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The point-of-care colorimetric detection of the biomarker of phenylamine in the human urine based on Tb^{3+} functionalized metal-organic framework

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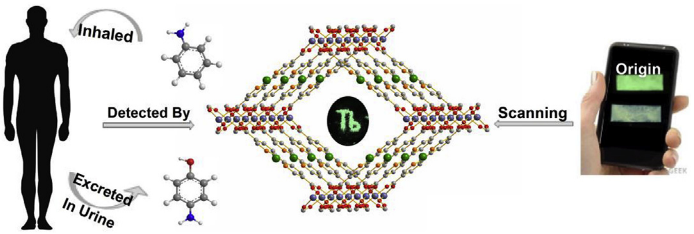
HIGHLIGHTS

- A probe to PAP, biomarker of phenylamine in human urine.
- Sensing with high sensitivity, high selectivity and quick response.
- A simple and cost-effective smartphone-based medical portable tool for at home monitoring of PAP.
- The sensor based on the luminescent Tb^{3+}-loaded MOFs through the post-synthetic loading.

GRAPHICAL ABSTRACT



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ABSTRACT

Phenylamine has been recognized as one of the most important industrially relevant ingredient and a crucial intermediate in chemical products. Yet, its internal exposure detection in human remains largely elusive due to the lack of potent monitoring method. Hereby this issue is addressed with a probe based on lanthanide functionalized organic-inorganic hybrid material Al(OH)(bpydc) (**1**) through post-synthetically modified metal-organic framework. The as-synthesized Tb^{3+}@**1** exhibits the strong luminescence of Tb^{3+} originated from efficient energy transfer from the ligand, which can sense the biological metabolite *p*-aminophenol (PAP) of the phenylamine in the human urine. Linear correlation between the integrated fluorescence intensity and the concentration of PAP was investigated, enabling quantitative analysis of PAP in physiologically ranges (0.005–5 mg mL^{-1}) with low detection limit (5 μg mL^{-1}). This probe demonstrates excellent sensitivity, high selectivity, good reusability and quick response to PAP. Furthermore, a simple and rapid smartphone-based medical portable test paper was developed, whose quantitative color change can be easily distinguished visually. Hence, the PAP sensing platform can serve as a potential diagnostic tool for home monitoring of PAP.

1. Introduction

Phenylamine is an important industrially relevant ingredient which is widely used in the synthesis of dyes, and also serves as a crucial intermediate in the producing of pesticides, rubbers, perfumes, oil paint, and other chemical products [1–3]. However, it is a highly toxic compound, which can quickly be absorbed into the human body through the skin, digestive tract and respiratory tract [4]. Because of their extensive utilization in industry, the phenylamine and its derivatives are also considered as the source of contaminants for soil and the aquatic environments [5,6]. Notably,

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the hazardous substances can be enriched through food-chain in the plants and animals. A short-time exposure with a megadose of the amine can produce acute intoxication; however, long-term exposure to such toxins has been associated with an elevated risk of cancer of the bladder cancer and hepatic carcinoma [7]. The *p*-aminophenol (PAP) is the primary urinary metabolite of phenylamine, acetophenetidin and acetaminophen, and unmeant tiny urinary PAP can arise from exposure to one or all of these medicine [8,9]. Therefore, a simple, reliable, and quick sensor system for the determination biomarker is desirable in occupational health care.

Exposure biomarkers are useful in environment epidemiology as indicators of internal dose that account for all routes of exposure [10]. Nowadays, biological monitoring of exposure is the most frequently used methodology for the detection of exposure to chemicals and particularly most effective in non-invasive samples including urine that are relatively simple to collect for population-based exposure studies [11]. This has been an alternative method to the conventional sampling method for the detection of the biomarker of exposure of the phenylamine. Nevertheless, the traditional methods for the diagnosis of biomarkers including ELISA and HPLC are expensive, time-consuming, and laborious and often require specialized facilities. Self-diagnostic tools for monitoring urine have been described for a long time, however, their widespread adoption has been limited by the relatively high cost of acquiring the equipment. Recently, a study demonstrated that the users need portable device to monitor the risk and the kits would frequently be used if they are efficient and relatively inexpensive to access [12].

Over the recent decade, the cell-phone based devices have been developed in bioanalytical sciences, including “read-out” colorimetric detection [13]. Moreover, a cell phone has been considered as potential promising electronic device for the point-of-care (POC) diagnostic [14]. The POC colorimetric device is used for detection and quantification of colorimetric test strips, which is based on chromaticity values in acquired images to analyze the concentration recorded by the cellphone camera [15–18].

Metal-organic frameworks (MOFs) are fabricated by linking metal ions with bridging organic ligands, which have been developed as a novel class of open framework of crystalline porous materials with high structural tunability and flexibility [19,20]. The luminescence properties arising from Laporte forbidden 4f-4f transitions of the lanthanide ions, exhibit a long-lived characteristic narrow bandwidth [21]. However, direct excitation of the lanthanide ions rarely emits strong luminescence. Furthermore, the organic ligands of MOFs often comprise of aromatic that can participate in energy transfer process to lanthanide ions, known as “antenna effect” [22]. The post-synthetic encapsulation of lanthanide ions into MOF provides a promising analytical method to recognize tunable luminescence and prepares luminescence sensing probes. Consequently, the lanthanide metal-organic frameworks have been recognized as an excellent platform for implementation in sensing [23,24], including oxygen [25,26], metal ions [27–29], explosive chemicals [30,31], and various aromatic compounds [32].

The present study aimed to investigate the effectiveness of a lanthanide-ion based MOF Al(OH)(bpydc) (**1**), which had not been described as an alternative sensor for efficient and highly sensitive detection of PAP in the simulated urinary sample and realistic assay. The MOF, prepared from an uncoordinated ligand, enabled and generated the luminescent lanthanide (III)-loaded MOFs through the post-synthetic loading. Besides, the porous Tb^{3+} loaded MOF with excellent stability and outstanding optical properties can be used as a potential luminescent probe for the detection of the metabolite of phenylamine in human urine and the results could be a warning sign before further screening. Furthermore, we developed a simple and cost-effective smartphone-based medical portable tool for at home monitoring of PAP. Moreover, the quantitative color change can be easily distinguished visually, which is proportional to the concentration of PAP absorbed in the test strip. Thus, in the present study, we have developed a potential promising system for the simple, accurate and instantaneous quantification of PAP concentration by measuring the quantitative color change in human urine for further practical application.

2. Experimental section

2.1. Materials and reagents

All chemical used were commercially available organic reagents and were of reagent grade. Unless otherwise specified, reagents were used as received without further purification. Deionized water was used throughout the experiments. $AlCl_3 \cdot 6H_2O$ (241.43 g mol^{-1}) and 2,2′-bipyridine-5,5′-dicarboxylic acid (H_2bpydc, 244.20 g mol^{-1}), and sodium acetate (136.03 g mol^{-1}) were procured from Sigma-Aldrich. Lanthanide chloride salts of Tb^{3+} were prepared by dissolving the corresponding oxide compounds quantitatively in 37.5% HCl followed recrystallization.

2.2. Experimental equipment

The structure was analyzed using X-ray diffraction (XRD), on a Bruker D8 diffractometer Germany with CuK α radiation (40 mA and 40 kV). The photoluminescence excitation and emission spectra for sensing of the PAP were obtained on an Edinburgh FLSP 920 luminescence spectrophotometer using a 450 W Xenon lamp as a source of excitation with an appropriate cut-off filter. The decays were determined employing pulsed flash lamps. The Fourier transform infrared (FTIR) spectra were recorded on a Nexus 912 AO445 spectrophotometer in the range 4000–400 cm^{-1} by using the KBr disk method. The UV–vis diffuse reflectance spectra were obtained by UV-visible absorption spectroscopy with BWS003. Thermal gravimetric analysis (TGA) was carried out with a Netzsch ST A 449C system with a temperature program from 40 °C to 800 °C at a heating rate of 5 K min^{-1} under nitrogen atmosphere in the Al_2O_3 crucibles. Scanning electronic microscope (SEM) images were recorded with a Hitachi S-4800. Transmission electron microscopy (TEM) was carried out on a JEOL JEM-2010F electron microscope and operated at 200 kV. Concentrations of Al and Tb were determined by using an X-7 series ICP-MS (Thermo Elemental, Cheshire, UK) after the nanostructure was decomposed with concentrated nitric acid. XPS experiments were performed on a RBD upgraded PHI-5000C ESCA system (Perkin Elmer) with MgKa radiation ($h\nu = 1253.6$ eV).

2.3. Synthesis of Al(OH)(bpydc)

Synthesis of Al(OH)(bpydc) (**1**) was synthesized according to the procedure described in literature [33]. Briefly, the $AlCl_3 \cdot 6H_2O$ (151 mg, 0.635 mmol), 2,2′-bipyridine-5,5′-dicarboxylic acid (153 mg, 0.625 mmol) and 10 mL N,N′-dimethylformamide (DMF) were placed in a Teflon-lined stainless steel reactor and stirred for 30 min. Then, sodium acetate was slowly added to the mixture. The resulting mixture was heated at 120 °C for 24 h. After that, the reaction mixture was cooled to room temperature, filtered and washed three times with DMF. The white microcrystalline powdered product was vacuum dried at 80 °C. The yield obtained was around 90%. The resulting solid was then washed with methanol by Soxhlet extraction for 24 h at 80 °C to eliminate the impurities in the pores of the framework. Then the samples were activated by drying at 80 °C overnight under vacuum.