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J Am Chem Soc. Author manuscript; available in PMC 2008 September 29.

Published in final edited form as:

J Am Chem Soc. 2006 July 19; 128(28): 9024–9025. doi:10.1021/ja0627444.

Nanoscale Metal-Organic Frameworks as Potential Multimodal Contrast Enhancing Agents

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Nanomaterials have been actively pursued as new molecular probes for biomedical imaging.¹ The vast majority of nano-sized imaging probes are based on purely inorganic materials such as quantum dots,² superparamagnetic metal oxides,³ and gold nanoparticles or nanoshells.⁴ Metal-organic frameworks (MOFs) are a new class of hybrid materials built from metal ions with well-defined coordination geometry and organic bridging ligands which have already shown promise in a number of applications including catalysis,⁵ nonlinear optics,⁶ and gas storage.⁷ In contrast to inorganic materials, the compositions and structures of MOFs are innumerable owing to the choice of a vast range of metal ions and organic linkers. We thus envision that new multimodal imaging probes can be designed by incorporating suitable metal ions and organic moieties into nanoscale metal-organic frameworks (NMOFs).

Although there is an extensive literature on the synthesis and characterization of bulk MOF materials, few reports have appeared on NMOFs.⁸ Wang *et al.* synthesized submicrometer-scale spherical colloids of the Pt(p-phenylenediamine) system by simply mixing the metal and organic components in aqueous solution,^{8a} whereas Mirkin *et al.* prepared spherical particles of a zinc MOF via precipitation induced by a poor solvent.^{8b} These methods are however not applicable to other metal-ligand combinations, and the amorphous nature of the resulting colloid particles prohibits a detailed understanding of these systems. Herein we wish to report a general water-in-oil microemulsion-based methodology for the synthesis of NMOFs and their preliminary evaluation as multimodal imaging probes.

Gd(BDC)_{1.5}(H₂O)₂ (**1**) nanorods (where BDC is 1,4-benzenedicarboxylate) were prepared by stirring an optically transparent microemulsion of GdCl₃ and bis(methylammonium)-benzene-1,4-dicarboxylate (in a 2:3 molar ratio) in the cationic cetyltrimethylammonium bromide (CTAB)/isooctane/1-hexanol/water system for 2 h. The nanorods of **1** were isolated in 84% yield by centrifugation and washing with ethanol and water. Scanning electron micrographic (SEM) images of **1** demonstrated the formation of nanorods of fairly uniform shape and size (Fig 1). The morphologies and sizes of the nanorods were influenced by the *w* value (defined as the water/surfactant molar ratio) of the microemulsion systems. For example, nanorods of **1** of 100 to 125 nm in length by 40 nm in diameter were obtained with *w*=5 and a Gd³⁺ concentration of 50 mM. As the *w* value was increased to 10, nanorods of **1** one to two μm in length and ~100 nm in diameter were obtained under otherwise identical conditions. We have carried out numerous syntheses and have observed very consistent morphologies and sizes for nanorods of **1** under identical conditions. The particle size of **1** was also affected by the reactant concentration and the reactant ratio. A decrease in the

E-mail: wlin@unc.edu.**Supporting Information Available:** Experimental procedures and 9 figures. This material is available free of charge via the Internet at <http://pubs.acs.org>.

concentration of reactants or a deviation of the metal to ligand molar ratio from 2:3 typically resulted in a decrease of the particle size. Powder X-ray diffraction (PXRD) studies showed that the nanorods of **1** were crystalline and had the same diffraction pattern as the bulk phase of $\text{Tb}(\text{BDC})_{1.5}(\text{H}_2\text{O})_2$.⁹ The composition of **1** was further supported by thermogravimetric analysis which showed that **1** lost the two coordinated water molecules in the 125 to 140 °C range.

To probe the generality of NMOF synthesis in reverse microemulsions, we have carried out reactions of GdCl_3 and tri(methylammonium)benzene-1,2,4-tricarboxylate (1,2,4-BTC) in the CTAB/isooctane/1-hexanol/water microemulsion system. As shown in Fig 2, irregularly-shaped, crystalline nanoplates of $[\text{Gd}(1,2,4\text{-BTC})(\text{H}_2\text{O})_3]\cdot\text{H}_2\text{O}$, **2**, with a diameter of ~100 nm and an average thickness of 35 nm were successfully synthesized with a *w* value of 15. The identity and phase purity of the nanoplates of **2** were also confirmed by PXRD and TGA results (supporting info).¹⁰ Although reverse microemulsions have been successfully used for the synthesis of a range of nanomaterials including organic polymers, semiconductors, and metal oxides, these are the first examples of NMOF syntheses in reverse microemulsions.

The presence of the Gd^{3+} centers in **1** and **2** has prompted us to examine their utility as nanoscale contrast agents for magnetic resonance imaging (MRI). MRI is a powerful noninvasive medical diagnostic technique that can differentiate normal tissues from diseased tissues based on their varied NMR water proton signals arising from different water densities and/or nuclear relaxation rates.¹¹ Complexes of highly paramagnetic metal ions such as Gd^{3+} are often administered to enhance the image contrast by increasing water proton relaxation rates. Currently available metal chelate-based contrast agents however exhibit modest longitudinal (R1) relaxivities and large quantities (several grams per patient) must be administered to provide adequate MR contrast. We rationalize that **1** and **2** NMOFs contain a large number of Gd^{3+} centers and would therefore give very large relaxivities on a per particle basis. When conjugated to targeting moieties, such nanomaterials can be effective site-specific MR contrast agents owing to their large metal payload.

Relaxivity data obtained with suspensions of **1** in water containing 0.1% xanthan gum showed that nanorods of **1** of ~100 nm in length and ~40 nm in diameter (with $\sim 4.5 \times 10^5$ Gd^{3+} /nanorod) had an R1 value of 35.8 s^{-1} per mM of Gd^{3+} and $\sim 1.6 \times 10^7 \text{ s}^{-1}$ per mM of nanorod. **1** also exhibited a transverse relaxivity (R2) of 55.6 s^{-1} per mM Gd^{3+} and $\sim 2.5 \times 10^7 \text{ s}^{-1}$ per mM of nanorod. This level of R1 relaxivity is unprecedented and at least an order of magnitude higher than those of Gd^{3+} -containing liposomes which have been shown to be effective target-specific MR contrast agents for cancer and cardiovascular disease.¹² Nanorods of **1** of ~400 nm in length by ~70 nm in diameter (with $\sim 7.4 \times 10^6$ Gd^{3+} /nanorod) had an R1 value of 26.9 s^{-1} per mM Gd^{3+} and $\sim 2.0 \times 10^8 \text{ s}^{-1}$ per mM nanorod as well as an R2 of 49.1 s^{-1} per mM Gd^{3+} and $\sim 3.6 \times 10^8 \text{ s}^{-1}$ per mM of nanorod. A further increase in particle size to ~1 μm in length and ~100 nm in diameter ($\sim 5.6 \times 10^7$ Gd^{3+} /nanorod) resulted in an R1 of 20.1 s^{-1} per mM Gd^{3+} and $\sim 1.1 \times 10^9 \text{ s}^{-1}$ per mM nanorod and an R2 of 45.7 s^{-1} per mM Gd^{3+} and $\sim 2.6 \times 10^9 \text{ s}^{-1}$ per mM of nanorod. The inverse size dependence of per mM Gd^{3+} relaxivity observed for **1** is consistent with the decreasing surface to volume ratio for the larger nanorods. We believe that the Gd^{3+} centers at or near the surface are primarily responsible for the observed relaxivities. We also measured the relaxivities of nanoplates of **2** of a diameter of ~100 nm and an average thickness of 35 nm which exhibited an R1 of 13.0 s^{-1} per mM Gd^{3+} and $\sim 3.25 \times 10^7 \text{ s}^{-1}$ per mM nanoplate (with $\sim 2.5 \times 10^6$ Gd^{3+} /nanoplate) and an R2 of 29.4 s^{-1} per mM Gd^{3+} and $\sim 7.35 \times 10^7 \text{ s}^{-1}$ per mM of nanoplate.

As shown in Fig 3c, nanorods of **1** are much more efficient in enhancing the water signals in T1-weighted images than clinically used OmniScan. Interestingly however, very significant signal reduction was caused by nanorods of **1** in T2-weighted images (supporting information)

when a spin-echo pulse sequence was used. The very high R1 and R2 relaxivities exhibited by **1** and **2** thus allow their use as both T1- and T2-contrast agents depending on the MR pulse sequence employed.

We have also successfully synthesized luminescent nanorods of **1** by using Eu³⁺ or Tb³⁺ dopants. By mixing in 5 mol% of EuNO₃ or TbNO₃ during the syntheses, nanorods of similar sizes and morphologies to **1** were obtained and had the compositions of Gd_{0.95}(BDC)_{1.5}(H₂O)₂:Eu_{0.05} (**1a**) and Gd_{0.95}(BDC)_{1.5}(H₂O)₂:Tb_{0.05} (**1b**). Ethanol dispersions of these doped nanorods are highly luminescent upon UV excitation with characteristic red and green luminescence from Eu³⁺ and Tb³⁺, respectively (Fig 3d). These results suggest that NMOFs such as **1** can be used as potential contrast agents for multimodal imaging.

In summary, we have developed a general reverse microemulsion-based methodology for the synthesis of NMOFs. These NMOFs exhibit large R1 and R2 relaxivities on a per mM of Gd³⁺ basis and extraordinarily large R1 and R2 relaxivities on a per mM of nanoparticle basis. Doping of luminescent lanthanide ions was also demonstrated. Molecular targeting of such NMOFs 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENT

We acknowledge financial support from NSF (CHE-0512495) and NIH grants (U54-CA119343-01 and P20 RR020764-01). WJR thanks NSF for a graduate fellowship and WL is a Camille Dreyfus Teacher-Scholar.

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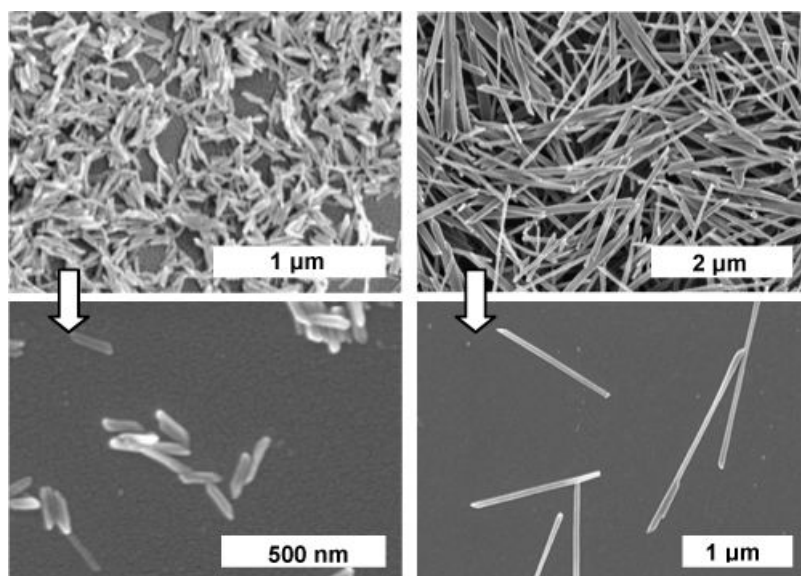


Figure 1. SEM images of $\text{Gd}(\text{BDC})_{1.5}(\text{H}_2\text{O})_2$ (**1**) nanorods synthesized with $w=5$ (left) and $w=10$ (right).

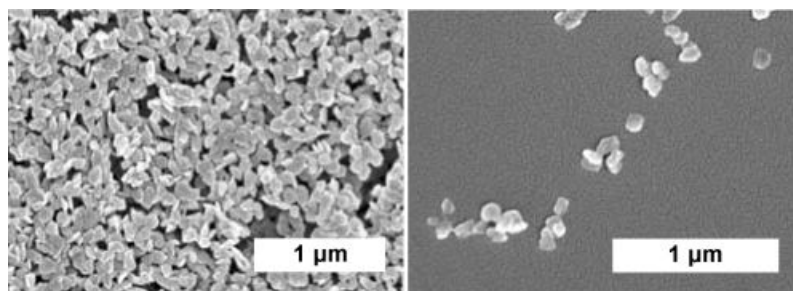


Figure 2. SEM images of irregularly-shaped, crystalline $[\text{Gd}(1,2,4\text{-BTC})(\text{H}_2\text{O})_3]\cdot\text{H}_2\text{O}$ (**2**) nanoplates.

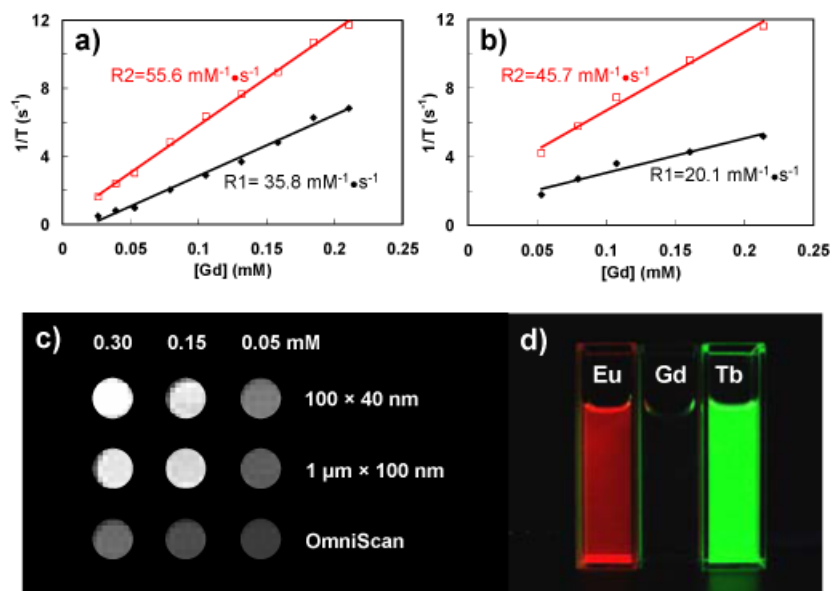


Figure 3. (a) R1 and R2 relaxivity curves of **1** of ~ 100 nm in length by ~ 40 nm in diameter. (b) R1 and R2 relaxivity curves of **1** of $\sim 1 \mu\text{m}$ in length by ~ 100 nm in diameter. In comparison, OmniScan gave an R1 of $4.1 \text{ mM}^{-1} \cdot \text{s}^{-1}$ under these conditions. (c) T1-weighted MR images of suspensions of **1** in water containing 0.1% xanthan gum. (d) Luminescence images of ethanolic suspensions of **1**, **1a** (**1** doped with 5 mol% Eu^{3+}), and **1b** (**1** doped with 5 mol% Tb^{3+}).