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Metal–organic framework biosensor with high stability and selectivity in a bio-mimic environment†

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A water-stable copper metal–organic framework (MOF), $\{[Cu_2(HL)_2(\mu_2\text{-}OH)_2(H_2O)_5]\cdot H_2O\}_n$ (1, H_2L = 2,5-dicarboxylic acid-3,4-ethylene dioxythiophene), was applied for the electrochemical detection of ascorbic acid (AA) without further post-modification. A glass carbon electrode covered with 1 was used as a biosensor for the simultaneous detection of AA and L-tryptophan (L-Trp) from both a single-component solution and a bio-mimic environment.

In the last few decades, metal–organic frameworks (MOFs) have rapidly developed as a class of crystalline inorganic–organic hybrid materials with fantastic potential applications covering different areas, including environmental, energy, biological and material fields.[1–5] Recently, as a new application for MOFs, several research groups have been trying to apply MOFs as electrode materials, which are essential in food chemistry and biochemistry for developing electrochemical methods with high selectivity and sensitivity for efficiently detecting trace amounts of biologically related compounds,[6–11] because of the advantageous properties of MOFs, such as their various pore sizes, high surface areas, manipulatable surface properties and naked active sites, which make them ideal biosensor candidates for electrochemical reactions.[12–14] Most MOF electrode sensors are based on post-modified methods, such as linking $-NH_2$ or –SH functional groups and doping other dopants,[7–11] which increases the experimental complexity and difficulty. As far as we know, MOFs possessing electrochemical activity for electro-biosensors without post-modification have rarely been reported until now.[15] On the other hand, the poor water stability of most electro-active MOFs limits their application in the field of electrochemistry detection because related reactions are usually carried out in a water environment.[16]

Herein, an electro-conducting MOF was designed and synthesized with a formula of $\{[Cu_2(HL)_2(\mu_2\text{-}OH)_2(H_2O)_5]\cdot H_2O\}_n$ (**1**, H_2L = 2,5-dicarboxylic acid-3,4-ethylene dioxythiophene). **1** exhibits excellent stability towards air and water as well as a simulated biological system, and can be applied as an electrochemical sensor for ascorbic acid (AA) in both a single-component solution and a bio-mimic environment. To the best of our knowledge, this is the first application of using a MOF material directly as an electrochemical biosensor, which demands no post-modification.

1 was obtained as block blue crystals from the reaction of the thiophene derivative ligand, H_2L, and $CuCl_2$ by a hydrothermal method. The morphology of **1** was characterized using high resolution TEM after dispersing in ethanol, as shown in Fig. 1. The images show uniform regular hexagon crystals with a size in the range of 100–400 nm. Single crystal X-ray diffraction reveals that **1** crystallizes in the triclinic space group $P\bar{1}$. The asymmetric unit consists of three penta-coordinated Cu^{2+} ions (the occupancy of Cu2 and Cu3 is 0.5 each), two HL^- ligands, two μ_2-OH bridges and three H_2O molecules. Cu1 is penta-coordinated by O atoms

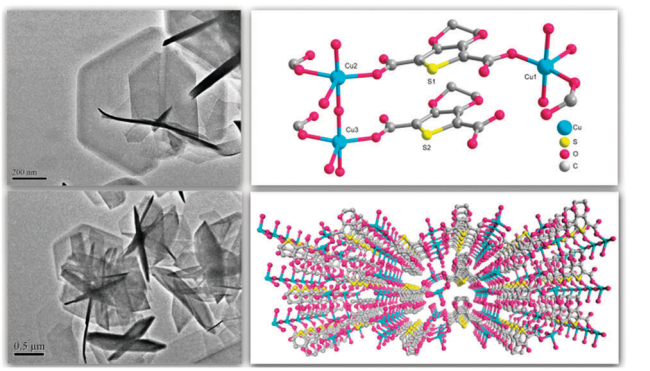

Fig. 1 Left: TEM images of **1** with different scale bars. Right: coordination environments of the Cu(II) ions and the crystal structure of **1**.

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from two HL^- ligands and three water molecules. Both Cu2 and Cu3 are penta-coordinated by O atoms from one water molecule, two HL^- ligands, and two μ_2-OH atoms, and a $\{Cu_2C_2O_4\}$ cluster is formed. This binuclear cluster is further extended along the *a* axis by μ_2-OH bridges to afford a 1D chain, which is further connected to Cu1 by HL^- along the *c* axis to form a 2D layered structure (Fig. 1).

The phase purity and stability of **1** were examined by powder X-ray diffraction (PXRD) patterns (see ESI†). After being immersed in water for at least three months, an excellent water stability of **1** was observed, as confirmed by PXRD. When immersing the crystals of **1** in aqueous solutions with the pH value ranging from 3 to 8 for one month, the PXRD patterns of these crystals were still in conformity with the simulated one from the single-crystal data (see ESI†), which indicated that **1** was extremely stable in the neutral and weakly acidic environments of a normal organism.

The electrochemical behavior of **1** was investigated by cyclic voltammetry (CV) measurements after coating unmodified **1** on the surface of a glass carbon electrode (GCE, Φ = 3 mm). The CV curve of this MOF coated electrode, named as **1-GCE**, in K_2HPO_4–KH_2PO_4 buffer solution (PBS, pH 6.8) is shown in Fig. 2a. Compared to the bare glass carbon electrode, a pair of quasi-reversible peaks was observed with E_{pa} = −0.039 V and E_{pc} = −0.344 V *versus* Ag/AgCl, which is attributed to the Cu^{2+}/Cu^{+} redox process.[15] The peak to peak separation (ΔE_p) was 0.305 V, and the half-wave potential of −0.192 V was calculated according to the following equation:[17]

$$E_{1/2} = (E_{pa} + E_{pc})/2$$

CV measurements on **1-GCE** were carried out for a further twenty cycles. The peak current density decreased slightly at the beginning, and was then constant after ten cycles (see ESI†), which indicated the good reproducibility of **1-GCE**, originating from the high stability of **1**.

The influence of the scan rate (ν) was investigated as well. The CV measurements of **1-GCE** in PBS (pH 6.8) with a scan rate from 0.02 V s^{-1} to 0.14 V s^{-1} are shown in Fig. 2b. The peak current densities of both the oxidation and reduction processes increase gradually with increasing scan rates. The anodic (i_{pa}) and cathodic (i_{pc}) peak current densities are directly proportional to $\nu^{1/2}$ (see ESI†), which indicates a surface controlled process.[18]

To characterize the proton conductivity of **1-GCE**, electrochemical impedance spectroscopy (EIS) analysis was performed on **1-GCE** with 0.1 M KCl solution containing 5 mM potassium ferricyanide. The Nyquist plot of the EIS spectra for **1-GCE** is shown in Fig. 3. The diameter of the semicircle represents a charge transfer resistance (R_{ct}) of 2.966 kΩ on the **1-GCE** surface.

The electron transfer rate constant (K_{et}) at the **1-GCE** interface is 2.461, which can be estimated using the EIS data and the equation as follows:[19–21]

$$K_{et} = \frac{1}{2(R_{ct})(CPE)}$$

where CPE is a constant phase element and the value is 6.851 μF s^{-1}. A Warburg coefficient value for **1-GCE** of 204.6 Ω cm^2 $s^{-1/2}$ was obtained.

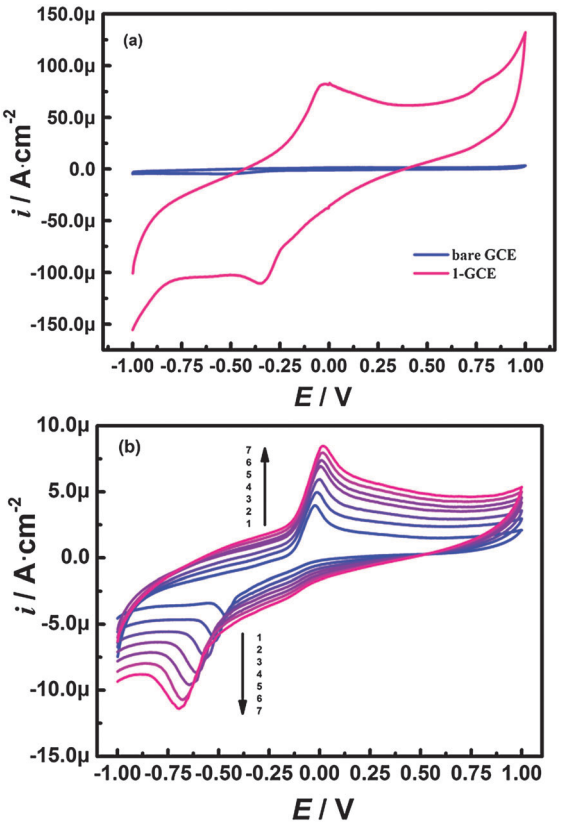

Fig. 2 (a) Cyclic voltammetry measurements in phosphate buffer solution (pH 6.8) for the bare GCE (blue) and **1-GCE** (pink). (b) Cyclic voltammograms of **1-GCE** in pH 6.8 PBS at different scan rates from 0.02 V s^{-1} to 0.14 V s^{-1}.

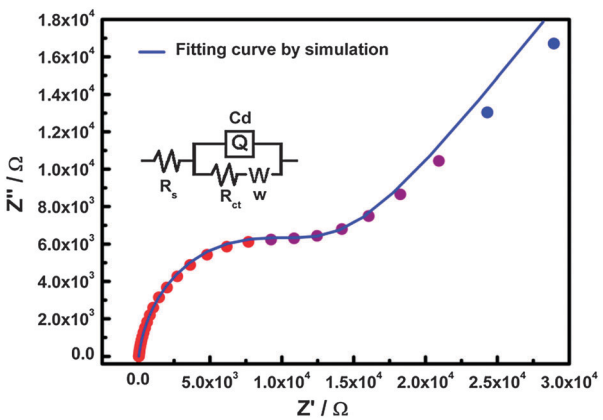

Fig. 3 Nyquist plot of **1-GCE** in 0.1 M KCl solution containing 5 mM potassium ferricyanide. Inset: equivalent circuit for **1-GCE**.

Ascorbic acid (AA), which is a common water-soluble vitamin with great importance in biomedical chemistry, diagnostics, and pathological research as well as numerous biological reactions,[22,23] was selected as the target biomolecule to study the capacity of **1** as a biosensor. AA is electrically active with different modified electrodes, however, its oxidation involves undesirable high overvoltage and poor selectivity.[24–27] In order to obtain efficient electrodes for AA detection, the oxidation potentials should be

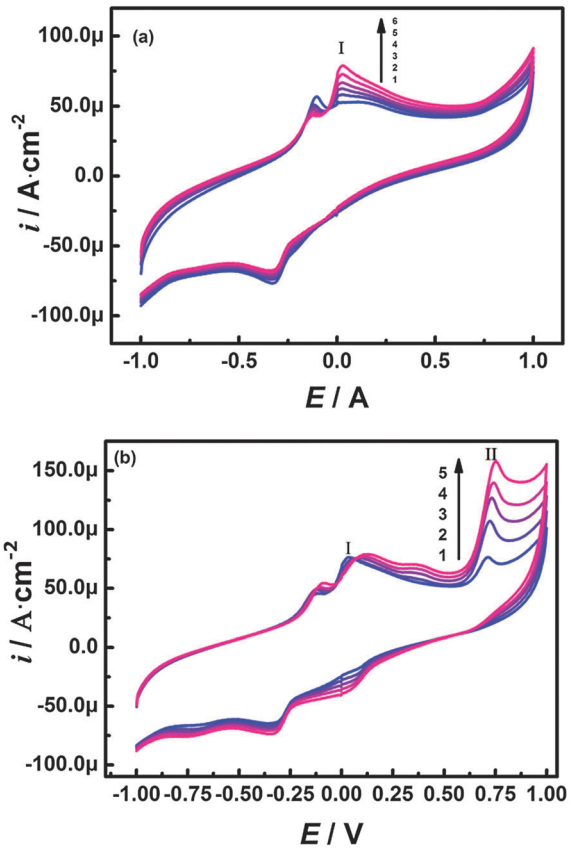

Fig. 4 (a) Cyclic voltammograms of **1-GCE** in phosphate buffer solution (pH 6.8) obtained with AA concentrations of 0.25, 0.5, 0.75, 1.0, 1.25, and 1.5 mM. (b) Cyclic voltammograms of **1-GCE** in PBS (pH 6.8) obtained with L-Trp concentrations of 0.1, 0.2, 0.3, 0.4, and 0.5 mM.

lowered and the selectivity should be improved. Fig. 4a shows the CV response of **1-GCE** in pH 6.8 PBS with different AA concentrations. The current density of the oxidation peak I was observed at E_{pa} = 0.023 V, which is much lower than the previously reported value of 0.360 V for the MIL-101(Cr) post-modified electrode.[10] The current density of peak I increases gradually with the increase of AA concentration in the range of 0.25 mM to 1.5 mM. Sharp and distinct oxidation peaks were obtained for AA. i_{pa} exhibits a nearly linear variation (see ESI†) with the concentration of AA, following the equation:

$$i_{pa} = 24.501c_{AA} + 8.589, \quad R^2 = 0.976$$

where i_{pa} is the anodic peak current of peak I, c_{AA} is the concentration of AA (μA cm^{-2}), and R is the correlation coefficient. The sensitivity is 24.501 μA M^{-1}. The results indicate that **1** further lowered the oxidation potential of AA sensing. Before being oxidized, AA molecules should be adsorbed onto the surface of **1** and interact with the active sites in the framework firstly. The numerous active sites provided by **1** can lower the energy barrier for AA oxidation and act as mediators to promote the electron transfer between AA and the GCE. The peak I potential of AA is much closer to the **1** anode peak potential (ΔE = 0.062 V). This feature indicates that **1** is an excellent chemical sensor with a fast response for AA detection.

Subsequently, selectivity tests were performed with the **1**-modified electrode. The major problem for AA determination is the interference from other species, such as amino acids, which usually coexist with AA in real systems and occur at almost the same potential at the bare electrode.[28] Initially, tests with AA mixed with one or several types of amino acids, including L-alanine, D-alanine, L-glutamine, L-tryptophan, L-histidine, L-aspartic acid, L-proline, D-proline, L-tyrosine, L-cysteine, L-serine, L-lysine, L-threonine, DL-isoleucine, D-valine and L-arginine, were performed with **1-GCE**. In all cases, an excellent selectivity was observed. Among these amino interferents, it was found that L-tryptophan (L-Trp) could be detected on this modified electrode as well. As shown in Fig. 4b, the CV curves for **1-GCE** were measured for a mixture of 1.5 mM AA and different concentrations of L-Trp in pH 6.8 PBS. High current values and well separated oxidation peaks of L-Trp (peak II) were obtained. The anode peak current density increased at E_{pa} = 0.710 V as the L-Trp concentration increased. The peak current density of AA (peak I) was hardly reduced. The linear regression equation (see ESI†) is shown as follows:

$$i_{pa} = 110.835\log c_{L\text{-}Trp} + 138.201, \quad R^2 = 0.998$$

where i_{pa} is the anodic peak current of peak II, $c_{L\text{-}Trp}$ is the concentration of L-Trp (μA cm^{-2}), and R is the correlation coefficient. The sensitivity is 110.835 μA M^{-1}. The results indicate that the appearance of L-Trp does not disturb the detection of AA, and **1** can be used as a good sensor for L-Trp as well.

In summary, we have successfully synthesized a new water-stable Cu-MOF based on the 2,5-dicarboxylic acid-3,4-ethylene dioxythiophene ligand, which provides abundant active sites and an excellent electrochemical performance for AA detection. An impressive selectivity towards AA in a simulated biological system containing plenty of amino acids is exhibited by this MOF material. This is the first attempt to directly apply a MOF as an electrochemical biosensor, avoiding the complexity and difficulty of post-modifications. The new sensor provides a promising platform for studying the application of MOFs in areas such as electrochemistry and biochemistry.

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