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# Cation-Triggered Drug Release from a Porous Zinc−Adeninate Metal−Organic Framework

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Porous materials are used for a variety of biomedical applications.[1] Recent studies point toward the potential biomedical utility of porous metal-organic frameworks (MOFs).[2] For example, lanthanide-based MOFs have been used as multimodal cellular probes[3] and drug storage and release has been evaluated for some $Tb^{3+}$, $Fe^{2+}$, and $Cr^{3+}$-based MOFs.[4] However, for biomedical applications, it is important to consider not only the function but also the biocompatibility of a material. Some MOFs may thus present concerns due to potential leaching of toxic metal ions and other harmful constituents. For this reason, we have chosen to construct bio-MOFs, MOFs that incorporate simple biomolecules and biocompatible metal cations in their structures.[5]

Here, we use rigid biomolecules as building blocks for constructing permanently porous bio-MOFs and introduce bio-MOF-1 as a representative of this class of MOFs. We describe its structure and show that it is stable and maintains its crystallinity for weeks in biological buffers. We exploit the intrinsic anionic nature of bio-MOF-1 by demonstrating that it can serve as a host for adsorbing cationic drug molecules. Further, we demonstrate that exogenous cations from biological buffers can be used to affect the controlled release of the adsorbed drug molecules from the pores.

For this study, we chose adenine, a purine nucleobase, as a biomolecular ligand. Adenine is an ideal ligand for constructing bio-MOFs because (a) it is rigid, (b) it has multiple possible metal binding modes, and (c) its molecular coordination chemistry is well-developed.[6] Initial reactions between adenine and zinc salts resulted principally in the formation of condensed materials with small, inaccessible pores. These results prompted us to include auxiliary linking molecules into our syntheses to promote the formation of larger accessible pores.

Specifically, we found that introducing biphenyldicarboxylic acid to reactions between adenine and zinc acetate dihydrate in dimethylformamide (DMF) yielded a single crystalline material formulated as $Zn_8(ad)_4(BPDC)_6O{\bullet}2Me_2NH_2$, 8DMF, $11H_2O$, heretofore referred to as bio-MOF-1 (ad = adeninate; BPDC = biphenyldicarboxylate). Single crystal X-ray analysis revealed that bio-MOF-1 consists of infinite zinc−adeninate columnar secondary building units (SBUs) composed of apex-sharing zinc−adeninate octahedral cages (Figure 1A). Each cage consists of four adeninates which occupy alternating faces of the octahedran and eight $Zn^{2+}$ tetrahedra, four at the corners of the equatorial plane of each cage and two at each apical position. The $Zn^{2+}$ comprising the apexes constitute half of a $Zn_4O$ cluster that links adjacent octahedral cages together. Pairs of $Zn^{2+}$ within each $Zn_4O$ cluster are bridged by two adeninates through the N3 and N9 positions. N1 and N7 of each adeninate coordinate to the $Zn^{2+}$ in the equatorial plane. The zinc−adeninate columns are interconnected via multiple BPDC linkers. One carboxylate from each linker coordinates in a monodentate fashion to a $Zn^{2+}$ in the $Zn_4O$ cluster, while the other carboxylate binds in a monodentate fashion to one of the equatorial $Zn^{2+}$ on an adjacent column. This connectivity pattern results in large channels that run along the *c* crystallographic direction (Figure 1B). The zinc−adeninate columns pack in parallel according to the **pcu** network topology.[7]

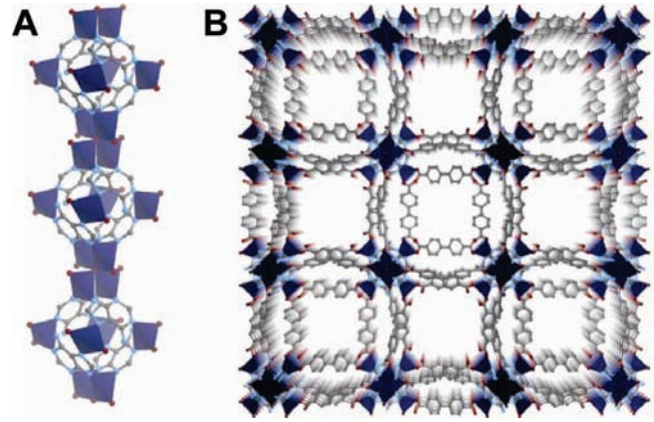


***Figure 1.*** The crystal structure of bio-MOF-1 consists of zinc−adeninate columns (A) which are linked together into a 3-D framework by biphenyldicarboxylate linkers to generate a material with 1-D channels along the *c* crystallographic direction (B) ($Zn^{2+}$, dark blue; C, dark gray; N, light blue; O, red; H omitted for clarity).

Overall, the framework structure is anionic, and dimethylammonium cations (the product of DMF decomposition) as well as DMF and water guests reside in the channels, as determined by elemental analysis (EA) and thermogravimetric analysis (TGA). The TGA data reveal a weight loss of 26% from room temperature to 125 °C, which can be attributed to the loss of solvent guest molecules. Thereafter, we observe a small weight loss (2.8% at 180 °C) prior to decomposition, which corresponds to the loss of dimethylammonium cations. Solvent exchange experiments performed on the as-synthesized material reveal that the DMF and water guest molecules can be completely exchanged from the pores without loss of framework crystallinity. Indeed, bio-MOF-1 maintains its crystallinity after soaking for several weeks in various organic solvents, water, and, importantly, biological buffers such as phosphate-buffered saline (PBS buffer), as evidenced by powder X-ray diffraction (PXRD) experiments (see Supporting Information). TGA data for chloroform-exchanged samples revealed a region of thermal stability following the initial loss of solvent guest molecules. Collectively, these results prompted us to evaluate the permanent porosity of bio-MOF-1. Nitrogen adsorption studies yielded a type-I isotherm characteristic of a microporous material (Figure 2A). The BET surface area is ~1700 $m^2/g$.

The anionic nature of bio-MOF-1 pointed toward its potential utility as a material for the storage and release of cationic drug molecules. We reasoned that cationic drugs could be loaded into the pores via cation exchange with the dimethylammonium cations. Exogenous cations in biological fluids could then affect the controlled release of the cationic drug molecules from the pores.



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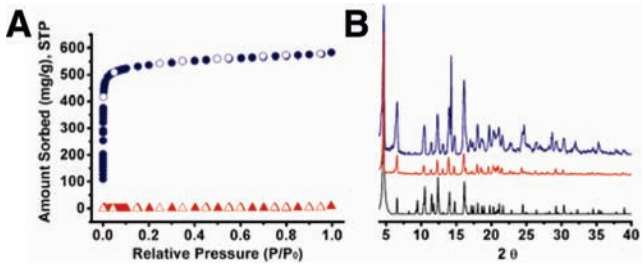


***Figure 2.*** (A) $N_2$ adsorption isotherms (77 K) for as-synthesized bio-MOF-1 (blue circles; filled adsorption, empty desorption) and procainamide-loaded bio-MOF-1 (red triangles; filled adsorption, empty desorption). (B) X-ray powder diffraction patterns for bio-MOF-1 (black, simulated; red, as-synthesized material; blue, procainamide-loaded material).

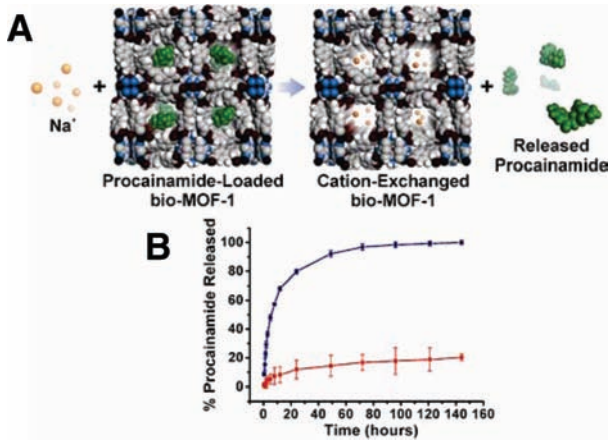


***Figure 3.*** (A) Scheme depicting cation-triggered procainamide release from bio-MOF-1. (B) Procainamide release profiles from bio-MOF-1 (blue, PBS buffer; red, deionized nanopure water).

For our initial studies, we chose to study storage and release of procainamide HCl, an antiarrythmia drug. Procainamide HCl has a short half-life in vivo and must be dosed every 3−4 h.[8] It is therefore an ideal candidate for controlled release administration, and several controlled release formulations are currently available.[9] Procainamide HCl was introduced into the pores of bio-MOF-1 through a cation exchange process (see Supporting Information) which does not affect the crystalline integrity of the material (Figure 2B). Complete loading (0.22 g/g material) was achieved after 15 days, as determined by elemental analysis, TGA, and gas adsorption studies (Figure 2A and Supporting Information). The procainamide-loaded material was formulated as $Zn_8(ad)_4(BPDC)_6O{\bullet}3.5(\text{procainamide-}H^+)$, $1.5Cl^-$, $16.5H_2O$ (Supporting Information). We estimated that ~2.5 procainamide molecules per formula unit reside in the pores, while the remaining procainamide molecules likely adhere to the exterior surfaces of the material.

Because of the ionic interactions between procainamide and bio-MOF-1, cations can be used to trigger procainamide release from the framework (Figure 3A). To determine the release profile, we placed a sample of the procainamide-exchanged material in 0.1 M PBS buffer (pH = 7.4) and monitored the release of procainamide via HPLC. At each time point, aliquots of buffer were removed from the buffer/bio-MOF-1 suspension and replaced with fresh buffer. The aliquot was then analyzed for procainamide. Steady procainamide release was observed over the course of 20 h, and complete release was realized after 72 h (Figure 3B). The crystalline integrity of the framework is maintained throughout the release process, as evidenced by PXRD studies (Supporting Information).

To verify that procainamide release was mediated by the buffer cations, we performed a control experiment in which drug-loaded bio-MOF-1 was placed in nanopure water (18.2 mΩ), and the solution was assayed for procainamide content in the same fashion as described above. In this case, only 20% of the procainamide was released, which likely corresponds to the molecules which are associated to the exterior surfaces of bio-MOF-1.

In conclusion, we have shown that a permanently porous bio-MOF can be constructed using biomolecular building blocks. Further, we have exploited the anionic nature of this bio-MOF for the storage and release of an important cationic drug molecule. To our knowledge, this is the first example of cation-triggered drug release from a metal−organic framework and also the first demonstration of a potential biomedical application for an MOF constructed with biomolecule building blocks. We expect that construction and study of bio-MOFs will become increasingly important as more biomedical applications of MOFs are uncovered.

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**Supporting Information Available:** Experimental procedures, crystallographic data, and additional supporting data. This material is available free of charge via the Internet at http://pubs.acs.org.

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