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SUBJECT AREAS:

METAL-ORGANIC
FRAMEWORKS

FLUORESCENT PROBES

Received
20 January 2014Accepted
19 February 2014Published
13 March 2014

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A malonitrile-functionalized metal-organic framework for hydrogen sulfide detection and selective amino acid molecular recognition

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A novel porous polymeric fluorescence probe, MN-ZIF-90, has been designed and synthesized for quantitative hydrogen sulfide (H₂S) fluorescent detection and highly selective amino acid recognition. This distinct crystalline structure, derived from rational design and malonitrile functionalization, can trigger significant enhancement of its fluorescent intensity when exposed to H₂S or cysteine molecules. Indeed this new metal-organic framework (MOF) structure shows high selectivity of biothiols over other amino acids and exhibits favorable stability. Moreover, in vitro viability assays on HeLa cells show low cytotoxicity of MN-ZIF-90 and its imaging contrast efficiency is further demonstrated by fluorescence microscopy studies. This facile yet powerful strategy also offers great potential of using open-framework materials (i.e. MOFs) as the novel platform for sensing and other biological applications.

Metal-organic frameworks (MOFs)^{1–3}, self-assembled from metals ions or clusters and polydentate bridging ligands, have emerged as promising materials for gas storage and separation applications^{4–7}. Zeolitic imidazolate frameworks (ZIFs), a subfamily of MOFs, combine desirable properties of both zeolites and MOFs, such as permanent porosity, diverse structures, and high thermal and chemical stability^{8–11}. Notably, the adjustable pore size/geometry and flexible chemical tunability of MOFs/ZIFs offer unlimited potential for sensing and detection applications^{12–18}. One current interest of these open framework materials is on their luminescent, magnetic or colorimetric properties^{19–21}. Significant advances, such as good selectivity, quick responsibility, and low detection limits, have been reported in the sensing of targeted analytes using small-molecule probes and polymeric materials^{22–24}. In recent years, some interesting MOF structures also exhibited great potential in sensing²⁵, molecular recognition^{26–29}, and biological applications^{30–35}. However, the detection of hydrogen sulfide (H₂S) and biothiols using open frameworks, in spite of its great importance in environmental and biological systems, remains largely unexplored (Fig. 1)^{36–39}.

An exponentially growing body of evidence points H₂S and biothiols to have a significant signaling role in biological systems and pathological processes^{40,41}. In particular, H₂S, which is produced in the cardiovascular system of mammals, is found to lead to dilation of blood vessels and the lowering of blood pressure. Cysteine (Cys), on the other hand, can be converted into a powerful antioxidant and thus prevent free radical damage to the deoxyribonucleic acid and membranes of cells and reduce the risk caused by an acetaminophen overdose. Hence recognizing thiol-containing species, especially signaling them in living cells is crucial for the understanding of biological processes. To address the challenge in developing a new MOF system that could efficiently uptake and response to thiol-containing molecules, one needs to design a host network equipped with special functional groups. Despite fast developments in the areas of MOFs functionalization, a system that exhibits specific response to H₂S and cysteine has not been demonstrated.

The key design element in the present case is the anchoring of malonitrile functional sites to the walls of ZIF-90 skeleton (Fig. 2). We envisioned that a host framework containing the malonitrile moiety should be reasonably conceivable for thiol compound determination. The advantages of such a pore surface engineering are obvious: the

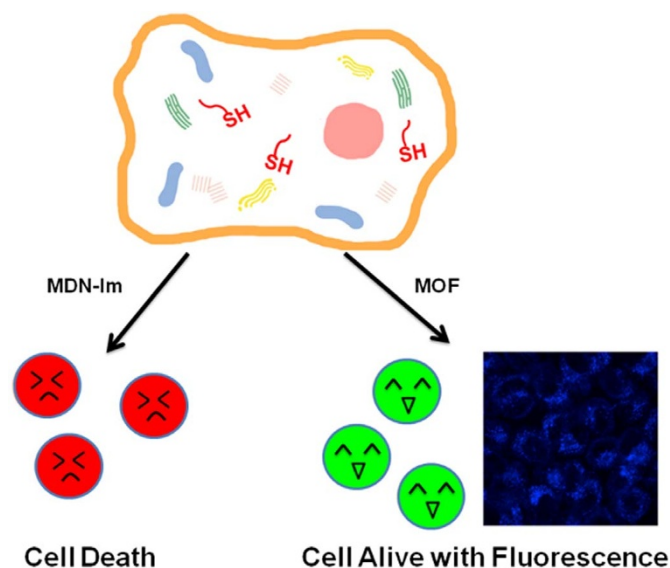


Figure 1 | Concept of the recognition of biothiols in living cell. Biothiols recognition by using model compound, MN-Im, caused cell death, whereas the utilization of biocompatible and functionalized MOFs may provide opportunities for non-toxic and high-contrast signal of biothiols in living cells. This figure was created by Dr. X.F. and co-authors and the inset image is the fluorescent photo from our experiment.

free aldehyde groups in the ZIF-90 framework allow the covalent functionalization with malonitrile groups through a Knoevenagel condensation reaction⁴²; the malonitrile units can then undergo a specific reaction with thiol compounds with an enhancement of photoluminescence, constituting a base for sensing; moreover, the ZIF-90 skeleton, with its distinct chemical stability and porous framework nature, tends to gather small molecules preferentially without structural deterioration, thus providing the potential for non-toxic molecular recognition in living cells with higher selectivity.

As a proof of this idea, malonitrile functional units were covalently connected to ZIF-90 prepared through a mechanochemical method by simply stirring them in toluene at room temperature. In order to get rid of the excessive malonitrile that are in the pores and those attached on the surface of the ZIF-90 particles, thus-obtained solids were extensively washed with large amounts of toluene, and were further soaked in CH_2Cl_2 for three days. The resulting functionalized host, MN-ZIF-90, was fully characterized through fourier-transform infrared (FT-IR) spectroscopy, $^1\text{H-NMR}$ spectroscopy, powder X-ray diffractions (PXRD), and gas sorption measurements.

Results

FT-IR spectra (Supplementary Fig. S1) confirmed the formation of the double-bond linkages between malonitrile and aldehyde group in ZIF-90. Two absorption peaks at 2202 and 2128 cm^{-1} revealed the existent of $\text{C}\equiv\text{N}$ band, while the appearance of absorption peak at 1622 cm^{-1} can be assigned to $\text{C}=\text{C}$ band. $^1\text{H-NMR}$ spectroscopy of digested MN-ZIF-90 (Supplementary Fig. S2) indicated that about one third of the aldehyde groups within the frameworks were participated in the Knoevenagel reaction. PXRD pattern of the modified ZIF-90 matched well with that of the as-prepared ZIF-90 (Supplementary Fig. S3), which demonstrated that MN-ZIF-90 retained the SOD topology within the crystalline framework. The particles of MN-ZIF-90 were about 148 nm in diameter, as confirmed by field-emission scanning electron microscopy (FE-SEM) (Supplementary Fig. S4) and dynamic light-scattering (DLS) measurement (Supplementary Fig. S5).

The inner porosities of MN-ZIF-90 were investigated by gas sorption measurements. Calculated from N_2 sorption isotherms, non-local density function theory (NLDFT) analyses for the pore-size distribution demonstrated that the micropore volume of MN-ZIF-90 is significantly decreased compared with the pristine ZIF-90 (Supplementary Fig. S6). The micropores with diameters around 0.7 nm in ZIF-90 was almost vanished in MN-ZIF-90 due to the occupancy of the malonitrile moieties, while the mesopores around 3.3 nm originated from the defects in mechanochemically prepared

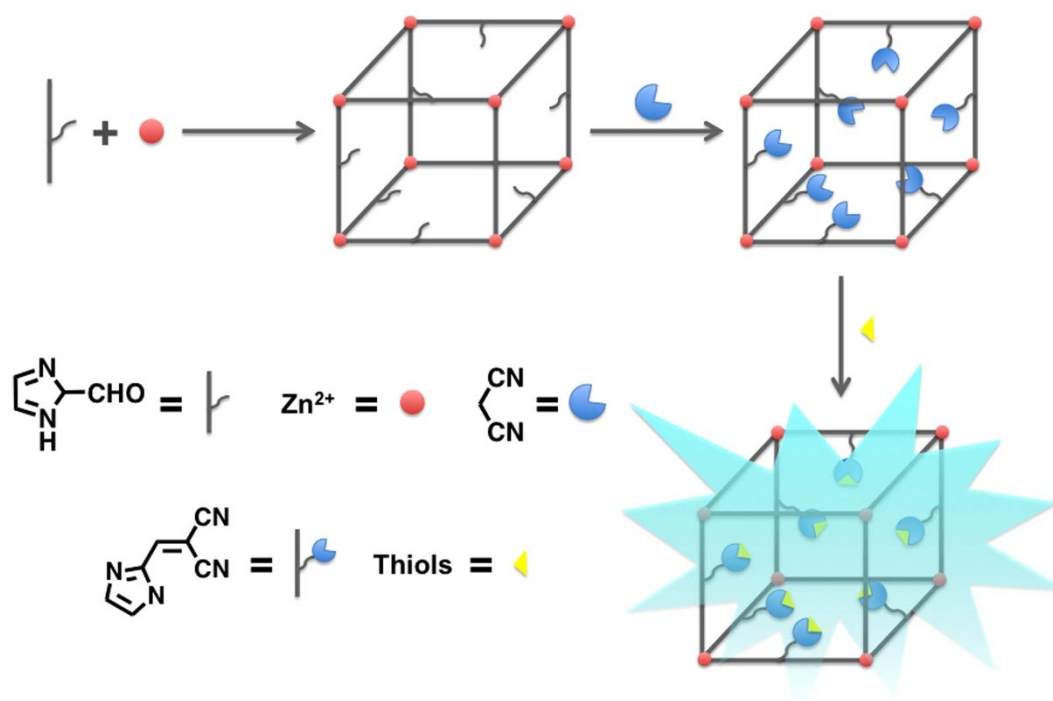


Figure 2 | Schematic illustration of the synthesis and functions of MN-ZIF-90. Reagents and conditions for the synthesis and detection can be obtained in the Supplementary Information section 2.

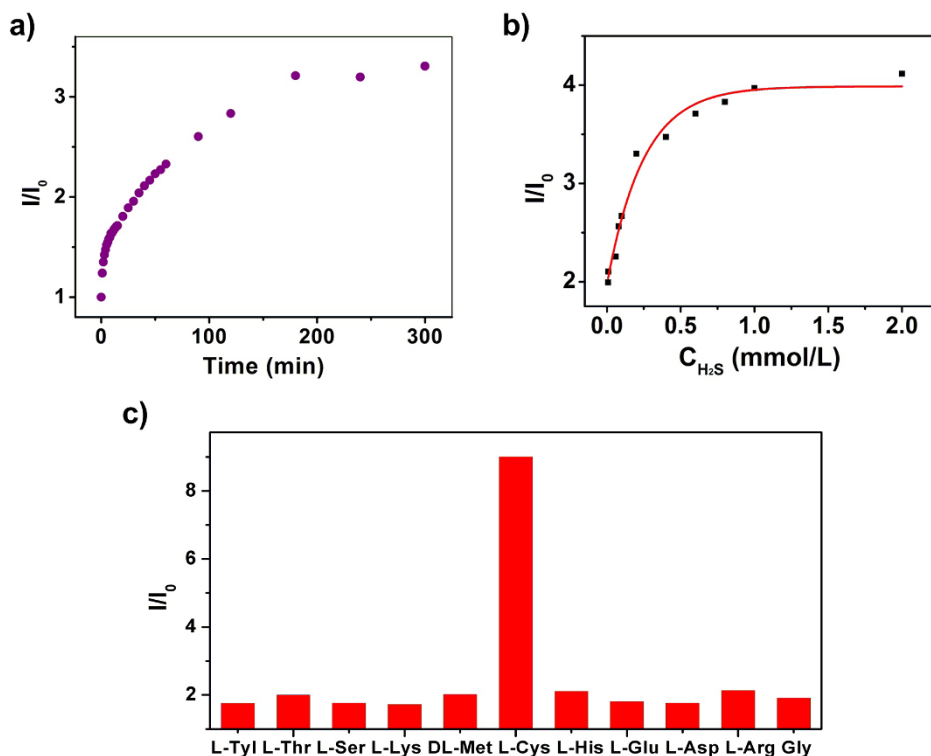


Figure 3 | H_2S and amino acids detection. (a) Time-dependent fluorescent intensity changes of MN-ZIF-90 with H_2S (0.2 mM) at r.t. (b) Fluorescence enhancement of MN-ZIF-90 with various H_2S concentrations. (c) Fluorescence enhancement of MN-ZIF-90 in the presence of different amino acids at r.t. [MN-ZIF-90] = 0.2 mM.

ZIF-90 were reduced to 2.8 nm in MN-ZIF-90. The decrement of the pore volume after the introduction of malonitrile groups was also confirmed by NLDFT pore volume simulation calculated from CO_2 sorption isotherms (desorption branch) (Supplementary Fig. S7).

The malonitrile moieties conjugated to the host through double bonds can serve as quenchers of the host fluorescence through intramolecular photoinduced electron transfer. The resulting α,β -unsaturated malonitrile is susceptible to thiol compounds, which will lead to a broken of the double bond^{43,44}. Not only in the pores, but also on the surface of the nanoparticles, MN-ZIF-90 is equipped with malonitrile functions. As the result, the fluorescence of the host will be recovered once the thiol compounds are introduced into the system. This motivated us to test the fluorescent responsibilities of MN-ZIF-90 to the thiol compounds.

Upon immersion of MN-ZIF-90 in a solution of H_2S , a hypsochromic shift of 7 nm in the UV spectroscopy was observed (Supplementary Fig. S8), indicating the double-bond conjugation was broken. Meanwhile, a “turn-on” ratio over 3.3-fold in FL intensities was triggered with the addition of 1.0 equiv. of H_2S (Fig. 3a and Supplementary Fig. S9) within 180 min. In addition, the relationship of its fluorescence intensity with H_2S concentration in the range from 0.008 to 2 mmol/L can be established as a function of $I/I_0 = -2.02 \times \exp(-C_{H_2S}/0.25) + 3.99$ (Fig. 3b), suggesting that H_2S can be detected quantitatively using MN-ZIF-90.

Beyond H_2S , several molecules of biological importance were also screened to verify the selectivity of MN-ZIF-90 in aqueous solution (Fig. 3c). As expected, among eleven different amino acids, only cysteine, a thiol-containing amino acid, induced fluorescence recovery of the solution with an activation ratio that is up to 8.5 times of magnitude higher than its original fluorescence (Supplementary Fig. S10–S11). The probe detects cysteine at concentration as low as 25 $\mu\text{mol/L}$ with a noticeable change in fluorescence intensity (signal/noise ratio of 3 : 1). Other amino acids, such as L-Tyr, L-Thr, L-Ser, L-His, etc., only lead to a small enhancement of the fluorescence.

For a probe to be used in live cells, biocompatibility is always the first property to examine. To evaluate the potential use of MN-ZIF-90 as a contrast agent for optical imaging and a probe for biothiol recognition, we conducted in vitro viability assays on HeLa cells. The cytotoxicity of MN-ZIF-90 was evaluated using a 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium (MTS) assay. Treatment of HeLa cells with MN-ZIF-90 did not lead to any appreciable cell death even after 48 h of incubation when an MN-ZIF-90 concentration as high as 0.5 mg/mL was used in the Dulbecco’s Modified Eagle’s medium (DMEM, containing 10% FBS) (Fig. 4c). In contrast, 2-((1-methyl-1H-imidazol-2-yl)methylene)malonitrile (MN-Im) (Supplementary Information, Section 1), as a model compound, exhibited much higher cytotoxicity. To test their in vitro imaging contrast efficiency, laser scanning

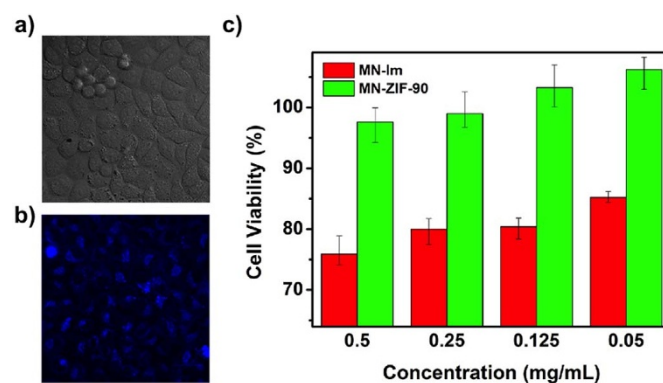


Figure 4 | In vitro viability assays on HeLa cells with MN-ZIF-90 and MN-Im. (a–b) Bright field image and fluorescence image after treating the HeLa cells with MN-ZIF-90 (0.05 mg/mL) after 48 h of incubation. (c) In vitro HeLa cell viabilities after 48 h of incubation with MN-Im and MN-ZIF-90 at different concentrations.



confocal microscopy studies were performed. As shown in Fig. 4, significant blue luminescent signal was observed for HeLa cells incubated with MN-ZIF-90, and overlay of bright field and fluorescent images further demonstrate that the fluorescence was evident in the intracellular region (Supplementary Fig. S12). These observations confirm the capability of MN-ZIF-90 for high-contrast in vitro cell imaging with negligible background.

Discussion

In summary, we have designed and synthesized a novel open framework fluorescent probe, MN-ZIF-90, based on rational design and post-synthetic modification^{12,45} of ZIF-90. H₂S, as well as Cys, can trigger significant enhancement of its fluorescent intensity in aqueous solution. The probe showed high selectivity of biothiols over other amino acids, and exhibited favorable biocompatibility. These features, along with the facile yet powerful method of preparation, make the probe attractive for recognition of biothiols in biological systems. This work highlights the potential of using nano-scale functional MOFs as the novel platform for the design of nontoxic targeting biomolecules and long-term labeling of cells. Applying this strategy in developing thiol detection and recognition systems based on open framework materials, such as MOFs, ZIFs, and covalent organic frameworks (COFs)⁴⁶, are in process and will be reported in a timely manner.

Methods

Materials. All reagents and starting materials were obtained commercially and were used as received without any further purification. Zn(NO₃)₂·6H₂O was purchased from Sinopharm Chemical Reagent Co. Ltd. Imidazole-2-carbaldehyde and malonitrile were purchased from J&K Chemical Co. Toluene and N,N-dimethylformamide were purchased from Beijing Chemical Works. Dulbecco's Modified Eagle Medium (DMEM), Fetal bovine serum (FBS) were purchased from Biodee Co., 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium (MTS) were purchased from Promega Co.

Synthesis of ZIF-90. A mixture of ZnO (0.42 g, 5 mmol), imidazole-2-carboxyaldehyde (0.96 g, 10 mmol) and N,N-dimethylformamide (DMF, 500 μL) in a metal jar mill was ball-milled for 15 min, then another 500 μL DMF was added into the jar and further ground for 15 min. After that, the crystalline powder obtained was centrifuged and washed with DMF (5 × 20 mL), followed by soaking the crystals in CH₂Cl₂ (10 mL) for 24 h. The product was then rinsed 3 × 10 mL of CH₂Cl₂ and left to soak for 3 days with fresh CH₂Cl₂ added every 24 h before being dried under vacuum (10⁻² Torr) overnight at 150°C.

Synthesis of MN-ZIF-90. A mixture of malonitrile (38 mmol, 2.5 g) and ZIF-90 (2 mmol, 0.5 g) in toluene (100 mL) was stirred at r.t. for 48 h. Then the solid was obtained by centrifugation and washed with DMF (5 × 20 mL), followed by soaking the crystals in CH₂Cl₂ (10 mL) for 24 h. The product was then rinsed 3 × 10 mL of CH₂Cl₂ and left to soak for 3 days with fresh CH₂Cl₂ added every 24 h before being dried under vacuum (10⁻² Torr) overnight at 150°C.

Cell viability test. HeLa cells were cultured in DMEM (containing 10% FBS) in a humidity incubator at 37°C with 5% CO₂ for 72 h. Cells were seeded in 96-well plates at density of 8 × 10³ cells/well. After overnight culture, medium in each wells were replaced by fresh medium containing different concentrations of MN-ZIF-90 or MN-Im. After 48 hours treatment, into each well, 20 μL MTS solution was added. After 4 hours incubation at 37°C, the absorbance of each well at 492 nm was recorded by the plate reader.

Cell imaging. HeLa cells were seeded in a 15 mm petri dish with a glass cover slide. After overnight culture, cells were stained with 0.05 mg/mL MN-ZIF-90 for 48 h. Before imaging, the cells were washed with phosphate buffered saline (PBS) (pH 7.4) solution for two times. For confocal image: the data was acquired with a Zeiss laser scanning confocal microscope (ZIESS, LSM 780).

Characterization. Fourier transform infrared (FT-IR) spectra were recorded on an IRPrestige-21 spectrophotometer. Powder X-ray diffraction (PXRD) patterns were analyzed with monochromatized Cu-Kα (λ = 1.54178 Å) incident radiation by a D8 Advance Bruker powder diffractometer operating at 40 kV voltage and 50 mA current. UV-visible absorption spectra were measured by TU-1901 spectrophotometer. Fluorescence spectra were obtained using an F-7000 fluorescence spectrophotometer. ¹H-NMR spectra were recorded on a Varian mercury-plus 400 spectrometer. Particle size measurements were carried out by dynamic light scattering (DLS) spectrometer (Malvern Zen3600 + MPT-2). Field-emission scanning electron microscopy (FE-SEM) was performed on a JEOL model JSM-7500

F operating at an accelerating voltage of 5.0 kV. Nitrogen sorption isotherm was measured at 77 K on a Quantachrome Instrument ASIQMVH002-5 after pretreatment by heating the samples under vacuum at 150°C for 6 h. CO₂ sorption isotherm was performed at 273 K.

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Acknowledgments

We are grateful to the 973 Program 2013CB834704, the National Natural Science Foundation of China (Project No. Grant NO. 21201018), the 111 Project (B07012).

Author contributions

X.F. and B.W. conceived the research project. H.L., Y.G., D.C., R.L. and X.R. conducted experiments. X.J. and Y.D. gave advice on experiments. X.F., B.W. and H.L. wrote the manuscript. All authors reviewed the manuscript.

Additional information

Supplementary information accompanies this paper at <http://www.nature.com/scientificreports>

Competing financial interests: The authors declare no competing financial interests.

How to cite this article: Li, H.W. *et al.* A malonitrile-functionalized metal-organic framework for hydrogen sulfide detection and selective amino acid molecular recognition. *Sci. Rep.* **4**, 4366; DOI:10.1038/srep04366 (2014).



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