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Coloring ultrasensitive MRI with tunable metal-organic frameworks
Coloring ultrasensitive MRI with tunable metal–organic frameworks†

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As one of the most important imaging modalities, magnetic resonance imaging (MRI) still faces relatively low sensitivity to monitor low-abundance molecules. A newly developed technology, hyperpolarized $^{129}$Xe magnetic resonance imaging (MRI), can boost the signal sensitivity to over 10 000-fold compared with that under conventional MRI conditions, and this technique is referred to as ultrasensitive MRI. However, there are few methods to visualize complex mixtures in this field due to the difficulty in achieving favorable “cages” to capture the signal source, namely, $^{129}$Xe atoms. Here, we proposed metal–organic frameworks (MOFs) as tunable nanoporous hosts to provide suitable cavities for xenon. Due to the widely dispersed spectroscopic signals, $^{129}$Xe in different MOFs was easily visualized by assigning each chemical shift to a specific color. The results illustrated that the pore size determined the exchange rate, and the geometric structure and elemental composition influenced the local charge experienced by xenon. We confirmed that a complex mixture was first differentiated by specific colors in ultrasensitive MRI. The introduction of MOFs helps to overcome long-standing obstacles in ultrasensitive, multiplexed MRI.

Introduction

Multicolor imaging provides a method for investigating complex biological processes in living samples. Target analytes that are labeled with different dyes can be clearly distinguished by color differentiation.1 Multicolor imaging has been widely explored in chemical, biological, and medical fields; this technique can visualize T lymphocytes, bacteria, and tumors in the whole body,2 constantly monitor drug release from cargos,3 intensively investigate the spatiotemporal dynamics of differentiated by specific colors in ultrasensitive MRI. The introduction of MOFs helps to overcome long-standing obstacles in ultrasensitive, multiplexed MRI.

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technology can monitor gas–gas\textsuperscript{16–20} and gas–blood\textsuperscript{21–24} exchange in the lungs, as well as evaluate brain function.\textsuperscript{25,26} Because of the much higher sensitivity, hyperpolarized \(^{129}\text{Xe}\) MRI is referred to as ultrasensitive MRI.\textsuperscript{27,28} To confer targeting ability to chemically inert xenon, host “cages” with high xenon affinity are introduced and modified with targeting groups.\textsuperscript{29} The resulting \(^{129}\text{Xe}\) in cages produces new signals that can be separated from the dissolved free \(^{129}\text{Xe}\) signals in tissues and blood. Some nanostructures, such as porous nanoparticles,\textsuperscript{30} nanoemulsions,\textsuperscript{31} dendrimers,\textsuperscript{32} proteins,\textsuperscript{33} and genetically encoded reporters,\textsuperscript{34,35} could provide host cavities for xenon binding and exchange. Nevertheless, \(^{129}\text{Xe}\) signals in most of the developed nanocages are broad, due to the complicated exchange processes and the intricate chemical microenvironments. Some supramolecular and superstructural cages, such as cryptophane\textsuperscript{36–38} and metal–organic capsules,\textsuperscript{39–41} show narrower signal peaks than nanocages because their pores bind only one xenon atom and exhibit an intermediate exchange rate at room temperature. By using targeted cryptophane as a cage, a low detection limit of \(10^{-10}\) M was achieved to trace intracellular biothiol with hyperpolarized \(^{129}\text{Xe}\) chemical exchange saturation transfer (Hyper-CEST) MRI.\textsuperscript{42} The multiplexing capacity of \(^{129}\text{Xe}\) NMR has been exploited by modifying or replacing the linker of cryptophane.\textsuperscript{43} However, \(^{129}\text{Xe}\) MRI biosensors in real samples were physically separated from each other.\textsuperscript{44,45} There are very few reports on detecting complex mixtures by \(^{129}\text{Xe}\) MRI, which may be due to the unacceptable biocompatibility, negligible chemical shift differences, or complicated synthesis procedures of cryptophane. Hence, searching for better host cages remains a challenge in exploiting the applications of ultrasensitive MRI for multitarget imaging.

Metal–organic frameworks (MOFs) are synthetic materials with controllable pores that have been widely studied in environmental,\textsuperscript{46,47} energy,\textsuperscript{48,49} and nanomedicine\textsuperscript{50,51} fields. Compared with other nanomaterials, MOFs have unique advantages because their skeleton, structure, and pore function can be carefully designed and controlled by the selection of starting derivatives and metals. It is worth mentioning that MOFs have been successfully applied in xenon separation,\textsuperscript{52} which demonstrates the high affinity between xenon and MOFs and inspires us to develop MOF-based \(^{129}\text{Xe}\) biosensors. Besides, it was reported that the \(^{129}\text{Xe}\) NMR chemical shift was increased from the larger isoreticular MOF (UiO-67) to the smaller one (UiO-66).\textsuperscript{53} If we can find an MOF that permits only a single xenon atom exchange per pore, such as cryptophane, a favorable signal may be obtained in ultrasensitive MRI. This would overcome the issue that \(^{129}\text{Xe}\) signals in nanomaterial-based cages are typically too broad and weak. More importantly, the \(^{129}\text{Xe}\) atom is extremely sensitive to its local environment; its MR chemical shift spans over 5000 ppm, which is a much wider range than that of \(^{1}\text{H}\) (\(\sim 20\) ppm). On the basis of the above theories, we expect to develop a series of MOFs with different pore structures to offer diverse chemical surroundings for \(^{129}\text{Xe}\) atom thrusts and achieve different MR signals. Inspired by semiconductor quantum dots, which can generate diverse emission colors by simply controlling the dot’s inner core shell,\textsuperscript{54} a distinguishable \(^{129}\text{Xe}\) MR signal resulting from each edited MOF may also be “stained” with its own color to show the signal difference. Thus, the introduction of MOFs may provide comparable \(^{129}\text{Xe}\) MRI labels for multitarget analysis.

In this study, we investigated the potential of modifying the MOF pore structure to gain multiple signals for coloring ultrasensitive MRI (Scheme 1). A class of MOF nanoparticles was formed by similar octahedral Zn–O–C clusters and benzene

![Scheme 1](image-url)  MOF pore structures are altered to provide diverse microenvironments for \(^{129}\text{Xe}\) atom hosting and produce distinguishable MR signals. Multicolor \(^{129}\text{Xe}\) MR images are introduced by staining the unique signal in each altered MOF with a specific color.
links, and their pore size was expanded by extending the molecular struts. It was shown that the exchange rate of the $^{129}$Xe atom in MOF pores increased as the organic link was extended, and the resulting signal differences between any two MOFs were large enough to be completely separated. To better understand the inherent key factors that led to these unique properties, we performed theoretical calculations of $^{129}$Xe in each MOF pore. The results illustrated that the pore sizes and charge numbers contributed to the different chemical micro-environments, which manifested as diverse chemical shifts. Based on the above experimental and theoretical studies, the MOF family was developed as a favorable contrast agent for ultrasensitive MRI. Furthermore, three types of MOF nanoparticles with different pore sizes and structures were mixed. The $^{129}$Xe NMR and MRI results showed that the signals in the three MOFs could be totally received and completely discriminated. To the best of our knowledge, this is the first time that large $^{129}$Xe MR signal differentiation is obtained in a complex mixture by using a class of “nanocages” with similar chemical compositions. These results prove the concept of achieving distinguishable caged $^{129}$Xe MR signals by regulating the MOF structure and encoding ultrasensitive MRI with multiple colors that resulted from the different chemical shifts. Hence, ultrasensitive MRI with tunable MOFs opens a new approach for imaging complex mixtures without invasiveness, radiation, and depth limitations.

## Results

### Production of MOF nanoparticles

MOFs with similar structures were solvothermally prepared by mixing carboxylate benzene organic links with metallic node zinc ions and the stabilizing reagent polyvinyl pyrrolidone (PVP) in dimethylformamide (DMF)/ethanol. Their pore sizes were regulated with expanded link lengths. We introduced 1,4-benzenedicarboxylic acid, 2,6-naphthalenedicarboxylic acid, and biphenyl-4,4′-dicarboxylic acid as the organic links, and the produced MOFs were named IRMOF-1, IRMOF-8, and IRMOF-10, respectively. As shown in the transmission electron microscopy (TEM) and scanning electron microscopy (SEM) (Fig. 1) images, the spherical nanoparticles indicated the morphology and structural features of the as-prepared IRMOF-1, IRMOF-8, and IRMOF-10 nanoparticles. When the visual field was further enlarged (Fig. S1–S3†), obvious lattice structures were observed (Fig. S4–S6†), and numerous small nanoparticles (~10 nm) accumulated and formed IRMOF nanospheres. By counting the particle sizes in the TEM images, the IRMOF nanoparticles showed diameters of approximately 110 nm (Table S1†), while the dynamic light scattering (DLS) results showed particles that were ~40 nm larger (Table S2†). The fabrication of these structures might be induced by a surface-energy-driven mechanism. The X-ray diffraction (XRD) (Fig. S13–S15†) and Fourier transform infrared (FTIR) spectroscopy (Fig. S16–S18†) results further revealed the successful formation of IRMOF nanoparticles.

### Modification of the MOF pore structure to achieve different cages for $^{129}$Xe hosting

The free volume in crystals in the MOF could be varied by regulating the molecular linkers, and the produced MOFs would provide different pores as hosts for small molecules. In the present study, the free volume was expanded with extended benzene links, and the free diameters of pores in IRMOF-1, IRMOF-8, and IRMOF-10 were 7.93, 9.17, and 12.15 Å,

![Fig. 1](image-url)  
**Fig. 1** Characterization of the morphology of the MOF nanoparticles. (a) TEM and (b) SEM images of IRMOF-1, IRMOF-8, and IRMOF-10 showed spherical structures and relatively uniform size distributions. Scale bar, 100 nm.
The nanoscale pores may offer cavities for $^{129}$Xe atom hosting and then produce various MR signals due to the diverse microenvironments provided by the different-sized pores in each MOF. To investigate their potential as host cages to capture $^{129}$Xe atoms and produce new signals, we performed NMR studies of the designed MOFs with a 9.4 T spectrometer with a homemade $^{129}$Xe hyperpolarizer. In a typical CEST procedure, a series of RF irradiations was applied to saturate the MR signal of $^{129}$Xe in the cage, and the dissolved $^{129}$Xe signal was decreased when the free $^{129}$Xe atom was thrust and exchanged. As hypothesized, the $^{129}$Xe atom in each MOF produced an MR signal at its unique chemical shift; IRMOF-1, IRMOF-8, and IRMOF-10 were saturated at 48, 17, and 26 ppm, respectively (Fig. 2a). These irradiation differences were large enough to excite the signal from only one MOF under its particular frequency. For example, under 13 $\mu$T RF saturation at 48 ppm, IRMOF-1 produced sufficient contrast in ultrasensitive MRI (Fig. 2b), whereas signals from IRMOF-8 and IRMOF-10 samples remained silent. This phenomenon occurred because the RF at 48 ppm could only saturate the MR signal from $^{129}$Xe in IRMOF-1, and one irradiation at a defined chemical shift corresponded to one specific $^{129}$Xe cage. Simultaneously, ultrasensitive $^{129}$Xe MRI could be further colored by IRMOF-8 and IRMOF-10 with RF irradiation at 17 and 26 ppm, respectively. The MRI results showed that the three signals from the designed MOFs could be excited separately (Fig. 2b).

**The pore size determines the exchange rate**

We evaluated the interaction of $^{129}$Xe atoms with MOFs by quantitative Hyper-CEST analysis. A series of full Hyper-CEST spectra were obtained by saturating $^{129}$Xe in MOFs under the

Fig. 2  Manipulation of the MOF pore structure to produce unique $^{129}$Xe MR signals. (a) Frequency-dependent saturation spectra of IRMOF-1, IRMOF-8, and IRMOF-10. To eliminate the influence of solvent, chemical shifts were referenced to the dissolved free $^{129}$Xe atom. (b) Coloring ultrasensitive MRI with three types of MOF nanoparticles. Each MOF is saturated at its unique chemical shift, thus enabling discrimination from others in ultrasensitive MRI. (c) Calculating the charge in an edge of an MOF pore. Charge numbers contribute to the differences in chemical shifts. (d) A mixture containing IRMOF-1, IRMOF-8, and IRMOF-10 showed separated signals. (e) MOF nanoparticles provide diverse contrast agents for complex mixture imaging. The MOF mixture showing ultrasensitive MRI in three colors, thus enabling the labeling of three different targets in a single sample.
Interestingly, the irradiation frequency (at a specific chemical shift) that saturates $^{129}$Xe in a nanocage was not related only to the pore size.\cite{4.6,4.5} The pore size gradually expanded from IRMOF-1 to IRMOF-10. The $^{125}$Xe atoms in the smallest pore of IRMOF-1 had the largest chemical shift difference compared with free $^{129}$Xe atoms (0 ppm). While the corresponding frequency of $^{129}$Xe in the other two MOFs did not behave as expected, the chemical shift of $^{125}$Xe in IRMOF-8 was 9 ppm smaller than that of IRMOF-10. We considered that the linker structure, length, and chemical composition might collectively influence the interaction between xenon and the cages.

To explain the disorder phenomenon, we further investigated the effect of electron clouds based on the IRMOF pore structures. We took one triangle and three edges in one lattice of IRMOF and stretched along the diagonal line of the lattice to calculate the Mulliken charge change. As shown in Fig. S29, the calculated chemical shift of $^{129}$Xe decreased in the order of IRMOF-1, IRMOF-10, and IRMOF-8 under the same R value. This trend fits well with the Hyper-CEST results (Fig. 2a). Then, the charge of each atom in the three systems was studied along with different R values. The atoms with charge root mean square changes larger than 0.01 in the three structures are shown in Fig. S4. Those atoms in IRMOF-1 were close to those in IRMOF-10 due to the similar geometric structures of the edges. However, IRMOF-8 had fewer effective atoms than IRMOF-1 and IRMOF-10. We also noted that the absolute values of the charges on Zn and O for IRMOF-8 were smaller than those of IRMOF-1 and IRMOF-10; this led to a smaller interaction between IRMOF-8 and xenon than that between IRMOF-1 and IRMOF-10 with xenon. The charge on Zn, O, C, and H for IRMOF-1 was larger than those for IRMOF-10, and the pore size of IRMOF-1 was smaller than that of IRMOF-10. Thus, xenon has a higher probability of being close to the edges and the triangle in IRMOF-1. All these factors resulted in dispersed chemical shifts, that is, IRMOF-1 > IRMOF-10 > IRMOF-8.

<table>
<thead>
<tr>
<th>Xenon host</th>
<th>Particle diameter/nm</th>
<th>Interior pore diameter for Xe hosting/Å</th>
<th>$^{129}$Xe exchange rate/s$^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>IRMOF-1</td>
<td>106.3</td>
<td>7.93</td>
<td>429 ± 152</td>
</tr>
<tr>
<td>IRMOF-8</td>
<td>105.2</td>
<td>9.17</td>
<td>1176 ± 937</td>
</tr>
<tr>
<td>IRMOF-10</td>
<td>116.6</td>
<td>12.15</td>
<td>2496 ± 548</td>
</tr>
<tr>
<td>Gas vesicle\cite{37}</td>
<td>519</td>
<td>—</td>
<td>19 300 ± 1800</td>
</tr>
<tr>
<td>Cryptophane-A\cite{57,58}</td>
<td>—</td>
<td>5.4</td>
<td>16 ± 3</td>
</tr>
</tbody>
</table>

Table 1. $^{129}$Xe-host interaction parameters obtained from quantitative Hyper-CEST. The free diameter of MOF pores was expanded as the organic length was extended from IRMOF-1 to IRMOF-10. The exchange rate of the $^{129}$Xe atom in the MOF increased with the expanding MOF pore diameter. The exchange rate of $^{129}$Xe in the MOF was considerably smaller than that in gas vesicles and larger than that in supermolecular cryptophane-A due to the intermediate pore space for Xe hosting.
A linear response was obtained over the concentration range from 0.05 mg mL\(^{-1}\) to 1 mg mL\(^{-1}\) (Fig. 3b). The corresponding ultrasensitive MRI also showed a concentration-dependent intensity (Fig. 3c). Hence, the exploited MOF nanoparticles could be used as ultrasensitive MRI stains with diverse colors, making it possible to analyze complex samples qualitatively and quantitatively in the future.

Conclusions

In this study, a complex mixture was first distinguished by color differentiation in ultrasensitive MRI, which was achieved by the introduction of MOF nanoparticles as contrast agents. Compared to other hard-to-obtain \(^{129}\)Xe cages, MOF nanoparticles with uniform pores could be easily fabricated by altering the length of the starting organic links. The produced MOF nanoparticles provided three types of pore spaces with different chemical microenvironments to capture the signal source of \(^{129}\)Xe atoms. As the \(^{129}\)Xe atom was extremely sensitive to the surrounding environment, the designed MOF nanoparticles produced distinct \(^{129}\)Xe MR signals under three irradiation frequencies, resulting in three colors for ultrasensitive MRI stains. These colors could be completely separated because the \(^{129}\)Xe chemical shift differentiation between any two MOFs was over 9 ppm.

We carefully investigated the relationship between the MOF pore structure and the resulting \(^{129}\)Xe MR signals, expecting to find laws that might help us explore more types of ultrasensitive MRI contrast agents. The pore size was expected to be one of the important factors that considerably affect the exchange rate of \(^{129}\)Xe atoms. As anticipated, the exchange rates of \(^{129}\)Xe in IRMOF-1, IRMOF-8, and IRMOF-10 increased with increasing pore size. However, the variation in relevant chemical shifts did not show a similar trend. The pore structure was mimicked, and the charge of the system was calculated. The results showed that the geometric structure and the number of atoms combined to act on the charge of each atom, which led to dispersed chemical shifts (IRMOF-1 > IRMOF-10 > IRMOF-8).

In conclusion, we successfully explored a new type of nanocage that circumvents the difficulty of fabricating \(^{129}\)Xe host cages and can be used as an ultrasensitive MRI stain with three individual colors. This approach may serve as a new strategy to analyze complex mixtures by combining the advantages of modifiable MOFs and ultrasensitive MRI without depth limitations. Numerous studies are expected to be conducted in the future, and they include but are not limited to the following: (1) Additional pore structures can be designed and fabricated by replacing organic links and/or metals, which may provide additional colors for ultrasensitive MRI. (2) The designed MOFs produced MR signals upfield of soluble free \(^{129}\)Xe atoms; other types of MOFs, which may lead to signals downfield, could be explored by utilizing the shielding electron effect. (3) The ultrasensitive MRI signal may be enhanced by improving the dispersity of MOF nanoparticles. (4) Real biological samples could be detected by introducing targeting groups. (5) Insoluble MOFs could be prepared in the form of spray and then inhaled for lung imaging.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Notes and references


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