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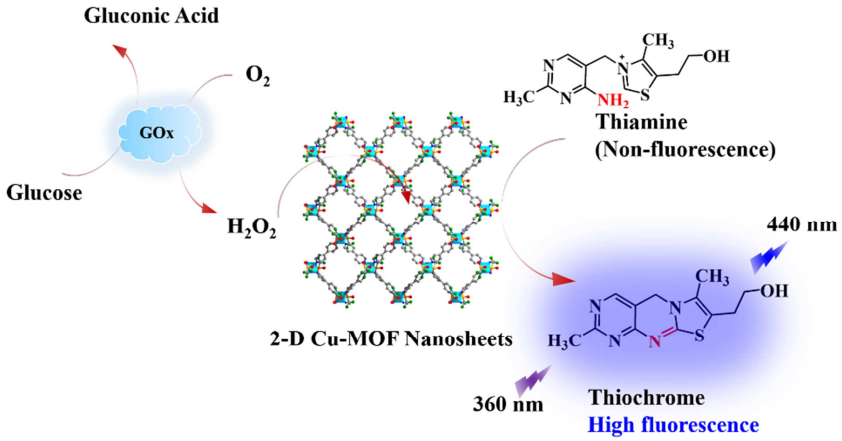
Graphical Abstract



Copper-based Two-Dimensional Metal-Organic Framework Nanosheets as Horseradish Peroxidase Mimics for Glucose Fluorescence Sensing

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ABSTRACT

Ultrathin two-dimensional (2D) metal-organic framework (MOF) nanosheets have attracted numerous attention due to their unparalleled advantages such as unique structures, large surface areas, good stability and high catalytic efficiency. In this paper, 2D $Cu(bpy)_2(OTf)_2$ nanosheets (Cu-MOF, bpy = 4,4-bipyridine, OTf = trifluoromethanesulfonate) are first utilized to achieve the fluorescent detection for H_2O_2 and glucose with their intrinsic peroxidase-like activity. The fluorescent biosensor Cu-MOF nanosheets were achieved by the efficient catalysis of non-fluorescent thiamine (TH) to strong fluorescent thiochrome in the presence of H_2O_2. With the combination of glucose oxidase, highly selective and sensitive fluorescent detection for glucose could be established with a detection limit of 0.41 μM and two separate linear ranges of 10–100 μM and 100–1000 μM, respectively. Furthermore, the developed method has been applied to human serum for the quantitative determination of glucose as a clinical diagnosis indicator of diabetes mellitus.

Keywords: fluorescence; metal-organic frameworks; nanosheets; H_2O_2; glucose

INTRODUCTION

Natural enzymes are recognized as one of the most efficient catalysts for a wide variety of biochemical reactions[1]. With high activity and specificity, natural enzymes have attracted significant attention in the applications such as medicine, biotechnology, and environmental engineering [2]. However, the applications of enzymes in industry are limited because of the high cost, specific reaction conditions and the fragile nature of enzymes themselves [3]. It is highly desirable to develop biocompatible materials to mimic the functions of nature enzymes. Therefore, many artificial enzymes have been reported to possess enzyme mimetic activity previously [4].

Natural horseradish peroxidase (HRP) is an important heme-containing enzyme with extensively practical and commercial applications [5]. In 2007, Fe_3O_4 nanoparticles was first reported as artificial peroxidase by Yan and co-workers [2]. Subsequently, other metal oxide nanomaterials such as CuO [6], CeO_2 [7], Co_3O_4 [8], and ZnO [9] were also reported. Meanwhile, gold nanoparticles [10], transition metal dichalcogenides (TMDs) [11], carbon nanoparticles [12], and graphene oxide have been demonstrated to possess peroxidase-like activity previously and successfully applied in the sensing area. Compared with HRP, these artificial enzymes are low cost, stable, and have tunable catalytic activity [13-14]. However, the synthetic procedures of artificial peroxidases are usually complicated and some of peroxidase mimics suffer from low catalytic activity [15-17]. Therefore, developing new artificial peroxidases with high catalytic activity, easy synthesis, and excellent stability has

important practical significance.

Metal–organic frameworks (MOFs) are a typical class of crystalline porous materials [18]. Because of their high specific surface areas, tunable pores, and diverse functionalities, MOFs are widely used in gas capture and storage, chemical sensing, biomedical imaging and catalysis [19-22]. Moreover, MOFs were emerged as one of the most promising materials to develop novel artificial enzymes due to their tunable structures and water-stable properties [23-24]. Up to now, bulk MOFs have successfully been reported as artificial enzymes [25-27]. However, the bulk crystals of these MOFs gave inhomogeneous dispersion in water, meanwhile, the active sites on the inner surface were usually limited because of the confined pore size. To solve these problems, 2D MOF nanosheets have attracted increasing interest, recently [28]. Compared to the bulk MOF crystals, 2D MOF nanosheets possess larger surface area which can facilitate the approaching of substrate molecules towards the active sites on their surface with minimal diffusion barriers, and thus improve their performance in catalysis and sensing application [29-30]. Therefore, 2D MOF nanosheets with unique properties might have better performance in enzymatic catalytic reaction, which has been rarely explored in the fluorescence detection system.

In this work, we demonstrated that the Cu-based 2D MOF nanosheets, also known as $Cu(bpy)_2(OTf)_2$ (Cu-MOF, bpy = 4,4-bipyridine, OTf = trifluoromethanesulfonate) [31], have peroxidase-like activity and could be used for H_2O_2 and glucose sensing. The selection of this Cu-based MOF nanosheets over common Cu-carboxylate MOFs was primarily based on the stability because the

coordination between pyridine and copper of this nanosheets was stable in basic conditions while copper carboxylate MOFs were less stable in basic solution. The choice of ligands in the MOF nanosheets was also critical. The ligand of bpy was stably connected to form 2-D networks with the coordination of Cu(II), while the OTf acted as spacing ligand during the exfoliation. The 2D Cu-MOF nanosheets were used as an artificial peroxidase and thiamine (TH), namely vitamin B_1, was used as a substrate [32]. The non-fluorescent substrate TH could be readily converted to intensely fluorescent product thiochrome (TC) in basic solution with the appearance of H_2O_2 and peroxidase [33-34]. This principle can be used to directly detect the H_2O_2 as well as detect the glucose indirectly by coupling glucose oxidase (GOx) by fluorescence sensing [35]. Compared with colorimetric detection, fluorescence has higher sensitivity, better selectivity and wider linear range. Herein, a sensitive fluorescent method for the determination of H_2O_2 and glucose would be developed with the detection limit as low as 0.32 μM for H_2O_2 and 0.41 μM for glucose. Furthermore, the developed method has been successfully applied to quantitative determination of glucose for human serum, which is in accordance to the conventional results.

EXPERIMENTAL SECTION

Chemicals and Instrumentation

Copper trifluoromethanesulfonate ($Cu(OTf)_2$), 4,4-bipyridine (bpy), TH, glucose, sodium hydroxide, sodium carbonate, sodium bicarbonate, 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES), glucose, maltose,

maltotriose, maltotetraose and fructose were purchased from Aladdin Industrial Inc (Shanghai, China). Glucose oxidase (GOx, 100 U/mg) from Aspergillus Niger was also purchased from Aladdin and stored in a refrigerator at -18 ^{o}C. H_2O_2 (30%), tryptophane (Trp), ethanol (EtOH) and acetone were obtained from Sinopharm Chemical Reagent Co., Ltd (Shanghai China). After the standard clinical procedures, the serum samples were obtained from Jiangsu Province Hospital of TCM (Affiliated Hospital of Nanjing University of Chinese Medicine). All other reagents were used without further purification. Ultrapure water was prepared in the lab (18 MΩ·cm) by an ELGA purification system (Veolia Water Solutions & Technologies, UK).

An F-4600 fluorescence spectrophotometer (Hitachi High-Tech Science Co. Japan) was used to measure fluorescence spectrum. Rigaku D/MAX-2500 diffractometer was used to obtain an X-ray diffraction (XRD) pattern with a Cu Kα radiation (1.54056 Å). Scanning electron microscope (SEM) images were obtained on a JSM-7600F (JEOL Ltd) scanning electron microscope. Transmission electron microscopy (TEM) analyses were performed on H7650 with an accelerating voltage of 120 kV. Atomic force microscopy (AFM) measurement was performed with a PicoPlus in tapping mode (Agilent, US).

Synthesis of $Cu(bpy)_2(OTf)_2$

The 2D Cu-MOF nanosheets were prepared by exfoliation from the bulk MOFs. Bulk Cu-MOF was prepared according to the previous reports with only a few changes [31, 36]. Typically, 10.0 mL of 30.0 mM $Cu(OTf)_2$ aqueous solution was added to a 22 mL glass vial upon which 1 mL of pure ethanol was layered

meticulously. Then, 10.0 mL of ethanol solution of bpy (60.0 mM) was layered onto the ethanol layer which was left to stew for 3 weeks at room temperature. The dark blue crystals were obtained by centrifugation, and washed five times with acetone and ethanol. To obtain 2D Cu-MOF nanosheets, the Cu-MOF were placed in distilled water and stirred for 9 h. A dispersed solution was obtained after removal of the precipitate. The collected 2D Cu-MOF nanosheets were obtained by centrifugation at 12000 rpm for 20 min and dried at room temperature.

H_2O_2 and Glucose Sensing

H_2O_2 detection was performed as follows: (a) 50 μL of 10 mM TH, 50 μL of 0.02 $mg \cdot mL^{-1}$ Cu-MOF and H_2O_2 with different concentrations were added to Na_2CO_3-$NaHCO_3$ buffer (0.1 M, pH=10.0) to reach a final volume of 1.0 mL. (b) The mixed solution was incubated at 55 ^oC for 3 min and then used for determination of H_2O_2. The fluorescence spectrum of oxidized product TC at 440 nm with a 370 nm excitation from TH was measured to quantify the concentrations of H_2O_2.

Glucose sensing was performed by the hybrid of enzymatic oxidation of glucose and above H_2O_2 detection: (a) 10 μL of 4.0 $mg \cdot mL^{-1}$ GOx and 10 μL to 100 μL of glucose stock solutions (1 mM and 10 mM, respectively) were added to 1 M HEPES buffer (pH=7.0) to reach final volume of 150 μL. Then, the mixed solution was incubated at 37^oC for 30 min. (b) 50 μL of 10 mM TH, 50 μL of 0.02 $mg \cdot mL^{-1}$ Cu-MOF and 750 μL of 0.1 M Na_2CO_3-$NaHCO_3$ buffer were added into the above solution to get final glucose concentrations from 0.01 mM to 1 mM. (c) The fluorescence spectrum of oxidized product TC from TH at 440 nm with a 370 nm

excitation was measured to quantify the concentrations of glucose after the incubation at 55^{o}C for 3 min.

Preparation of Serum Samples

The standard addition method was used for the detection of glucose in serum samples. Firstly, 25 μL of serum samples with standard clinical procedures were added in centrifuge cubes. Then, acetonitrile (acetonitrile : serum= 3:1, v/v) was added to remove the high-abundance proteins by the collection of supernatant after centrifugation (3000 rpm) for 10 min. Thereafter, different concentrations of glucose (1, 2, 3 and 4 mM) were added to the above mixtures.

RESULTS AND DISCUSSION

Characterization of Bulk Cu-MOF and Cu-MOF Nanosheets

The successful synthesis of Cu-MOF and its exfoliation to 2D Cu-MOF nanosheets were fully characterized before the MOF nanosheets were used for the sensing experiments. The prepared bulk Cu-MOF showed the same XRD pattern as the simulated one (Fig. 1a), confirming the successfully synthesis of bulk Cu-MOF. The SEM images of the bulk Cu-MOF showed the layered structures (Fig. S1a). The bulk Cu-MOF exhibited a non-typical adsorption isotherm at 77 K with Brunauer–Emmett–Teller (BET) surface area of 10.3 $m^2 \cdot g^{-1}$ and a total pore volume of 0.175 $cm^3 \cdot g^{-1}$, indicating the framework flexibility (Fig. S2) [36]. Subsequently, 2D Cu-MOF nanosheets with a thickness of few layers were successfully obtained after exfoliation and confirmed by SEM and TEM (Fig. 1b and 1c). To confirm the stability of 2D Cu-MOF nanosheets in aqueous solution with pH of 10, TEM images of 2D

Cu-MOF nanosheets after socking into pH = 10 Na_2CO_3-$NaHCO_3$ buffer for 2 h were measured by directly loading the nanosheet suspension onto carbon coated TEM grid (Fig. 1d). Obviously, the TEM image performed almost no difference. Meanwhile, the Tyndall scattering of this 2D nanosheets in the same buffer was unchanged after 18 h, which indicated the good stability of the material in our experimental conditions. (Fig. S1b). AFM image also revealed the synthesized material was 2-D Cu-MOF nanosheets with ultrathin thickness of 1.0 nm rather than 3-D aggregates (Fig. S3). It was worth noting that without the formation of 3-D aggregates, the porosity of 2-D nanosheets were usually very low, when measured with N_2 gas molecules. The high solubility of the nanosheets in water guaranteed the exposure of the active sites and their contact with substrate molecule during the catalysis although low surface area was measured in the solid phase. The good solubility resulted in the difficulty in the recycling experiments in which the nanosheets were hard to be collected from the centrifugation.

Peroxidase-Like Activity of $Cu(bpy)_2(OTf)_2$ Nanosheets

The peroxidase-like activity of 2D Cu-MOF nanosheets was evaluated by catalyzing the peroxidase substrate TH in the presence of H_2O_2. The catalytic mechanism of Cu(II) in basic conditions for the oxidation of TH has been established as the generation of hydroxyl radicals (·OH) from the decomposition of H_2O_2 [34, 37]. At the meantime, Cu could also stabilize the intermediate dihydrothiochrome, which is generated by the rapid and reversible deprotonation from TH [38]. Stabilization of this dihydrothiochrome intermediate with thiophilic metals, such as Cu(II), Ag(I) and

Hg(II) is crucial because it prevents side reaction leading to non-fluorescent thiamine disulfide (TDS). Further oxidation of the dihydrothiochrome intermediate by ·OH to TC is quite similar to the peroxidase-activated process. As shown in Fig. 2, the substrate TH performed no fluorescence, while only after adding the 2D Cu-MOF nanosheets and H_2O_2, the strong emission of TC at 440 nm was obtained, confirming the peroxidase-like activity of Cu-MOF nanosheets. It is worthwhile to know that a very weak fluorescence can be observed from the Cu-MOF-TH system and TH-H_2O_2 system, which represents the practical background in the applications for the detection of H_2O_2. Thus, the above control experiments further confirm the biomimetic catalytic activity of 2-D Cu-MOF in the presence of H_2O_2.

Optimization of Experimental Conditions

The fluorescence intensity of Cu-MOF is optimized with the changes of pH, reaction time and temperature. As shown in Fig. 3a, from pH of 7 to 11.5, a volcano plot was obtained with the maximum catalytic activity of Cu-MOF at pH of 10. This is probably because the mild alkaline condition is beneficial to the faster generation of hydroxyl radical from H_2O_2, thus rendering high catalytic activity and fluorescence intensity. However, when the solution pH was above 10, the decreased fluorescence intensity is observed and probably due to the low stability of 2D Cu-MOF nanosheets at high alkaline media. Meanwhile, time-dependent fluorescence of Cu-MOF nanosheets showed that the reaction was almost finished within 1 min. However, 3 min was chosen to make sure the stability of the experiment results (Fig. 3c). In addition, the temperature could change the reaction kinetics with the fixed time of 3

min. Higher temperature is favorable for the faster reaction rate within a certain range, resulting in higher fluorescence intensity. While, when the reaction temperature was higher than 55 ^{o}C, the fluorescence intensity performed almost no difference. To obtain the maximum fluorescence, 55 ^{o}C were recognized as the optimized temperature for the following experiments (Fig. 3b). For the sensing of glucose, the concentration of GOx was also optimized as 40 μg·mL^{-1}(Fig. S4). Under the optimal condition, the fluorescence catalyzed by Cu-MOF nanosheets was higher than the bulk Cu-MOF and HKUST-1 [39] (Fig. S5) due to the ultrathin thickness and large numbers of exposed active sites (Fig. 3d). We have also performed control experiments with ligand bpy and Cu ions. The bpy ligand showed no catalytic activity, while higher fluorescence intensity was obtained with Cu-MOF nanosheets than Cu ions, possibly due to the hydrolysis of Cu ions in the basic conditions and the formation of less active Cu hydroxide (Fig. S6).

Steady-State Kinetic Assay of 2D Cu-MOF nanosheets

The steady-state kinetic experiments were performed to investigate the kinetic mechanism for the peroxidase-like activity of Cu-MOF nanosheets by changing the concentrations of H_2O_2. Kinetic experiments were monitored at 55 ^{o}C for the initial reaction period (10, 20, 30, 40, 50 and 60 s) using 20 μg·mL^{-1} Cu-MOF in a volume of 1.0 mL of Na_2CO_3-$NaHCO_3$ buffer solution (0.1 M, pH=10) with 0.5 mM TH as substrate (Fig. S7). The kinetic parameters such as the maximal reaction rate and the Michaelis-Menten constant, were calculated based on Lineweaver–Burk plots.

$$\frac{1}{v} = \frac{K_m}{v_{max}[C]} + \frac{1}{v_{max}}$$

where v is the initial reaction rate, C is the H_2O_2 concentration. In essence, a lower value of K_m and a higher value of V_{max} demonstrated the relatively stronger affinity between the catalyst and substrate as well as higher catalytic activity, respectively. The V_{max} value of the 2D Cu-MOF nanosheets with H_2O_2 as substrates was significant smaller than that of natural horseradish peroxidase (HRP) and other biomimetic materials, possibly due to the very different pH conditions [40-41]. In addition, it was remarkable that the K_m value for our 2D MOF-based nanosheets was much lower than HRP and the most of reported peroxidase mimics [17, 41], suggesting that a relatively lower concentration of H_2O_2 was competent to achieve the maximum peroxidase-like catalytic activity in our nanosheets system. This is a strong indicative parameter to show the affinity between H_2O_2 substrate and the 2D Cu-MOF nanosheets.

H_2O_2, TH and Glucose Sensing based on Cu-MOF Nanosheets

The Cu-MOF nanosheet has the intrinsic peroxidase properties, so a fluorescent sensing platform for detection of H_2O_2 has been established. Since the catalytic activity of the Cu-MOF nanosheet is highly dependent on the concentration of H_2O_2 in the solution, the method could be used for the quantitative measurement of H_2O_2. After the reaction for 3 min at 55 ^oC, the fluorescent intensity of mixture was recorded at 440 nm with a 370 nm excitation for the quantitation of H_2O_2. As shown in Fig. 4, there is the good linear correlation between the fluorescent intensity and the H_2O_2 concentrations in two ranges of 10-100 μM (R^2=0.998) and 100-1000 μM (R^2=0.992),

respectively. The phenomenon of two ranges of linearity is due to the enzyme-like saturation effect of Cu(II) sites on the heterogeneous surface at 2-D Cu-MOF nanosheets, which is often observed in nanoparticle-based sensors and enzyme-linked immunosorbent assay.[42] It is also worth noting that the linear range of 2-D Cu-MOF nanosheet is much wider than HRP (Fig. S8), which could only catalyzes H_2O_2 at low concentrations (0-60 μM). The detection limit is 0.32 μM on the basis of a single-to-noise ratio of 3:1. Compared with HRP, Cu NCs[17] and CuNPs@C [41], Cu-MOF nanosheet has lower detection limit. The 2-D Cu-MOF nanosheets could also be utilized as sensor for TH (Vitamin B1) with the fixed H_2O_2 concentration (Fig. S9).

Monitoring blood glucose is important for the diagnosis and management of diabetes, while H_2O_2 is the main product of the glucose oxidation by glucose oxidase (GOx). It means that the proposed fluorescent method could be used for the determination of glucose with the coupling of GOx. Fig. 4b showed typical glucose concentration-response curves. The liner range for glucose was from 10-100 μM (R^2=0.995) and 100-1000 μM (R^2=0.993), respectively, with a detection limit of 0.41 μM.

Selectivity and determination of Glucose in Serum Samples

To determine the selectivity of glucose, 1 mM K^+, sucrose, maltose, fructose, tryptotriose, maltotriose, uric acid and glucose were added into the solution. It shows that the glucose results in a significant fluorescence intensity comparing with others. The selectivity of the proposed method works well for the determination of glucose.

To demonstrate the applicability of this system, the proposed method was applied to the determination of glucose in human serum samples (Table 2). The results of our method were in good agreement with those obtained by the conventional glucose meter method, confirming the feasibility and reliability of the proposed method.

CONCLUSIONS

In conclusion, the water-stable 2D Cu-MOF nanosheets possessed intrinsic peroxidase-like activity, which had the features of low cost, high stability and easy preparation. With the optimized pH, temperature and reaction time, the simple fluorescent method for glucose detection had been developed, which showed high sensitivity and excellent selectivity. The design and fabrication of porous and ultrathin 2D MOF materials as biomimetic catalyst will be promising in the future applications.

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Figure legends

Fig. 1. (a) The Cu-MOF XRD patterns of the simulation one (black) and as-synthesized (red). (b) SEM image and (c) TEM image of the 2D Cu-MOF nanosheets. (d) TEM image of 2D Cu-MOF nanosheets in aqueous solution with pH of 10 after 2 hours.

Fig. 2. Emission spectra of TH alone (black), in the presence of H_2O_2 (green), in the presence of Cu-MOF (red) and in the presence of Cu-MOF and H_2O_2 (blue).

Fig. 3. The influence of (a) pH, (b) temperature and (c) reaction time on fluorescence intensity. (d) The comparison of biomimetic catalyst 2D Cu-MOF nanosheets with bulk Cu-MOF and HKUST-1. 50 μL of 10 mM TH, 50 μL of 0.02 mg·mL^{-1} Cu-MOF and 10μL 1M H_2O_2 were added to Na_2CO_3-$NaHCO_3$ buffer (0.1 M) to reach a final volume of 1.0 mL.

Fig. 4. The calibration curve for H_2O_2 and glucose. (a) 50 μL of 10 mM TH, 50 μL of 0.02 mg·mL^{-1} Cu-MOF and H_2O_2 with different concentrations were added to Na_2CO_3-$NaHCO_3$ buffer (0.1 M, pH=10.0) to reach a final volume of 1.0 mL. (b) 10 μL of 4.0 mg·mL^{-1} GOx, glucose with different concentrations, 50 μL of 10 mM TH, 50 μL of 0.02 mg·mL^{-1} Cu-MOF and 750 μL of 0.1 M Na_2CO_3-$NaHCO_3$ buffer were added into the solution to get final glucose concentrations from 0.01 mM to 1 mM. Error bars represent the standard deviation for three measurements.

Fig. 5. The selectivity test for glucose. The analytes are K^+, sucrose, maltose, fructose, tryptophane, maltotriose, uric acid and glucose with the concentration of 1 mM.

Table 1. Comparison of the kinetic parameters for the H_2O_2 as substrate catalyzed by HRP, Cu NCs, CuNPs@C and the 2D Cu-MOF nanosheets.

Catalyst	Solution pH	V_{max} (10^{-8} M·s^{-1})	K_m (mM)	Reference
HRP	4.0	8.71	3.7	[2]
Cu NCs	6.0	4.22	29.16	[17]
CuNPs@C	4.0	5.3	1.89	[37]
2-D Cu-MOF nanosheets	10.0	0.16	0.385	This work

Table 2. Results of glucose concentrations in the diabetic and control serum samples

No.	this method (mM)	glucose oxidase method (mM)
diabetic 1	14.31	14.13
diabetic 2	11.78	10.45
diabetic 3	11.54	11.38
diabetic 4	7.60	7.56
control 1	4.74	5.08
control 2	5.61	5.32

Figure 1

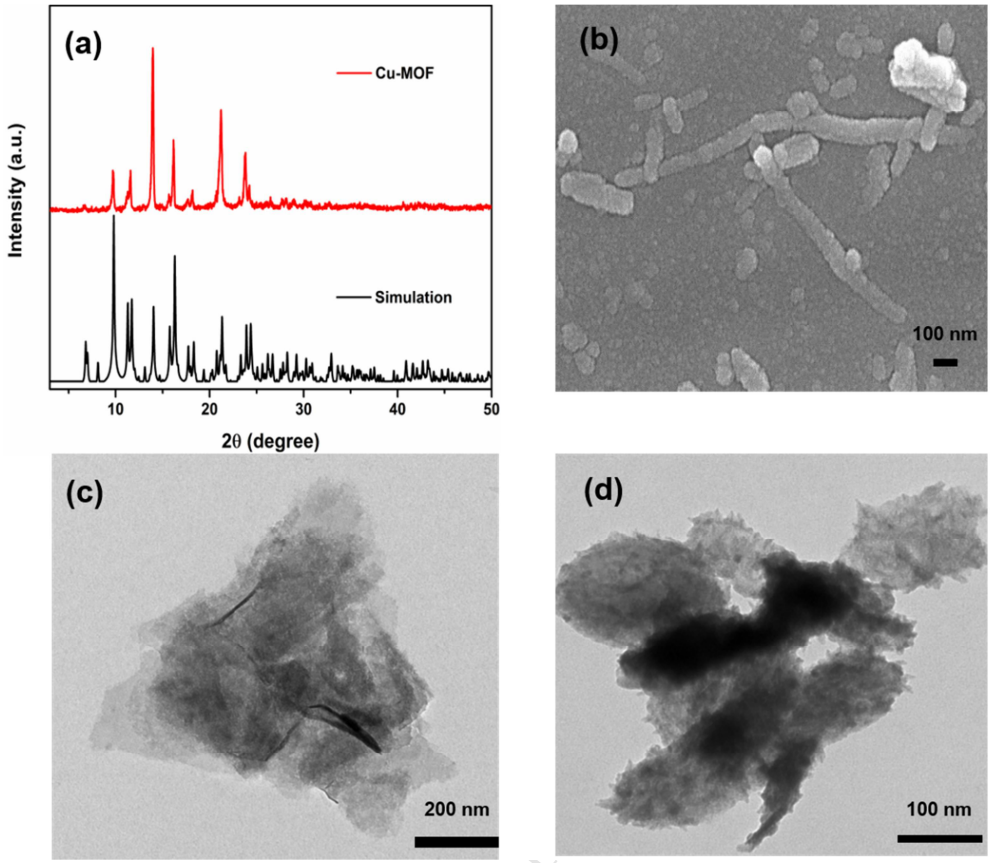


Figure 2

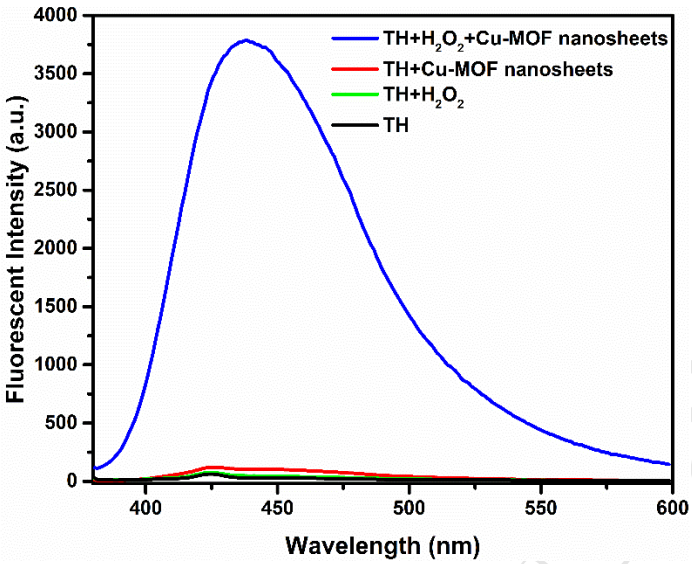


Figure 3

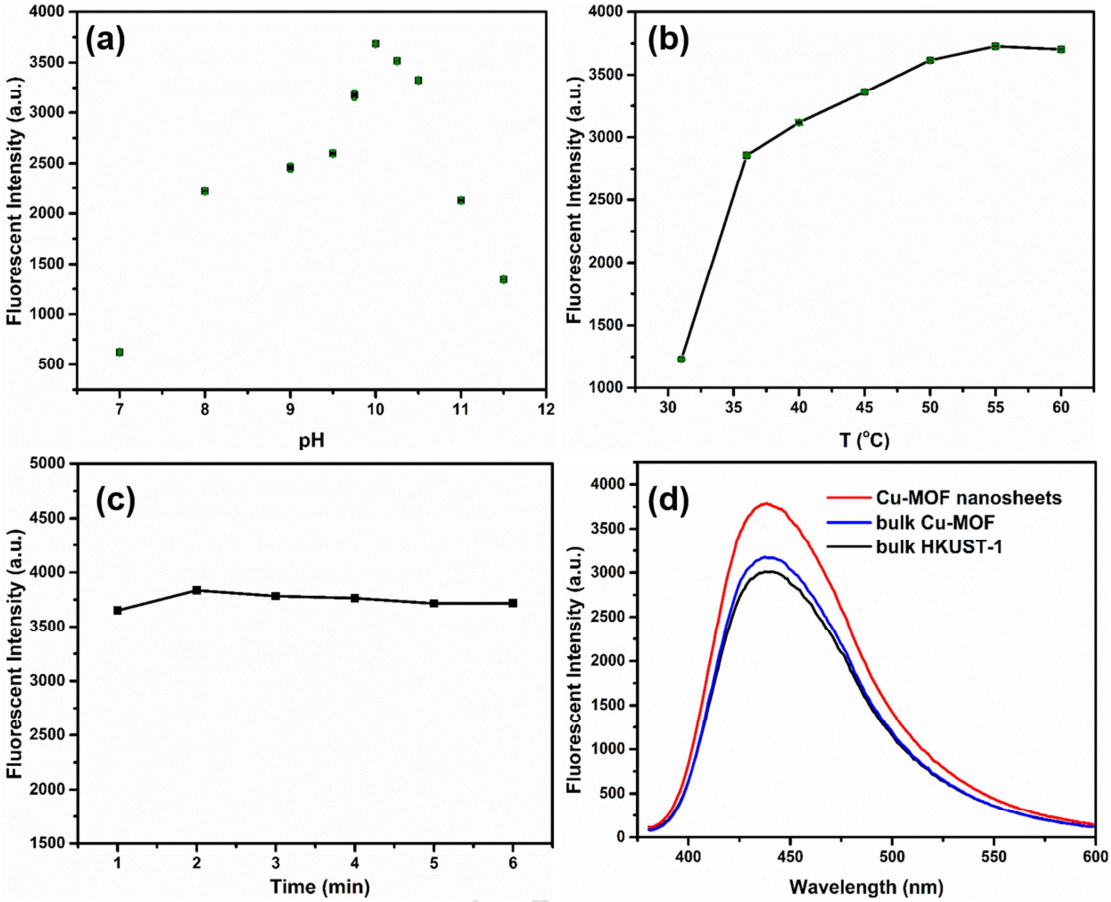


Figure 4

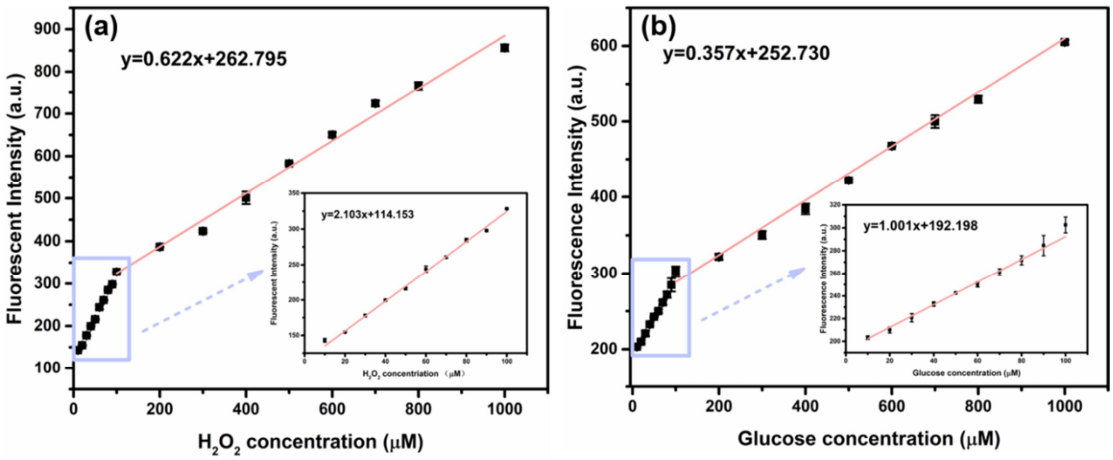
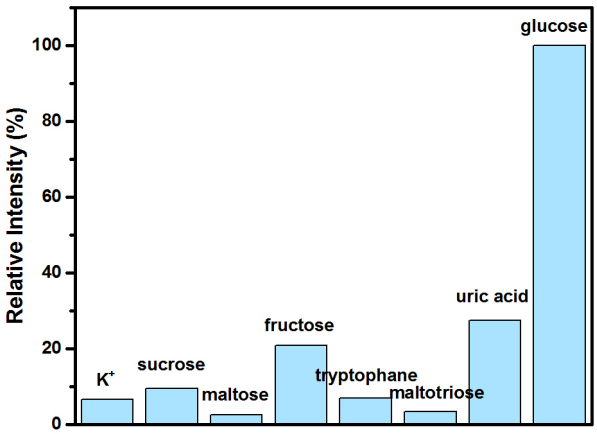
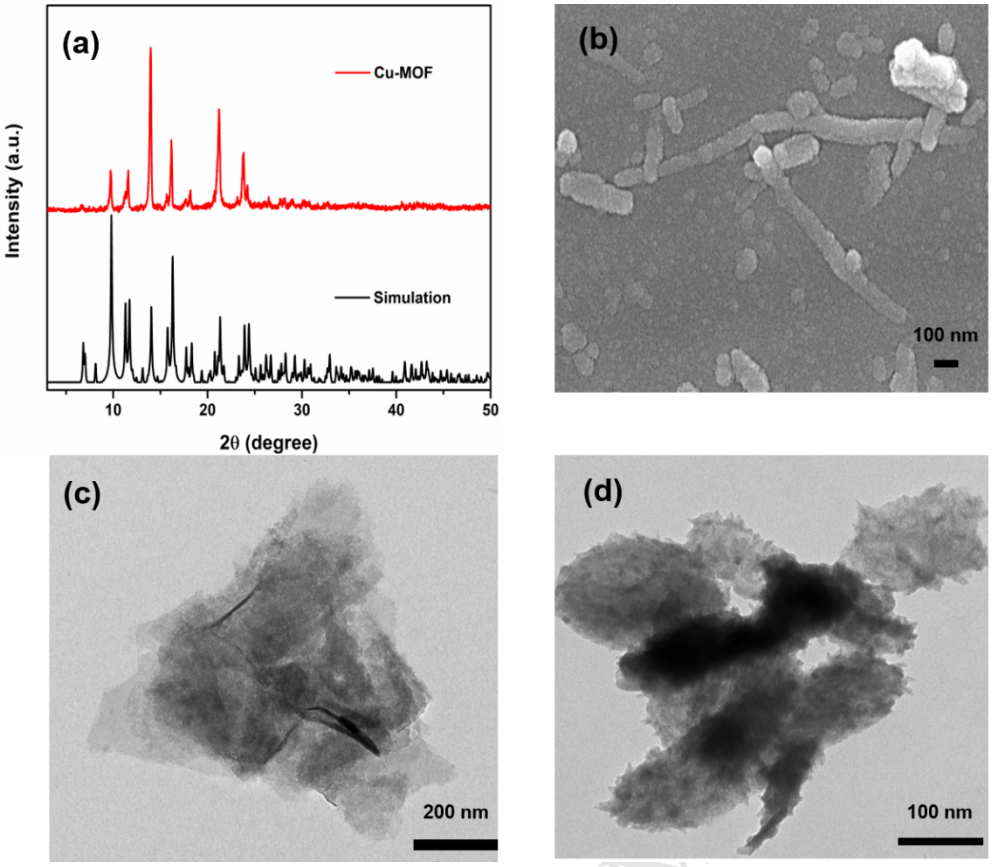
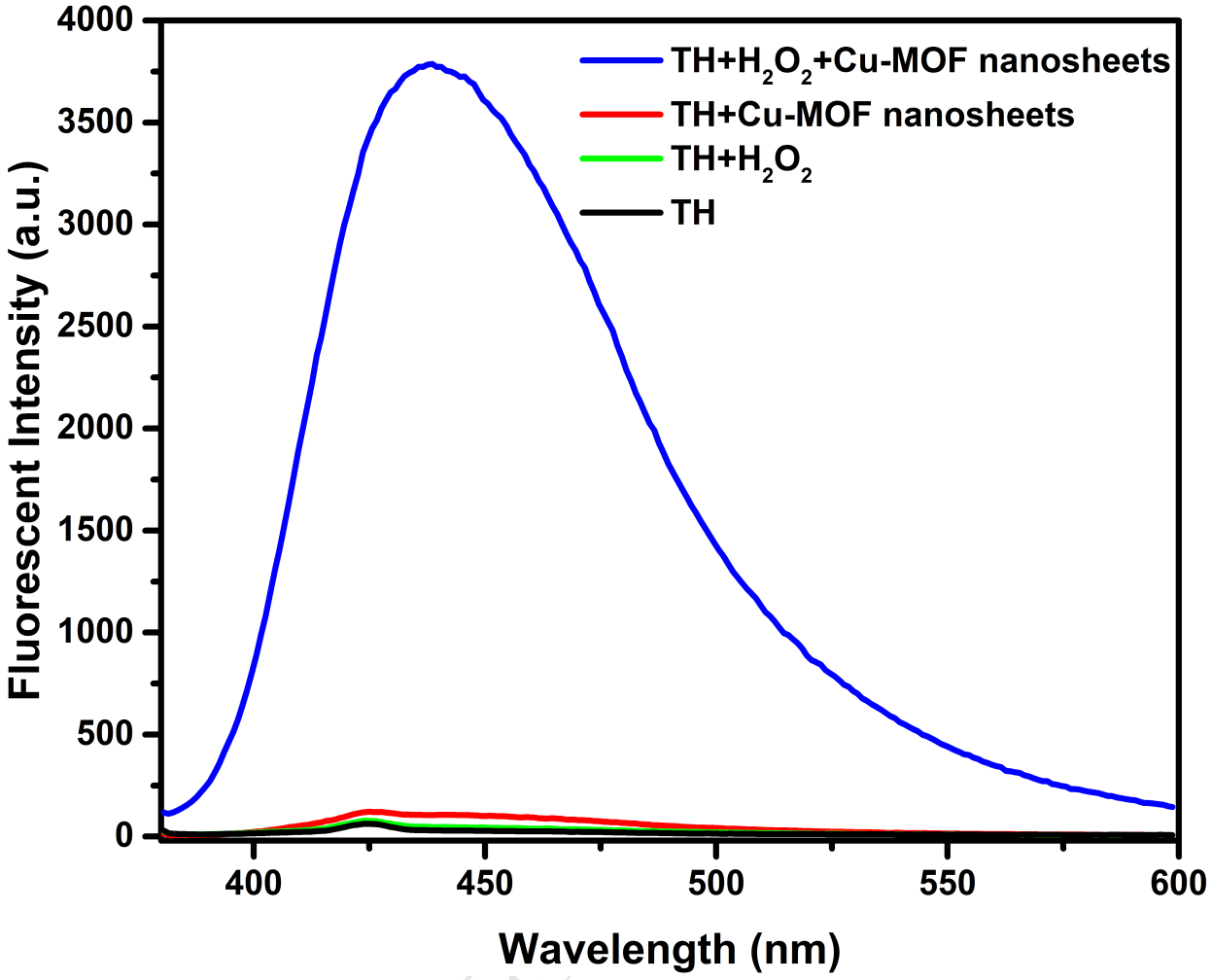
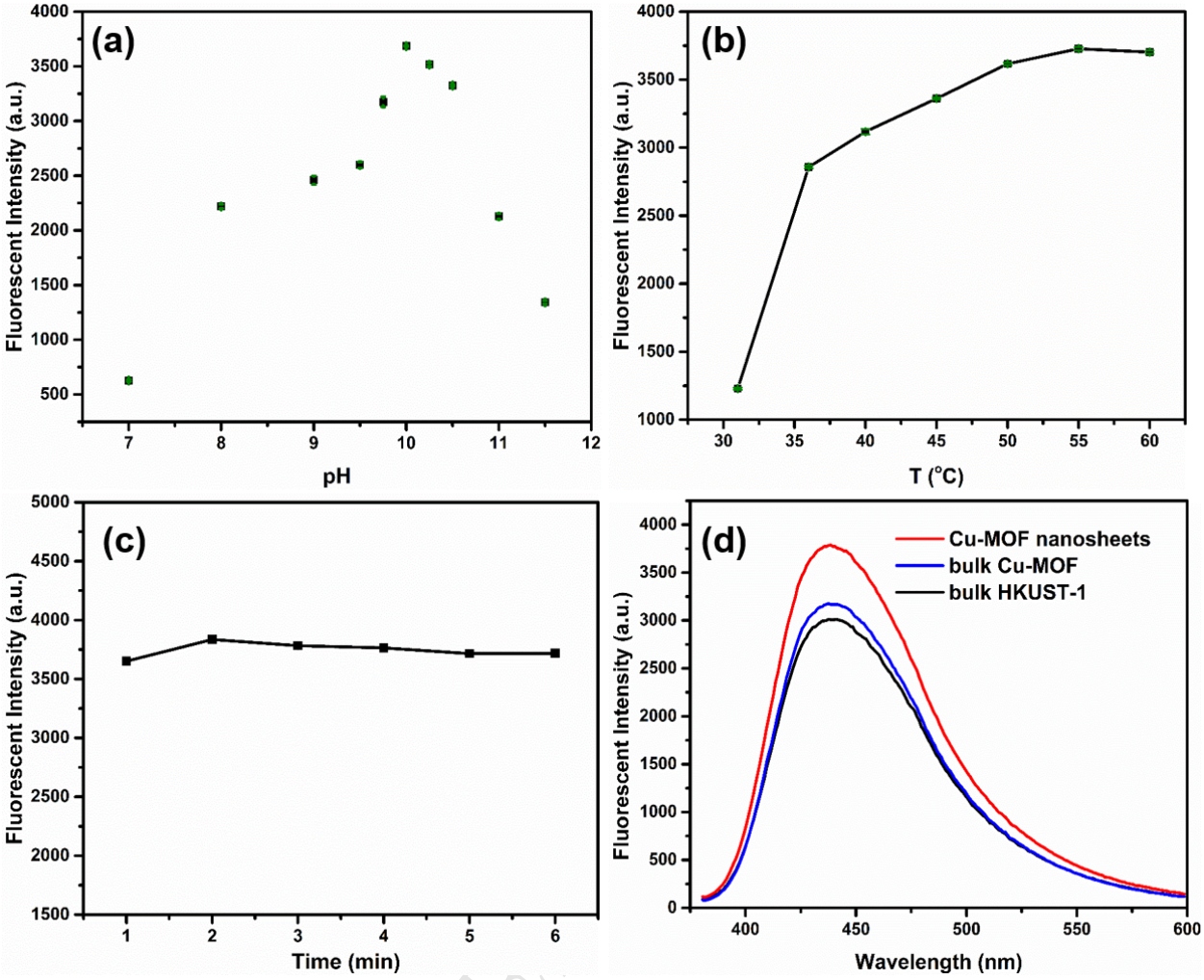


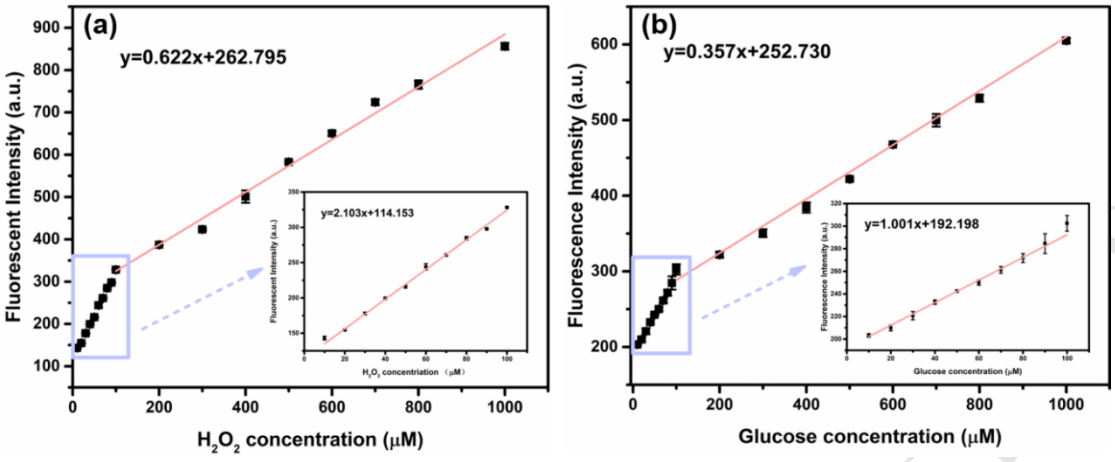
Figure 5

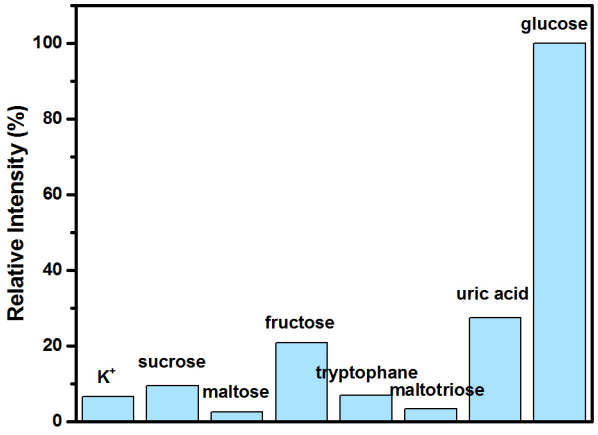







(a)
Fluorescent Intensity (a.u.)
pH
(b)
Fluorescent Intensity (a.u.)
T (°C)
(c)
Fluorescent Intensity (a.u.)
Time (min)
(d)
Cu-MOF nanosheets
bulk Cu-MOF
bulk HKUST-1
Fluorescent Intensity (a.u.)
Wavelength (nm)





Highlights

- Two-Dimensional $Cu(bpy)_2(OTf)_2$ metal-organic framework nanosheets are first utilized to achieve the fluorescent detection for H_2O_2 and glucose with their intrinsic peroxidase-like activity.

- Non-fluorescent thiamine is converted to intense fluorescent thiochrome by $Cu(bpy)_2(OTf)_2$ nanosheets in the presence of H_2O_2 for selective and sensitive detection of glucose with the combination of glucose oxidase.

- The fluorescent biosensor 2-D $Cu(bpy)_2(OTf)_2$ nanosheets is developed with detection limit as low as 0.32 μM for H_2O_2 and 0.41 μM for glucose, respectively.

- Quantitative determination of glucose for human serum is established for the diabetic and healthy serum samples.

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: