

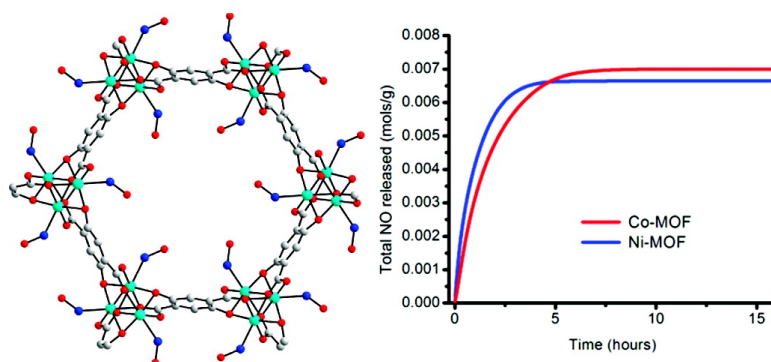
Article

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## Exceptional Behavior over the Whole Adsorption–Storage–Delivery Cycle for NO in Porous Metal Organic Frameworks

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**Abstract:** Two porous metal organic frameworks (MOFs),  $[M_2(C_8H_2O_6)(H_2O)_2] \cdot 8H_2O$  ( $M = Co, Ni$ ), perform exceptionally well for the adsorption, storage, and water-triggered delivery of the biologically important gas nitric oxide. Adsorption and powder X-ray diffraction studies indicate that each coordinatively unsaturated metal atom in the structure coordinates to one NO molecule. All of the stored gas is available for delivery even after the material has been stored for several months. The combination of extremely high adsorption capacity ( $\sim 7$  mmol of NO/g of MOF) and good storage stability is ideal for the preparation of NO storage solids. However, most important is that the entire reservoir of stored gas is recoverable on contact with a simple trigger (moisture). The activity of the NO storage materials is proved in myography experiments showing that the NO-releasing MOFs cause relaxation of porcine arterial tissue.

### Introduction

Gas-delivery technologies using porous solid storage materials are of increasing importance in many areas of science,<sup>1</sup> with emerging applications that include storage of hydrogen<sup>2,3</sup> and methane<sup>4</sup> as energy carriers and delivery of nitric oxide (NO) for medical therapies.<sup>5</sup> A perfect gas-storage solid should have high adsorption capacity and fast kinetics at workable temperatures, and the gas should interact strongly enough with the material that it is not lost from the solid on storage but not so strongly that it cannot be released from the material for use at the required time. The release should also occur at the appropriate rate for the desired application, and control over the release kinetics is an added advantage. Most suggested gas-storage materials fail to meet one or more of these criteria. Here we describe the use of porous coordination polymers as almost ideal gas-storage materials, as they perform exceptionally over the whole adsorption–storage–delivery cycle. They adsorb, and store without significant loss, large quantities of NO. Significantly, the entire stored NO reservoir can be released via a simple triggering mechanism, and its size is almost 7 times greater than that of any other porous material known<sup>6</sup> and over 7000 times larger than previously studied porous coordination

polymers.<sup>7</sup> We also show that the flux of NO released from the material is biologically active for the relaxation of vascular smooth muscle.

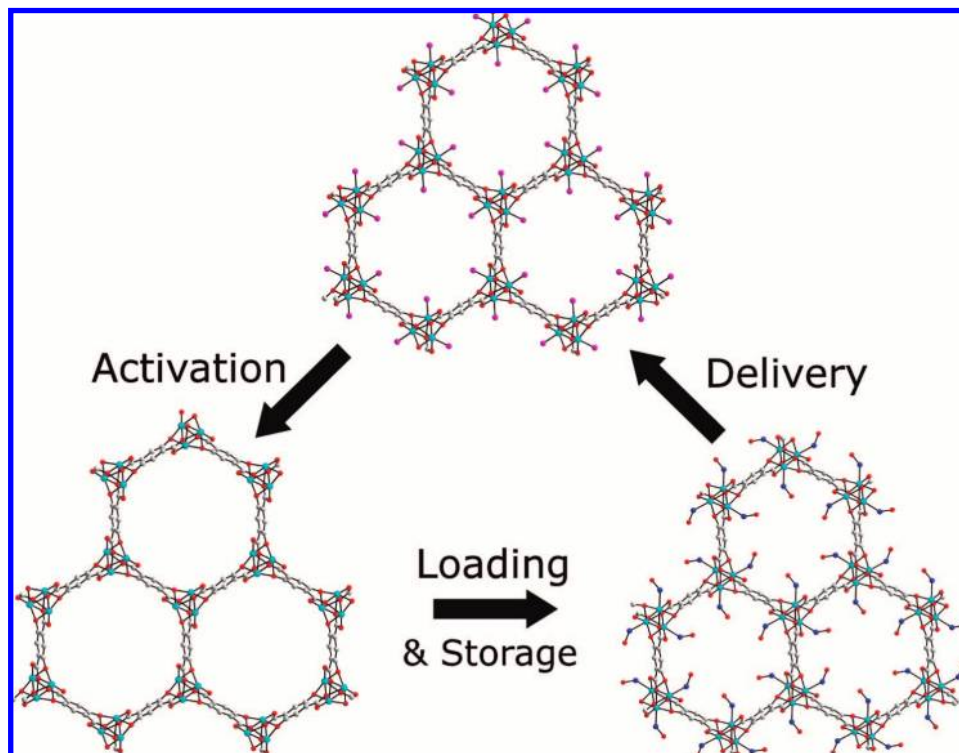
NO is an extremely important biological signaling molecule, and its delivery from a storage material is attractive for many in vitro and in vivo antibacterial, antithrombotic, and wound-healing applications.<sup>8,9</sup> The characteristics of NO dictate that release from a material is a method of generating local rather than systemic effects, which also has the advantage of reducing unwanted side effects. In recent times, polymers,<sup>10–13</sup> functionalized silica nanoparticles,<sup>14,15</sup> and zeolites<sup>6</sup> have all been used to deliver vastly different amounts of NO for different functions. Unfortunately, many of these NO donors also deliver carcinogenic or pro-inflammatory side products, which may limit their applicability in certain circumstances.<sup>16</sup>

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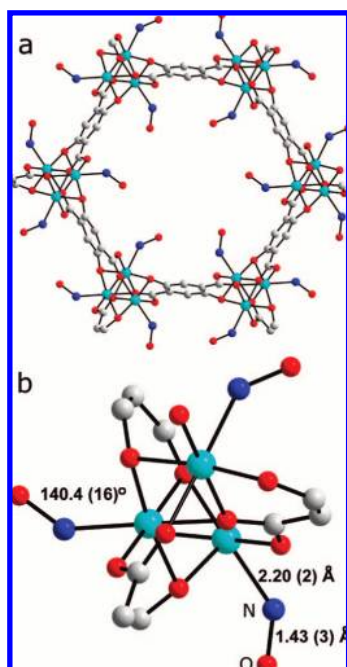
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**Figure 1.** Cycle of activation, loading, storage, and delivery that determines the success of a gas-storage material (Co- and Ni-MOF). Great care must be taken to ensure that the activation stage (i.e., removal of all guest molecules) is done carefully and completely to allow access to all of the coordinatively unsaturated sites in the structure. In turn, for the most effective gas-storage materials, delivery of the entire reservoir of stored gas must be possible. Color key: cyan, Ni/Co; red, oxygen; gray, carbon; pink, oxygen of coordinated water molecules. Hydrogen atoms and noncoordinated guest molecules have been omitted for clarity.



**Figure 2.** Crystal structure of NO-loaded Co-MOF from Rietveld refinement of X-ray diffraction data. (a) Binding of NO to the CUSs in Co-MOF. The nitrogen and oxygen atoms of NO were located from difference Fourier maps. (b) Enlarged view of NO bound to the cobalt atoms in NO-loaded Co-MOF, showing the bent mode of NO binding that is very similar to that seen in cobalt-loaded zeolites.<sup>24</sup> The color key is the same as in Figure 1.

Porous coordination polymers, sometimes known as metal organic frameworks (MOFs), are materials with extremely high

porosities that exceed those of any other known class of material.<sup>17–20</sup> Some porous coordination polymers have coordinatively unsaturated metal sites (CUSs) on the walls of the pores that are available to bind molecules, including gases (after activation to remove any guest molecules present in the synthesis).<sup>21–23</sup> The presence of CUSs in a coordination polymer has a particularly pronounced effect on the NO adsorption and release characteristics of the material. Solids with large numbers of accessible CUSs strongly bind NO on adsorption, which is ideal for stable, long-shelf-life gas-storage applications. However, there is a balance to be struck. A useful gas-storage material must perform effectively over the whole cycle shown in Figure 1, and recovering the gas easily when it is needed must be possible—for the most effective materials, the entire reservoir of stored gas must be releasable by some trigger under suitable conditions. The preferred trigger for NO release is exposure to water at room/body temperature.

The search for materials that perform well over the whole adsorption–storage–delivery cycle is one of the holy grails in

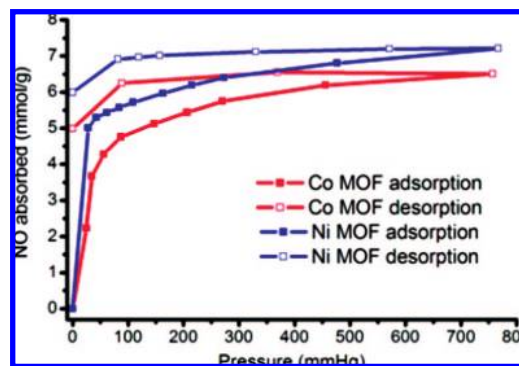
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all of gas-storage science, but is a particular problem for storage materials that interact strongly with the gas in question. The classic example of this is hydrogen storage using hydrides, where poor reversibility is a serious issue. NO-storing solids, in which metal–NO interactions are relatively strong (up to  $\sim 90$  kJ mol $^{-1}$ ; see ref 7), suffer from similar problems, and materials such as zeolites release only a portion of the adsorbed gas for use.<sup>6</sup> Porous coordination polymers with CUSs also bind NO strongly, and while HKUST-1 (a porous benzenetricarboxylate-based coordination polymer material with coordinatively unsaturated copper sites) adsorbs large quantities of NO (up to  $\sim 3$  mmol NO/g of material at room temperature), it releases only  $1 \mu\text{mol NO/g}$  of material.<sup>7</sup> In this paper, we report the NO adsorption and delivery properties of two coordination polymers, one based on Co and the other on Ni, with 2,5-dihydroxyterephthalic acid as the organic linker:  $[\text{M}_2(\text{C}_8\text{H}_2\text{O}_6)(\text{H}_2\text{O})_2] \cdot 8\text{H}_2\text{O}$  (M = Co, Ni) (hereafter called Co-MOF and Ni-MOF, respectively). These materials adsorb twice as much NO as HKUST-1 at room temperature and boast almost perfect releasability of the adsorbed NO upon exposure to moisture, leading to delivery of  $\sim 7$  mmol NO/g of material, an amount 7000 times greater than that by HKUST-1 and 7 times greater than that by the best zeolite. It is clear from our results that the materials release pure NO, a situation that has recently been shown to be necessary in order to limit inflammatory responses in human tissue.<sup>24</sup>

## Results and Discussion

Samples of Co-MOF and Ni-MOF were prepared as described in the literature by Dietzel and co-workers,<sup>25</sup> who called the materials CPO-27-Co and CPO-27-Ni, respectively. Figure 1 shows the structure of the as-made materials (excluding the eight molecules of water that are guests in the voids). Thermal activation of the material at 110 °C (see Materials and Methods) removes the guest molecules and the two molecules of water per formula unit that are coordinated to the metals in the structure, leaving in the structure  $\sim 0.0064$  mol of CUSs/g of activated material. Exposure to NO led to immediate changes in color, from red to almost-black in Co-MOF and from yellow to dark-green in Ni-MOF, indicative of the interaction of the gas with the CUSs. Powder X-ray diffraction (XRD) of the two MOFs revealed that the crystallinity of the original samples is retained, and Rietveld refinement of the XRD data for the NO-loaded Co-MOF material (see the Supporting Information) clearly indicated that the gas molecules are coordinated to the metal sites in the structure with a geometry (Figure 2) similar to that seen in NO-loaded Co-zeolites.<sup>26</sup>

Gravimetric adsorption measurements revealed that the materials adsorb in the region of 7.0 mmol NO/g of activated material at room temperature (Figure 3). The desorption arm of the experiments showed considerable hysteresis, which is explained by the strong interaction of nitric oxide with CUSs,



**Figure 3.** Adsorption/desorption isotherms at 25 °C for NO on Co- and Ni-MOF. The hysteresis in the isotherms is typical of materials in which the NO binds relatively strongly to the metals.

similar to that seen in other materials with coordinatively unsaturated metal ions such as zeolites<sup>6</sup> and HKUST-1.<sup>7</sup> The amount of adsorption is  $\sim 1$  NO molecule per CUS, although one must remember that there will also be a small amount of weakly adsorbed (physisorbed) NO on the walls of the polymer in addition to the strongly held (chemisorbed) metal-coordinated NO. Recent IR studies of NO on CPO-27-Ni confirm the 1:1 Ni–NO adduct in the material.<sup>25d</sup>

The large adsorption capacity of the coordination polymers is useful only if the storage is stable over time and if the gas can be recovered for use at a later time. The NO-loaded materials can be stored under dry atmospheres and then exposed to moisture to trigger the release of the NO for use. Water molecules replace the coordinated NO, releasing it from the material. Figure 4 shows the release profiles for the two materials when contacted by a wet gas [11% relative humidity (RH)] after storage for 2 weeks. The total amount of NO released was also  $\sim 7$  mmol NO/g of material, illustrating that the entire NO store was still recoverable after this time. Storage for up to 20 weeks showed no significant change in the amount of releasable NO. This behavior is vastly different from that of NO-loaded HKUST-1, where only a small fraction of the NO is recoverable.<sup>6</sup> Figure 4 also shows the effect of the different metals on the kinetics of release. Co-MOF releases NO significantly more slowly than Ni-MOF. The inset in Figure 4a shows that beyond 14 h, the two MOFs are still releasing significant amounts of NO under these conditions.

An expanded view of the first hour of release (Figure 5) shows that the physisorbed NO is released very quickly (within the first few minutes) as a sharp spike, while the release of the chemisorbed NO is very much slower. The total measurable amount of physisorbed NO accounts for  $\sim 1\%$  of the total amount of NO released from the sample.

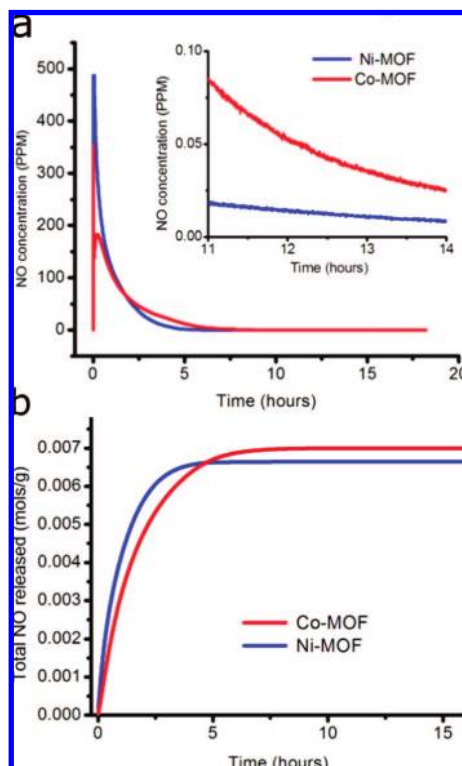
Contact with a flowing wet gas is an excellent method of reproducibly mimicking “scarce water” situations, such as delivery of NO topologically to the skin. However, on contact with phosphate-buffered saline (PBS, pH 7.4), which is a better mimic of blood or other physiological solutions, the delivery rate increased markedly. The half-life of NO delivery was reduced from several hours for flowing gas to  $\sim 10$  min for pressed pellets in contact with PBS for both the Co- and Ni-MOF samples.

Given the powerful vasodilator, antithrombotic, and anti-atherogenic properties of NO generated by the endothelium of blood vessels,<sup>9</sup> it is important to investigate whether NO stored in MOFs can be released under physiological conditions and

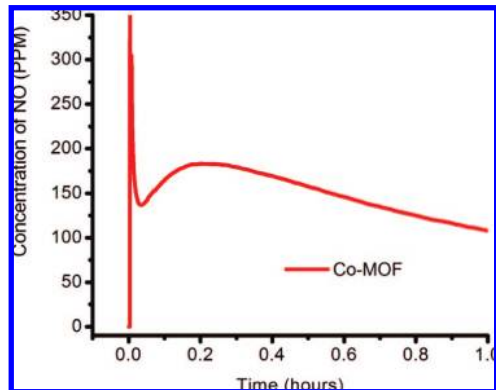
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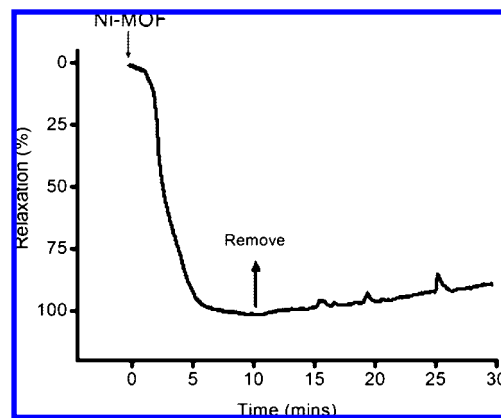


**Figure 4.** (a) Delivery of NO on contact with wet gas (11% RH), as measured by chemiluminescence. The inset shows that the materials are still releasing NO at and beyond 14 h under these conditions. (b) The total amounts of NO released by the two materials normalized per gram of activated solid.



**Figure 5.** The first hour of the release curve shown for Co-MOF in Figure 4, showing the sharp spike of NO due to the very fast release of physisorbed gas followed by the much slower release of the chemisorbed NO. The physisorbed gas accounts for less than 1% of the total amount of NO released by the material.

cause a relevant tissue response. To this end, we investigated the impact of a pressed pellet of Ni-MOF (5 mg) on precontracted pig coronary arteries *in vitro* (Figure 6). Placement of pellets a distance of 2 mm from the vessel in the 10 mL organ bath resulted in rapid 100% relaxation of the vessel. The pellet could be seen to generate bubbles of gas for ~10 min of submersion, although the relaxation remained maximal for >1 h. In some experiments (Figure 6), the pellet was removed from the bath after 10 min and the relaxation was seen to gradually recover. Parallel control experiments with NO-free Ni-MOFs failed to cause relaxation and did not generate bubbles on



**Figure 6.** Representative trace (of  $n = 3$ ) showing the vasodilatory effect of Ni-MOF in a precontracted porcine coronary artery. A pellet (~5 mg) of Ni-MOF was placed in the organ bath (10 mL) and removed as indicated. Within 4 min of the addition of the pellet, 100% relaxation was achieved, and the relaxation slowly recovered upon pellet removal. In experiments where the pellet was left in the bath, no recovery was seen even at times longer than 1 h after pellet addition.

submersion, indicating that NO release from the loaded MOF is responsible for the relaxing effect.

Biological applications of MOFs are only just being developed, and early indications are that carboxylate MOFs show very favorable toxicology for *in vivo* applications.<sup>27</sup> Given their properties of very high adsorption capacity, long shelf life, stable storage, and triggered release at biologically useful fluxes, the Ni- and Co-MOF materials described here are almost ideal gas-storage materials. The only property of the solids that is not perfect is the toxicology of the two metals, particularly cobalt. However, the toxicologically much more suitable zinc analogue of the two materials (MOF-74/CPO-27-Zn) is known from the work of Dietzel et al.<sup>25c</sup> and Rowsell and Yaghi.<sup>28</sup> The activation stage for this material is, unfortunately, not as easy as those for other MOFs, and even after extensive solvent extraction and thermal activation, only ~5 mmol NO/g of material is adsorbed. The recent paper by Dietzel et al.<sup>25c</sup> explains why the Zn analogue is not easy to activate fully: this material exhibits several phase transitions, and the framework undergoes considerable strain upon dehydration. However, the amount of NO adsorbed is still significantly greater than that for any other porous material, so this material remains a very interesting candidate for further biological applications.

One particularly important aspect of NO donors is their biocompatibility. Many currently proposed NO donors have significant drawbacks, particularly those regarding the codelivery of toxic, carcinogenic, or pro-inflammatory side products.<sup>16</sup> Controlled delivery of pure NO is therefore a prerequisite for applications, as this significantly reduces unwanted side reactions. Recent work has shown that pure NO delivered by zeolites is noninflammatory on contact with human tissue.<sup>24</sup> The exceptional behavior over the whole adsorption–storage–delivery cycle indicates that the MOFs reported in this paper deliver only pure NO. This combination of large capacity with biocompatibility based on the delivery of pure NO opens up exciting possibilities for MOF-based NO donors. While the metals in the present study (Co and Ni) are not toxicologically ideal, it is

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possible to envisage applications where the material is separated from human tissue by a gas-permeable membrane, rendering the toxicity of the material itself much less of an issue. Examples of this type of possible application are delivery to the skin through gas-permeable dressings.

Of course, the gases of interest in storage technologies have properties that differ markedly from each other, making the transfer of strategies among technologies unlikely unless the gases themselves are very similar. However, we have shown in this work that paying attention to the whole cycle can produce large-step changes in the deliverable capacity of NO. Similar advances over the adsorption–storage–delivery cycle with materials in other areas, such as hydrogen storage, could lead to technological advances that are not possible at the present time.

## Materials and Methods

**Synthesis and Activation.** All of the materials were synthesized according to literature methods.<sup>25</sup> To activate the materials, they were first placed under vacuum until ~29% of the mass (the uncoordinated water) was lost. They were then carefully heated to 110 °C while still under vacuum for 36 h in order to ensure that all of the coordinated water molecules were removed, leaving a fully activated material.

**Absorption/Desorption Experiments.** The absorption/desorption of NO gas in various samples was measured using a gravimetric adsorption system. A CI Instruments microbalance was thermally stabilized to eliminate effects from external environment. The microbalance had a sensitivity of 0.1  $\mu\text{g}$  and a reproducibility of 0.01% of the load. The pressure of the absorption system was monitored by two BOC Edwards active gauges with ranges of  $1 \times 10^{-8}$  to  $1 \times 10^{-2}$  and  $1 \times 10^{-4}$  to  $1 \times 10^3$  mbar, respectively. The sample (~25 mg) was initially subjected to the vacuum before being degassed at the required temperature (which depended on the sample's activation temperature and stability) under a pressure of  $1 \times 10^{-4}$  mbar until no further weight loss was observed. The sample temperature was then decreased to 25 °C and kept constant by a circulation water bath with temperature accuracy of  $\pm 0.02$  K. The counterbalance temperature was kept the same as that of the sample in order to minimize the influence of temperature differences on weight readings, and the sample temperature was monitored using a K-type thermocouple located close to the sample bucket (<5 mm). The variation in sample temperature was minimal (<0.1 K) throughout the experiment. NO gas was introduced into the adsorption system until the desired pressure was achieved, and the mass uptake of the sample was measured as a function of time until the adsorption equilibrium was achieved. In this manner, an adsorption isotherm was collected by incrementally increasing the pressure and noting the mass gain of the sample after equilibrium was reached. Desorption of the NO gas absorbed in the samples was performed by gradually decreasing the system pressure to  $2 \times 10^{-2}$  mbar.

**Loading and Measurement of NO Release by Chemiluminescence.** Powdered samples of the MOFs (~0.03 g) were activated as described above. They were cooled to room temperature and exposed to ~2 atm of dry NO (99.5%, Air Liquid) for 30 min,

evacuated, and exposed to dry argon. The cycle of evacuation and exposure to NO was repeated three times.

NO release measurements were performed using a Sievers NOA 280i chemiluminescence nitric oxide analyzer. The instrument was calibrated by passing air through a zero filter (Sievers, <1 ppb NO) and 89.48 ppm NO gas (Air Products, balance nitrogen). The flow rate was set to 180 mL/min with a cell pressure of 8.5 Torr and an oxygen pressure of 6.1 psig. To measure NO release from different samples, nitrogen gas of controlled humidity (11% RH) was passed over the powders, the resultant gas directed into the analyzer, and the concentration of NO recorded.

For experiments in contact with PBS, calculated amounts of each MOF were ground together with Teflon (10 wt %), and this mixture was then pressed into 5 mm pellets, which were then dehydrated and loaded with NO in the same way as for the powder samples. The pellets were placed in a capped sample vial, and then PBS buffer solution (4 mL) was injected. The NO released was measured in the same manner as above.

**Powder X-ray Diffraction.** Samples of Co-MOF were loaded into capillaries, exposed to 1 atm of NO, and then sealed. X-ray diffraction data were collected on a Stoe Stadip diffractometer using Fe K $\alpha$  radiation (to avoid fluorescence). The Rietveld refinement was based on the dehydrated Co-MOF structure reported in ref 25a. The NO atoms were located using Fourier maps and included in the refinement. The final refinement converged to  $wR_p = 0.0784$ ,  $R_p = 0.0582$ , and  $R(F^2) = 0.2166$ .

**Vascular Relaxation Experiments.** Pig hearts were obtained from the local abattoir within 5 min of slaughter and placed in ice-cold Krebs buffer solution (119 mM NaCl, 4.7 mM KCl, 2.5 mM CaCl<sub>2</sub>, 1 mM MgCl<sub>2</sub>, 25 mM NaHCO<sub>3</sub>, 1.2 mM KH<sub>2</sub>PO<sub>4</sub>, 11 mM D-glucose, 95% O<sub>2</sub>, 5% CO<sub>2</sub>) prior to dissecting free the left anterior coronary artery. Rings of artery (5 mm) were mounted on wire supports in a myograph (Danish Myo Technology, Aarhus, Denmark) and allowed to equilibrate for 1 h prior to application of a passive tension of 15 mN. The rings were then contracted using the thromboxane A<sub>2</sub> analogue U46619 (80 nM) in order to generate tensions of 30–50 mN. Once a steady level of contraction was attained, compressed pellets of NO-loaded Ni-MOF (~5 mg) were added to the organ bath at a distance of ~2 mm from the precontracted ring. The pellet was subsequently removed after 10 min of incubation or left in the organ bath for 1 h in order to ascertain the reversibility of the observed relaxations as well as the durability of the effect. A total of three independent experiments were conducted; data was recorded via an analog/digital converter and Chart Software (AD Instruments).

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**Supporting Information Available:** Crystallographic information for NO-loaded MOFs. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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