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MOF modified pencil electrode for hydrogen peroxide detections

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Abbreviations
***MOF**, Metal organic frame work*
***CDH**, Cellobiose dehydrogenase*
***PGE,** Pencil graphite electrode*
***LOD,** Limit of detection*

ABSTRACT

Background: Hydrogen peroxide is a key component of fungal biomass degradation. Fungal extracellular enzymes can produce this reactive oxygen species or depend on it as a co-substrate. The measurement of H_2O_2 in proximity of enzymes bound to biomass is important to elucidate its production rate by oxidases, its consumption rate by peroxidases. **Objectives** This work reports the fabrication and characterization of pencil graphite electrode (PGE) and its application to measure the H_2O_2 production by cellobiose dehydrogenase (CDH). **Methods:** The limit of detection (LOD) and the sensitivity of pencil graphite electrode were detected for both of bare and modified PGE, respectively. The H_2O_2 generation of cellulose immobilized CDH was measured using the MOF modified PGE. CDH produces H_2O_2 in the presence of cellobiose as a substrate. **Results:** MOF modified PGE exhibited low LODs (571 µM) and high sensitivities (2.35µA $mM^{-1}mm^{-1}$). The lower acquisition costs and higher simplicity compensate for the higher LODs and lower sensitivities when compared to platinum electrodes. **Conclusions:** PGE was easy to fabricate, multiply usable and cost effective which make it a strong and promising tool for H_2O_2 measuring.
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INTRODUCTION:

H_2O_2 is considered the most common reactive oxygen species (ROS) and by-product of the oxidative metabolic pathway (Lu, Wen, and Li 2006). Simple and reliable hydrogen peroxide (H_2O_2) measurements are needed in different fields in recent years, because of the important role of H_2O_2 in chemicals production, fuel cells, biotechnology, environmental, pharmaceutical and clinical applications (Jia et al. 2014; Reza and Bagheri 2014; Sawangphruk et al. 2014; Tang, Yuan, and Chai 2006; Toniolo et al. 2011).

Many approaches were introduced to detect H_2O_2 including chromatography (Toyo, Kashiwazaki, and Kato 2003), spectrometry (Matsubara, Kawamoto, and Takamura 1992), fluorescence, chemiluminescence (Taylor et al. 2006) and titrimetry (Hurdis and Romeyn 1954). Among all techniques, electrochemical methods in H_2O_2 detection are still the affordable choice due to their advantages (low cost, fast response and high

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sensitivity). Thus, many achievements in electrochemical detection of H_2O_2 have been reported (Chemishy 1989; Guascito et al. 2008; Lvovich and Scheeline 1997; MasuoAizawa, IsaoKarube 1974; Wu et al. 2006), of which the enzymatic and nonenzymatic hydrogen peroxide electrochemical sensing are the most common techniques in H_2O_2 detection (Zhenting Zhao, Qibiao Ou 2017).

Due to the high surface area and the porosity of MOF, many molecules could be loaded on it, which catalyze the target with a high catalytic activity that affords inherent sensitivity for the electrochemical detection. In the face of the enticing features of MOFs introduce them as an excellent material for electrode modification, still there are two challenges to be addressed: the design of redox active MOFs and the improvement on MOF conductivity(Pauliukaite et al. 2008). Moreover, because of their high surface areas, naked active sites, specific adsorption affinity and various pore sizes MOFs were used for electrode surface modification in order to detect trace amounts of compounds (Dong et al. 2016; Kung et al. 2015; Li et al. 2013; X. Wang et al. 2015; D. Zhang et al. 2015).

Due to the wide potential window, chemical inertness and low cost, carbon-based materials have been considered as an important electrode material for electrochemical biosensors. Different carbon allotropes have been used for biosensor fabrication for the detection of H_2O_2. Among the carbon-based electrodes, pencil graphite electrodes (PGE), glassy carbon electrodes (GCE) and carbon fiber electrodes (CFE) are three of the most widely used electrodes. Pencil graphite electrodes (PGEs) are carbon-based electrodes that are identified by their cost-effectiveness, simplicity, commercial availability, high surface area, and high conductivity. PGEs are attractive materials for electrochemical sensing owing to their exclusive feature of "disposability" compared to other commonly used carbon-based electrodes (A.-N. Kawde, Baig, and Sajid 2016). In addition, PGEs are mechanically rigid and easy to modify and miniaturize (David, Badea, and Radu 2013). Modification of PGE with nanomaterials or direct formation of NPs on PGE surface enhances its surface area, which in turn results in high sensitivity and improved electrochemical activity towards the detection of target species (A.-N. Kawde, Baig, and Sajid 2016). A variety of nanomaterials have been applied for modifications of PGE such as metal nanoparticles (Aziz and Kawde 2013a), conducting polymers, carbon-based materials (Kuralay, Dumangöz, and Tunç 2015). Due to high selectivity and sensitivity, portability, rapid analysis, and ease of availability, modified PGEs offer excellent opportunities for detections of many environmental and biological samples (Alipour, Reza, and Saadatirad 2013; Rezaei 2014; Tadi, Motghare, and Ganesh 2014). Moreover as reported very recently, modified PGEs show a high electrocatalytic activity toward H_2O_2 detection. (Aziz and Kawde 2013b; A. Kawde, Baig, and Temerk 2015; J. Zhang and Zheng 2015). Herein, sensors using pencil graphite were fabricated through a very simple process and modified with UiO-66 MOF. In addition, design, fabrication, and operation of a 2D scanning electrochemical micros-copy cell for the amperometric detection of enzymatically produced H_2O_2.

MATERIALS AND METHODS:

Materials and enzymes

The MDA-MB-231 cell line, known as a wild-type for BRCA human triple-negative breast cancer cell line, was obtained from Vacsera (Dokki, Giza, Egypt) and processed in National Cancer Institute, Cairo University. The MDA-MB-231 cells were cultured in DMEM medium (Sigma, St Louis, MO, USA) containing 10% fetal bovine serum along with 100 mg/ml streptomycin and 100 units/ml penicillin G (Sigma, St Louis, MO, USA). Cells were incubated in a

humidified atmosphere with 5% (v/v) CO_2 at 37°C. For drug treatment, 10mg of olaparib (LKT Laboratories, USA) was dissolved in 1ml DMSO and stored at -4^{o} C upon usage.

CDH assay using cytochrome c and DCIP

CDH activity was measured based on monitoring the reduction of 20 µM cytochrome c (cyt c) (ε550 = 19.6 mM-1 cm-1) or 0.3 mM 2,6-dichlorophenolindophenol (DCIP) (ε520 = 6.8 mM-1 cm-1. 100 µL of the electron acceptor solution and 100 µL lactose solution (30 mM in distilled water) was added to 780 µL 100 mM phosphate buffer, pH 6.0. Cuvettes were incubated in a water bath at 30°C for 20 min. The reaction was monitored at 550 or 520 nm for 3 min at 30°C in a Lambda 35 UV-visible (UV-Vis) spectrophotom.

Fabrication of MOF modified Pencil Graphite Electrode (PGE).

All leads with a diameter of 0.5 mm were used as received. A copper wire was soldered to the pencil leads for electrical contact. Contacted leads of ~ 1 cm length were put into standard borosilicate glass capillaries with filament (OD 1.50 mm, ID 0.86 mm, Sutter Instrument, Novato, CA, USA) leaving out ~ 1 mm at one side of the capillary. At this side, the nozzle, including the salient part of the lead, was sealed using graphite conductive adhesive 154 (Electron Microscopy Sciences). The sealed leads were then polished using wet emery paper (P400 and P2500) until they were in the plane with the surrounding glass capillary. The electrode was then rinsed with distilled water and dried at room temperature overnight. PGE microelectrode were modified with simple way. A solution of 1.5 mg ml^{-1} UIO-66(Zr) MOF in HQ-H_2O was prepared by sonicating for 15 min. The prepared electrodes were immersed in a 3mL tube containing 1 ml of the synthesized UIO-66 (Zr) MOF and sonicated for 30 min at room temperature. The UIO-66(Zr) modified electrodes were then washed gently with distilled water and dried at room temperature before use.

Electrochemical Measurements.

All electrochemical measurements were performed with a standard three-electrode setup employing an Ag/AgCl-reference electrode (3 M KCl), a platinum wire as a counter electrode and a pencil electrode as a working electrode using a PGSTAT204 Potentiostat/Galvanostat (Metrohm Autolab, Utrecht, The Netherlands). Calibration curves were obtained by using chronoamperometry applying a potential of -0.4 V vs Ag/AgCl (3 M KCl) adding aliquots of H_2O_2 to 50 mL stirred KPP buffer solution, pH 6.0, at defined time intervals and plotting the current I versus the respective H_2O_2 concentrations.

RESULTS:

Characterization of UiO-66 and modification of carbon electrodes.

The Zr-based MOF UiO-66 was synthesized as mentioned above in materials and methods section. The resulting white powder was collected and the crystal structure of the prepared UIO-66 MOF was examined using Powder X-ray diffraction (PXRD). XRD pattern, FTIR spectra and FE SEM of the synthesized UIO-66 MOF is shown in (**Figure 1a, b and 2)**.

Fabrication of MOF modified Pencil Graphite Electrodes (PGEs)

Briefly, (PGEs) as a sensor were simply designed by connecting graphite pencil (0.5 mm diameter, 2mm length) with copper wire as an electrical conductor in glass capillary. A PGE was immersed in the synthesized UIO-66 MOF solution for 15 min at room temperature. After washing and drying, chronoamperometry was applied in 50 mM of KPP pH 6.0 for both bare PGE and modified electrode.

Amperometric response of working electrode.

The amperometric responses of the bare and MOF modified Pencil Graphite Electrodes (PGEs) microelectrodes in

comparison with platinum microelectrode were measured by successive injections of different concentrations of H_2O_2 in 50 mM KPP (pH 6.0) under stirring at an applied potential of -0.4 V with a time interval of 60 s as indicated in Fig 3. (**Figure 3a)** shows the stable amperometric response of Pt microelectrode with a 25 µM diameter. The steady-state current was obtained after a very reasonable time (2 second) of additions of H_2O_2**. (Figure 3b)** shows the amperometric responses of the bare PGE (solid red line) UIO-66 modified PGE (solid black line) at -0.4V upon successive additions of H_2O_2 with interval time 30 s. The UIO-66 modified PGE **(Fig. 3b black)** offered a very well-defined and sensitive signal for each addition of H_2O_2, in comparison with the bare PGE **(Figure. 3b red)** that showed a weak signal.

Calibration curve of working electrodes, determination of LOD and sensitivity.

A calibration curve observed at the different types of microelectrode was undertaken to assess the potential impact of MOF modifications on microelectrode. **Figure 4** shows the calibration data for the different types of microelectrodes over the range of 0.25- 5.0 mM H_2O_2. For a Pt microelectrode (25µm in diameter) the active surface area of Pt, assuming a disk-shaped surface, was calculated according to $A= \pi r^2 = 0.000490874$ mm^2. The quality of the calibration data obtained for the Pt microelectrode is remarkable. A linear response is observed for the Pt microelectrode. Weighted regression of the data ($R^2 = 0.996$) over the range of 0.25-5.0 mM yields a sensitivity of the Pt microelectrode calculated from the slope of the calibration plot between 0.25 and 5 mM of 4.16 µA mM^{-1} mm^{-2}. The limit of detection (LOD), considered as the limiting current for H_2O_2 detection and measured as 3 times the standard deviation of the blank divided by sensitivity was found to be 200.45 µM. The Limit of quantification (LOQ), was calculated as 10 times the standard deviation of the blank divided by sensitivity was found to be 668.12 µM. The surface area of a graphite pencil electrode (0.5 mm in diameter), assuming a disk-shaped surface, was calculated according to $A= (\pi r^2) = 0.1964$ mm^2. Figure 4b shows the electrocatalytic activity of bare PGE and the UIO-66/GPE for amperometric detection of H_2O_2 at an operating potential of -0.4V upon successive additions of 0.25, 0.5, 0.75, 1, 2, 3, 4, and 5 mM H_2O_2. Weighted regression of the data for the UIO-66/GPE and the bare PGE ($R^2 = 0.996$ and 0.995, respectively) over the range of 0.25-5 mM yielded in a sensitivity of 2.16 µA mM^{-1} mm^{-2} and 0.751 µA mM^{-1} mm^{-2}, respectively. The LODs were 610 and 0.214 µM, respectively. The LOQs were 2070 and 803 µM, respectively. A comparison of the limit of detection, the linear range and the sensitivity of the here prepared microelectrodes with MOFs modified H_2O_2 sensors from the literature are given in (**Table 1).**

2D-scanning electrochemical microscopy for measuring H_2O_2 as a by-product of enzymatic reactions.

The SECM set-up used in the electrochemical enzymatic reaction measurements was described previously in published work(Sun 2012)**.** The main components of a SECM set-up are the micromanipulator used for positioning of the SECM tip in x-, y-, and z- direction, a potentiostat, a computer and an ultramicroelectrode. Here, we used MOF modified carbon electrodes as SECM tips in the homemade electrochemical cell. All SECM measurements were performed in 50 mM KPP, pH 6.0. A buffered solution has been chosen to be suitable with the enzyme conditions used in the measurements. Experiments were carried out applying a standard three-electrode setup comprising a Ag/AgCl (3M KCl) silverchloride electrode was used as a reference electrode, a Pt wire as a counter electrode and MOF modified and unmodified pencil as working electrode. A cellulose filter paper was used as the basis

for protein immobilization. Fig 5 schematically illustrates the enzymatic reaction occurring in the electrochemical cell. It shows that CDH catalyzes the oxidation of cellobiose to cellobionic acid followed by the reduction of H_2O_2 to O_2.

MOF/Pencil electrode as amperometric sensor for the detection of H_2O_2 produced from CDH immobilized on cellulose.

The collected amperometric response is proportional to the concentration of the present H_2O_2. With the help of the respective calibration curves, the actual concentration of H_2O_2 was calculated. For the SECM experiments we defined and keept constant a specific scan rate for the forward and backward scans (μm s^{-1}). Thus, we were able to convert the raw data from the chronoamperometric experiments (current and time) to concentrations of H_2O_2 and distance. Plotting of these variables reveals a spatial resolution of H_2O_2 concentrations in the bulk solution and is shown in (**Figure 6)** for the tested electrode.

DISCUSSION:

The structure of the synthesized sample is confirmed by the good agreement between the XRD patterns of the sample and the simulated pattern. FTIR spectra of the MOF sample were collected in the range of 400-400 cm^{-1} as KBr pellets (Figure 1b). The stretching vibration and bending vibration bands around 1607 and 1408 cm^{-1} are attributed to ν_{as} (COO) and ν_s (COO) which confirms the presence of terephthalate ligands. The band centered at 3391 cm^{-1} in the frequency region between (3800-3100 cm^{-1}) can be assigned to the hydrogen-bonded adsorbed water and ν(C-H) stretching modes of DMF molecules. The aromatic and aliphatic ν(C-H) modes of the benzene ring and DMF are indicated by the presence of the weak bands in the 3100-2850 cm^{-1} region. The low frequency region is dominated by an intense band centered at 1658 cm^{-1} and two narrow bands at 1255 and 1102 cm^{-1}. These bands could be assigned to the $\delta(OH_2)$, $\delta(CH_3)$ and δ(C-O) vibration of the physisorbed water and DMF molecules, respectively. The morphological structure of the pristine sample was examined using FE-SEM at different magnification scales (2μm and 5μm). As shown in Fig 2. 1c, 2c, and 3c, the prepared UiO-66 appears as relatively uniform particles with a particle size in the nanoscale range (100-200 nm).

Fig 3a shows the stable amperometric response of Pt microelectrode with a 25 μM diameter. The steady-state current was obtained after a very reasonable time (2 second) of additions of H_2O_2. Fig 3b shows the amperometric responses of the bare PGE (solid red line) UIO-66 modified PGE (solid black line) at -0.4V upon successive additions of H_2O_2 with interval time 30 s. The UIO-66 modified PGE (Fig. 3b black) offered a very well-defined and sensitive signal for each addition of H_2O_2, in comparison with the bare PGE (Fig. 3b red) that showed a weak signal. This is a direct effect of the MOF surface modifications on the electrocatalytic properties of the prepared electrode. The data from Fig 3b for both bare PGE and UIO-66/PGE confirmed that the bare PGE displayed poor electrocatalytic properties with respect to the reductions of H_2O_2 compared to that observed for the UIO-66/PGE. The reduction of H_2O_2 at the UIO-66/PGE could be attributed to the excellent electrocatalytic properties of the UIO-66 MOF. Moreover, the UIO-66 MOF played as suitable mediators to shuttle electrons between H_2O_2 and PGE, and they facilitated the electrochemical generation following electron exchange with H_2O_2.

The accuracy of the data is very reasonable, which make Pt microelectrode sensor able to quantitatively measure H_2O_2 amperometrically. This fact gives a suggestion for the potential use of Pt microelectrode in a wide range of applications from very low levels of

hydrogen peroxide produced in vivo due to oxidative cell stress to the millimolar levels presented in some industrial processes (Amatore et al. 2000). Moreover, the range of linearity offered covers more than that obtained by field strips common in commercial use (Evans et al. 2002)**.**

With UIO-66 modification, the sensitivity of a pencil graphite electrode could thus be improved by almost a factor of four. The high sensitivity of modified electrode comes from the fact that MOF on the surface of PGE increases the surface area of the electrode, therefore, increases the electrocatalytic performance of the electrode towards H_2O_2 reduction. The above discussion indicates that UIO-66 - PGE offers higher electrocatalytic properties towards the detection of H_2O_2 in comparison with the bare PGE. A comparison of the limit of detection, the linear range and the sensitivity of the here prepared microelectrodes with MOFs modified H_2O_2 sensors from the literature are given in Table 1. Based on this comparative study, it was found that the UIO-66/carbon electrodes can offer affordable LOD and high sensitivity for the detection of H_2O_2.

Recently, new approaches were applied based on PGE for sensing of H_2O_2 (A.-N. Kawde, Baig, and Sajid 2016). Modification of PGE with nanomaterials has aroused great attention in H_2O_2 detection owing to its high sensitivity. For measuring H_2O_2 produced from cellobiose dehydrogenase we used a UIO-66 MOF modified PGE. A very fine drop of CDH enzyme was immobilized on the middle of a cellulose paper with a length of 2.5 cm fixed on the bottom of the homemade electrochemical cell. The cell was filled with 50 mM KPP, pH 6.0, serving both as buffer solution and electrolyte, and 10 mM cellobiose solution serving as a substrate for CDH. UIO-66/PGE was used as SECM tip. The measurement started by moving UIO-66/PGE above the immobilized enzyme in the electrochemical cell using the micromanipulator. The electrode was then scanned successively forwards and backwards along the y-axes over the whole length of the cell, thereby screening over the immobilized H_2O_2 producing (CDH) and H_2O_2 consuming (CDH/LPMO) enzymes. The CDH catalyzed generated H_2O_2 travels vertically out from the immobilized CDH in a hemispherical shape and is amperometrically detected with the positioned UIO-66/PGE tip at a very close distance to the immobilized CDH.

Figure 6. represents the data collected from the amperometric detection of H_2O_2 at the applied potential of -0.4V using a MOF modified PGE as working electrode. The solid line represents the data collected from the 1st forward scan and the dotted line refers to the 2nd forward scan. The data show that in the beginning of 1st forward scan (far away from the immobilized enzyme) almost no change in current was observed. In close vicinity of the immobilized CDH the current starts to increase reaching a peak maximum, when the electrode tip is positioned above the enzyme. Continuing the scan and thus moving the electrode further away from the immobilized CDH, the current decreases and soon reaches its initial background level. The higher background current in the 2nd forward scan may be attributable to further diffusion of the generated H_2O_2 into the bulk solution over the whole cell distance. The lower peak maximum in the 2nd forward scan simply results from a shorter, in terms of time, stop in scanning in order to reach a maximum current right above the enzyme (as was done in the 1st forward scan). From the data in **Figure 6** and the explanations mentioned above, we can conclude that a UIO-66 MOF modified PGE is a suitable detector for H_2O_2 produced from cellobiose fueled CDH.

CONCLUSION:

The fabrication of a MOF modified pencil graphite microelectrode with high sensitivity to detect the enzymatic production and conversion of H_2O_2 by cellulose bound enzymes and to determine the concentration and diffusion of H_2O_2 were achieved. CDH produces H_2O_2 in the presence of cellobiose as a substrate. Comparisons between Pt microelectrode and both of bare and modified pencil graphite electrode used for H_2O_2 detections were done.

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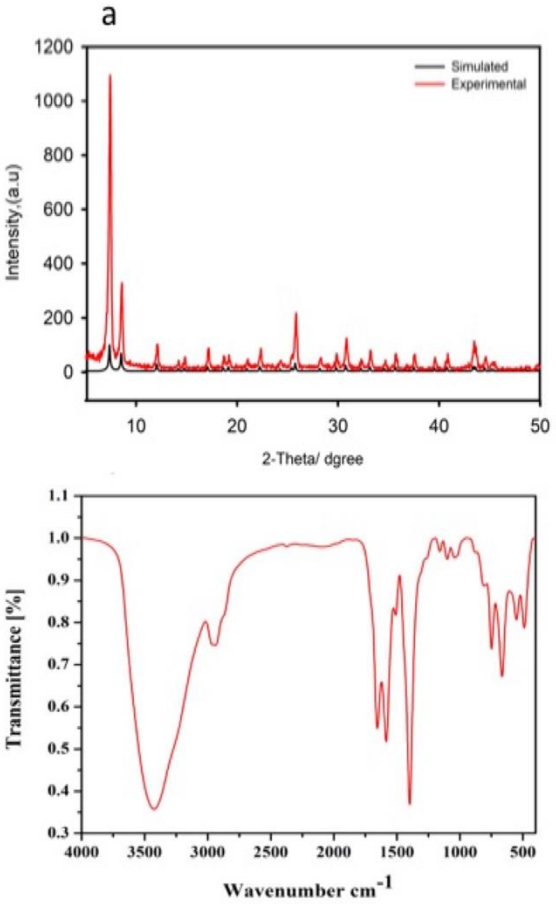

Figure (1): XRD patterns of prepared UIO-66 MOF and simulated UIO-66 MOF (a), FTIR spectra (b).

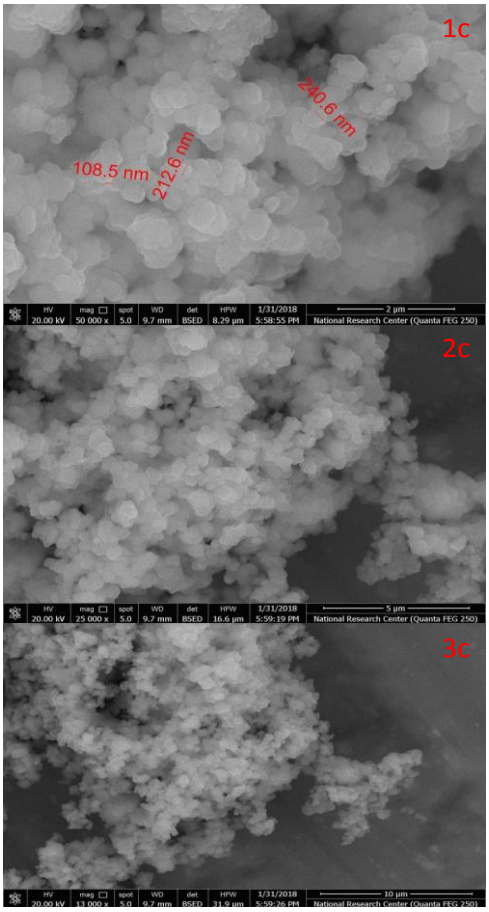

Figure (2): FE SEM of prepared UIO-66 MOF at different magenifications scale (1c 2µm,2c 5µm,3c 10 µm).

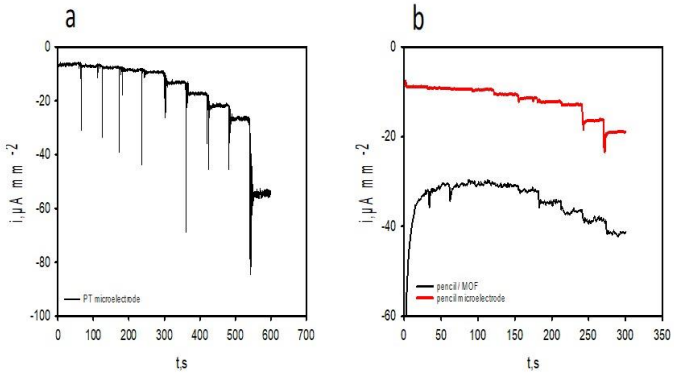

Figure (3): The amperometric response of indicated microelectrodes upon successive injection of H_2O_2 in 50 mM KPP, pH 6.0, at -0.4 V. (a) platinum microelectrode with a diameter of 25 µm, (b) pencil electrode with a diameter of 0.5 mm unmodified and modified with MOF.

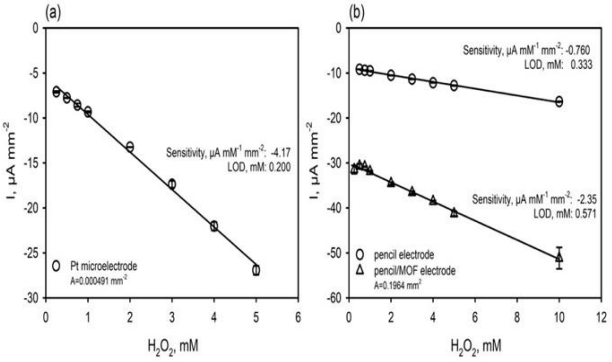

Figure (4): Calibration curves of indicated microelectrodes for hydrogen peroxide detection. (a) platinum microelectrode with a diameter of 25 µm, (b) pencil electrode with a diameter of 0.5 mm unmodified and modified with MOF.

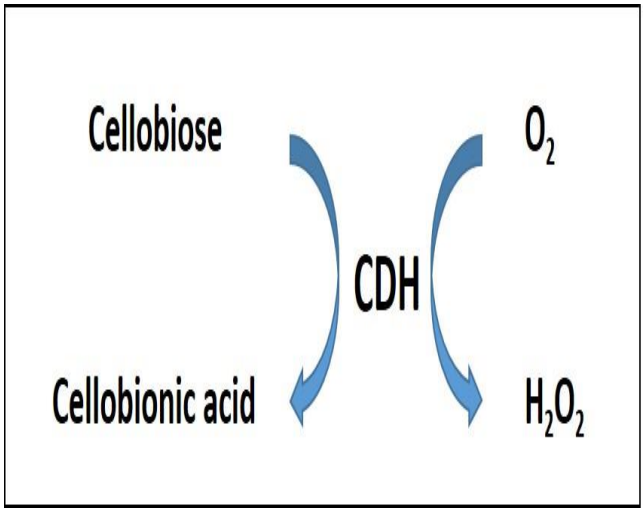

Figure (5): Schematic representation of reactions taking place between pencil electrode and CDH immobilized on surface of cellulose paper in the electrochemical cell.

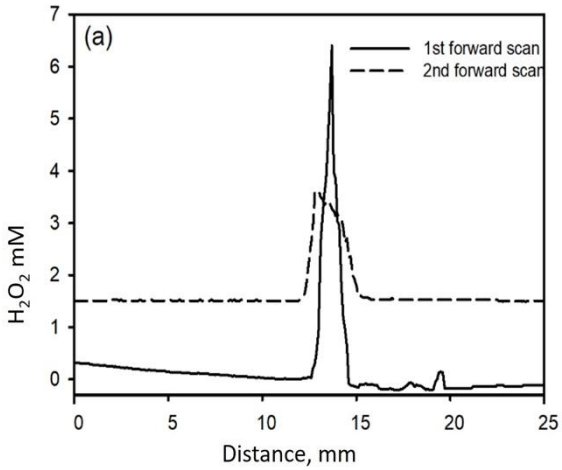

Figure (6): 2D-scanning electrochemical microscopy for detection H_2O_2 produced by CDH using (a) modified pencil electrode/CDH.

Table 1 Comparison of the analytical parameters values of MOF modified electrode for hydrogen peroxide detections

Modified electrode	**Linear range (mM)**	**Limit of detection (LOD), [µM]**	**Sensitivity**	**Ref [a]**
UIO-66/PGE[2]	0.5-20	610	2.16 µA mM^{-1} mm^{-2}	This work
AP-Ni-MOF/CPE[3]	0.004-60	0.9	NP	(Sherino et al. 2018)
AgNPs-Zn- MOF/GCE[4]	0.001-5	0.067	NP	(Arul and John 2017)
Cu-hemin MOFs/CS-rGO	0.00006 – 0.41	0.019	14.5 µAM^{-1}	(L. Wang et al. 2016)
Pt@UiO-66/GCE	0.005-14.75	3.06	75.33 µA $mM^{-1}cm^{-2}$	(Xu, Yang, and Xu 2015)
Cu-MOF-MWCNT/ GCE	0.03-0.07	0.46	NP	(Zhou et al. 2014)
Cu-MOF/CPE	0.001–0.9	1.0	NP	(D. Zhang et al. 2015)
Co-MOF/GCE	0.005-9.0	3.76	83.10 A mM^{-1} cm^{-2}	(Yang et al. 2015)