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Design of a calix[4]arene-functionalized metal-organic framework probe for highly sensitive and selective monitor of hippuric acid for indexing toluene exposure

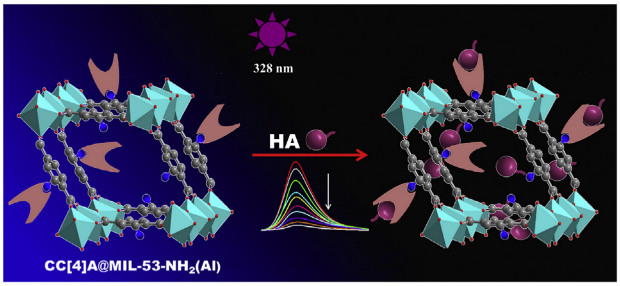
Yaran Du [a], Xiqian Li [b], Haijiao Zheng [a], Xueju Lv [a], Qiong Jia [a, *]

[a] College of Chemistry, Jilin University, Changchun 130012, China
[b] China-Japan Hospital of Jilin University, Changchun 130033, China

HIGHLIGHTS

- Fluorescent CC[4]A@MIL-53-NH_2(Al) was prepared using post-synthetic modification of MOF.
- CC[4]A could simultaneously increase the fluorescence performance and recognition ability.
- CC[4]A@MIL-53-NH_2(Al) displayed fast response, wide detection range, high sensitivity, and selectivity toward HA.
- CC[4]A@MIL-53-NH_2(Al) had potential for naked-eye monitoring HA in urine for judging the degree of toluene intoxication.

GRAPHICAL ABSTRACT



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ABSTRACT

In the present work, a novel metal-organic framework (MOF) fluorescent probe was prepared by post-synthetic modification of MIL-53-NH_2(Al) with carboxylatocalix[4]arene (CC[4]A). The introduced CC[4]A could not only enhance the fluorescence performance and the recognition ability of the probe, but also sustain the high stability under UV light and moisture conditions. A method based on the as-synthesized CC[4]A@MIL-53-NH_2(Al) probe was established for sensing hippuric acid. The detection limit was determined to be as low as 3.7 μg mL^{-1}. Over the concentration range of 0.005–3 mg mL^{-1}, the calibration curve was obtained with a satisfactory linearity ($R^2 = 0.993$). The method was successfully used for rapid and highly selective direct monitor of hippuric acid in human urine. The sensor had great potential to be used as a simple diagnostic tool for hippuric acid in human urine which is regarded as a biological index of toluene exposure.

1. Introduction

Metal-organic frameworks (MOFs), constructed from the coordination of metal ions with organic ligands, have gained increasing attention because of their intriguing framework topology, high surface area, and permanent porosity [1–3]. Such advantages contribute to their extensive applications in the field of gas storage [4,5], drug delivery [6,7], catalysis [8,9], separation [10,11], and chemical sensing [12,13]. For instance, the performances of gas sorption and drug delivery mainly depend on the

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* Corresponding author.
E-mail address: jiaqiong@jlu.edu.cn (Q. Jia).

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high surface area and microporous structure of MOFs. The applications as chemical sensors of MOFs are raised from their composition, *i.e.*, the coordination of metal ions with organic ligands [14,15]. As an alternative, incorporating functional groups into the ligands or opening metal sites may further facilitate MOFs as preferred sensing materials [16].

Post-synthetic modification (PSM) provides a valuable approach for introducing functional groups into MOFs to exploit new materials-based sensors [17–19]. Various PSM methods have been reported in the past decades, most of which were focused on the enhancement of recognition ability toward targets [20]. It is of great significance to develop PSM strategies for simultaneously improving the fluorescence intensity and recognition ability. Lanthanoids and dyes have been employed for this goal, in which lanthanoids-functionalized MOFs were widely reported and used for sensing metal ions, anions, small molecules, and temperature [21]. However, lanthanoid complexes suffer from the limitations of being induced by their relatively poor stability under UV light and moisture conditions [22,23].

As a member of calix[*n*]arenes family, calix[4]arene and its derivatives are well-known since they can be easily synthesized and possess different binding centers such as sulfur, oxygen, and nitrogen sites, benefitting their high selectivity and binding efficiency toward various targets [24,25]. Besides their superior recognition ability, π-conjugated units contained in calix[4]arenes make them competitive when used as fluorescence sensors [26,27]. It can be expected that calix[4]arenes may act as good candidates for PSM of MOFs. Nevertheless, to the best of our knowledge, there have been no reports about the synthesis and utilization of fluorescence sensors combining the advantages of both calix[4]arenes and MOF.

Bearing these points in mind, we herein reported the synthesis of a novel fluorescent material based on the covalent attachment of MOFs and carboxylatocalix[4]arene (CC[4]A) *via* a PSM strategy. CC[4]A was introduced into the framework of MIL-53-NH_2(Al) to increase the fluorescence intensity, active sites, and interaction interface. With this novel CC[4]A@MIL-53-NH_2(Al) fluorescent material, a sensing platform was established for the detection of hippuric acid (HA). HA was selected as the target since it can act as a biological indicator in the monitoring of toluene exposure. As is well known, toluene is a toxic ingredient in solvents, paints, and other household products. Whether the urinary HA level is greater than 2.0 mg mL^{-1} or not is usually used to indicate whether one is over-exposed to toluene according to the ACGIH recommendation [28]. Thus, the fast and efficient detection of HA is critical for reflecting the real toluene exposure and intoxication of human beings. Traditional detection approaches such as gas chromatography, high-performance liquid chromatography, and electrochemical immunoassay are not convenient for practical use because they often involve expensive instruments and complicated procedures [29–31]. In view of these drawbacks, Yan et al. developed a sensing platform based on lanthanide-MOF for the fast fluorescent detection of HA [32]. However, studies about MOF-based probes for HA sensing have been seldom investigated except the above-mentioned literature. It still remains a great challenge to develop simple, facile, and sensitive methods for HA detections. The present work is the first attempt to design a MOF-based fluorescent probe by introduction of macrocyclic compounds and apply it to HA sensing. The introduced CC[4]A could not only enhance the fluorescence performance, but also improve the recognition ability of the probe. Moreover, the probe was determined to be stable under UV light and moisture conditions.

2. Experimental section

2.1. Chemical and materials

Aluminum chloride hexahydrate ($AlCl_3 \cdot 6H_2O$), *N*-hydroxysulfosuccinimide (sulfo-NHS), 1-ethyl-3-(3-(dimethylamino)propyl)carbodiimide (EDC), and *N*,*N*-dimethylformamide (DMF) were purchased from Aladdin Reagent (Shanghai, China). 2-Amino-1,4-benzenedicarboxylic acid (NH_2-BDC) and HA were obtained from Sigma-Aldrich Company (St. Louis, MO, USA). Creatinine (Cre), creatine, urea, uric acid (UA), and glucose (Glu) were supplied by J&K Scientific Ltd. (Beijing, China). Methanol (MeOH), sodium sulfate (Na_2SO_4), sodium chloride (NaCl), potassium chloride (KCl), and ammonium chloride (NH_4Cl) were purchased from Beijing Chemical Works (Beijing, China). CC[4]A was synthesized and purified by recrystallization according to a previous report [33].

2.2. Characterizations

Powder X-ray diffraction (PXRD) patterns were recorded using a D/Max-IIIC instrument (Rigaku, Japan) with Cu Kα radiation and the range of 2θ was 5–40°. XPS data were collected with an X-ray photoelectron spectrometer (Thermo Electron, USA). Elemental analysis was conducted with a Vario EL cube (Elementar Analysensysteme GmbH, Germany). Fourier-transform infrared (FT-IR) spectra were obtained using a Spectrum One FT-IR spectrometer (Perkin-Elmer, USA) with the recorded range of 4000–450 cm^{-1}. The thermogravimetric analysis/derivative thermogravimetric determinations (TGA-DTG) were obtained with an STA-449C thermal gravimetric analyzer (Netzsch Company, Germany). Surface area measurements were taken on an ASAP 2420 gas adsorption instrument (Micromeritics, Atlanta, USA). A UV light with an irradiation of 365 nm was used to investigate the fluorescence performance. The fluorescence emission spectra of different samples were collected on an FL5301 fluorescence spectrophotometer (Shimadzu Company, Japan). The fluorescence lifetime and absolute fluorescence quantum yield were determined with an FLS920 fluorescence spectrophotometer (Edinburgh Instruments, England).

2.3. Synthesis of MIL-53-NH_2(Al)

MIL-53-NH_2(Al) was synthesized according to a previous report [34]. Briefly, 3 mmol NH_2-BDC was dissolved in 20 mL water under the magnetic stirring. 10 mL water containing 3 mmol $AlCl_3 \cdot 6H_2O$ was dropped into the above mixture and stirred for 1 h. Then the as-obtained mixture was placed in a Teflon-lined steel autoclave and heated at 150 °C for 5 h. After the acquired yellowish was cooled overnight, it was separated and rinsed with water thoroughly. Then, the product was dispersed in 20 mL DMF and stirred for 24 h to remove the unreacted reagents. Thereafter, the product was soaked in MeOH for 72 h and then dried at 70 °C in vacuum for 24 h.

2.4. PSM of CC[4]A@MIL-53-NH_2(Al)

Firstly, 50 mg CC[4]A was completely dispersed in 50 mL water by ultrasonication for 3 h. Then 50 mg EDC and 20 mg sulfo-NHS were added and stirred for 15 min to activate the carboxyl groups of the composites followed by the addition of 20 mg MIL-53-NH_2(Al) under stirring for 72 h. After the filtration step, the solid was washed with water and soaked in MeOH to remove the unreacted reagents. Thereafter, the product was dried under vacuum at 55 °C to obtain a yellowish powder.

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