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## Biocompatible metal–organic frameworks for the storage and therapeutic delivery of hydrogen sulfide†

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Hydrogen sulfide ( $H_2S$ ) is an endogenous gasotransmitter with potential therapeutic value for treating a range of disorders, such as ischemia-reperfusion injury resulting from a myocardial infarction or stroke. However, the medicinal delivery of  $H_2S$  is hindered by its corrosive and toxic nature. In addition, small molecule  $H_2S$  donors often generate other reactive and sulfur-containing species upon  $H_2S$  release, leading to unwanted side effects. Here, we demonstrate that  $H_2S$  release from biocompatible porous solids, namely metal–organic frameworks (MOFs), is a promising alternative strategy for  $H_2S$  delivery under physiologically relevant conditions. In particular, through gas adsorption measurements and density functional theory calculations we establish that  $H_2S$  binds strongly and reversibly within the tetrahedral pockets of the fumaric acid-derived framework MOF-801 and the mesaconic acid-derived framework Zr-mes, as well as the new itaconic acid-derived framework CORN-MOF-2. These features make all three frameworks among the best materials identified to date for the capture, storage, and delivery of  $H_2S$ . In addition, these frameworks are non-toxic to HeLa cells and capable of releasing  $H_2S$  under aqueous conditions, as confirmed by fluorescence assays. Last, a cellular ischemia-reperfusion injury model using H9c2 rat cardiomyoblast cells corroborates that  $H_2S$ -loaded MOF-801 is capable of mitigating hypoxia-reoxygenation injury, likely due to the release of  $H_2S$ . Overall, our findings suggest that  $H_2S$ -loaded MOFs represent a new family of easily-handled solid sources of  $H_2S$  that merit further investigation as therapeutic agents. In addition, our findings add Zr-mes and CORN-MOF-2 to the growing lexicon of biocompatible MOFs suitable for drug delivery.

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## Introduction

Hydrogen sulfide ( $H_2S$ ) is a colorless, flammable gas with a distinctive “rotten-egg” odor that is pervasive in industrial processes such as petroleum refining, natural gas processing, and wastewater treatment.<sup>1,2</sup> Because  $H_2S$  is an irritant to respiratory linings and a chemical asphyxiant, it has a recommended Immediately Dangerous to Life and Health (IDLH) value of 100 ppm, above which prolonged exposure can be fatal. In addition to being toxic to humans at high concentrations,  $H_2S$  impurities in gas streams are highly corrosive to piping and

other equipment.<sup>3,4</sup> In spite of its toxic and corrosive nature,  $H_2S$  is also an important gasotransmitter in mammals with proposed roles in calcium homeostasis, long-term potentiation, and mediation of oxidative stress.<sup>5–7</sup> As such,  $H_2S$  has been invoked as a potential therapeutic for numerous disorders, including bone disease, brain injury, inflammation, Parkinson’s disease, high blood pressure, cancer, and ischemia-reperfusion injury.<sup>8–15</sup>

The toxicity and flammability of  $H_2S$  limit the viability of inhalation as a therapeutic delivery pathway.<sup>9</sup> Indeed, studies regarding the potential biological role and therapeutic value of  $H_2S$  rarely employ this gas directly. Instead, researchers have designed small molecule donors that decompose to generate  $H_2S$  or related species under physiological conditions.<sup>9,10,12,13,16,17</sup> However, the application of these donors is complicated by the concomitant production of reactive byproducts and other sulfur-based species upon  $H_2S$  release.<sup>9</sup> A promising alternative strategy is to design biocompatible porous solids capable of storing and controllably releasing gaseous  $H_2S$ , avoiding the formation of biologically-active byproducts. In particular, metal–organic frameworks (MOFs),

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which are porous materials constructed from organic “linkers” and inorganic “nodes,” are promising materials for the controlled delivery of bioactive molecules,<sup>18–20</sup> such as the gasotransmitter nitric oxide (NO).<sup>21</sup> The chemical tunability of MOFs achievable through linker modification and surface functionalization is a promising feature which could potentially enable control over the rate and location of H<sub>2</sub>S delivery.<sup>22</sup> Nonetheless, the potential application of MOFs as H<sub>2</sub>S donors in medicine remains almost completely unexplored.<sup>22,23</sup>

To be useful for H<sub>2</sub>S delivery *in vivo*, MOF-based platforms must meet several criteria, including: (1) construction from non-toxic metals and linkers; (2) stability towards H<sub>2</sub>S; (3) high H<sub>2</sub>S capacities with controlled release under physiological conditions; and (4) stability under physiological conditions (e.g., serum at 37 °C). However, *none of the MOFs that have been studied for H<sub>2</sub>S adsorption to date fulfill all of these criteria*, as many are limited by framework destruction upon irreversible H<sub>2</sub>S binding,<sup>22–30</sup> low capacities,<sup>26,31</sup> poor biocompatibility, or harsh H<sub>2</sub>S desorption conditions.<sup>2,23,24,30,32</sup> In addition, many previously studied MOFs are constructed from toxic metals (e.g., Ni, Cr)<sup>22,30</sup> or complex organic linkers<sup>33</sup> that could lead to unwanted side effects *in vivo*. For example, the only MOF that has been explored for therapeutic H<sub>2</sub>S delivery to date, namely, Zn-MOF-74, fails to meet several of these criteria.<sup>23</sup> We have found that H<sub>2</sub>S adsorption in Zn-MOF-74 is completely irreversible, which precludes its application for H<sub>2</sub>S delivery. This framework was also found to be highly toxic to HeLa cells (see ESI or ESI Section 15† for details). Therefore, there remains a critical need to identify biocompatible MOFs that display strong yet reversible H<sub>2</sub>S adsorption for application as next-generation H<sub>2</sub>S donors.

A promising strategy to identify new MOFs capable of reversibly adsorbing H<sub>2</sub>S is to leverage its properties as a hydrogen-bond donor and weak hydrogen-bond acceptor, similar to water.<sup>34</sup> As such, we were inspired by the recent deluge of MOFs designed for reversible water capture<sup>35–38</sup> to identify potential frameworks for H<sub>2</sub>S storage. In particular, we hypothesized that the surprisingly strong binding of water ( $-\Delta H_{\text{ads}} \approx 60 \text{ kJ mol}^{-1}$ ) in Zr<sub>6</sub>O<sub>4</sub>(OH)<sub>4</sub>(fumarate)<sub>6</sub> or MOF-801 (Fig. 1, left), which is due to ordered hydrogen-bonding interactions within the tetrahedral cavities,<sup>39</sup> may translate to strong binding of H<sub>2</sub>S within this MOF as well. In addition, Zr is a non-toxic metal<sup>40</sup> and fumaric acid occurs naturally as part of the Krebs cycle,<sup>41,42</sup> suggesting that MOF-801 and closely related frameworks should also be biocompatible.<sup>43</sup> Here, through combined experimental and computational analyses we demonstrate that MOF-801, as well as the related biocompatible mesaconate-based framework Zr-mes<sup>44,45</sup> and itaconate-based framework CORN-MOF-2 (CORN = Cornell University)<sup>46,47</sup> undergo strong but reversible adsorption of H<sub>2</sub>S with minimal framework degradation (Fig. 1). In addition, these frameworks are capable of delivering H<sub>2</sub>S under physiologically relevant conditions, allowing for the therapeutic benefits of H<sub>2</sub>S to be accessed using easily-handled solids. Taken together, these features make the frameworks described here promising H<sub>2</sub>S donors for biomedical applications.

## Results and discussion

### Preparation of MOFs

The MOFs Zr<sub>6</sub>O<sub>4</sub>(OH)<sub>4</sub>(fumarate)<sub>6</sub> and Zr<sub>6</sub>O<sub>4</sub>(OH)<sub>4</sub>(mesaconate)<sub>6</sub> are also known as MOF-801 (ref. 39) and Zr-mes,<sup>44</sup> respectively. Herein, we refer to these frameworks as Zr-fum and Zr-mes, respectively, for clarity. Following procedures adapted from the literature, we prepared Zr-fum and Zr-mes under solvothermal conditions on 10 mmol scale (see ESI Sections 3–6† for details). Specifically, these frameworks were synthesized from ZrOCl<sub>2</sub>·8H<sub>2</sub>O and the corresponding dicarboxylic acid in either *N,N*-dimethylformamide (Zr-fum-DMF,<sup>39</sup> Zr-mes-DMF<sup>44</sup>) or water (Zr-fum-H<sub>2</sub>O,<sup>48</sup> Zr-mes-H<sub>2</sub>O<sup>48</sup>) using formic acid as a modulator. After optimization, 30 equivalents of formic acid were found to produce Zr-fum and Zr-mes with high crystallinity, as determined by powder X-ray diffraction (PXRD; ESI Fig. S1 and S2†). Notably, higher concentrations of formic acid led to the formation of significant impurities.

The PXRD patterns of solvated Zr-fum and Zr-mes prepared in DMF and in H<sub>2</sub>O are shown in Fig. 2. The PXRD patterns for Zr-fum-DMF and Zr-fum-H<sub>2</sub>O match the predicted pattern corresponding to the single-crystal X-ray diffraction (SCXRD) structure of MOF-801.<sup>39</sup> Likewise, the patterns for Zr-mes match the predicted pattern based on the density functional theory (DFT)-calculated ideal structure of this framework (see ESI Section 14† for details). The Langmuir surface areas determined from N<sub>2</sub> adsorption isotherms of all four frameworks are in good agreement with previously reported values (ESI Fig. S7, S13, S19, and S25†). Unlike Zr-fum-H<sub>2</sub>O, Zr-mes-H<sub>2</sub>O was found to undergo partial amorphization upon complete desolvation under high vacuum (<10  $\mu\text{bar}$ ) at 100 °C, although this did not impact its porosity. Notably, synthesis under aqueous conditions produced nanocrystals of Zr-fum-H<sub>2</sub>O less than 100 nm in size (ESI Fig. S15†), suitable for applications in medicine,<sup>49</sup> whereas synthesis in DMF produced larger crystallites approximately 500 nm in size (ESI Fig. S9†). The framework Zr-mes was obtained as crystallites of intermediate size (100–200 nm) under both sets of conditions (ESI Fig. S21 and S27†). Owing to the similar properties of frameworks prepared in water and in DMF, we employed Zr-fum-H<sub>2</sub>O and Zr-mes-H<sub>2</sub>O for subsequent studies to bypass the use of toxic DMF.

After preparing Zr-fum-H<sub>2</sub>O and Zr-mes-H<sub>2</sub>O, we next investigated whether the naturally-derived and inexpensive dicarboxylic acid itaconic acid<sup>46,47</sup> can be used to synthesize an isostructural MOF, which we term CORN-MOF-2 and refer to as Zr-ita herein for consistency (Fig. 1; see ESI Sections 7 and 8† for details). Produced *via* the fermentation of carbohydrates by fungi from the genus *Aspergillus*, itaconic acid is a desirable linker because of its very low cost and lack of toxicity.<sup>46</sup> Unfortunately, solvothermal synthesis using ZrCl<sub>4</sub> and itaconic acid in DMF produced amorphous material, as confirmed by PXRD (Fig. 2). Several acid modulators were evaluated to enhance the crystallinity of Zr-ita-DMF, including acetic acid, L-proline, concentrated HCl, pivalic acid, and formic acid, but none led to crystalline MOF. In addition, N<sub>2</sub> sorption isotherms of Zr-ita-DMF prepared without an acid modulator revealed minimal



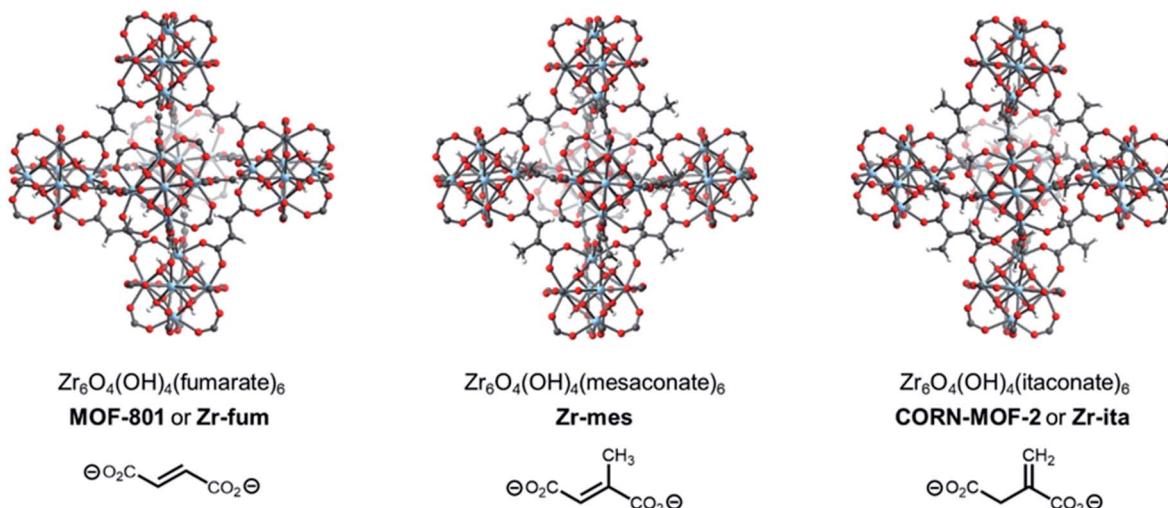


Fig. 1 Density functional theory-calculated ideal structures of known and new sustainably-derived metal–organic frameworks prepared from fumaric, mesaconic, and itaconic acid as part of this work. Gray, white, red, and pale blue spheres correspond to carbon, hydrogen, oxygen, and zirconium, respectively.

porosity and a Brunauer–Emmett–Teller (BET) surface area of only  $33 \text{ m}^2 \text{ g}^{-1}$  (ESI Fig. S30†). Insight into the poor quality of amorphous Zr-ita-DMF was obtained from  $^1\text{H}$ -NMR spectra of samples digested using a saturated  $\text{K}_3\text{PO}_4/\text{D}_2\text{O}$  solution in  $\text{DMSO-d}_6$  (ESI Fig. S31†). Peaks due to itaconate and residual solvent were observed as expected. However, additional peaks ascribed to the isomeric mesaconate were also observed. We hypothesize that basic *N,N*-dimethylamine generated by the hydrolysis of DMF mediates the isomerization of itaconate to mesaconate during framework self-assembly, leading to an amorphous structure. In addition, residual DMF was observed by  $^1\text{H}$ -NMR even after extensive soaking in tetrahydrofuran. Therefore, the significant linker isomerization and difficulty in removing DMF from the pores together account for the low surface area of Zr-ita-DMF.

We hypothesized that the key to preparing high-quality Zr-ita was to avoid the use of base during MOF synthesis.

Consistently, employing water as the solvent instead of DMF produced semi-crystalline Zr-ita- $\text{H}_2\text{O}$  for the first time (Fig. 2). The modest crystallinity of Zr-ita- $\text{H}_2\text{O}$  compared to Zr-fum- $\text{H}_2\text{O}$  and Zr-mes- $\text{H}_2\text{O}$  is likely due to the  $\text{sp}^3$ -hybridized carbon in the backbone of this flexible linker. Because of these characteristics, Zr-ita- $\text{H}_2\text{O}$  is likely an amorphous MOF (aMOF), which have found application for toxic gas capture and drug delivery.<sup>50</sup> Because the DFT-calculated structure of Zr-ita- $\text{H}_2\text{O}$  is idealized and does not account for linker flexibility, the PXRD pattern simulated from this structure in Fig. 1 does not reflect the amorphous nature of Zr-ita- $\text{H}_2\text{O}$ . When prepared on 10 mmol scale, Zr-ita- $\text{H}_2\text{O}$  exhibited improved porosity compared to Zr-ita-DMF, with a 77 K  $\text{N}_2$  BET surface area of  $235 \pm 2 \text{ m}^2 \text{ g}^{-1}$  and a Langmuir surface area of  $487 \pm 22 \text{ m}^2 \text{ g}^{-1}$  (ESI Fig. S35†). Marked hysteresis was also observed upon  $\text{N}_2$  desorption in Zr-ita- $\text{H}_2\text{O}$ . Analysis of the pore size distribution from the  $\text{N}_2$  sorption isotherm revealed micropores approximately  $6.6 \text{ \AA}$  in

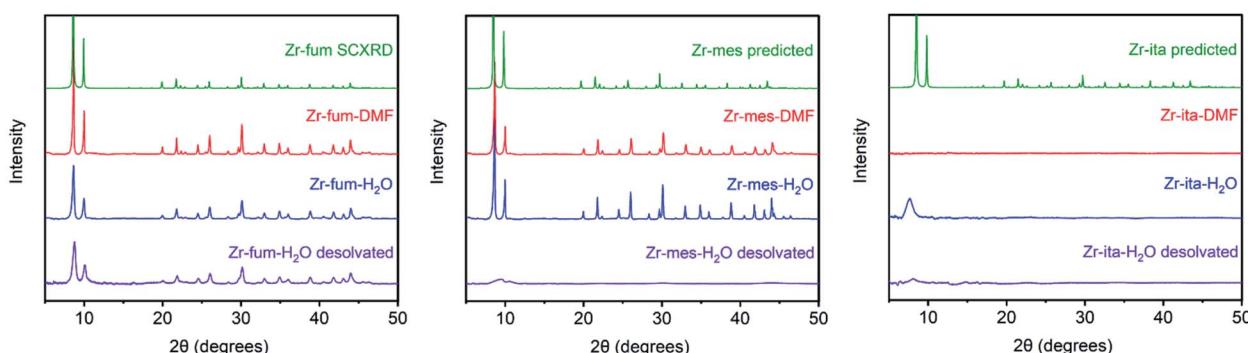


Fig. 2 Comparison of PXRD patterns of Zr-fum, Zr-mes, and Zr-ita prepared in DMF and in water. The patterns for MOFs prepared in DMF (red) and  $\text{H}_2\text{O}$  (blue) were obtained after activation at  $100^\circ\text{C}$  under vacuum ( $<100 \text{ mbar}$ ) using a Schlenk line and were found to still contain ethanol by  $^1\text{H}$ -NMR digestion. Further desolvation at  $100^\circ\text{C}$  under stronger vacuum ( $<10 \mu\text{bar}$ ) led to partial amorphization of Zr-mes and Zr-ita, but not Zr-fum (purple). The predicted patterns based on the previously reported single crystal X-ray diffraction pattern of Zr-fum and from the DFT-calculated ideal structures of Zr-mes and Zr-ita are included for reference (green).



diameter (ESI Fig. S39†), as expected based on the idealized structure, along with mesopores 20–100 Å in size. Thus, we attribute the observed hysteresis to mesoporous defects or cavities between particles. Consistent with the hypothesis outlined above, the  $^1\text{H}$ -NMR spectra of Zr-ita- $\text{H}_2\text{O}$  digested using a saturated  $\text{K}_3\text{PO}_4/\text{D}_2\text{O}$  solution in  $\text{DMSO-d}_6$  revealed only resonances attributed to the itaconate linker, residual formate from defect sites, and solvent (ESI Fig. S36†). To further illustrate the scalability of Zr-ita- $\text{H}_2\text{O}$ , we prepared this new framework on 0.5 mol scale, resulting in a total yield of approximately 87 g (73% yield) of activated framework (see ESI Section 8† for details). Thus, Zr-ita- $\text{H}_2\text{O}$  was employed for subsequent  $\text{H}_2\text{S}$  adsorption studies to compare with Zr-fum- $\text{H}_2\text{O}$  and Zr-mes- $\text{H}_2\text{O}$ .

### $\text{H}_2\text{S}$ adsorption in MOFs

After preparing Zr-fum- $\text{H}_2\text{O}$ , Zr-mes- $\text{H}_2\text{O}$ , and Zr-ita- $\text{H}_2\text{O}$ , we next evaluated the reversible  $\text{H}_2\text{S}$  capture performance of all three frameworks by carrying out isothermal adsorption measurements at 25 °C, 40 °C, and 55 °C (Fig. 3; see ESI Section 10† for details). At 25 °C and 1 bar of  $\text{H}_2\text{S}$ , Zr-fum- $\text{H}_2\text{O}$  displayed the highest  $\text{H}_2\text{S}$  uptake (4.0 mmol g<sup>-1</sup>, 11 wt%) followed by Zr-mes- $\text{H}_2\text{O}$  (3.3 mmol g<sup>-1</sup>, 10 wt%) and Zr-ita- $\text{H}_2\text{O}$  (1.3 mmol g<sup>-1</sup>, 4.0 wt%), which trends with the frameworks' respective surface areas. These measurements indicate that Zr-fum- $\text{H}_2\text{O}$  and Zr-mes- $\text{H}_2\text{O}$  possess capacities comparable to those in MOFs that undergo (partially) reversible  $\text{H}_2\text{S}$  adsorption under similar conditions, such as UiO-66 (~3.0 mmol g<sup>-1</sup>; UiO = Universitetet i Oslo),<sup>21</sup> MIL-53 (Al) (~3.5 mmol g<sup>-1</sup>),<sup>13</sup> MIL-53 (Cr) (~3.5 mmol g<sup>-1</sup>),<sup>13</sup> and Ga-soc-MOF-1a (~4.5 mmol g<sup>-1</sup>; soc = square octahedral).<sup>22</sup> Moreover, the relatively smooth overlay of the adsorption and desorption data suggests that  $\text{H}_2\text{S}$  binds reversibly at every temperature (see below for further discussion). Although  $\text{H}_2\text{S}$  adsorption is readily reversible at 25 °C in all three frameworks, they were regenerated at 100 °C under high vacuum (<10  $\mu\text{bar}$ ) between experiments for consistency.

To investigate the thermodynamics of  $\text{H}_2\text{S}$  binding in Zr-fum- $\text{H}_2\text{O}$ , Zr-mes- $\text{H}_2\text{O}$ , and Zr-ita- $\text{H}_2\text{O}$ , we fit the adsorption data in Fig. 3 using both dual-site Langmuir and Langmuir-Freundlich models (ESI Fig. S46, S49, S52 and Tables S2–S4†).

Although both models provided adequate fits to the data, the empirical Langmuir-Freundlich fits (Fig. 3) were found to be superior and thus were employed for subsequent analysis. The differential enthalpies of adsorption were calculated as a function of isosteric  $\text{H}_2\text{S}$  loading using the Clausius-Clapeyron equation (eqn (1)), in which  $P_Q$  is the pressure at a constant uptake  $Q$ ,  $\Delta H_{\text{ads}}$  is the differential enthalpy of adsorption,  $R$  is the ideal gas constant,  $T$  is the temperature, and  $c$  is a constant.

$$\ln(P_Q) = \left(\frac{\Delta H_{\text{ads}}}{R}\right)\left(\frac{1}{T}\right) + c \quad (1)$$

The differential enthalpies of adsorption ( $-\Delta H_{\text{ads}}$ ) for all three frameworks are included in Fig. 4. The low-coverage adsorption enthalpies follow the trend Zr-ita- $\text{H}_2\text{O}$  ( $53.2 \pm 0.8 \text{ kJ mol}^{-1}$ ) > Zr-mes- $\text{H}_2\text{O}$  ( $44.7 \pm 0.6 \text{ kJ mol}^{-1}$ ) > Zr-fum- $\text{H}_2\text{O}$  ( $32.2 \pm 5.6 \text{ kJ mol}^{-1}$ ). The same trend was observed when the data were fit using dual-site Langmuir models as well (ESI Fig. S46, S49, and S52†). This difference is likely due to the smaller pores of Zr-ita- $\text{H}_2\text{O}$  and Zr-mes- $\text{H}_2\text{O}$ , which enable enhanced hydrogen-bonding interactions between  $\text{H}_2\text{S}$  and the

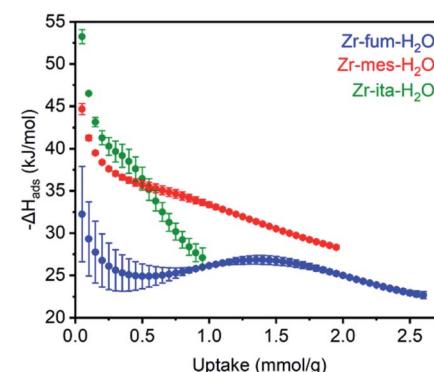


Fig. 4 Differential enthalpies of adsorption ( $-\Delta H_{\text{ads}}$ ) for  $\text{H}_2\text{S}$  as a function of uptake for activated Zr-fum- $\text{H}_2\text{O}$  (blue), Zr-mes- $\text{H}_2\text{O}$  (red), and Zr-ita- $\text{H}_2\text{O}$  (green), as determined using the Clausius-Clapeyron equation (eqn (1)) and Langmuir-Freundlich fits in Fig. 3. A data point was considered equilibrated after <0.01% pressure change occurred over a 45 s interval.

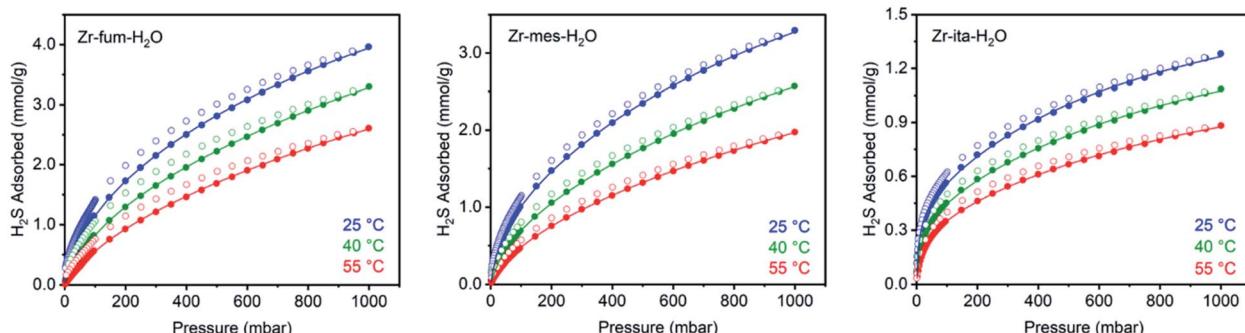


Fig. 3  $\text{H}_2\text{S}$  adsorption (closed circles) and desorption (open circles) isotherms at 25 °C (blue), 40 °C (green), and 55 °C (red) of activated Zr-fum- $\text{H}_2\text{O}$ , Zr-mes- $\text{H}_2\text{O}$ , and Zr-ita- $\text{H}_2\text{O}$ . Solid lines represent fits of the adsorption data to a Langmuir-Freudlich model. A data point was considered equilibrated after <0.01% pressure change occurred over a 45 s interval.



framework.<sup>31,33,51-53</sup> Consistently, preliminary *in situ* diffuse reflectance infrared Fourier transform spectroscopy (DRIFTS) measurements of H<sub>2</sub>S-dosed Zr-fum-H<sub>2</sub>O are indicative of hydrogen-bonding interactions between H<sub>2</sub>S and the framework upon adsorption (ESI Fig. S106; see ESI Section 16† for details).<sup>52</sup> The data in Fig. 4 are among the first experimentally-derived differential enthalpies of H<sub>2</sub>S adsorption in MOFs, and they are comparable to or higher than those predicted computationally for previously-reported frameworks.<sup>24,31,33</sup> The comparatively strong binding of H<sub>2</sub>S in Zr-fum-H<sub>2</sub>O, Zr-mes-H<sub>2</sub>O, and Zr-ita-H<sub>2</sub>O bodes well for their ability to store H<sub>2</sub>S prior to release upon exchange with water under physiological conditions.

The reversibility of H<sub>2</sub>S adsorption and long-term stability towards H<sub>2</sub>S are also critical criteria for prospective H<sub>2</sub>S-storage materials. As such, we carefully evaluated the stability of Zr-fum-H<sub>2</sub>O, Zr-mes-H<sub>2</sub>O, and Zr-ita-H<sub>2</sub>O towards H<sub>2</sub>S in both the gas and solution phases. To characterize the stability of Zr-fum-H<sub>2</sub>O, Zr-mes-H<sub>2</sub>O, and Zr-ita-H<sub>2</sub>O to H<sub>2</sub>S in solution, we soaked each MOF in a 0.8 M solution of H<sub>2</sub>S in THF at 50 °C for 48 h. Negligible changes in the PXRD patterns, infrared spectra, and <sup>1</sup>H-NMR spectra after digestion with a saturated K<sub>3</sub>PO<sub>4</sub>/D<sub>2</sub>O solution were observed for the MOFs after exposure to H<sub>2</sub>S in solution, suggesting that, in contrast to Zn-MOF-74, little-to-no framework degradation occurred under these conditions (see ESI Section 11† for details).

Consistent with the desorption data in Fig. 3, the 77 K N<sub>2</sub> Langmuir surface areas of all three MOFs also remained essentially unchanged after exposure to gaseous H<sub>2</sub>S at 25 °C (Fig. 5). In contrast, water vapor binds strongly and only semi-reversibly to all three frameworks, leading to a partial reduction in their Langmuir surface areas after exposure to H<sub>2</sub>O vapor at 35 °C (see ESI Section 9† for details). To corroborate the reversibility of H<sub>2</sub>S adsorption in Zr-fum-H<sub>2</sub>O, Zr-mes-H<sub>2</sub>O, and Zr-ita-H<sub>2</sub>O, we also carried out cycling experiments in which the MOFs were repeatedly exposed to approximately 1 bar of H<sub>2</sub>S at 30 °C followed by desorption at 100 °C under vacuum (Fig. 6). The H<sub>2</sub>S cycling capacities of all three frameworks remained relatively constant over ten cycles, decreasing by only 3% for Zr-fum-H<sub>2</sub>O, 8% for Zr-mes-H<sub>2</sub>O, and 6% for Zr-ita-H<sub>2</sub>O, respectively. In addition, 77 K N<sub>2</sub> adsorption measurements confirmed that the Langmuir surface areas of all three frameworks

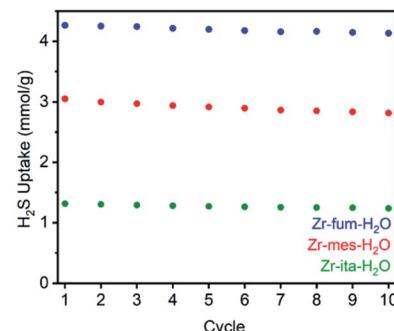


Fig. 6 Cycling capacities for H<sub>2</sub>S adsorption (1 bar, 30 °C) in Zr-fum-H<sub>2</sub>O, Zr-mes-H<sub>2</sub>O, and Zr-ita-H<sub>2</sub>O. The samples were regenerated at 100 °C under high vacuum (<10  $\mu$ bar) between cycles.

remained high after repeated cycling of H<sub>2</sub>S, and characterization by PXRD and <sup>1</sup>H-NMR after digestion with a saturated K<sub>3</sub>PO<sub>4</sub>/D<sub>2</sub>O solution confirmed that minimal degradation occurred during H<sub>2</sub>S cycling (see ESI Section 12† for details). Last, the lack of residual sulfur species in Zr-fum-H<sub>2</sub>O that had been exposed to H<sub>2</sub>S and subsequently activated under vacuum was confirmed by X-ray photoelectron spectroscopy (ESI Fig. S102 and S103†). Together, these experimental measurements confirm that H<sub>2</sub>S adsorbs reversibly and non-destructively within Zr-fum-H<sub>2</sub>O, Zr-mes-H<sub>2</sub>O, and Zr-ita-H<sub>2</sub>O, in contrast to Zn-MOF-74.<sup>22</sup> Indeed, the excellent performance of these materials upon H<sub>2</sub>S cycling places them among the upper echelon of frameworks that have been studied for H<sub>2</sub>S capture and/or delivery to date. Importantly, the lack of degradation upon H<sub>2</sub>S adsorption in these materials indicates that they should be capable of cleanly delivering pure H<sub>2</sub>S that is uncontaminated by any other sulfur-containing species.<sup>9</sup>

Due to the microcrystalline nature of the MOFs studied herein, we were unable to study the binding modes of H<sub>2</sub>S within each MOF by single-crystal X-ray diffraction. Thus, we turned to density functional theory (DFT) calculations to probe the structure of H<sub>2</sub>S bound within Zr-fum, Zr-mes, and Zr-ita (Fig. 7; see ESI Section 14† for details). Calculations were carried out using a plane-wave basis and projector augmented-wave (PAW) pseudopotentials and corrected for dispersive interactions.<sup>54-56</sup> The fidelity of our calculations was confirmed

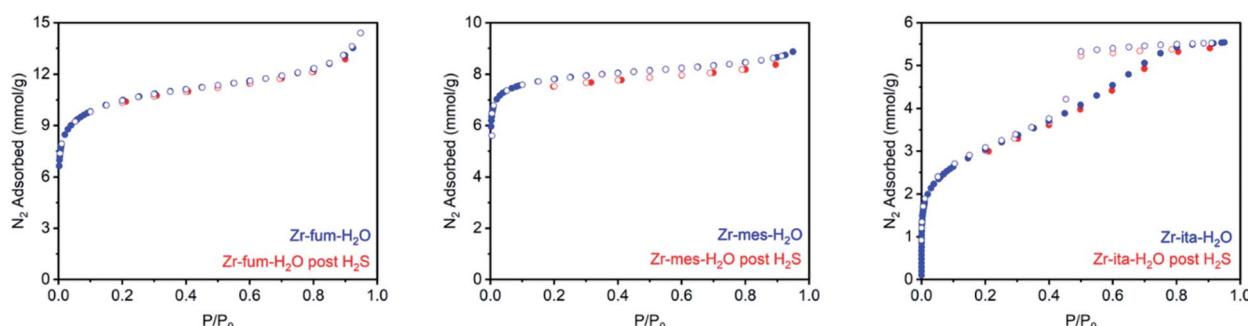


Fig. 5 77 K N<sub>2</sub> adsorption isotherms of activated Zr-fum-H<sub>2</sub>O, Zr-mes-H<sub>2</sub>O, and Zr-ita-H<sub>2</sub>O before (blue) and after treatment with H<sub>2</sub>S at 25 °C (red). After H<sub>2</sub>S adsorption, the MOFs were regenerated at 100 °C under vacuum (<10  $\mu$ bar) for 48 h.



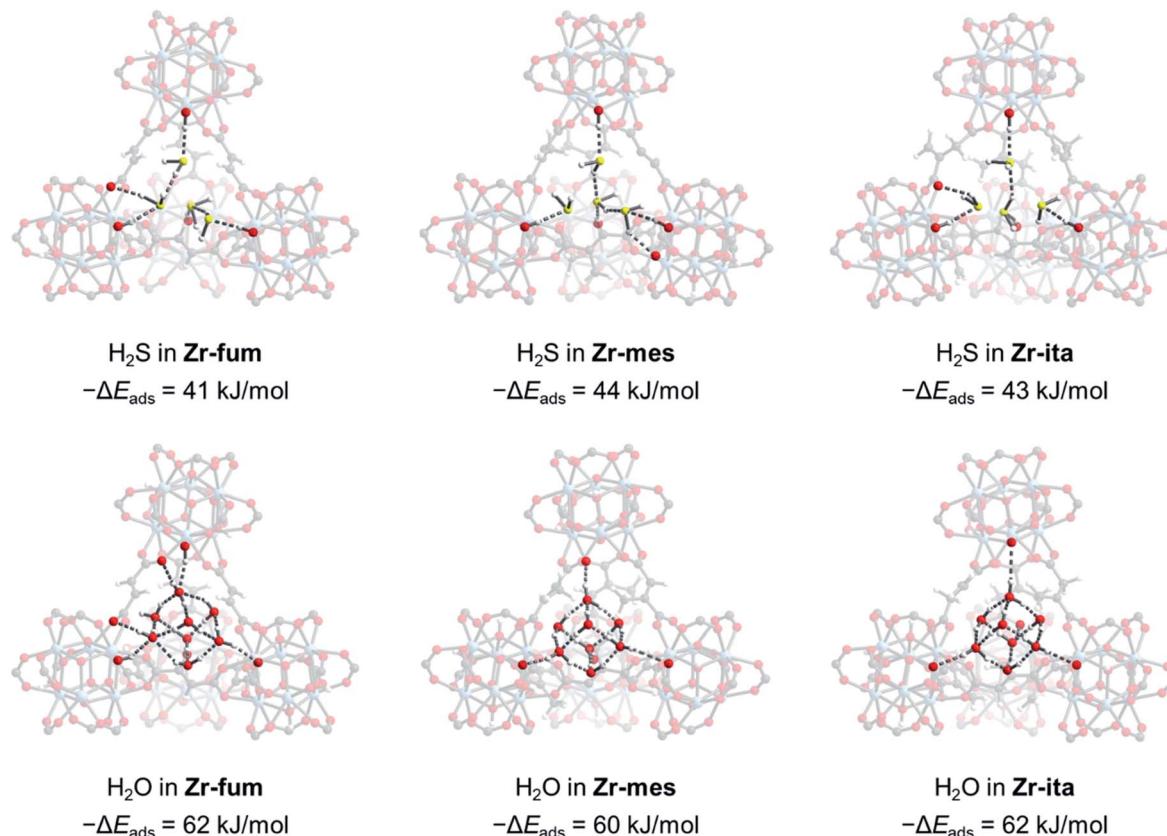


Fig. 7 DFT-calculated structures of  $\text{H}_2\text{S}$  binding in Zr-fum, Zr-mes, and Zr-ita with calculated energies of adsorption ( $-\Delta E_{\text{ads}}$ ) indicated. The DFT-calculated structures and energies of  $\text{H}_2\text{O}$  adsorption in all three MOFs are included for comparison. Gray, white, red, yellow, and pale blue spheres correspond to carbon, hydrogen, oxygen, sulfur, and zirconium, respectively.

by comparing the calculated structure for Zr-fum with the previously reported single-crystal X-ray diffraction structure (ESI Fig. S86†).<sup>39</sup> As expected,  $\text{H}_2\text{S}$  was found to preferentially bind within the tetrahedral cavities of all three frameworks (Fig. 7, top; see ESI Fig. S89† for space-filling model). Comparing the activated and  $\text{H}_2\text{S}$ -bound structures yielded 0 K adsorption energies ( $-\Delta E_{\text{ads}}$ ) of 41, 44, and 43  $\text{kJ mol}^{-1}$  for Zr-fum, Zr-mes, and Zr-ita, respectively, which are comparable to the experimental enthalpies of adsorption (Fig. 4). The  $\text{H}_2\text{S}$  molecules are predicted to be anchored within the tetrahedral cavities by  $\text{O}-\text{H}\cdots\text{S}$  interactions with the  $\text{OH}^-$  groups on the  $\text{Zr}_6$  clusters (2.16–2.43 Å in length). Additional hydrogen-bonding interactions between adjacent  $\text{H}_2\text{S}$  molecules are predicted, with  $\text{S}-\text{H}\cdots\text{S}$  distances ranging from 2.38 Å to 2.54 Å. Notably, these distances are slightly shorter than the  $\text{S}-\text{H}\cdots\text{S}$  distance in  $(\text{H}_2\text{S})_2$  (2.78 Å),<sup>44</sup> likely due to the increased polarization of  $\text{H}_2\text{S}$  molecules interacting with the framework pores. The favorable packing of  $\text{H}_2\text{S}$  within the tetrahedral cavities accounts for its strong yet reversible adsorption in all three frameworks.

For comparison, we also predicted the preferred binding modes for  $\text{H}_2\text{O}$  in Zr-fum, Zr-mes, and Zr-ita (Fig. 7, bottom). Similar to  $\text{H}_2\text{S}$ ,  $\text{H}_2\text{O}$  was found to preferentially bind within the tetrahedral cavities of all three frameworks, albeit with more favorable binding energies in every case. The calculated binding energy for water in Zr-fum ( $-\Delta E_{\text{ads}} = 62 \text{ kJ mol}^{-1}$ ) is similar to

the previously reported experimental enthalpy of adsorption ( $-\Delta H_{\text{ads}} = 60 \text{ kJ mol}^{-1}$ ),<sup>39</sup> validating our predictions. Notably, the stronger nature of  $\text{O}-\text{H}\cdots\text{O}$  interactions compared to  $\text{S}-\text{H}\cdots\text{S}$  interactions favors binding additional water molecules within the tetrahedral cavities, leading to a higher predicted uptake in addition to more thermodynamically favorable binding for  $\text{H}_2\text{O}$  over  $\text{H}_2\text{S}$ . The stronger overall binding of  $\text{H}_2\text{O}$  suggests that it should be able to displace  $\text{H}_2\text{S}$  from the tetrahedral cavities of MOFs, providing an avenue to trigger  $\text{H}_2\text{S}$  release under physiological conditions.

## $\text{H}_2\text{S}$ delivery from MOFs

Prior to evaluating the ability of  $\text{H}_2\text{S}$ -loaded Zr-fum, Zr-mes, and Zr-ita to release  $\text{H}_2\text{S}$  under physiologically relevant conditions, we evaluated the stability of these frameworks under aqueous conditions as well as their biocompatibility. Similar to other Zr-MOFs,<sup>57,58</sup> all three frameworks were found to be stable in neutral deionized water (pH 7.0) and cell culture medium (pH 7.4) prepared from Dulbecco's Modified Eagle's Medium (DMEM) supplemented with 10% fetal bovine serum (FBS) over extended periods (3–10 days) (ESI Fig. S73–S75; see ESI Section 13† for details). Based on its high  $\text{H}_2\text{S}$  capacity and stability under physiological conditions, we selected Zr-fum- $\text{H}_2\text{O}$  as the most promising framework to study further for  $\text{H}_2\text{S}$  delivery. The biocompatibility of Zr-fum- $\text{H}_2\text{O}$  was assessed by exposing

HeLa cells to varying amounts of activated framework suspended in DMEM supplemented with 10% FBS for 72 h at 37 °C (Fig. 8; see ESI Section 13† for details). Viabilities were determined by incubating the exposed cells with (4,5-dimethylthiazol-2-yl)-2,5-diephenyltetrazolium bromide (MTT) followed by colorimetric quantification in comparison with cells that were not treated with MOF (100% viability).<sup>59</sup> Near 100% viabilities were observed up to concentrations of 0.2 mg mL<sup>-1</sup>, and >90% viability was observed for Zr-fum-H<sub>2</sub>O at concentrations as high as 0.5 mg mL<sup>-1</sup>. This is in contrast to other MOFs such as Zn-MOF-74, which was found to be highly toxic to HeLa cells at concentrations greater than 0.1 mg mL<sup>-1</sup> (ESI Fig. S101†).<sup>60</sup> Assuming Zr-fum-H<sub>2</sub>O is capable of delivering 4 μmol of H<sub>2</sub>S per mg of MOF (Fig. 3), a concentration of 0.1 mg mL<sup>-1</sup> corresponds to a deliverable concentration of H<sub>2</sub>S of up to 400 μM, which is comparable to or above endogenous concentrations (e.g., 50–160 μM in the brain).<sup>7</sup> This highlights the potential benefit in using a porous solid to deliver H<sub>2</sub>S: low concentrations (<0.1 mg mL<sup>-1</sup>) of framework can be employed to release therapeutic levels of H<sub>2</sub>S, minimizing any potential side effects from the framework itself. Promisingly, our results suggest that Zr-mes and Zr-ita are also relatively non-toxic to HeLa cells (ESI Fig. S80†).

Having established the biocompatibility of Zr-fum-H<sub>2</sub>O, we next evaluated its ability to release H<sub>2</sub>S upon subjection to aqueous solution (Fig. 9 and 10). First, a known amount of H<sub>2</sub>S-dosed MOF was submerged into a large volume of phosphate buffered saline (PBS) with stirring (~1 mg MOF per mL PBS). Aliquots from the suspension were quenched with a large excess (>20 equiv.) of the fluorescent probe 1,5-dansyl azide (DNS-az), which exhibits rapid turn-on fluorescence ( $\lambda_{\text{max}} = 520$  nm) upon reaction with H<sub>2</sub>S.<sup>61</sup> The release of H<sub>2</sub>S from H<sub>2</sub>S-Zr-fum-H<sub>2</sub>O into PBS was reproducibly confirmed by fluorescence spectroscopy (Fig. 9, upper; ESI Fig. S78†). The concentration of H<sub>2</sub>S in solution reached saturation in approximately 30 seconds; given the large excess of free DNS-az present in solution, this suggests

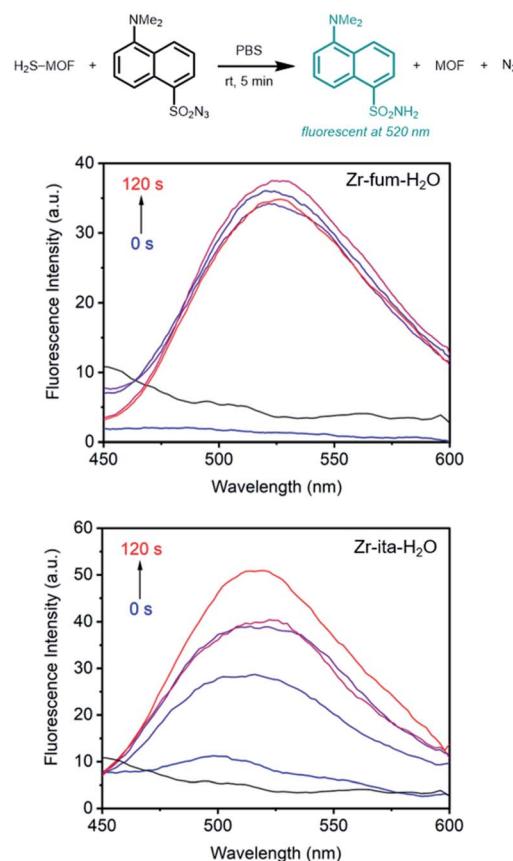


Fig. 9 Fluorescence assay (excitation at 340 nm) using the turn-on fluorescence probe dansyl azide (DNS-az) to confirm the release of H<sub>2</sub>S from Zr-fum-H<sub>2</sub>O (upper) and Zr-ita-H<sub>2</sub>O (lower) upon submersion in phosphate buffered saline (PBS). The black line corresponds to a control experiment lacking MOF. The data were smoothed by adjacent-averaging (15 points).

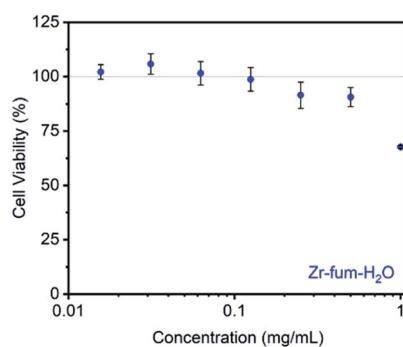


Fig. 8 Viability of HeLa cells upon exposure to suspensions of activated Zr-fum-H<sub>2</sub>O at a range of concentrations in DMEM supplemented with 10% FBS for 72 h at 37 °C. Viabilities were determined by incubating the cells with MTT followed by colorimetric analysis using a microplate reader. Results are reported as the average cell viability of 6 wells/concentration compared to untreated cells from three independent trials, with the standard deviation (SD) reported as the error (±SD).

that the release of H<sub>2</sub>S from Zr-fum-H<sub>2</sub>O is complete in less than 30 s. Importantly, a control experiment in which H<sub>2</sub>S was dosed into a tube lacking MOF and then “poured” into PBS following the same procedure produced no detectable amounts of H<sub>2</sub>S, confirming that all of the H<sub>2</sub>S was released from Zr-fum-H<sub>2</sub>O (black line, Fig. 9). We also reproducibly confirmed the release of H<sub>2</sub>S from H<sub>2</sub>S-Zr-ita-H<sub>2</sub>O using the same assay (Fig. 9, lower; Fig. S79†). In contrast to Zr-fum-H<sub>2</sub>O, H<sub>2</sub>S release from Zr-ita-H<sub>2</sub>O took 120 s to reach saturation, indicating that H<sub>2</sub>S release from Zr-ita-H<sub>2</sub>O may be slower than from Zr-fum-H<sub>2</sub>O. Unfortunately, due to unavoidable loss of gaseous H<sub>2</sub>S to air this assay cannot be used to reliably quantify the concentration of H<sub>2</sub>S released into solution.

Notably, while the release of H<sub>2</sub>S from Zr-fum-H<sub>2</sub>O and Zr-ita-H<sub>2</sub>O into PBS is relatively rapid, H<sub>2</sub>S release under ambient conditions from all three MOFs is quite slow. As assessed by exposure to strips of filter paper soaked in lead chloride solution, all three frameworks were found to still contain H<sub>2</sub>S after standing for at least four days in humid air, with Zr-fum-H<sub>2</sub>O still containing H<sub>2</sub>S after six days in humid air (ESI Fig. S81–S83†). In contrast, both Na<sub>2</sub>S·9H<sub>2</sub>O and NaSH were found to completely hydrolyze and degrade in less than 5 h under



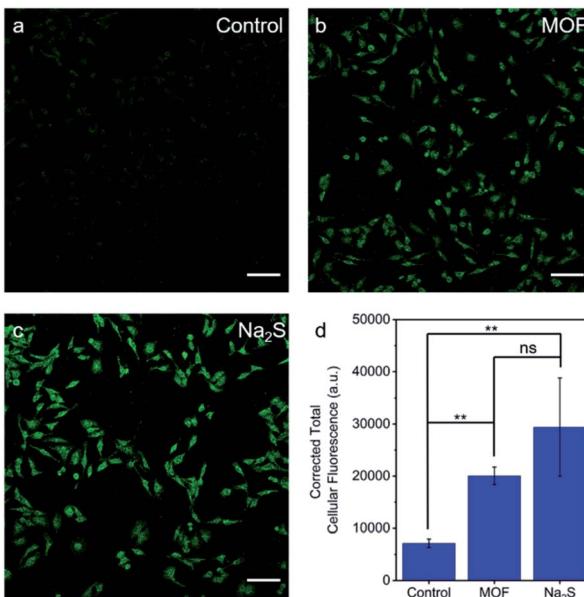


Fig. 10 Representative fluorescence microscopy images of  $\text{H}_2\text{S}$  release in WSP5-loaded HeLa cells treated with (a) water, (b)  $0.05 \text{ mg mL}^{-1}$   $\text{H}_2\text{S-Zr-fum-H}_2\text{O}$ , or (c)  $200 \mu\text{M}$   $\text{Na}_2\text{S}$  for 1 h at  $37^\circ\text{C}$ . (d) Quantification of total cellular fluorescence of HeLa cells incubated under the conditions described. The scale bar indicates  $100 \mu\text{m}$ . ns indicates not significant, \*\* indicates  $p < 0.01$ .

ambient conditions (Fig. S84†). The clean release of  $\text{H}_2\text{S}$  into water and the long-term stability of these MOFs in humid air makes them ideal solid sources of  $\text{H}_2\text{S}$  that can be easily handled in the laboratory.<sup>9</sup>

The ability of  $\text{H}_2\text{S-Zr-fum-H}_2\text{O}$  to deliver  $\text{H}_2\text{S}$  to cells under physiologically-relevant conditions was further probed using confocal fluorescence microscopy (Fig. 10). Specifically, HeLa cells were incubated first with DMEM containing WSP5 (WSP = Washington State Probe), a selective fluorescence probe for intracellular  $\text{H}_2\text{S}$ ,<sup>62</sup> followed by rinsing and exposure to water (Fig. 10a),  $\text{H}_2\text{S-Zr-fum-H}_2\text{O}$  (Fig. 10b), or  $\text{Na}_2\text{S}\cdot 9\text{H}_2\text{O}$  (Fig. 10c). For both  $\text{H}_2\text{S-Zr-fum-H}_2\text{O}$  and  $\text{Na}_2\text{S}\cdot 9\text{H}_2\text{O}$ , a statistically significant enhancement in corrected total cellular fluorescence (CTCF) was observed compared to the control experiment, validating the release and cellular uptake of  $\text{H}_2\text{S}$  in both cases. Together, these fluorescence experiments (Fig. 9 and 10) confirm the ability of  $\text{H}_2\text{S-Zr-fum-H}_2\text{O}$  to release  $\text{H}_2\text{S}$  under physiologically relevant conditions for subsequent uptake by cells.

One of the primary proposed therapeutic modes of  $\text{H}_2\text{S}$  is its ability to mediate oxidative stress within cells.<sup>13,63</sup> For example,  $\text{H}_2\text{S}$  has been shown to limit the oxidative damage to tissue that occurs following the temporary blockage of blood flow during a stroke or myocardial infarction when a period of ischemia or hypoxia is followed by a return of normoxic blood flow, known as ischemia-reperfusion injury (R).<sup>63,64</sup> We evaluated the ability of Zr-fum- $\text{H}_2\text{O}$  to deliver  $\text{H}_2\text{S}$  and mitigate reperfusion injury using an *in vitro* model of this condition, hypoxia-reoxygenation, in H9c2 rat cardiomyoblast cells (Fig. 11). As expected, cardiomyoblast cells incubated under normoxic

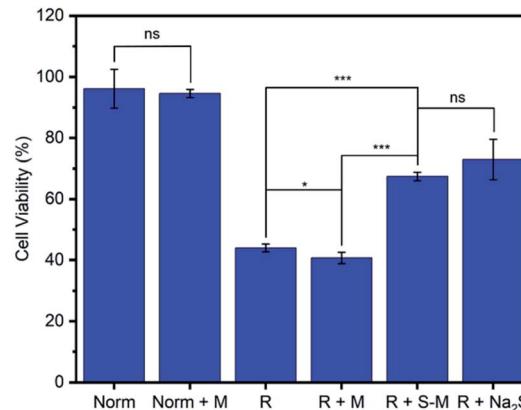


Fig. 11 Hypoxia-reoxygenation model of ischemia-reperfusion injury using H9c2 rat cardiomyoblast cells to confirm the ability of Zr-fum- $\text{H}_2\text{O}$  to deliver  $\text{H}_2\text{S}$  under physiological conditions. Norm = normoxic conditions; Norm + M = normoxic conditions with activated MOF; R = hypoxia followed by normoxic conditions, simulating reperfusion injury; R + MOF = hypoxia followed by normoxic conditions with activated MOF; R + S-M = hypoxia followed by normoxic conditions with  $\text{H}_2\text{S}$ -loaded Zr-fum- $\text{H}_2\text{O}$ ; R + Na<sub>2</sub>S = hypoxia followed by normoxic conditions with Na<sub>2</sub>S·9H<sub>2</sub>O. \* indicates  $p < 0.05$ , \*\*\* indicates  $p < 0.001$ , and ns indicates not significant.

conditions in the absence (Norm) or presence of desolvated Zr-fum- $\text{H}_2\text{O}$  (Norm + M) demonstrated similar viabilities ( $96 \pm 6\%$  and  $94 \pm 1\%$ , respectively). The latter result is consistent with the lack of toxicity observed for this material with HeLa cells (Fig. 9). In contrast, cells incubated under hypoxic conditions ( $5\% \text{ CO}_2$  in  $\text{N}_2$  for 10 minutes) followed by a return to normoxic conditions, simulating a reperfusion injury (R), demonstrated significantly reduced viabilities ( $44 \pm 1\%$ ). However, subjecting cells to this reperfusion injury model in the presence of  $\text{H}_2\text{S-Zr-fum-H}_2\text{O}$  (R + S-M) led to a significant improvement in their viabilities ( $67 \pm 1\%$ ), confirming the potential of Zr-fum- $\text{H}_2\text{O}$  as a delivery vessel for therapeutic  $\text{H}_2\text{S}$ . Importantly, the presence of activated MOF (R + M) did not lead to an increase in viability compared to cells in the absence of MOF ( $41 \pm 1\%$ ), corroborating that the therapeutic value of  $\text{H}_2\text{S-Zr-fum-H}_2\text{O}$  is likely due to  $\text{H}_2\text{S}$  release. Likewise, a statistically identical improvement in cell viabilities ( $73 \pm 7\%$ ) was observed using Na<sub>2</sub>S·9H<sub>2</sub>O in place of  $\text{H}_2\text{S-Zr-fum-H}_2\text{O}$  (R + Na<sub>2</sub>S), confirming that  $\text{H}_2\text{S}$ -loaded MOFs provide similar therapeutic value as traditional sources of  $\text{H}_2\text{S}$  but with enhanced stability in the solid state. Overall, our results suggest that Zr-fum- $\text{H}_2\text{O}$ , as well as Zr-mes- $\text{H}_2\text{O}$  and Zr-ita- $\text{H}_2\text{O}$ , represent promising vehicles for the delivery of biologically active  $\text{H}_2\text{S}$  under physiological conditions.

## Conclusions

The controlled delivery of  $\text{H}_2\text{S}$  is an unsolved challenge in medicine and biology.<sup>9</sup> Here, we demonstrate that biocompatible MOFs that are completely stable to  $\text{H}_2\text{S}$ , including Zr-fum, Zr-mes, and Zr-ita, present a promising new direction for the design of vehicles for  $\text{H}_2\text{S}$  release under physiological



conditions. In particular, given its excellent stability, high H<sub>2</sub>S capacity, lack of toxicity, ambient stability, and performance in a cellular hypoxia-reoxygenation injury assay, Zr-fum-H<sub>2</sub>O represents a next-generation platform for the therapeutic delivery of H<sub>2</sub>S. In addition to Zr-fum-H<sub>2</sub>O, this work also adds Zr-mes-H<sub>2</sub>O and Zr-ita-H<sub>2</sub>O to the growing lexicon of biocompatible MOFs for drug delivery applications. Future work will focus on functionalizing the surface of these frameworks to further control the rate and location of H<sub>2</sub>S delivery under physiological conditions.

## Author contributions

P. J. M., J. J. Wilson, R. M. M., F. E. C., and J. J. Woods conceived the project. R. M. M. and F. E. C. synthesized and characterized MOFs and carried out all gas adsorption measurements. J. J. Woods carried out all cellular experiments with assistance from R. M. M. J.-H. L. carried out DFT calculations. J. K. designed the DRIFTS cell and carried out experiments with assistance from R. M. M. J. H. H. preliminarily optimized the synthesis of MOFs. J. J. F.-R. carried out SEM measurements. The final version of the manuscript was written with contributions from all co-authors.

## Conflicts of interest

P. J. M. is listed as a co-inventor on several patents that include functionalized metal-organic frameworks.

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