

Biomedical Applications of Metal Organic Frameworks

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ABSTRACT: We have witnessed a rapid growth in the field of a new nanoporous material group, metal organic frameworks (MOFs), over the past decade. MOFs possess a wide array of potential applications in chemical engineering, chemistry, and materials science, including gas storage, gas separation, and catalysis. One of the areas MOFs started to appear recently is biomedical applications. The unique physical and chemical characteristics of MOFs make them promising candidates for drug storage and drug delivery, nitric oxide storage and delivery, imaging, and sensing. In this review, we outline the recent progress of using MOFs as a promising platform in biomedical applications due to their high drug loading capacity, biodegradability, and versatile functionality. We also demonstrate the potential of MOFs for continuous development and implementation in biomedical applications by discussing issues including stability, toxicology, and biocompatibility. Although significant progress has been made in utilizing MOFs for biomedical applications, further improvements must still occur before MOFs can become viable therapeutics options.

1. INTRODUCTION

Nanoporous materials have attracted the interest of both academia and industry in various applications such as gas storage, gas separation, shape/size selective catalysis, drug storage and delivery, imaging, and sensing. Metal organic frameworks (MOFs) can be considered as a relatively new crystalline nanoporous material family including thousands of different structures. MOFs are self-assemblies of metal ions which act as coordination centers and organic ligands which act as linkers between metal centers. MOFs, one of the most exciting recent developments in nanoporous material science, have been also termed as coordination polymers, hybrid organic–inorganic materials, metal organic polymers, or porous coordination networks in the literature. Although they have been known since 1965, the interest in this field was kindled in late 1999 when MOFs were synthesized based on the concept of reticular design.¹ The unique combination of high porosity, lack of nonaccessible bulk volume, very large surface areas, wide range of pore sizes and topologies, and infinite number of possible structures made MOFs attractive alternatives to the traditional nanoporous materials in many scientific and industrial fields.^{2,3}

MOFs have attracted a great deal of attention in the past decade and the number of publications related with MOFs has increased remarkably (Figure 1). Most of the MOF research is experimental in nature and directed to synthesis of new structures. Several reviews exist for experimental synthesis and characterization of MOFs.^{4–10} A large number of molecular modeling studies have been conducted specifically in the area of gas storage and gas separations, which can be considered as the most mature application areas of MOFs.^{11–17} Interesting physical and chemical properties of MOFs make them also promising candidates in applications of drug storage and delivery,¹⁸ sensors, and luminescent materials;¹⁹ however these areas have not been explored as broadly as gas storage and gas separation applications in the literature. In this review, we examine the current state of the knowledge surrounding the possibility of using MOFs in biomedical applications. In the next section, synthesis and structural properties

of MOFs are briefly described, while the following sections focus on the use of MOFs in drug storage and delivery, nitric oxide (NO) storage and delivery, imaging, and sensing. In each section, we first provide a brief assessment of the current state of these applications and then list both the opportunities and challenges of using MOFs in biomedical applications to get insights into whether MOFs can play a useful role in this area.

2. SYNTHESIS, STRUCTURES, AND PROPERTIES OF MOFS

MOFs are essentially formed with a building-block approach by connecting metal ions with organic linkers as can be seen in Figure 2. Rowsell and Yaghi²⁰ mentioned that three inherent attributes are required to label a solid as a MOF: strong bonding providing robustness, linking units, and geometrically well-defined structure which implies that these solids must be highly crystalline. MOFs typically have low density ($0.2–1\text{ g/cm}^3$), very high surface area ($500–4500\text{ m}^2/\text{g}$), high porosity, and reasonable thermal and mechanical stability. The greatest advantage of MOFs over other well-known nanoporous materials such as zeolites and carbon nanotubes is the ability to tune the structure and functionality of MOFs directly during synthesis. This tunability is significantly different from that of traditional zeolites whose pores are confined by rigid tetrahedral oxide skeletons that are difficult to alter. By choosing appropriate building blocks during synthesis, solids with cavities of predefined shapes and functionalities can be formed for a desired application. This type of conceptual design approach is known as reticular synthesis.^{20,21} For example, Figure 3 shows the unit cell structure of one of the most widely studied MOFs in the literature, isoreticular metal organic framework-1 (IRMOF-1). This MOF has zinc oxide clusters as the metal corners and it is a three-dimensional cubic network

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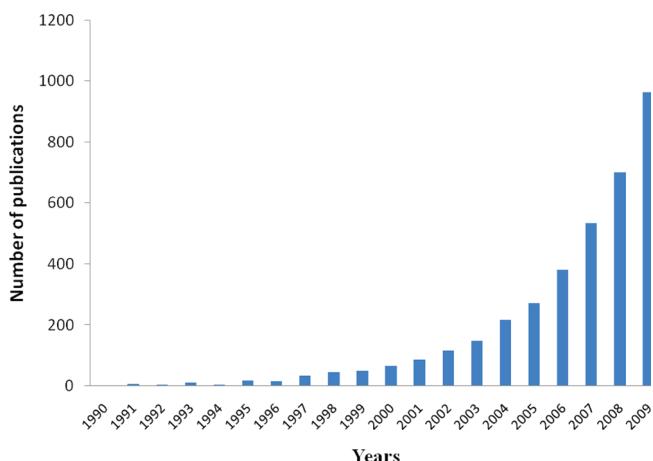


Figure 1. Number of publications featuring the term “metal organic frameworks” in their topics (Source: ISI Web of Science, retrieved December, 3 2010).

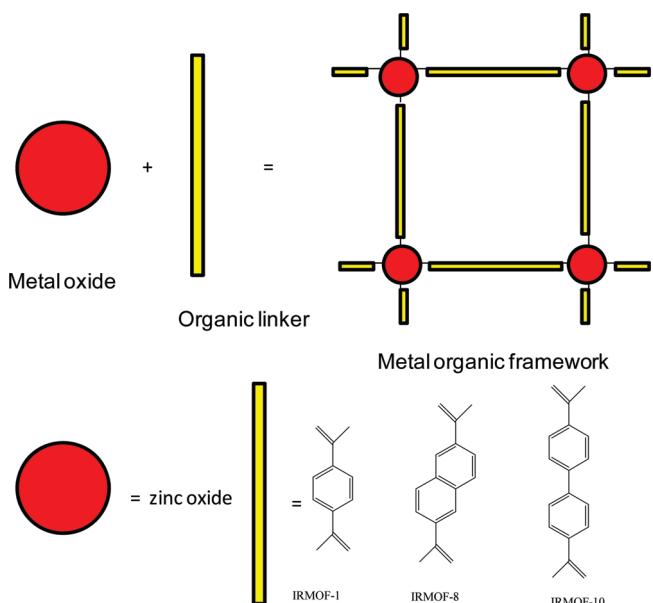


Figure 2. Building blocks of metal organic frameworks.

connecting the large cages at the center of each unit cell. Other IRMOF materials share the same octahedral $Zn_4O(CO)_2$ clusters linked by different organic dicarboxylate linkers. As Figure 3 demonstrates, by changing the organic linker type different IRMOFs named as IRMOF-8, IRMOF-10, and IRMOF-14 can be obtained.²² Variations in the organic linkers not only changes the pore size but also generates materials with different chemical functionalities and affinities for guest molecules.²³ For example, the type of organic linkers in IRMOFs affects the adsorption and diffusion of hydrogen significantly in the pores of the material.²⁴

Thousands of different MOFs have been synthesized and categorized in the Cambridge Structural Database (CSD) to date.^{25–29} This number of course represents only a small fraction of imaginable materials due to the large variety of possible linker and corner unit combinations. The wide choice of metal corners and organic linkers offers a theoretically infinite number of materials with a broad range of structural properties in addition

to chemical, optical, magnetic, and electrical properties. The enormous numbers of distinct MOFs that are known present both a challenge and an opportunity for implementation of MOFs in practical applications. The wide range of available pore sizes, topologies, and functionalities strongly suggests that existing MOFs will have useful properties in several fields of biomedical applications. On the other hand, these hybrid inorganic–organic compounds are a growing area of research and it is still a challenge to predict which MOF among thousands of candidates will be appropriate for a specific biomedical application.

Many MOFs can be synthesized easily and quickly at low cost. MOFs are generally synthesized by hydrothermal or solvothermal techniques in which crystals slowly grow from a hot solution of metal precursor.^{1,21,27,29} One important issue is the activation of MOFs after synthesis. Solvents used during synthesis usually remain in the pores of the materials, and usually activation by heating is required to remove these solvent molecules. Studies have shown that activation at elevated temperatures can cause sample decomposition, whereas activation at lower temperatures greatly minimizes the danger of reducing metal ions.³⁰ There have been continuous efforts to improve the synthesis and activation of MOFs since obtaining a material that is free of defects and solvent molecules is of paramount importance for guest uptake performance of MOFs in gas storage and drug loading. Some MOFs have unsaturated metal sites, which are also referred to as “open metal sites”, on the walls of the pores. These open metal sites are available to bind guest molecules after activation. Both experiments and molecular simulations have shown that the existence of open metal sites has a pronounced effect on the guest adsorption.^{31–33} MOFs are generally characterized by X-ray since these materials are highly crystalline and porous. Their surface areas are calculated via nitrogen adsorption experiments. Characterization of guest molecules in the pores of MOFs after an uptake experiment is generally done by infrared, Raman spectroscopy, and/or UV-vis.

Many different variations of MOFs have yielded the appearance of subgroups in the past several years. Cote and co-workers constructed porous crystalline covalent organic frameworks (COFs) solely from light elements such as H, B, C, N, and O that are known to form strong covalent bonds in well established and useful materials such as diamond, graphite, and boron nitride.³⁴ COFs have been studied for gas storage, photonic, and catalytic applications due to their lightweight structures. These materials have rigid structures, exceptional thermal stabilities (up to 600 °C), and low densities and they exhibit permanent porosity with specific surface areas surpassing those of well-known zeolites and porous silicates.^{34,35} Another subgroup of MOFs is zeolite imidazolate frameworks (ZIFs), which have zeolite framework topologies in which all tetrahedral atoms are transition metals, and all bridging ones are imidazolate units.³⁶ ZIFs also show high thermal stability and remarkable chemical resistance to organic solvents. For example, Park et al.³⁶ reported that high thermal stability of ZIFs (up to 550 °C in N₂ atmosphere) is well beyond that of the permanently porous cubic structure of IRMOF-1, which decomposes at 450 °C in N₂ atmosphere. Mantion et al. recently synthesized the first peptide-based MOF, a metal peptide framework (MPF), constructed from an oligovaline peptide family.³⁷ Metal peptide frameworks (MPFs) are designed to be “bioinspired” analogs to MOFs in which the linker is a peptide. Due to the unlimited structural diversity offered by peptide chemistry, it is likely to witness synthesis of new MPFs in the near future.

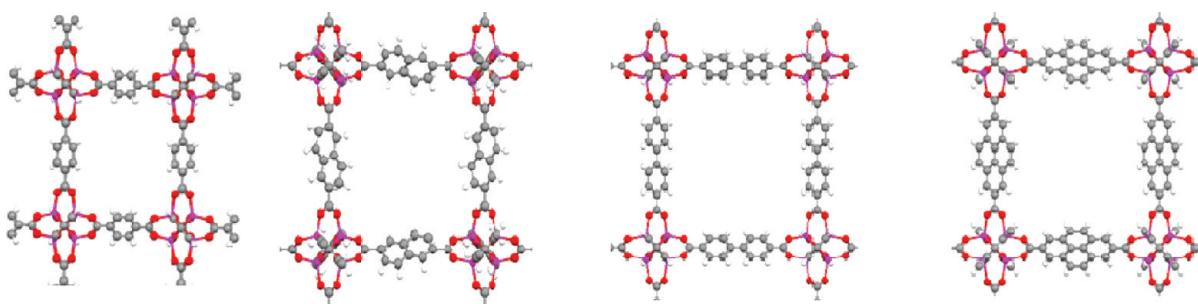


Figure 3. Unit cell crystal structures of IRMOF-1, IRMOF-8, IRMOF-10, and IRMOF-14 viewed along the [100] direction (from left to right). Zn: violet, O: red, C: gray, and H: white.

MOFs can also be arbitrarily categorized as rigid or flexible. The rigid ones possess permanent porosity and robust porous frameworks similar to inorganic porous materials. The flexible MOFs possess dynamics and respond to external factors such as guest molecules, temperature, and pressure. Structural flexibility, also known as “breathing”, allows these MOFs to reversibly modulate their pore size according to the guest molecules adsorbed into the pores, therefore these MOFs are considered to be promising in applications of molecular sieving and sensing.^{15,38} MOFs can be further categorized as catenated, interpenetrated, or interwoven MOFs. In catenation, two or more identical frameworks are intergrown at the expense of pore volume. In the interpenetrated MOFs, the networks are maximally displaced from each other, whereas in interwoven MOFs they are minimally displaced and show close contact which may result in mutual reinforcement. Studies show that catenated MOFs can give better adsorption properties compared to their counterparts.^{39,40}

One of the main issues to be discussed when considering the use of MOFs in biomedical applications is their stability. Because there are thousands of different MOF structures, it is hard to make a general comment on the stability of MOFs. For example, one of the most widely studied MOFs, IRMOF-1, is quite unstable under humid environment. Molecular dynamic simulations and experiments have shown that the framework of IRMOF-1 collapses at water content of 3.9% and higher because of the replacement of oxygen atoms of IRMOF-1 by oxygen atoms of water in the Zn coordination shells.^{41–43} On the other hand, Ni-CPO-27 which was left in bovine serum for days showed only a small amount of dissolution. After 4 days, less than 10% of this MOF was dissolved in the serum.⁴⁴ Horcajada et al.^{45,46} showed that Fe-MIL-100 and Fe-MIL-101 are stable in the biological solutions for extended periods without any deterioration in their performance for drug delivery purposes. Park et al.³⁶ observed that both ZIF-8 and ZIF-11 are able to maintain their crystal structures in water at 50 °C for 7 days. However, only ZIF-8 maintained its structure for 7 days in boiling water, whereas ZIF-11 was transformed to another crystalline material after 3 days.³⁶ Therefore, it could be concluded that the behavior of MOFs in solutions varies widely from materials that irreversibly degrade due to water under mild conditions to examples that are highly stable in boiling water or in biological solutions.

Another property of MOFs which has to be taken into account is toxicology since MOFs contain transition metal ions. Toxicology of materials is of paramount importance specifically when these materials are utilized in health, biomedical, or biological applications. Hinks et al.⁴⁴ reported that iron fumarete, which has the same chemical composition as the MOF designated Fe-MIL-88A, is approved as an oral iron supplement. This approval

supports the optimistic view on toxicology of MOFs. Toxicology studies on Fe-MIL-88 and Fe-MIL-101 indicated similar results.⁴⁴ It is important to note that the toxicology studies of MOFs have started recently and those carried out so far specifically on carboxylate materials are encouraging. More research is needed to get further insight into the use of MOFs in healthcare applications. We begin our discussion on potential use of MOFs in biomedical applications with one of the most promising fields: drug storage and delivery.

3. MOFS AS DRUG DELIVERY VEHICLES

One of the most important challenges in drug delivery research is the efficient delivery of drugs in the body using nontoxic nanocarriers. Some of the requirements for an efficient therapy with nanocarriers are to (1) control the release and avoid the “burst effect”, (2) control matrix degradation and engineer its surface, (3) be detectable by various imaging techniques, (4) efficiently entrap drugs with high loading capacity. In addition to these requirements, toxicity and biocompatibility are the two other important criteria related to the material considered as a potential novel drug carrier. For example, some metals are known to be highly toxic yet they still exist in appreciable amounts in the body. For example, hemoglobin contains iron which is about 22 μm in the blood, whereas others such as copper (68 μm), manganese (180 μm), zinc (180 μm), and nickel (2 μm) are found in tissue.⁴⁷ Currently, various materials such as liposomes, nano-emulsions, nanoparticles, functional hydrogels, or micelles are being used as drug delivery vehicles.^{47–53} These delivery routes can be classified as organic systems and inorganic systems. Even though organic systems have the advantage of providing biocompatibility and the ability to uptake many drugs, a controlled release mechanism is usually missing. Inorganic delivery materials such as mesoporous silica and silicon can deliver the adsorbed drugs in a more controlled manner due to their porous and ordered network; however, they have less drug loading capacity. Therefore, better routes are necessary to address the limitations of the current techniques.

MOFs can be regarded as optimal drug delivery materials due to the possibility of adjusting the framework’s functional groups and tuning of the pore size. Even though the major interest in MOFs has been in the area of high-density gas storage for potential use in separations, fuel cells, and other energy-related applications, recent reports suggest that MOFs may have a significant role in drug delivery (see Figure 4a and b). The ability to engineer controlled localized delivery of drugs might both contribute to the efficiency of the treatment and reduce side effects.

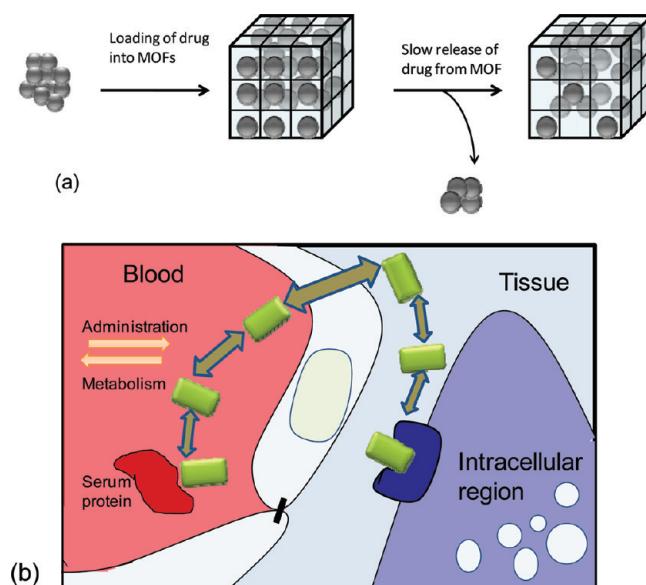


Figure 4. (a) Generalized scheme for the use of MOFs as drug delivery vehicles. (b) *In vivo* conditions involved in the slow release of drugs.

The first group of MOFs considered as potential drug delivery systems is the MIL (Materials of Institut Lavoisier) family which was developed by Ferey and colleagues.⁵⁴ The MIL family, synthesized from trivalent metal centers and carboxylic acid bridging ligands, is a very promising family of MOFs in drug delivery due to their large pore sizes (25–34 Å), outstanding surface areas (3100–5900 m²/g), and the possibility for further functionalization.

Organic materials (such as carboxylates, imidazolates, or phosphonates) in the hybrid structure of MOFs provide biocompatibility and capacity of a large amount of drug uptake, while inorganic groups may be optimized for controlled release profiles.³⁸ Moreover, the adaptation of porosity to the shape of the guest molecule is possible for some MOFs due to their high structural flexibility.^{55,56} However, the design of MOFs in the mesoporous range is crucial, as small pore size of MOFs in the microporous range limits the uptake and drug loading capacity.⁴⁶ To this end, Horcajada et al. have prepared MOFs MIL-100 and MIL-101 for the delivery of ibuprofen with well-defined structure and ordered porosity. MIL-100 contains pore diameters of 25–29 Å with pentagonal window openings of 4.8 Å, and hexagonal windows of 8.6 Å. MIL-101, on the other hand, contains 29–34 Å pore size with a large window opening of 12 Å for the pentagonal and 16 Å for the hexagonal windows. The authors found that MIL-100 could uptake 0.35 g of ibuprofen/g of dehydrated MIL-100, whereas MIL-101 could uptake 1.4 g of ibuprofen/g of dehydrated MIL-101. The fact that ibuprofen could fit in both pentagonal and hexagonal windows of MIL-101, but not into the smaller pentagonal window of MIL-100, resulted in higher loading capacities with MIL-101 which underscores the importance of materials' pore size in drug loading.³⁸ Apparent loss of crystallinity or decomposition of the framework structure was not observed as evidenced by X-ray diffraction even at these high drug loadings. The authors monitored the kinetics of ibuprofen release by using HPLC in a simulated body fluid solution. Duration of desorption was also longer by 3 d for MIL-101 compared to MIL-100. The steady release of the drug was observed during the first 8 h for MIL-101, and the release was complete at

the end of 6 d. The elongated delivery time was attributed to the π–π interactions between the aromatic rings and the ibuprofen. Because these MOFs contain toxic chromium, a less toxic analog, Fe-MIL-101, has been developed as a biocompatible alternative which may be a more appropriate drug carrier.⁵⁷

Horcajada et al. also studied drug delivery from a flexible MOF, MIL-53, which has a “breathing effect” due to its capability to expand its structure upon heating (Figure 5a).⁴⁵ The authors also found that the aluminum and chromium MIL-53lt (lt = low temperature) solids exhibited a reversible pore opening which involves atomic displacements by 5.2 Å upon dehydration, whereas the iron analogue^{58,59} opened its pores during the adsorption of molecules. The fact that Al and Cr solids undergo structural change upon dehydration was explained by the formation of hydrogen bonds between the water molecules and the inorganic hydrophilic parts of the pore.⁶⁰ The complete delivery of ibuprofen from MIL-53 took approximately 3 weeks, where 20 wt % of ibuprofen loading was achieved at high temperature within a maximum volume of 1500 Å³ (Figure 5b). The long duration of delivery was explained by the flexibility of the material to bend around the drug molecules such that bonding interactions would be maximized and steric hindrance would be minimized.⁴⁵ Comparison of the release profile of ibuprofen through different MOF structures has shown that the longest duration of delivery of this drug was maintained for about 20 d in MIL-53 compared to that in MIL-101, MCM-41_{Prop-NH₂}, and MCM-41, where the delivery of the drug was maintained for 6, 5, and 1 d, respectively (Figure 6). Here, it is important to note that MCM-41 is one of the most widely studied inorganic compounds for drug delivery and MCM-41 modified with aminopropyl groups (MCM-41_{Prop-NH₂}) has enhanced drug delivery properties compared to its counterpart.^{61–63}

Another interesting biomedical application of porous MOFs includes materials incorporating simple biomolecules and biocompatible metal cations in their structures (also known as bioMOFs). These permanently porous MOFs have been constructed with rigid biomolecules as building blocks, and have stable, crystalline structure in biological buffers for several weeks. McKinlay and co-workers⁶⁴ recently discussed the possibility of directly introducing a bioactive molecule as the linker or a bioactive metal as the inorganic part to form a bioMOF material, and commented that imaging properties could pave the way for the use of bioMOFs for theranostics. The intrinsic anionic nature of MOFs allowed the absorption of cationic drugs, and furthermore, cations from biological buffers could be used for controlled release of the adsorbed drug molecules from the pores. This recent study by Rosin and colleagues represents the first example of cation-triggered drug release from a MOF structure, and demonstrates the potential biomedical application of a MOF constructed with biomolecule building blocks.⁶⁵ The study involves anionic MOF which includes zinc(II) ions, adenine, and *para*-biphenyl-dicarboxylic acid. The anionic nature of the MOF was investigated for storage and release of cationic drugs via exchange with cations in biological fluid. The anionic MOF was loaded with 0.22 g/g of the hydrochloride salt of procainamide (an antiarrhythmia drug) and the release behavior of the MOF was monitored by HPLC. Current clinical limitation of procainamide therapy is the rapid clearance from the blood, which requires administration of this drug every 3–4 h. The authors observed the complete release of the drug at 72 h in phosphate buffered saline (PBS), whereas only 20% of the drug release was observed when drug-loaded MOF was dialyzed against pure water. This suggested that

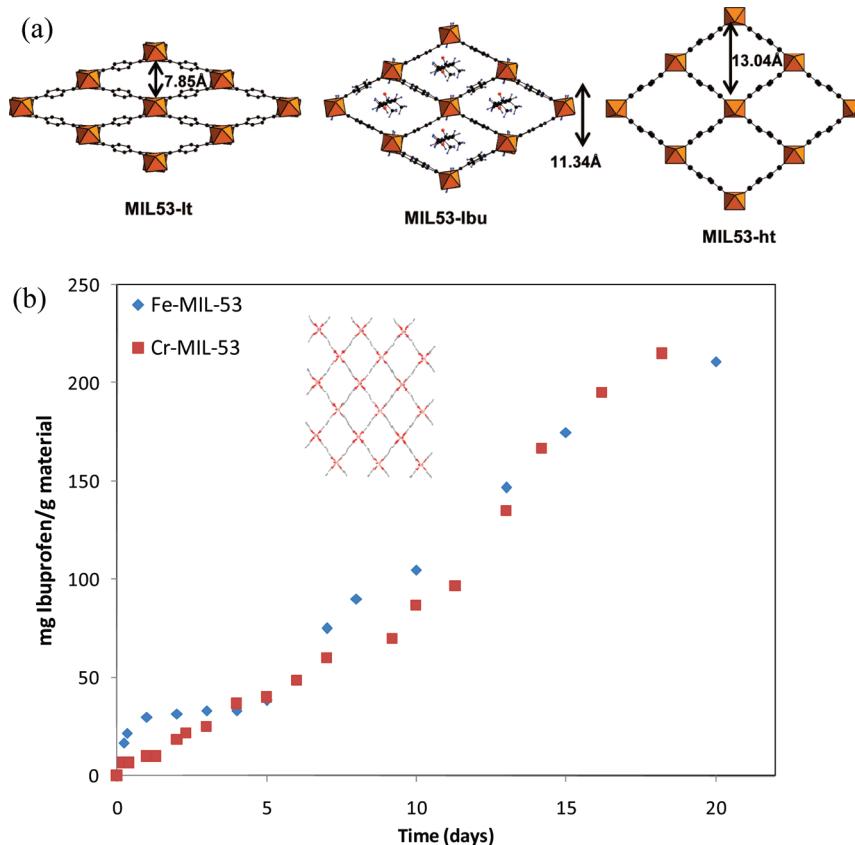


Figure 5. (a) Schematic representation of the breathing effect of the Cr-MIL-53 hybrid solid upon dehydration–hydration.⁴⁵ (b) Ibuprofen delivery from Cr-MIL-53 and Fe-MIL-53.

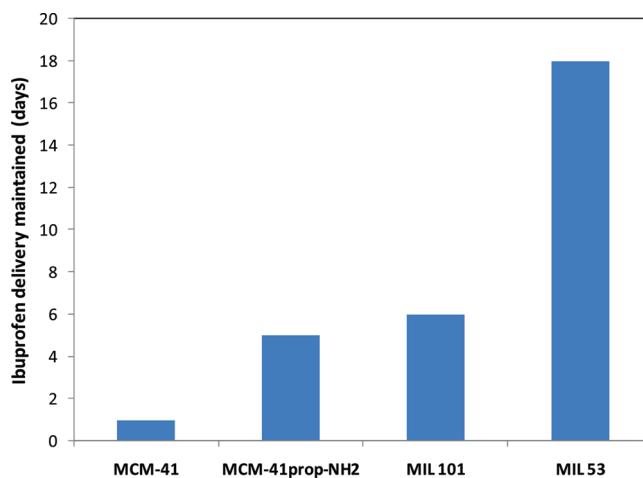


Figure 6. Comparison of ibuprofen delivery from MCM-41, MCM-41_{Prop-NH₂}, MIL-101, and MIL-53.

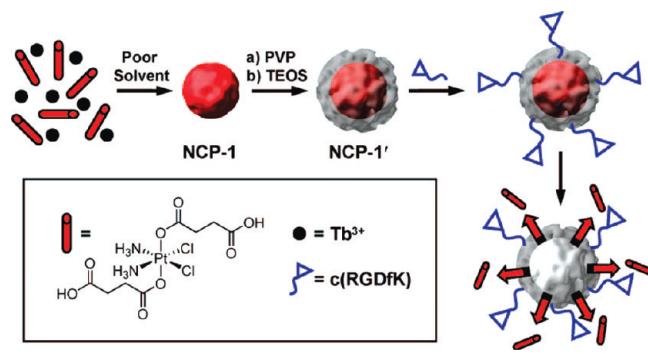
the majority of the procainamide was released by the cations present in PBS.

Although the systems discussed so far illustrate the potential of MOFs as drug delivery vehicles, bulk MOFs have limited *in vivo* application as they are not appropriate for systemic circulation. Therefore, the sizes of MOFs needed to be reduced down to the nanoscale so that nanoscale MOFs as drug carriers can circulate in the blood. Recently, Horcajada et al. synthesized nontoxic porous iron(III) based MOFs (MIL-53, MIL-88A, MIL-88Bt, MIL-89,

MIL-100, and MIL-101_NH₂) with engineered cores and surfaces as nanocarriers for the efficient delivery of challenging antitumoral and retroviral drugs (busulfan (Bu), azidothymidine triphosphate, doxorubicin, or cidofovir) against cancer and AIDS (see Table 1).⁶⁶ For example, the amphiphilic antitumoral drug Bu, widely used in combination with high-dose chemotherapy regimens for leukemias, represents a good alternative to total-body irradiation.^{67,68} The fact that Bu possesses a poor stability in aqueous solution and hepatic toxicity due to its microcrystallization in the hepatic microvenous system,⁶⁹ previous efforts toward encapsulation of Bu in known drug nanocarriers such as liposomes or polymeric nanoparticles never exceeded 5–6 wt %.⁷⁰ Recent study by Horcajada et al. demonstrated exceptionally high Bu loading in the rigid mesoporous MIL-100 (25 wt %), which is five times higher than that of the best system of polymer nanoparticles (5–6 wt %⁷⁰) and 60 times higher than with liposomes (0.4 wt %^{69,71}). Due to the lower pore volumes of microporous flexible structures of MIL-88A, MIL-53, and MIL-89, lower entrapment of Bu was obtained compared to the entrapment in MIL-100, and still the loading capacities were higher than those of the existing materials. The authors also investigated the toxicity, biocompatibility, drug-loading efficiency, and drug-release profiles for these MOFs. The cytotoxicity of MOFs has been investigated *in vitro* on mouse macrophages using MTT assay,⁷² and *in vivo* through intravenous administration of MOFs in Wistar female rats. Different indicators such as the animal behavior, body and organ weights, and serum parameters evaluated up to 3 months after injection did not show significant differences from the control group. Therefore, the lack

Table 1. Particle Size, Drug Loading (Wt %) in Several Porous Iron(III) Carboxylate Nanoparticles

	MIL-89	MIL-88A	MIL-100	MIL-53	MIL-101_NH ₂
organic linker	muconic acid	fumaric acid	trimesic acid	terephthalic acid	aminoterephthalic acid
pore size (Å)	11	6	25	8.6	29
particle size (nm)	50–100	150	200	350	120
anticancer or antiviral drugs	busulfan loading (%)	9.8	8.0	25.5	14.3
	azidothymidine triphosphate loading (%)		0.60	21.2	0.24
	cidofovir loading (%)	14	2.6	16.1	41.9
	doxorubicin loading (%)			9.1	
pain reliever	ibuprofen loading (%)			33	22

Scheme 1. Construction of Silica-Coated NCP-1 Particles and Further Functionalization with c(RGDfk)⁷³

of toxicity was confirmed with the absence of immune or inflammatory reactions. In the biomedical sense, these MOFs have been obtained in aqueous and ethanolic solutions, and can act as molecular sponges due to the possibility of encapsulating drugs with different polarities, sizes, and functional groups by immersion in corresponding solutions. These nanocarriers may open new perspectives for improved treatment with anticancer and antiviral drugs.

Rieter et al. have developed a new strategy to formulate highly degradable nanoparticles based on Pt-containing nanoscale coordination polymers (NCPs) in order to demonstrate the anticancer efficiency of Pt-based NCPs *in vitro*.⁷³ NCPs are constructed from metal ion connectors and polydentate bridging ligands, and have the potential to be engineered for a variety of applications including heterogeneous catalysis,^{36,74} imaging,⁷⁵ and sensing.⁷⁶ The nanoscale MOFs, designated as NCP-1 nanoparticles, were 58.3 ± 11.3 nm in diameter and were coated within silica for enhanced stability. These silica-coated NCP-1 particles were further functionalized with c(RGDfk), a cyclic peptide that targets $\alpha_v\beta_3$ integrin, and is overexpressed in many cancers (Scheme 1). The authors investigated cytotoxicity of the nanoparticles against HT-29 human colon adenocarcinoma cells, and observed improved cytotoxicity of the c(RGDfk)-functionalized particles, which suggested that the particles were taken up by receptor-mediated endocytosis, followed by reduction to the active Pt(II) species by reducing the cell environment. The capability of reducing a relatively nontoxic prodrug to a potent anticancer drug is promising as it delivers anticancer drugs to cancerous cells, which can reduce the dose-limiting side-effects of the existing anticancer chemotherapies. The release of Pt drug which was controlled by encapsulating the NCPs in shells of amorphous silica should allow for the design of NCPs as effective

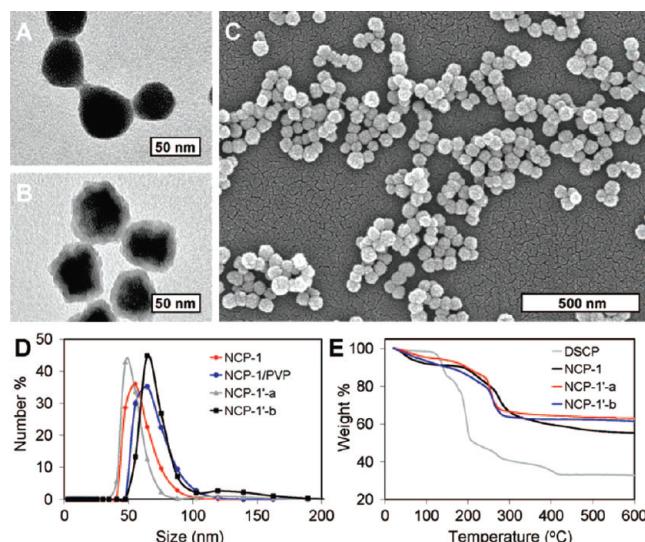


Figure 7. (A) TEM micrograph for as-synthesized NCP-1. (B) TEM and (C) SEM micrographs for polyvinylpyrrolidone (PVP)-functionalized NCP-1 intermediates, and NCP-1 treated with tetraethyl orthosilicate (TEOS) in a 4% (v/v) aqueous ammonia/ethanol mixture to yield silica-coated particles NCP-1'-b. (D) Dynamic light scattering curves for NCP-1, PVP-functionalized NCP-1, and NCP-1'. (E) TGA curves for DSCP, NCP-1, and NCP-1'.⁷⁷

delivery vehicles for a variety of biologically and medically important therapeutic or imaging agents (Figure 7).⁷³

Another novel strategy of delivering an imaging contrast agent and an anticancer drug by postsynthetic modifications of highly porous nanoscale MOFs was reported by Taylor-Pashow et al.⁷⁷ Researchers functionalized Fe(II) nanoscale MOF particles (MIL-101) with amine groups by incorporating 2-aminoterephthalic acid (NH_2-BDC) which resulted in similar MIL-101 structure or MIL-88B structure depending on the level of NH_2-BDC incorporation. The presence of amine groups was utilized for loading an optical imaging contrast agent (1,3,5,7-tetramethyl-4,4-difluoro-8-bromomethyl-4-bora-3a,4a-diaza-s-indacene (Br-BODIPY)) with a loading capacity of 5.6–11.6 wt %. Confocal microscope images of the BODIPY-loaded particles with HT-29 cells demonstrated fluorescence, which was an indication for the penetration of the particles through cell membrane and release of the fluorescent cargoes. The ethoxysuccinato-cisplatin (ESCP), which is a prodrug of cisplatin, was also loaded into amino functionalized MIL-101 by postsynthetic modification (Figure 8). Their findings established that the amino-functionalized Fe-MIL-101 nanoparticles provided an efficient platform also for the delivery

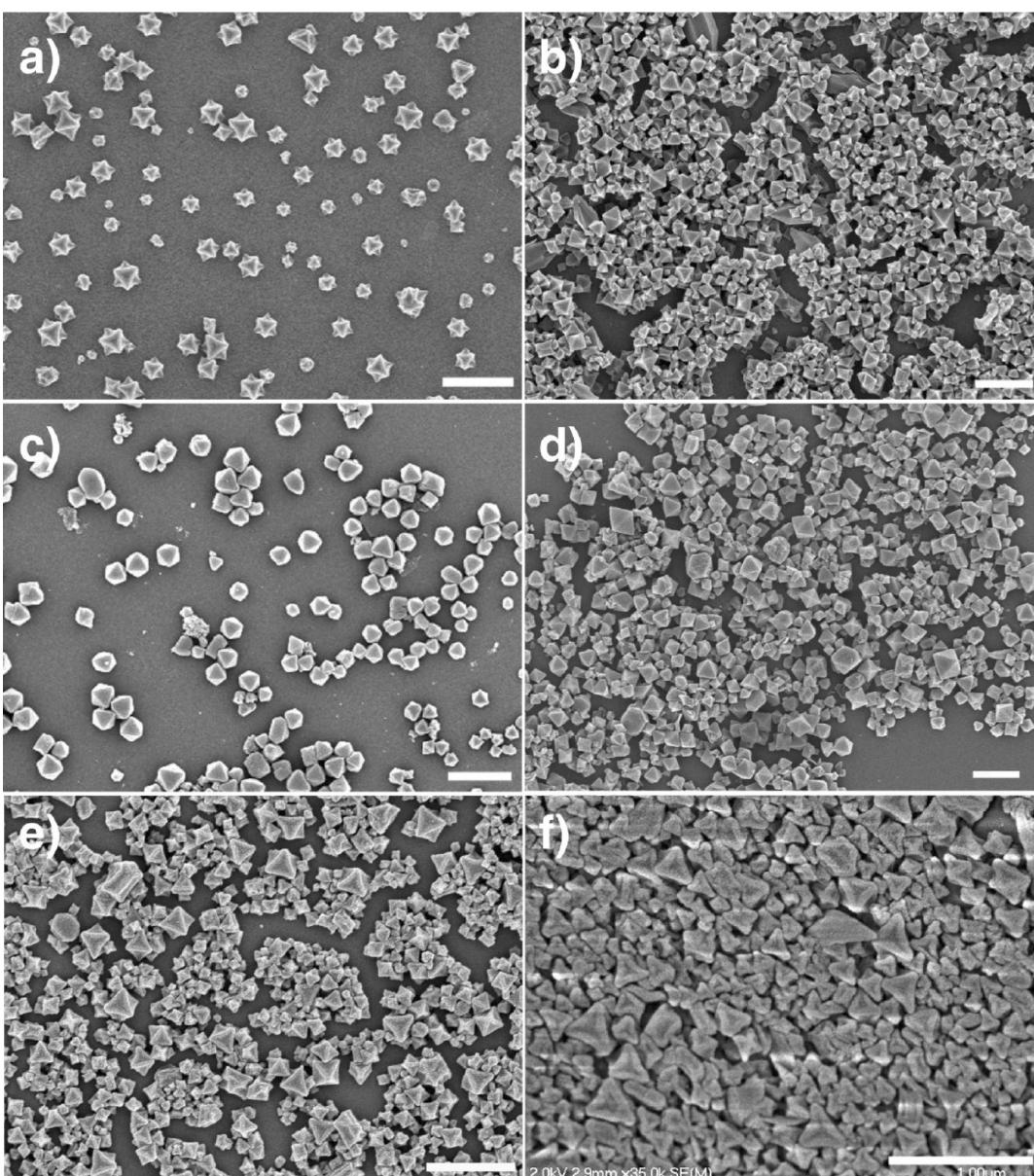


Figure 8. (a) SEM image of $\text{Fe}_3(\mu_3\text{-O})\text{Cl}(\text{H}_2\text{O})_2(\text{BDC})_3$ nanoparticles (**1**). Particles of **1** have an unusual octahedron morphology and an average diameter of ~ 200 nm. (b) SEM image of nanoparticles of **1a** with 17.4 mol % $\text{NH}_2\text{-BDC}$. (c) SEM of nanoparticles of **1a** loaded with the BODIPY dye (**1b**). SEM images show that the sizes and morphologies of the particles **1a** remain essentially unchanged after BODIPY loading. (d) SEM image of nanoparticles of **1a** loaded with $c,c,t\text{-[PtCl}_2(\text{NH}_3)_2(\text{OEt})(\text{O}_2\text{CCH}_2\text{CH}_2\text{CO}_2\text{H})]$ (ESCP) (**1c**). (e) SEM image of silica-coated nanoparticles of **1**. (f) SEM image of silica-coated nanoparticles of **1c**. SEM imaging showed no discernible change of the morphology upon subsequent coating steps. The scale bars represent $1 \mu\text{m}$.⁷³

of the ESCP prodrug with an overall payload of 12.8 wt %. These particles were further coated with silica for enhanced stability in vitro, which resulted a longer half-life of 14 h in PBS at 37 °C compared to 1.2 h of the uncoated particles. Further functionalization of silica-coated particles with cyclic peptide $c(\text{RGDfk})$ showed that these particles had cytotoxicity comparable to that of cisplatin when treated against HT-29 cells. The generality of this approach could be utilized for the design of a wide range of nanomaterials for imaging and therapeutic applications (Figure 9).

The energetic and dynamic properties of ibuprofen in mesoporous MIL-101 and UCMC-1 using molecular simulations and first-principle calculations have been also studied recently.⁷⁸ The researchers investigated the microscopic behavior of ibuprofen in

these two mesoporous MOFs. The experimental ibuprofen loading capacity agrees well with the computational model and is about four times greater than the one in silica MCM-41. Due to the existence of strong coordination between the carboxylic O atom of ibuprofen and the exposed Cr atom of MIL-101, the binding energy between ibuprofen and MIL-101 is two times as that in UCMC-1. This imposes a different spatial arrangement of ibuprofen in MIL-101 compared to the spatial arrangement in vacuum and UCMC-1. The mobility of ibuprofen has also been found smaller in MIL-101 compared to that in UCMC-1. This study highlights the importance of a clear molecular-level understanding for the development of novel drug delivery systems with better control of drug administration.⁷⁸

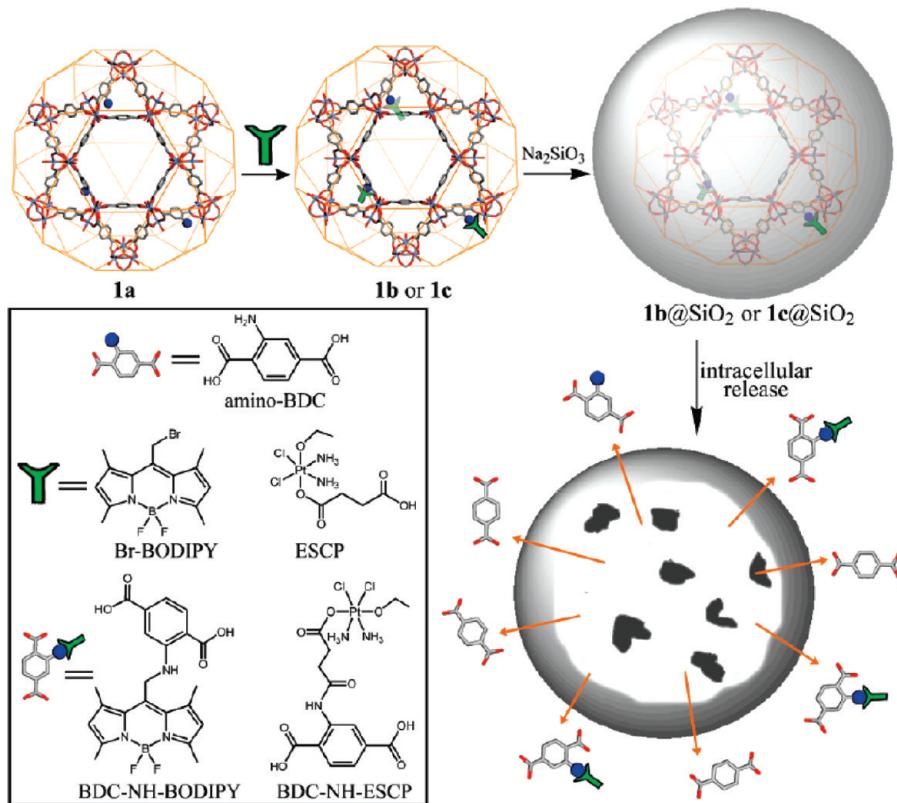


Figure 9. Covalent attachment of biologically relevant cargoes (BODIPY or ESCP) through amino groups on amino-functionalized particles of **1** (denoted as **1a**).⁷³

4. MOFS FOR NO STORAGE

MOFs have great potential in gas-storage applications due to their extremely high surface areas and porous structures. One of the important gas-storage applications in medicine is storage of nitric oxide (NO). NO is a crucial gas radical involved in various biological processes within the neuronal, immune, and vascular systems and an important neurotransmitter and neuromodulator in the central nervous system.⁷⁹ Delivery of NO from a storage material is attractive for many *in vitro* and *in vivo* antibacterial and antithrombotic applications.⁸⁰ Materials that can deliver NO are also of particular interest in preventing life-threatening complications associated with thrombosis formation at the surface of medical devices such as stents.⁸¹ Polymers and zeolites have been widely studied to deliver NO, yet many of these are found to deliver carcinogenic or pro-inflammatory side products which limited their applicability.⁸⁰ Therefore, development of new materials that can efficiently store and deliver significant quantities of NO into specific sites in the human body has vital importance. A good NO storage material should exhibit high adsorption affinity for NO, but the interaction between the storage material and gas should not be extremely high to prevent the release of NO from the storage material when it is needed. Fast kinetics and good thermal/mechanical properties are also required for storage materials so that release can occur at the desired time and rate for a certain application.

Xiao et al. performed gravimetric adsorption measurements of NO in HKUST-1 (also known as Cu-BTC).⁸² This MOF has unsaturated open metal sites that act as strong adsorption sites for NO molecules after activation. They reported adsorption capacity of 9 (3) mmol NO/g MOF at 196 (298) K and 1 bar. At

both temperatures 2.21 mmol NO/g MOF is reported not to desorb when the pressure of NO is reduced to zero. Their experiments showed that NO is released from HKUST-1 on contact with water vapor, however the total amount of NO released is around 1 μmol NO/g MOF, almost 2 orders of magnitude less than the amount initially adsorbed. McKinlay and co-workers⁸⁰ showed that CPO-27-Co and CPO-27-Ni adsorb twice as much NO as HKUST-1 at room temperature and boast almost perfect release trend of the adsorbed NO upon exposure to moisture. These two MOFs were able to release \sim 7 mmol NO/g of MOF, 7000 times higher than the amount released from HKUST-1. The strong affinity of these two MOFs toward NO is due to chemisorption of NO on the open metal sites of MOF as confirmed by IR studies. Experiments performed on MIL-53 underlined the importance of open metal sites in NO storage capacity of MOFs. Al-MIL-53 and Cr-MIL-53 do not possess open metal sites in their structure and they adsorb small amounts of NO at room temperature compared to CPO-27-Co, CPO-27-Ni, and HKUST-1 as shown in Figure 10. Adsorption isotherms of MOFs also support this idea: MOFs with open metal sites demonstrate large hysteresis on desorption of NO which indicates that NO is trapped on the open metal site, whereas NO adsorption isotherms of Al-MIL-53 and Cr-MIL-53 show little or no hysteresis.⁴⁴ Comparison among HKUST-1, CPO-27 series, and MIL-53 series highlights the fact that tunable structures of MOFs offer an advantage to control the rate of NO release for the desired biological applications. For example, antithrombogenic applications require a low flux of NO whereas higher fluxes are required for antibacterial effects.⁸³

Cohen et al.⁸⁴ incorporated diazeniumdiolate (NONOate) functional groups within MOFs using postsynthetic modification.

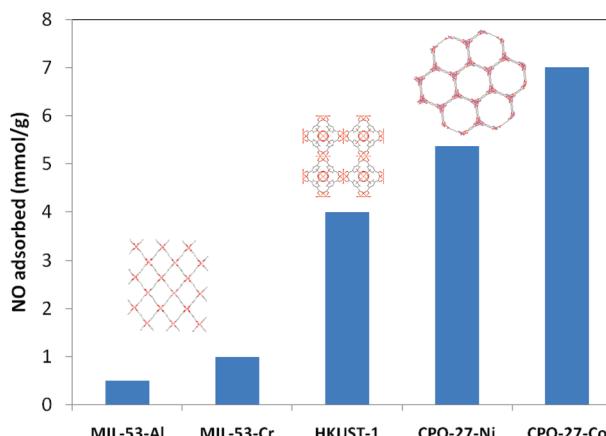


Figure 10. Experimental measurements for amount of NO adsorbed at room temperature at 1 bar in different MOFs.^{44,80,82}

as NONOate functional groups are attractive for NO release. They transformed MOFs containing pendant amines, IRMOF-3 and UMCM-1-NH₂, with NO into IRMOF-3-NONO and UMCM-1-NONO, respectively. They reported that modified MOFs visually showed no signs of degradation after treatment with NO and preserved their crystallinity. IRMOF-3-NONO (UMCM-1-NONO) released 0.51 ± 0.11 mmol (0.10 ± 0.01) NO per gram of material. IRMOF-3-NONO releases much more NO than HKUST-1, but 3.5 times less than the highest NO-releasing MOF (7 mmol NO per g of material). Results of this study demonstrated that NO release only occurs from amine-containing MOFs because structurally identical MOFs, IRMOF-1 and UMCM-1, which lack the pendant amine groups, showed no release of NO when treated under identical conditions. It is important to note that the NONOate functionality in IRMOF-3-NONO and UMCM-1-NONO shows some instability as a 20% decrease in NO release was observed when the samples were tested 10 days after the initial release study. The authors commented that this instability is not surprising since NONOate functionality within the MOF may be in its protonated form, which is more hygroscopic and less stable than the sodium salt analogs.

Because biological applications of MOFs are only starting, the number of experiments on NO storage and delivery capacity of MOF is limited to the studies we discussed above. One of the major issues raised when discussing the applications of MOFs is their stability. The requirement for the stability of MOFs for biomedical applications is that the material remain intact long enough for the delivery of the therapeutic agent. For the majority of applications related to the delivery of NO, delivery for a short period of time (a few days up to a week) is required, which seems not a difficult goal to reach based on the published studies in this area. For example, a recent study showed that CPO-27-Co and CPO-27-Ni can store NO up to 20 weeks without significant change in the amount of releasable NO,⁸⁰ which indicates that MOFs are promising candidates for NO storage given their high adsorption capacity. However, one issue that remains open is the toxicology of these MOFs, particularly CPO-27-Co. One can argue that the Zn analog of CPO series is much more suitable in terms of toxicology but it is known that some Zn-based MOFs such as IRMOFs can be unstable under humid environment.⁴¹ Experiments of Dietzel and co-workers' showed that CPO-27-Zn exhibits several phase transitions and undergoes considerable strain upon dehydration.⁸⁵ There is still a reason to be optimistic

for using CPO-27-Ni as a NO storage material since the preliminary experiments reported that ~ 5 mmol NO/g of material can be adsorbed after extensive activation of the material.

5. MOFs AS POTENTIAL IMAGING AGENTS

In the area of biomedical imaging, nanomaterials have been actively studied as new molecular probes.^{86,87} The typical nanosized imaging probes have been based on purely inorganic materials such as quantum dots, superparamagnetic metal oxides, gold nanoparticles, or nanoshells.^{88–94} MOFs as hybrid organic–inorganic materials have already shown promise in catalysis, gas storage, drug delivery, and nonlinear optics.^{95–99} For example, Li et al.¹⁰⁰ fabricated nanosheets of a fluorescent MOF, [Zn(BDC)-(H₂O)]_n, and reported that fluorescence property of this MOF is highly sensitive to ethylamine.

A recent study by Rieter et al. demonstrated the potential use of nanoscale MOFs as multimodal imaging probes designed by incorporation of suitable metal ions and organic moieties using a microemulsion-based approach.⁷⁵ This application resulted in nanoscale particle size as opposed to the macroscopic crystalline material achieved in typical MOF synthesis. In their approach, the researchers were able to synthesize nanorods and nanoplates using microemulsion of GdCl₃ and bis(methylammonium)-benzene-1,4-dicarboxylate in the cationic cetyltrimethylammoniumbromide (CTAB)/isooctane/1-hexanol/water or GdCl₃ and tri(methylammonium)benzene-1,2,4-tricarboxylate (1,2,4-BTC) in the TAB/isooctane/1-hexanol/water system, respectively. Due to the presence of Gd³⁺ centers in the nanoscale MOFs, these nanorods and nanoplates were investigated as contrast agents for magnetic resonance imaging (MRI). MRI is a powerful and noninvasive technique used to differentiate diseased tissues from normal tissues based on their varied NMR water proton signals, which occurs as a result of different water densities or nuclear relaxation rates. Therefore, when a magnetic field is applied, the capacity of metal-based MOFs to modify the relaxation times of water protons in the surrounding medium will be directly related to the relaxivity of the material. Metal ions such as Gd³⁺ are frequently used to improve image contrast by increasing water proton relaxation rates. Current metal-chelate-based agents exhibit modest longitudinal relaxivities, and require administration in large amounts in order to provide sufficient MR contrast. Rieter et al. have shown that nanorods were more efficient in enhancing water signals compared to the clinically used OmniScan. Furthermore, nanorods of ~ 100 nm long and ~ 40 nm in diameter (with $\sim 4.5 \times 10^5$ Gd³⁺/nanorod) had a modest longitudinal value (35.8 s^{-1} per mM of Gd³⁺ and $\sim 1.6 \times 10^7 \text{ s}^{-1}$ per mM of nanorod), at least an order of magnitude higher than those of Gd³⁺ containing liposomes which have been shown to be effective target-specific MR contrast agents for cancer and cardiovascular disease.¹⁰¹ These relaxivities that nanoscale MOFs exhibited were very high on a per mM of Gd³⁺ basis and per mM of nanoparticle basis which may allow their use as contrast agents depending on the MR pulse sequence. Molecular targeting of nanoscale MOFs to biomarkers that are associated with certain diseased cells should be feasible to potentially lead to a new class of target-specific multimodal imaging contrast agents.

Rieter et al. further demonstrated the possibility of surface modification and functionalization of MOF materials.⁷⁶ The authors developed a general technique to coat nanoscale MOFs with silica shells of variable thickness. These shells not only contribute to the core stability of nanoscale MOFs, but also allow for

the controlled release of metal constituents. Furthermore, the silica-coated nanoscale MOFs were functionalized for the detection of DPA which is an important molecular marker in spore-producing bacteria. Due to the tunable nature of nanoscale MOFs, this technique should allow for the synthesis of core–shell hybrid nanostructures for imaging, sensing, and drug-delivery applications.⁷⁶

The nanoscale MOFs developed via room-temperature reverse-phase microemulsion procedure allowed several metal/ligand combinations. However, such a synthetic procedure led to a gel-like amorphous material as a result of rapid and irreversible bond formation at room temperature. To obtain crystalline nanomaterials with a controlled aggregation, Taylor et al. studied surfactant-assisted synthesis of novel gadolinium nanoscale MOFs at elevated temperatures.^{102,103} Powder X-ray diffraction (PXRD), SEM, and TEM results showed that surfactant-assisted method resulted in the synthesis of two different nanoscale MOFs based on Gd and benzenehexacarboxylate moiety (bhc) building blocks. As a result of different metal–ligand coordination modes that were dependent on the pH value of the reaction medium, two nanoscale MOFs of different particle sizes and morphologies were obtained using identical building blocks. This strategy could be extended to the preparation of other new hybrid nanomaterials which will be useful for applications such as imaging, biosensing, and drug delivery. In an effort to search for optimum conditions for the synthesis of Gd-bhc-nano MOFs, authors discovered that nanoparticles with different morphologies and compositions could be obtained when reactions were carried out between GdCl_3 and mellitic acid. Powder X-ray diffraction (PXRD) studies showed that the crystal structure of nanoscale MOFs have nine-coordinate Gd centers bonded to two chelating and two bridging carboxylate groups from bhc ligands.

The first example of an iron-based MOFs as potential contrast agents has been investigated by Horcajada et al.⁶⁶ In addition to the promising results obtained with iron-based MOFs for the delivery of challenging antitumoral and antiviral drugs, iron-based MOFs have been studied as potential nanoparticle candidates for magnetic resonance imaging (contrast) agents. Authors studied *in vitro* cytotoxicity using an MTT assay, which showed low and comparable results with that of the currently available nanoparticulate systems. Magnetic resonance imaging measurements made on Wistar female rats 30 min after injection of various suspensions of an iron-based MOF, MIL-88A, have shown that the treated organs were darker than the untreated controls. The animals were monitored based on their behavior, body and organ weight, and serum parameters up to 3 months after injection. The appearance of the liver and spleen between control and treated rats were different, while 3 months after injection, the liver and spleen returned to an appearance similar to that of untreated animals. The higher spleen and liver weights observed for the treated animals compared to control groups was attributed to the fast sequestration by the reticuloendothelial organs of the nano-MOFs not protected by a polyethylene glycol (PEG) coating. The relaxivity values on the order of $50 \text{ s}^{-1} \text{ mM}^{-1}$, were considered sufficient for *in vivo* use.¹⁰⁴ The relaxivity values were related to the iron content and to the size of the nanoparticles. Therefore, when MIL-88A nanoparticles were PEGylated (bonded to polyethylene glycol), slightly higher relaxivity values were obtained compared to the non-PEGylated ones (95 versus $56 \text{ s}^{-1} \text{ mM}^{-1}$). The lack of toxicity was supported by the absence of immune or inflammatory reactions after nanoparticle administration. In addition,

the absence of activation of cytochrome P-450 suggested a direct excretion of the polyacids which was expected due to their high polarity. Finally, 150 mg of MIL-88A $\text{kg}^{-1} \text{ d}^{-1}$ was injected for 4 consecutive days to investigate *in vivo* subacute toxicity, and toxic effects were not observed up to 10 days after administration. These iron-based nanoscale MOFs are good candidates as magnetic resonance imaging (contrast) agents owing to their desirable relaxivity values and lack of toxicity.

6. MOFS FOR SENSING

MOFs having luminescent properties together with size/shape selective sorption properties can be considered as potential sensing devices. A few luminescent MOFs have been reported for ion monitoring.^{105,106} Even though MOFs have been studied for sensing various types of gases, development of MOFs that can sense oxygen, glucose, or biomolecules are of particular importance in biomedical applications, and yet this type of study does not exist in the literature. Here, some examples of MOFs as sensing materials are introduced, and potential of MOFs as sensors of biomolecules is highlighted.

Harbuzaru et al.¹⁰⁷ synthesized and studied sensing properties of a new MOF, ITQMOF-3-Eu. The good balance between absorption, energy transfer, and emission rate of this MOF allowed the fabrication of a miniaturized pH sensor prototype. MOF sensor responses were in the pH range of 5–7.5, which is required for work with biological fluids such as blood and culture cell media. The ITQMOF-3-Eu was reported to have good thermal stability up to 573 K in air. Achmann and co-workers¹⁰⁸ studied Al-BDC, Cu-BTC, and Fe-BTC MOFs for sensing applications in the gas phase and identified Fe-BTC as an appropriate sensor material for the detection of hydrophilic gases like ethanol, methanol, or humidity. The authors identified Fe-BTC as a selective online humidity sensor material for the detection of hydrophilic gases such as ethanol, methanol, or $\text{H}_2\text{O}_{(g)}$. The material was tested within the temperature range of 120–240 °C, where the material did not show any cross sensitivity toward O_2 , CO_2 , C_3H_8 , NO , and H_2 . Studies are underway to investigate differently doped MOF materials for evaluating the influence of special dopants on the sensor effect.

Allendorf et al. recently demonstrated the concept of stress-induced chemical detection through integration of a thin film of HKUST-16, a MOF composed of Cu(II) ions linked by benzene-tricarboxylate (BTC) ligands [$\text{Cu}_3\text{BTC}_2(\text{H}_2\text{O})_3$]_n with a microcantilever surface.¹⁰⁹ The authors showed that the energy of molecular adsorption within a porous MOF structure could be transformed to mechanical energy which could be utilized to create a responsive, reversible, and selective sensor. Even though the material still needs to be optimized, it is promising to be selective in sensitivity toward alcohols and CO_2 , while being insensitive to N_2 and O_2 . Further, the authors expect that higher sensitivities could be achieved using MOFs exhibiting greater structural flexibility.¹⁰⁹

Another recent technique developed by Lu and Hupp is among the few examples of reports of MOF-based sensing, and relies upon the changes in the refractive index of the sensing material.¹¹⁰ They have constructed MOF-based Fabry–Pérot devices that function as selective sensors for chemical vapors and gases. This device was based on fabrication of a simple, controllable and effective ZIF-8 films, which was obtained simply by immersing glass or silicon slides in a freshly prepared methanolic solution of 2-methylimidazole and $\text{Zn}(\text{NO}_3)_2$ at room temperature

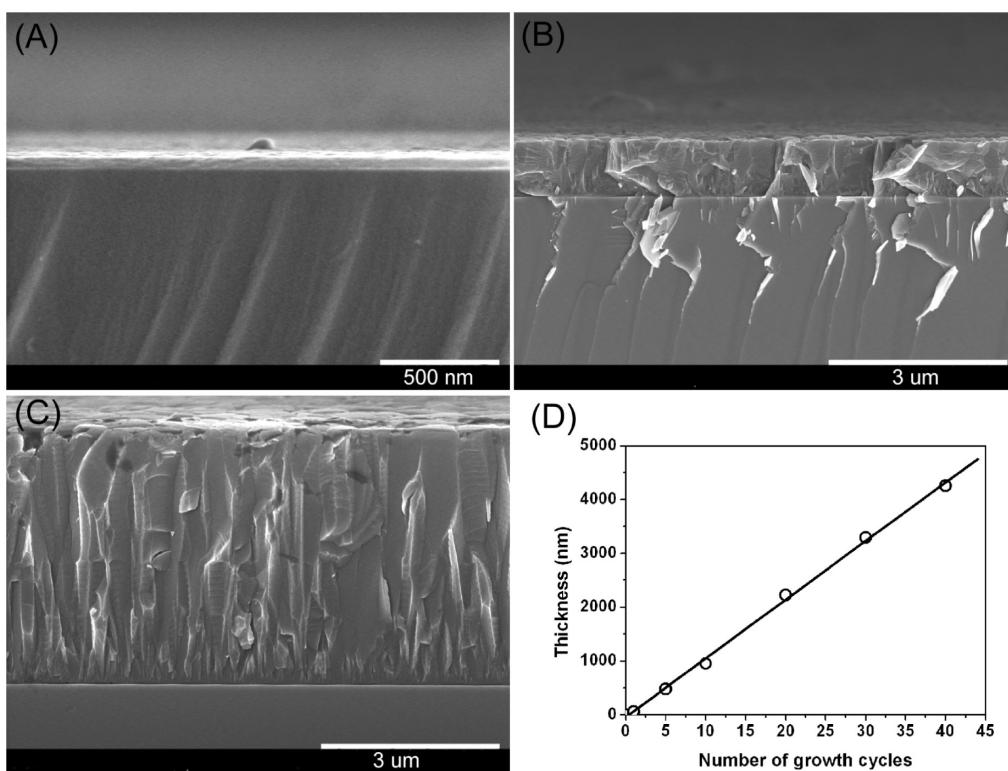


Figure 11. SEM images for the cross-sectional view of ZIF-8 films grown on silicon substrates with different numbers of cycles: (A) 1, (B) 10, and (C) 40. (D) Thickness of ZIF-8 film plotted as a function of numbers of growth cycles.¹¹⁰

(Figure 11). The advantages of this method include gentle reaction conditions (room temperature), rapid growth rate (~ 100 nm/30 min), good control over thickness (~ 100 nm/cycle), does not require surface modification of substrates, and allows for easy removal of solvent (methanol).

A thin film of $\text{Cu}_3(\text{BTC})_2(\text{H}_2\text{O})_3 \cdot x\text{H}_2\text{O}$ (HKUST-1) MOF on the gold electrode of quartz-crystal microbalance (QCM) was prepared by direct growth on a 11-mercaptopoundecanol self-assembled monolayer (SAM) by Biemmi and colleagues.¹¹¹ In their study, the authors addressed several key issues related to successful sensor design, including the formation of stable and compact thin films, interfacing with an appropriate transducer concept for sensitive detection, and characterization of the porous films by means of molecular sorption experiments. The attractive structural features of HKUST-1 include the available coordination sites on the constituent Cu(II) centers which have potential for selective adsorption of certain molecules. Water vapor sorption measurements recorded at different temperatures allowed the authors to directly characterize the sorption properties of the thin film grown on the electrode of the QCM-device.

7. CONCLUSION

Unique properties of MOFs are likely to make them promising material candidates in various applications and growing literature on synthesis and applications of MOFs support this forecast. MOFs currently play an important role in the areas of gas storage and gas separations, catalysis and these are the most mature fields of MOF applications. Research on biomedical applications of MOFs is gaining momentum and this emerging new class of porous materials is likely to replace the traditional nanoporous materials in drug delivery and storage in the future. However, lack

of data concerning critical issues such as the stability of MOFs under humid environment, toxicology and degree of biocompatibility may slow down implementation of MOFs in medicine. Early studies of toxicology of MOFs are encouraging and these fascinating materials may be suitable for further trials in different medical applications. Finally, the MOF research community has made a great progress in the past decade, and the future of the field seems very bright with the new opportunities that will become available for MOFs.

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Abbreviations

- Bu = Busulfan
- BTC = benzenetricarboxylate
- CSD = Cambridge Structural Database
- COF = covalent organic framework
- CPO = coordination polymer of Oslo
- HPLC = high-pressure liquid chromatography
- IRMOF = isoreticular metal organic framework
- MCM = mobile crystalline material
- MIL = materials of Institut Lavoisier
- MOF = metal organic framework
- MPF = metal peptide framework
- MTT = 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide (MTT) viability assay
- NCP = nanoscale coordination polymers
- NO = nitric oxide
- PEG = poly(ethylene glycol)

PBS = phosphate buffered saline
 PXRD = powder X-ray diffraction
 QCM = quartz-crystal microbalance
 SAM = self-assembled monolayer
 SEM = scanning electron microscope
 TEM = transmission electron microscope
 UV-vis = ultra violet-visible spectrophotometry
 ZIF = zeolite imidazolate framework

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