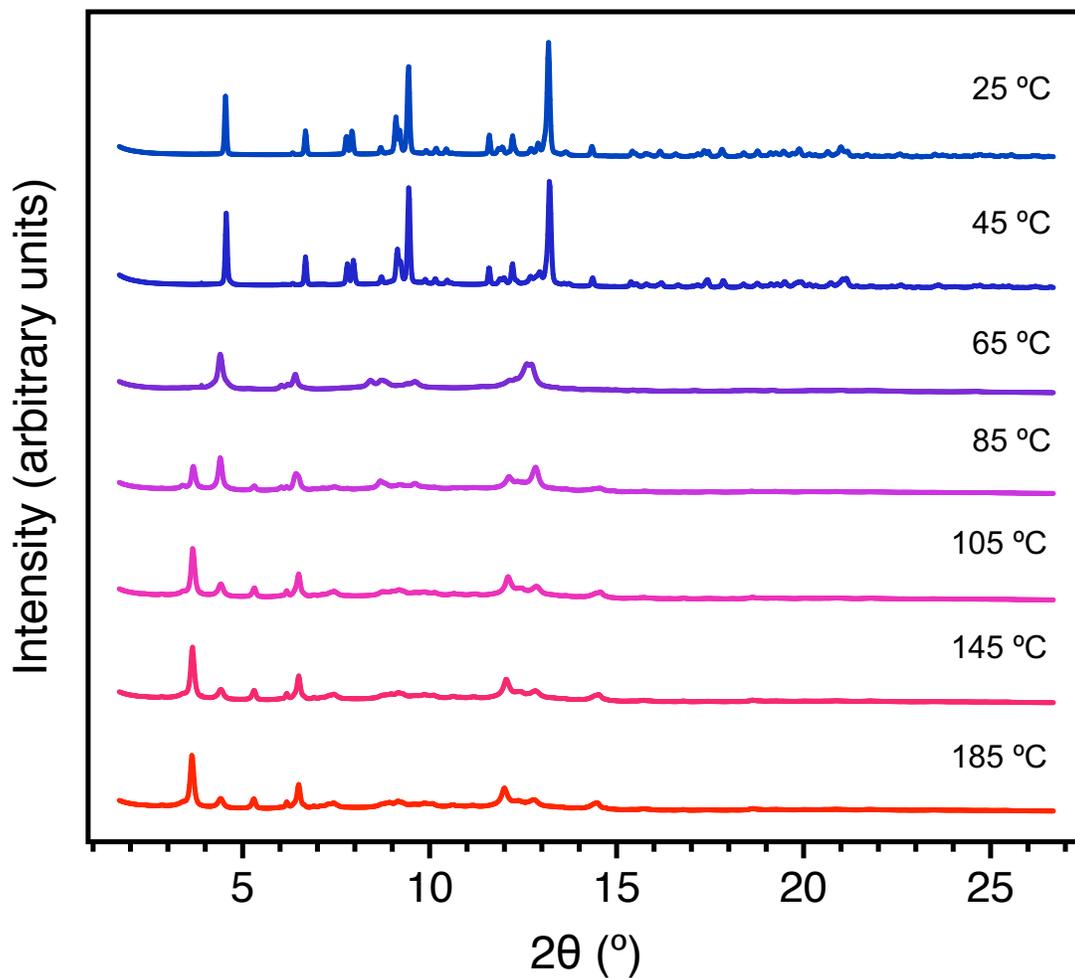
Figure S12. Effects of heating on $Ca(H_2olz) \cdot 2MeOH \cdot H_2O$ crystallinity (λ = 0.72768 Å). The sample of $Ca(H_2olz) \cdot 2MeOH \cdot H_2O$ was heated at the indicated temperature under nitrogen flow at increasing temperatures in a glass capillary. The material undergoes several phase transitions upon heating and changes from yellow to maroon in color, however, only the low-temperature phase could be indexed and resolved structurally. Porosity of the framework after activation at 65 °C and 100 °C was probed by N_2 and H_2, but isotherms did not show any gas uptake up to 1 bar.

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