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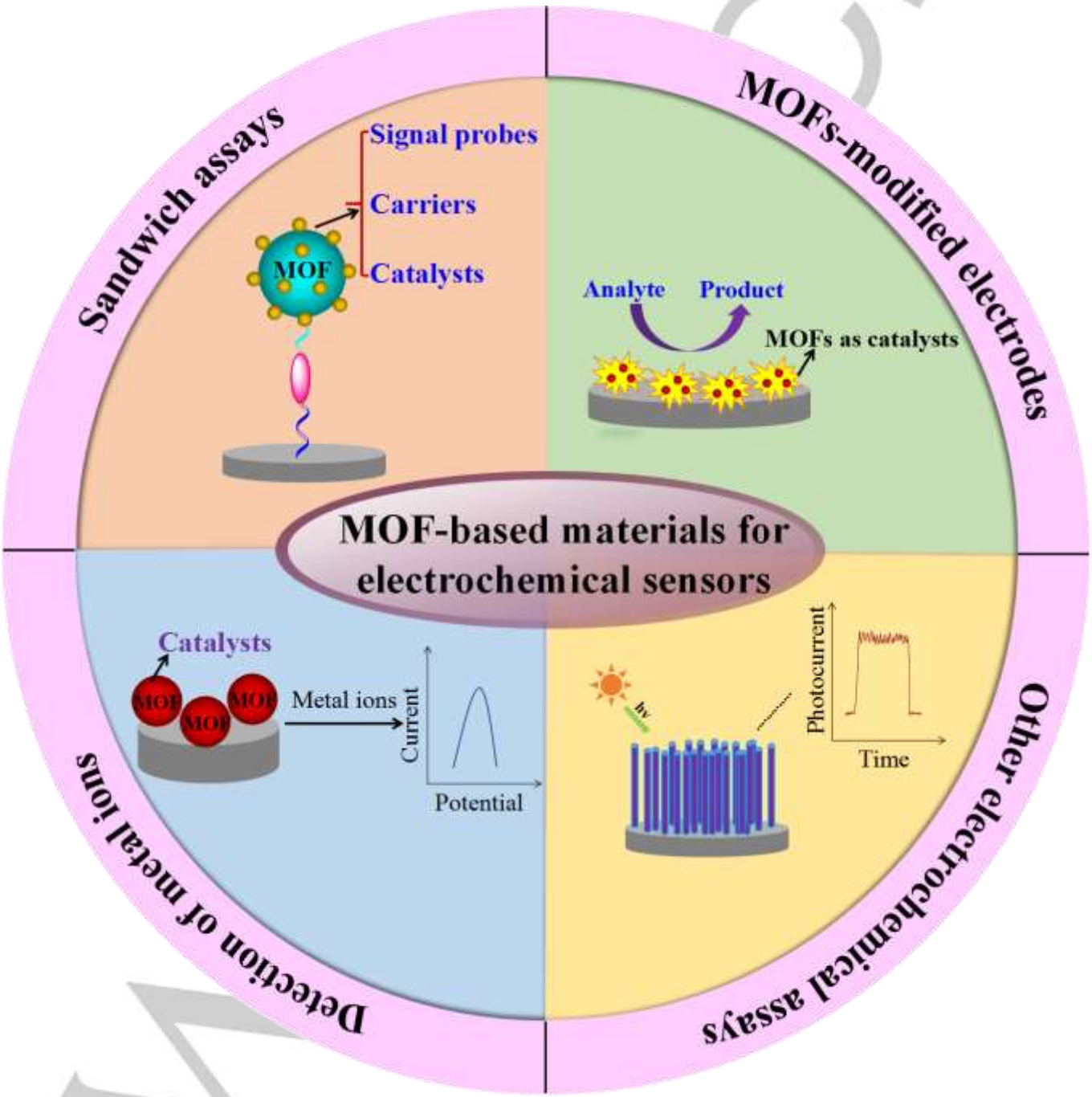
The Applications of Metal-Organic Frameworks in Electrochemical Sensors

Lantao Liu,[a] Yanli Zhou,*[b,c] Shuang Liu[a] and Maotian Xu*[b,c]



Dedication ((optional))

Abstract: Metal-organic frameworks (MOFs), synthesized by assembling metal nods with organic linkers, are highly ordered crystalline materials. MOFs have attracted much attention for applications in electrochemical sensors because of their unique chemical and physical properties including ultrahigh porosity, large surface area, tunable structure, and high thermal and chemical stability. Especially, redox and catalytic active sites introduced by use of active metal ions and/or ligands endow MOFs with the functions of electrochemical sensing. Moreover, precise chemical modification of functional molecules and immobilization with metal nanoparticles, carbon nanostructures and biomolecules could promote their electrochemical performances. In this review, we focus on recent progress achieved in MOF research with respect to general sensing principles and analytical performances of electrochemical sensors. The evaluation and challenges governing the detection of the assays are also discussed.

1. Introduction

The research on the synthesis and applications of metal-organic frameworks (MOFs), which are also known as porous coordination polymers, has been growing tremendously over the past few decades. MOFs exist as extended crystalline lattices comprising coupling units (metal centers or clusters) coordinated by electron-donating organic ligands. MOFs have the large internal pore volumes (up to 90% free volume) with well defined pore sizes and highest specific surface areas (beyond a Langmuir surface area of 10 000 $m^2 g^{-1}$) among the reported porous materials, which play a crucial role in functional applications, typically in gas storage and separation, drug delivery, and sensing.[1,2] Furthermore, their pore sizes of the microporous characters could be tuned from several angstroms to several nanometers based on the length control of the rigid organic linkers. Plenty of metal ions, organic linkers and structural motifs provide an essentially infinite number of possible combinations.[3,4] Thus, their structures could be designed for the different target molecules by the selection of the coordination nodes and organic linkers. Importantly, versatile framework functionalities beyond the accessible porosity could be produced from the metal centers (eg. electricity, catalysis, magnetism), organic ligands (eg. luminescence, fluorescence, chirality) or a combination of both.[5–8]

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Electrochemical sensors are widely applied for a range of applications including environmental monitoring, food quality control, medical diagnostics, and chemical treat detection. The sensitivity and selectivity are important elements to consider in optimizing the performance and utility of the electrochemical assay. The high porous and surface areas of MOFs could load the guest molecules and/or catalyze the targets with high catalytic activity, which affords inherent sensitivity for the electrochemical detection.[9] The porosity of MOF-based materials permits guest molecules to diffuse into the bulk structure, and the shape and size of the pores produce to shape- and size-selectivity over the incorporated guests.[9–11] Another source of selectivity is chemically specific interactions between the guest molecules and MOFs via hydrogen bonding, π-π interactions, open metal sites, and van der Waals interactions.

Despite the attractive properties of MOFs suggest them as ideal materials for the surface modification of electrodes, the signal transduction is one major challenge for the MOF-based electrochemical sensors. Nevertheless, only a part of MOFs meet the requirements of electrochemical sensing and are utilized as advanced electrode materials. The improvement in the conductivity and the design of redox-active MOFs are still required to enhance the properties to satisfy the realistic applications of MOF-modified electrodes. Fortunately, their porosity favors the introduction of nonnative conductivity by combining MOFs with a variety of functional materials such as metal nanoparticles, carbon nanostructures, polymers, and biomolecules.[1] The MOF composites/hybrids have the advantages of both MOFs (high porosity with ordered crystalline pores) and other active materials (electrical and catalytic properties), and the electrochemical performances are enhanced.[12–16] Consequently, the outstanding features of the composites from the synergistic combination of both MOFs and functional materials would further extend the applications of electrochemical analysis.

So far, the MOF-based electrochemical assay, which also has been widely reported, has not yet been summarized systematically. In this review, we begin with the design of electrochemical sandwich-type assays using MOFs as outer probes for the generation and/or amplification of electrochemical signal. On account of the electrocatalytic activity of MOFs, subsequent sections discuss the design of electrochemical sensors based on MOF composites modified on the electrode surfaces and MOF-modified electrodes for the detection of electrochemically active metal ions. Other types of electrochemical sensors are discussed briefly. Meanwhile, we focus on the recent progress toward the design and principles of MOF-based electrochemical sensors. In addition, the evaluations governing the detection of the assays are summarized. The improvements and challenges of these systems for practical applications are also discussed.

2. Electrochemical Sandwich Assays Using MOFs as Outer Probes

In a sandwich electrochemical sensor, signal enhancement and high selectivity could be achieved via the use of outer recognition probes conjugated to nanomaterials such as metal nanoparticles, graphene, and carbon nanotubes. MOFs with high specific surface areas as well as unique electronic and catalytic properties are increasingly utilized as electrochemical signal enhancers for the construction of sandwich assays. Moreover, the dopant modification, postsynthesis methods, and entrapping of functional molecules are commonly required for most MOFs to achieve the amperometric signal generation and/or amplification.

2.1. Electrochemically Active MOFs as Signal Probes

The bonding of metal ions as coordination centers forms infinite crystalline networks in MOFs. The Cu-MOFs are expected to have electroactive properties and can be used as electroactive materials because the Cu^{2+} possesses redox activity. The electrochemistry response of Cu-MOFs has been studied and well-defined reduction processes involve the stepwise reduction of the parent Cu(II) species to Cu(I) and Cu metal.[17] Large amounts of Cu^{2+} in MOFs could afford high electrochemical signals. Based on the electrochemical signal of Cu^{2+} from MOFs, Yuan's group reported a sensitive and efficient ratiometric electrochemical sensor for detection of lipopolysaccharide (LPS).[18] For the target-triggered quadratic cycles for signal amplification, the cleavage sites of ferrocene-labeled hairpin probes 2 (HP2) and the hybridization of gold nanoparticles (AuNPs) /Cu-MOFs labeled hairpin probes 3 (HP3) with capture probes generated the signal decrease of ferrocene and the signal increase of Cu-MOFs for ratiometric readout (Figure 1). AuNPs/Cu-MOFs were not only served as nanocarriers for modification of capture probe and as electroactive materials for signal probes but also worked as catalysts to glucose oxidation for enzyme-free signal amplification. Thus, this ratiometric electrochemical approach demonstrated a low detection limit (0.33 fg mL^{-1}) with high selectivity and accuracy for detection of LPS. This work represents the first report of utilization of MOFs themselves as the signal probes for application in the electrochemical biosensors.

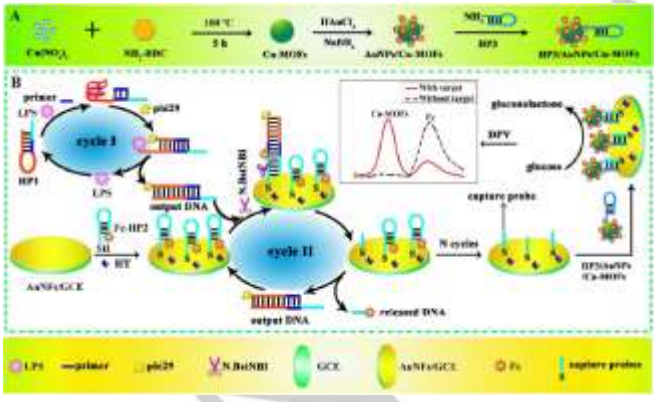

Figure 1. Schematic illustration of the fabrication of the aptasensor: (A) preparation procedure of AuNPs/Cu-MOFs labeled by HP3; (B) signal amplification strategy and the detection principle for LPS. Reproduced from Ref. [18]. Copyright 2015, American Chemical Society.

By the use of Cu-MOF nanomaterials as novel signal probes, a simple electrochemical immunoassay for C-reactive protein was developed, as shown in Figure 2.[19] Signal antibody-modified AuNPs-MOF composite, in which the antibodies, Cu-MOFs, AuNPs acted as a complexing agent for recognition layer, a signal probe, and a sensitive promoter, respectively, was constructed for fabrication of the electrochemical sensor. Compared with traditional probe, this new class of signal probe simplify the detection steps and reduce the detection time because of the direct detection of the signal of Cu^{2+} from MOFs

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without dissolution and preconcentration. Moreover, high sensitivity of the electrochemical immunoassay for C-reactive protein should be taken into account as the high electrochemical signals provided by large amounts of Cu^{2+} from MOFs. Based on this strategy, a similar sandwich-type immunoassay for carcinoembryonic antigen was also constructed using AuNPs loaded-Cu-MOFs as the electrochemical signal probes and was easy to operate with good sensitivity. [20]

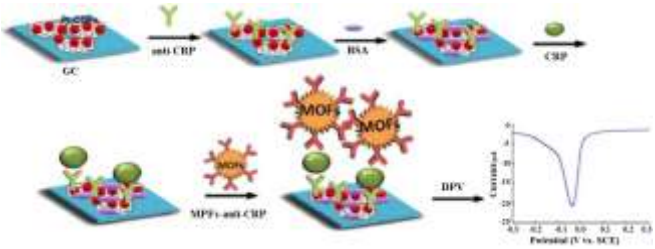

Figure 2. Schematic illustration of the electrochemical immunosensor using Cu-MOF nanomaterials as novel signal probes. Reproduced from Ref. [19]. Copyright 2016, American Chemical Society.

Inspired by this, Co-MOFs were also directly adopted as redox tags for fabrication of electrochemical aptasensor for thrombin detection because of the electron transfer from Co(II) to Co(III).[21] In the sandwich-type thrombin aptasensor, the thrombin aptamer bioconjugates with Co-MOFs and platinum nanoparticles (PtNPs) were synthesized. Firstly, the Co-MOFs were intrinsically used as electroactive materials to avoid the introduction of extra redox probes. Secondly, the special structure of two-layer PtNPs not only afforded the rapid pathway for electron-transporting but also increased the surface area to conjugate a large quantity of recognition molecules. Meanwhile, the addition of H_2O_2 enhanced the electron transfer from Co(II) to Co(III) by the catalysis of nanocomposites to H_2O_2 oxidation, producing distinct signal amplification. The electrochemical aptasensor based on the nanocomposites of Co-MOFs might represent a new paradigm for exploring the application of MOFs with redox-active metal centers in the construction of electrochemical sensors.

In brief, a high sensitivity was acquired by the use of MOFs as electrochemical signal probe because of high electrochemical signals provided by large of amounts of redox metal ions of MOFs. This principle with high sensitivity, simplicity, and accuracy paves a new avenue for the detection of various analysts and has the potential applications in bioassays. Nevertheless, considering the large number of reports about MOFs-based sensors, studies on the electrochemical sensors using MOFs as signal probes are still in the infancy owing to the low redox activity and catalytic activity of the organic ligands and the metal centers for the most MOF materials. Consequently, the further search of the MOF materials with superior redox activity and catalytic activity is still urgent for applications in electrochemical sensors.

2.2. Redox Active Species-modified MOFs as Signal Probes

The drawbacks including their poor electrical conductivity and redox activity restrict the applications of MOFs in electrochemical assays. It is noted that large specific surface area of MOFs and a large number of various sizes of pores could load electroactive molecules, which further extend the application ranges of MOF-based electrochemical sensors. As we know, hemin as a ferroprotoporphyrin, can act not only as a redox mediator based on the electrochemical activity of Fe(III)/Fe(II) reversible redox but also as a catalyst based on the peroxidase-like activity. Inspired by the excellent performances of MOFs and the high catalytic activity of hemin, MOFs as a new type of host matrix material to anchor hemin were studied.[22] Hemin-decorated MOFs exhibited high peroxidase activity and were applied in colorimetric and/or chemiluminescence detection of H_2O_2 or glucose. Integrating of the catalytic and redox properties of hemin, a new type of multifunctional MOF material by encapsulating hemin into an amino-contained Fe-MOFs was synthesized and further supported by AuNPs (Au/hemin@MOFs) for immobilization of recognition molecules.[22] The composites were conjugated with glucose oxidase (GOD) and aptamer, which were used as the secondary aptamer bioconjugates in the electrochemical aptasensor for detection of thrombin (Figure 3). The synthesized Au/hemin@MOFs could directly act as redox mediators for electrochemical signal generation, and then the addition of redox molecules was avoided. The electrochemical signal of hemin contained in hemin@MOFs was further amplified by the generation of H_2O_2 from glucose oxidation. Thus, the proposed aptasensor showed improved sensitivity due to plenty of hemin encapsulated by MOFs as signal probes and the excellent electrocatalytic activity of the Au/hemin@MOFs.

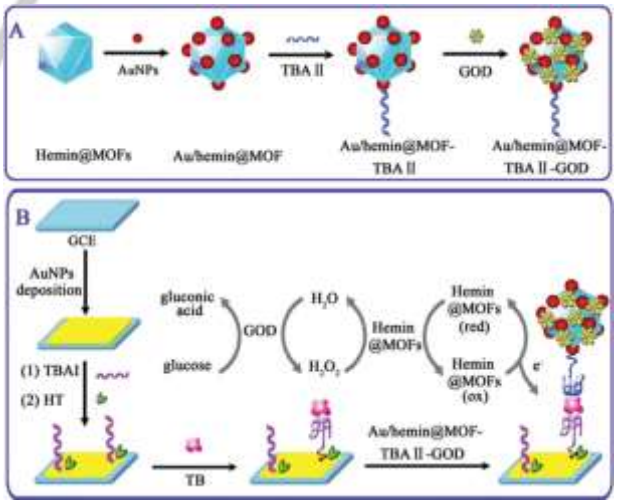

Figure 3. (A) The preparation of Au/hemin@MOF and the immobilization of recognition molecules. (B) Schematic representation of the stepwise assembly procedure and electrocatalysis detection principle of the proposed electrochemical aptasensor. Reproduced from Ref. [22]. Copyright 2015, Royal Society of Chemical.

Therefore, the proposed hemin@MOFs open up new opportunities for multifunctional roles of MOF composites as redox mediators, loading platforms, and catalysts. Other redox active molecules including methylene green, ferrocene were also employed as electron mediators in MOF nanocomposites for the construction of an electrochemical platform to detect glucose owing to their reversible electrochemical properties.[23,24]

2.3. MOFs as Catalysts and Carriers

In the sandwich structure of electrochemical sensor, the third type of MOF-based materials is that MOF composites act as a catalyst to catalyze the electrochemistry of redox mediators and as a nanocarrier to load the recognition probes due to the tunable pore voids and functional pore walls. MOFs created with porphyrin or porphyrin derivatives have been emerged as novel artificial enzymes because of the peroxidase-like catalytic activity. Especially, iron porphyrin-based MOFs could be applied as artificial enzymes to catalytic oxidation such as hydroxylation and epoxidation of hydrocarbons. Based on this principle, Ju and Lei's group reported the synthesis of a series of iron porphyrinic MOFs and employed them to construct electrochemical sensors.[25-27] Firstly, one-pot encapsulation of iron porphyrin into the cage of Cu-MOFs was conjugated with streptavidin (SA) as a recognition element, providing an efficient signal-transduction assay for DNA detection, as shown in Figure 4.[25] The detectable electrochemical signal was generated by the *o*-phenylenediamine oxidation in the presence of H_2O_2 and greatly enhanced by the MOF composites. The second example was that iron-porphyrinic MOFs were modified with AuNPs and further functionalized with DNA (GR-5).[26] The fabricated assay could selectively and sensitively detect Pb^{2+} owing to the affinity recognition property of GR-5 to Pb^{2+} and high peroxidase activity

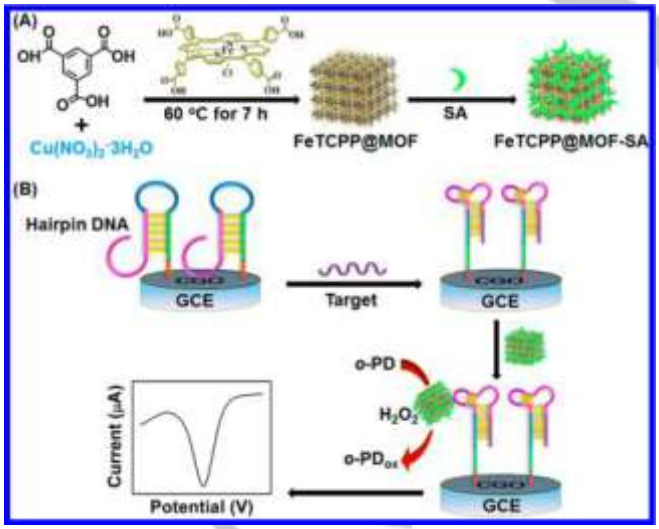

Figure 4. (A) Synthesis of Porphyrinic MOF-SA composite and (B) electrochemical DNA sensing via allosteric switch of hairpin DNA. Reproduced from Ref. [25]. Copyright 2015, American Chemical Society.

of iron-porphyrinic MOFs. Porphyrinic MOFs were also synthesized with Iron porphyrin as linker and Zr as node via solvothermal reaction, and sequentially modified with SA as recognition element.[27] Combination of the electrocatalysis of porphyrinic MOFs toward oxygen reduction and the telomerase-triggered extension was utilized for electrochemical detection of telomerase activity. The three examples indicated that iron porphyrion-based MOFs could catalyze the above oxidation process of electrochemical indicator for signal readout and thus an enhanced electrochemical performance was obtained. Besides, Yuan's group designed a Ce-based MOF decorated with AuNPs and the MOF composites were used to capture -SH terminated HP2.[28] A sensitive aptasensor for LPS detection was obtained based on the Ce-MOF composites and Zn^{2+} dependent DNAzyme-assisted recycling. Herein, the resultant Ce-MOF composites acted as nanocarriers to capture HP2 and also as catalysts to catalyze the oxidation of ascorbic acid due to the redox properties of Ce^{3+}/Ce^{4+}. In short, in the presence of redox mediators, MOF-based materials with high catalytic activity and load capacity provide a powerful platform for electrochemical signal transduction and are expected to extent the range of application for other analytes.[25-28]

3. Electrochemical Sensors based on the Modification of MOFs on Electrode Surface

To impart high sensitivity and some chemical specificity not available at the unmodified electrode, the electrode surfaces were widely modified with various materials. Recently, some groups have attempted to detect trace amounts of compounds using MOF bulk crystals with electrocatalytic activity for modification on the electrode surfaces because of their naked active sites, high surface areas, specific adsorption affinity and various pore sizes.[29-35] In addition to the direct modification of single component MOFs on the electrode surfaces, the introduction of other highly conductive and mechanically durable materials in MOFs has been developed to overcome the disadvantages such as poor stability in water, low electronic conductivity, and unsatisfactory electrocatalytic ability.

3.1. MOFs with Electrocatalytic Activity

The electrocatalytic activity within MOFs is divided two types including metal ions and organic ligands as the active sites. The metal content of inorganic nodes in MOFs plays a significant role in determining their electrocatalytic performances. Metal ions containing copper ion, cobalt ion, and chromium ion have been used as catalytic sites for electrochemical reactions. A porous Cu-MOF modified carbon paste electrode prepared by mixing was used as nonenzymatic sensor for the electrochemical determination of H_2O_2 and glucose.[29] Compared with the bare carbon paste electrode, the Cu-MOF modified electrode yielded an obvious reduction and oxidation current response after the addition of H_2O_2 and glucose, respectively. The high electrocatalytic activity of the Cu-MOF modified electrode was explained by the electron transfer process of Cu(II)-MOF/Cu(I)-

MOF couple. Similarly, a Cu-MOF modified carbon paste electrode and a Cu-MOF electrodeposited on a copper plate as amperometric detectors were fabricated for the detection of 2,4-dichlorophenol and bromate, respectively.[30,31] The above Cu-MOF modified electrodes showed high sensitivity and high stability for the analytes owing to excellent electrocatalytic ability of Cu-MOFs and effective immobilization of MOFs on the electrode surfaces. Co-MOF modified electrodes also showed a pair of reduction peaks corresponding to Co(III)-MOF/Co(II)-MOF couple, which demonstrated the high electrocatalytic activity towards the reduction of H_2O_2.[32,33] In addition, a Cr-MOF modified electrode was constructed for the simultaneous determination of dopamine and uric acid.[34] An increase in peak separation value was ascribed that the large pore volume of Cr-MOFs offered the site for oxidation reaction because of the two types of mesoporous cages with internal free diameters. Hence, the low detection limit of these electrochemical sensors could be ascribed that the Cu or Co-based MOFs with a reduction process catalyzed the electrochemical process of analytes.

Metalloporphyrins have been utilized as electrocatalytic materials for detection of a variety of substrates. Their stable and rigid structures are easily modified with active groups to coordinate metal ions. Kung et al. designed a uniform zirconium-based porphyrin MOF (MOF-525) thin films grown on conducting glass substrates via a solvothermal approach, and the prepared MOF-525 exhibited high electrocatalytic activity for nitrite oxidation.[35] This might be attributed to the catalytic action for the electrochemical oxidation of NO_2^- to NO_2 and rapid disproportionation of NO_2 into NO_2^- and NO_3^- by the oxidation of free-base porphyrin linkers, which produced the cation radical state of the porphyrin. The high catalytic action and perfect biocompatibility could promote the application of this system in biosensing systems.

In brief, the research of MOFs in the area of electroanalytical chemistry has drawn increasing attention, which is attributed to the redox behavior of metal ions and the tuning of the linker structure. Yet, their instability in aqueous phase impedes the electrochemical applications because the bonding of metal ions with ligands in MOFs is via the coordination bonds and/or weak cooperative interactions including π-π stacking, H-bonding, and Van der Waals forces. Up to now, some water-stable MOFs have investigated, but the major shortcoming of several classes of MOFs is their weak conductivity. To overcome these disadvantages of MOFs, the introduction of heterogeneous nanostructured materials with multi-nanocomponents has been proposed. An efficient strategy is the combination with highly conductive and mechanically durable materials such as, carbon nanostructures and metal nanocrystals. In addition, the immobilization of biomolecules on MOFs could meet the demand in biological applications.

3.2. Composites of MOFs with Carbon Nanostructures

From discovery to wide-ranging technological applications, graphene as a sp^2 carbon material with a two dimensional monoatomic thick, is an emerging multifunctional material owing to its excellent electrical conductivity, large theoretical specific surface area, high chemical stability, and low cost. The graphene, which was incorporated into other micro/nanostructured materials, promoted their electrical conductivity and dispersion and controlled their structures.[36] For example, a benzoic acid-functionalized graphene could act as a structure-directing template to influence the crystal growth and the performances of MOF.[37] Based on these considerations, Zhang et al. designed a polyoxometalate-based MOF and its composite with reduced graphene oxide (GO) via a simple one-pot approach.[38] The as-prepared hybrid material modified on the glassy carbon electrode (GCE) was used to detect dopamine. The dopamine sensor presented a good selectivity toward the dopamine oxidation due to the synergistic effect and the interaction of dopamine with C=C networks of the composites. The enhanced electron transfer from the abundant active sites, open channels, and aromatic planes in the composites could introduce a superior catalytic activity for dopamine oxidation. However, the above composite-modified electrode was prepared by drop-casting of GO/MOF on the electrode surface and further chemical reduction of GO sheets. Toxic reducing agents were employed in the method and a Nafion coating was needed to keep its stability. To overcome above drawbacks, a highly dispersible and stable GO/Cu-MOF was prepared by the cooperative interaction of π-π stacking, hydrogen bonding, and Cu-O coordination, as shown in Figure 5.[39,40] After casting on the GCE, the GO in the composite was transferred to the conductive reduced form (electrochemically reduced GO, ERGO) by an electrochemical reduction process with simple, fast and green nature. Compared with the Cu-MOF or ERGO modified electrode, the composite-modified electrode displayed significantly enhanced electrocatalytic activity toward the target molecules and also exhibited high stability and anti-interference

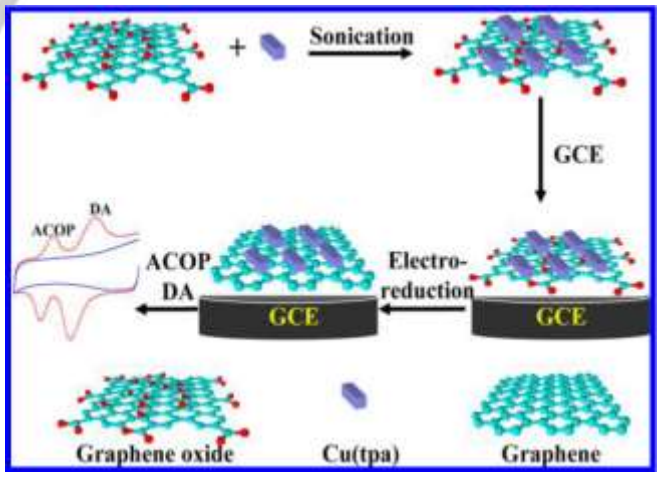

Figure 5. Illustration for the sonication-assisted preparation of the composites of Cu-MOFs and graphene, and its application for the simultaneous determination of acetaminophen and dopamine. Reproduced from Ref. [39]. Copyright 2014, American Chemical Society.

ability. Such good sensing performances could be ascribed by the synergistic catalysis from the excellent conductive property of ERGO and the outstanding porous structure and favorable electron transfer mediating function of the electroactive Cu-MOFs.

Carbon nanotubes (CNTs) are considered as another promising carbon-based material to improve the performances of MOFs because of their unique electrical conductivity, high surface areas and high thermal stability. The CNTs could combine with MOFs to form composite structures with tailored electrical and chemical properties.[41] A Ni-MOF was successfully anchored on carboxyl CNTs by in situ solvothermal method and the Ni-MOF nanoparticles with a diameter of 2-3 nm were uniformly dispersed on the surface of CNTs, which allowed the MOF crystals to be wired up to a current collector by the conductivity of CNTs.[42] Compared with the pure Ni-MOF modified electrode, the resultant Ni-MOF/CNT-modified electrode demonstrated a higher sensitivity and satisfactory stability for the H_2O_2 detection due to the synergistic catalytic activity of the composites.

Among all of the carbon materials, the porous carbon materials with particular properties including high surface areas, large pore volume and good electrochemistry have been also utilized for electrochemical sensing.[43] A hybrid of Cu-MOFs/porous carbon was synthesized by hydrothermal treatment and displayed excellent electrocatalytic ability for the reduction of hemoglobin and the oxidation of ascorbic acid compared to the individual counterparts.[44] A simple one-step hydrothermal method was also developed to synthesize porphyrinic iron-based MOF/porous carbon, and the hybrid materials provided more active sites to reduce H_2O_2.[45] In addition, acetylene black as one special type of carbon black was introduced to the Cu-MOFs and exhibited good electrocatalytic activity towards H_2O_2 reduction due to their active metal sites and diverse structures.[46]

In conclusion, the composites of carbon materials with MOFs showed excellent electrocatalytic activity toward targets due to the synergic effect of the accelerated electron transfer of carbon nanostructures and the superior catalytic performances of MOFs. The above MOF-based composites were utilized as artificial mimetic catalysts because of the low-cost alternatives to natural enzymes. Compared with natural enzymes, the artificial mimetic catalysts possess distinct advantages such as, simple synthesis, convenient modification, high stability and catalytic activity even over a wide range of temperatures and pH.

3.3. Composites of MOFs with Metal Nanocrystals

To develop a sensitive, selective, and effective electrochemical assay for the detection of a wide range of target analyte, the modification of suitable catalysts and catalyst support is very necessary on the bare electrodes. Large internal surface areas, well-defined pores, and chemical tenability of MOFs allow to be used as efficient catalytic supports. Catalytically active metal nanoparticles including gold, silver, copper, platinum, and palladium were loaded in the MOF materials, which could facilitate and improve catalytic efficiency. MOFs as a support could control the shape and size of metal nanoparticles and form highly active electrocatalysts to be used in the electrochemical routes.

There are there strategies for the incorporation of metal nanoparticles to generate metal nanoparticles/MOF composites. The first strategy prepares these composites by encapsulating pre-synthesized nanoparticles in MOFs. For example, Hosseini et al. synthesized Au-SH-SiO_2 and Cu-MOFs, and both of the materials were further incorporated under stirring conditions. The designed electrocatalyst showed an efficient electrocatalytic activity for the oxidation of hydrazine and L-cysteine in the phosphate buffer solution with pH value of 7.0 and 5.0, respectively.[47,48] A composite of AuNPs/ZIF-8 was constructed by embedding of AuNPs in the MOF for the detection of hydrazine.[49] In this method, the control of spatial distribution of presynthesized nanoparticles incorporated in the MOFs is difficult, which results in the low repeatability of the formed modified electrodes.[50]

The second strategy synthesizes nanoparticle/MOF composites by means of MOFs as templates to produce metal nanoparticles within their cavities. For instance, a Zn-MOF was synthesized by hydrothermal method and then incorporated with silver nanoparticles via in-situ reduction in the $AgNO_3$ aqueous solution.[51,52] The synthesized composite-modified electrode exhibited superior electrocatalytical activity for the reduction of H_2O_2. Other similar composites such as AuNPs/Zn-MOF, silver nanoparticles/Fe-MOF, AuPd alloy nanoparticles/Zr-MOF, and Cu nanoparticles/Zn-MOF, were also prepared by in-situ reduction of metal nanoparticles in the pre-formed MOFs and were employed for the design of electrochemical sensors.[53–56] Nevertheless, some inherent limitations including aggregation of nanoparticles on the external surface and potential collapse of the MOF structures via the post-reduction process of nanoparticles still exist.

In the third method, a simple one-pot approach for the preparation of metal nanoparticles-encapsulated MOFs as an electrocatalyst was developed for the detection of target molecules.[57] Both the spatial distribution of metal nanoparticles and the structure of MOFs could be controlled by the regulation of the condition of synthetic process. Recently, Pt nanoparticles (PtNPs)/MOFs were successfully synthesized by the one-pot encapsulation of PtNPs into prototypal MOFs, and the PtNPs were homogeneously distributed inside the MOFs (Figure 6).[58] The resulting composites displayed high efficient electrocatalysis for $NaBH_4$ oxidation, which was constructed for the detection of telomerase activity with high sensitivity and a wide dynamic range. Additionally, a novel template-engaged strategy was developed for the preparation a core-shell heterostructure of Cu_xO nanoparticles@ZIF-8 composites, and the composites showed high selectivity of H_2O_2 owing to the proper pore shape and pore size.[59] Thus, this strategy of one-pot strategy is convenient without the need for additional separation steps. Meanwhile, the nanoparticles can be uniformly dispersed inside the host material and provide active sites, and the MOFs keep the original structure as the molecular recognition.

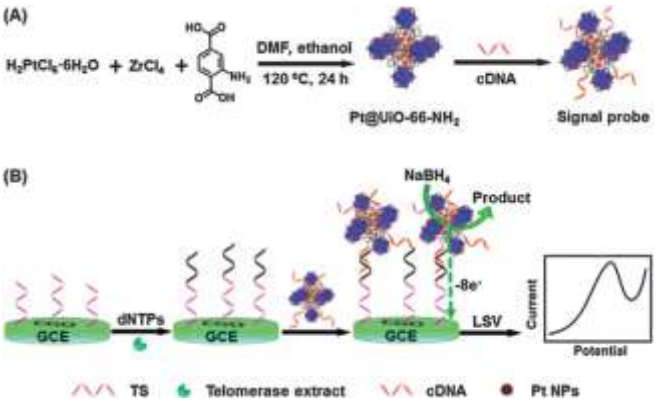

Figure 6. Schematic representation of (A) PtNPs/MOFs (Pt@UiO-66-NH_2) preparation and (B) sensing principle for the electrochemical detection of telomerase activity. Reproduced from Ref. [58]. Copyright 2016, Royal Society of Chemical.

In short, MOFs as excellent host matrices could not only provide a platform for loading metal nanoparticles but also guarantee the accessible MOF pores for the reactant and product. The porous structure of MOFs enhanced the mass transfer and improved the use efficiency of active metal nanoparticles. Moreover, MOFs could also be utilized to control shape and size of metal nanoparticles and to grow highly active electrocatalysis to be applied in electrochemical sensors. Therefore, the metal nanoparticles inserted in the MOFs could enhance the electrocatalytic activity towards the targets compared to metal nanoparticles alone. Combined with electrocatalytic properties of metal nanoparticles, MOFs with high surface area and porosity will display a new way in the modification of electrodes for fabricating new electrochemical sensors.

3.4. MOFs Immobilized with Biomolecules

In addition to catalytically active guest species encapsulated into porous MOFs, the immobilization of proteins has attracted immense attention with the demand of biological applications. One strategy for immobilizing proteins on MOFs employs the adsorption of proteins in the large cavities (large enough for accommodation protein molecules) of MOFs synthesized by special ligands. The other strategy is the direct encapsulation of protein in zeolitic imidazolate frameworks achieved by the procedure of the co-precipitation or biomimetic mineralization. For instance, a mesoporous MOF consisting of nanoscopic cages has been reported for the first time to immobilize microperoxidase-11 and it demonstrated high enzymatic catalysis performances compared to mesoporous silica counterpart.[60] The strong π-π interactions between microperoxidase and MOF facilitated the retention of enzyme molecules with the MOF pores, which was in contrast with the severe leaching of enzyme from the mesoporous silica because of the lack of specific interactions. Besides, Li et al. developed a water-stable Zr-MOF for the encapsulation of a nerve agent detoxifying enzyme and the immobilized enzymes had higher thermal and operational stability than their soluble form. [61]

Recently, the application of protein/MOF hybrid materials with high catalytic activity for electrochemical bioanalysis has gained increasing interest.[62–65] Chen's group synthesized a Cu-MOF and explored its application as a robust electrochemical biosensing platform by choosing tyrosinase as a model enzyme for rapid and sensitive detection of bisphenol A.[62,63] The resultant MOF with a large surface area could be used as ideal tyrosinase immobilization matrix and the π-π stacking interactions between bisphenol A and benzenedicarboxylate of MOF ligands enhanced the pre-enrichment of bisphenol A on the electrode surface. Zhang et al. also synthesized a zeolitic imidazolate frameworks-8 (ZIF-8) crystals to immobilize cytochrome c with an improved apparent substrate affinity due to mesoporous and microporous channels, and the fast detection of H_2O_2 in microliter food samples was achieved on this cytochrome c-coated screen-printed electrode.[64] Lei's group prepared porous carbon through direct carbonization of a N-rich MOF with a zeolite-type framework as both a precursor and a template, and the porous carbon was conjugated with porphyrin by π-π noncovalent interactions (Figure 7).[43] The prepared MOF-based composites were used to adsorb GOD and showed good electrocatalytic activity towards oxygen reduction, which was constructed as a glucose biosensor. Additionally, the composites of Tb-MOF and chitosan-AuNPs were modified on the electrode and the modified electrode was used as a new platform to load microperoxidase-11, as illustrated in Figure 8. This proposed sensor showed good electrocatalytic activity toward the reduction of H_2O_2.

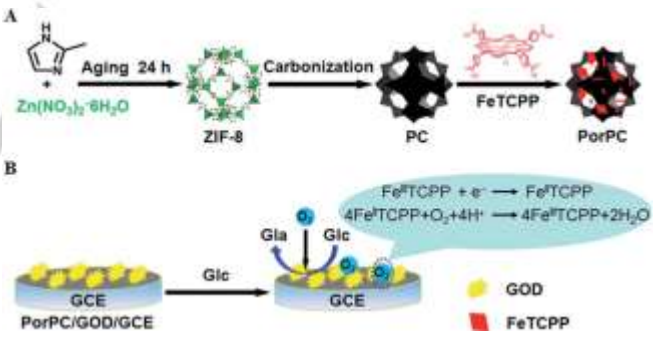

Figure 7. Schematic representation of (A) preparation of PorPC and (B) sensing mechanism for electrochemical detection of glucose. Reproduced from Ref. [43]. Copyright 2015, Royal Society of Chemical.

In general, thanks to their high porosities, functionalizable pore's walls and high surface area, MOFs can well capsulate numerous biomolecules into their mesopores and accordingly avoid the aggregation or cohesion. Thus, the bioactivity for target analytes are improved and high sensitivity can be obtained using the composite-modified electrodes, compared to native biomolecule-coated electrodes. Moreover, MOFs can selectively accumulate target molecules to enhance the specificity of the biosensors. Although there are some

successful applications, the merits of protein-MOFs hybrid materials and simple synthetic strategy have not yet fully demonstrated and the synthesis of protein-encapsulated MOFs remains a continuous challenge owing to the large size of protein molecules by comparison with the much smaller pore of most of MOFs. Further research is very urgent to address their disadvantages and explore their new applications.

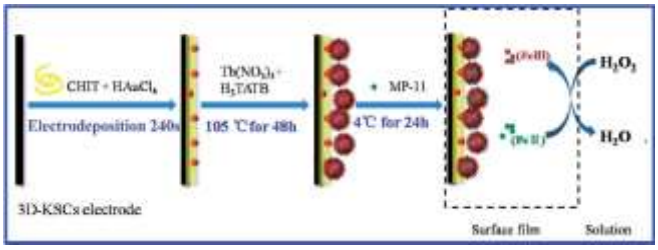

Figure 8. Schematic illustrating of the fabrication and sensing principle of the newly developed H_2O_2 biosensor. Reproduced from Ref. [65]. Copyright 2016, Royal Society of Chemical.

4. MOF-modified Electrodes for Detection of Electrochemically Active Metal Ions

Heavy metal ions have historically been, and remain today persistent contaminants that pose a serious threat to human health and the environment, even at low concentrations. The sensitive, simple, and reliable sensing systems for the heavy metal ions are still an indispensable necessity. MOF materials with tunable pore size, large surface area, and coordinative unsaturated or saturated metal sites, are promising in the selective adsorptive removal of heavy metal ions. The diverse compositions and structure types of MOFs could effectively adjust the adsorption ability compared with conventional adsorbents. Magnetic solid-phase extraction and solid-phase micro extraction based on MOF materials have been thoroughly explored for the detection of heavy metal ions.[66] Despite their accuracy, these approaches have practical disadvantages such as time consummation and high cost. The redox behavior of metal cations and the tuning of the linker structure inside framework of MOFs may provide a pathway for electrons and further lead to better charge transfer. Hence, recent efforts have been devoted to the MOF-based modified electrodes for electrochemical detection of heavy metal ions.

Electrochemical stripping voltammetry is a helpful technique for the trace heavy metal ion because of its effective preconcentration step of the accumulated analytes during the process of electrochemical measurement. Wang et al. prepared an amino-funcationalized Cu-MOF by solvothermal synthesis, and then the MOF-based materials were modified on the GCE by drop-casting.[67] The formed electrodes were used for the electrochemical detection of lead ions by differential pulse anodic stripping voltammetry. The results revealed that the MOFs on the electrodes were capable of selectively adsorption of lead ions from solution phase and showed a great improvement in sensitivity and selectivity for analysis of lead ions. The enhanced mechanism of the stripping voltammetric measurement is the following. Firstly, lead ions were accumulated from the aqueous solutions onto the surface of the amino-functionalized Cu-MOFs by selective complexation with free functional amino groups via the formation of a metal-ligand complex. The accumulated ions were reduced by applying a constant voltage and then were electrochemically stripped back into the solution upon scanning toward positive potential. Secondly, the shape and size of the pores could produce the shape- and size-selectivity over the lead ions when the ions penetrate into the Cu-MOF channels. Usage of the similar strategy, lead ions were also determined on the multi-wall carbon nanotubes/Cu-MOFs, Zn-MOFs, Cr-MOFs, Ni-MOFs, and Zn-MOFs/porous carbon modified electrodes.[68–72] Besides, Zr-MOF@conducting polymer and Zn-MOF based electrochemical sensor were demonstrated for cadmium ion detection with high performances by differential pulse voltammetry.[73,74]

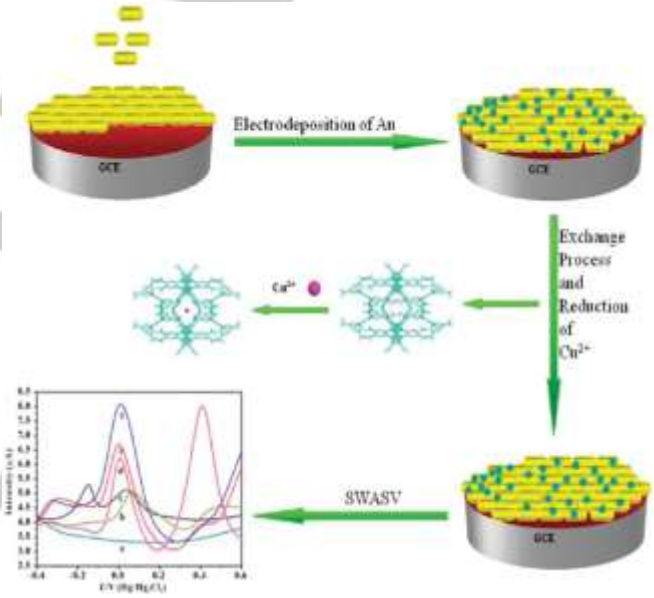

Figure 9. Schematic illustration of the preparation procedures of Au/Me_2NH_2@MOF-1/GCE and the procedures for the detection of copper(II) via the cation exchange process and nanoparticle synergy effect enhanced electrochemical signal. Reproduced from Ref. [76]. Copyright 2016, Royal Society of Chemical.

Recently, the pore MOFs with frameworks charges showed improved performances due to a post-synthetic modification by cationic exchange.[75] In Figure 9, Jin et al. prepared a novel microporous anionic Me_2NH_2@MOF-1, and used it as a modified electrode with AuNPs for detection of copper (II) ions by the use of square wave anodic stripping voltammetry (SWASV).[76] The anionic MOF in the modified electrode acted as a pre-concentrated trace of copper (II) ions. Combined with the benefit of a microporous framework, the copper (II) ions were filled with $[H_2N(CH_3)_2]^+$ ions. AuNPs as a binder increased the analytical signal and improved the sensitivity by ion-exchange. Thus, the

low detection limit of 1 pM for copper (II) ions was obtained by the use of SWASV. This strategy for generating new MOF-modified electrode will be useful for expanding the application range in the electrochemical sensing.

5. Other Electrochemical Assays based on the MOF-modified Electrodes

5.1. Photoelectrochemical Sensors

Photoelectrochemical (PEC) detection with simple instrumentation, high sensitivity, rapid analysis, and low cost is a quite promising analytical technique based on the photoelectric signal generation from the electron transfer among photoactive species, targets and electrode surfaces under photoirradiation. Porphyrins as dye sensitizers were utilized in the PEC systems to enhance photoelectric conversion efficiency. The production of cathodic and anodic photocurrent on the porphyrin-modified electrodes has been widely investigated due to strong optical absorption and emission, electrochemical performances for light harvesting-related electron transfer reactions, and widespread occurrence in nature. Specially, porphyrinic-based MOFs are expected to have excellent photochemical functions. Compared with the porphyrinic compounds, the porphyrin incorporated into the framework of MOFs offers some advantages: (1) higher chemical stability, (2) smaller HOMO-LUMO energy gap, (3) enhanced electron-hole recombination time because of the extended conjugation in the framework, and (4) a decisive oxygen reduction reaction.[77,78] The above features are beneficial for the photoinduced electron transfer process and enhance the photoelectric conversion efficiency. In this regard, Zhang et al. prepared a zirconium based porphyrinic MOF for the construction of a simple and rapid PEC assay on the indium tin oxide electrode.[79] The high porosity and tunable structures of the synthesized MOF as a visible light-harvesting unit could promote the enrichment of oxygen and dopamine. The developed sensor showed an enhanced photoelectronic activity towards dopamine under O_2-saturated aqueous solution because the dopamine molecules effectively inhibit charge recombination of electron-hole pairs. Furthermore, zirconium based porphyrinic MOF could be further utilized as PEC signal probes for a label-free phosphoprotein assay based on the steric hindrance effect from the coordination of the phosphate groups and Zr-O clusters as binding sites in these MOFs. Thereby, the proposed biosensor demonstrated high sensitivity and selectivity for detecting *α*-casein.

Much attention has been paid to the heterostructures integrating MOFs through embedding metal or semiconductor nanoparticles into the cavities because of the synergism effect. In contrast, a few works concerning with functional materials@MOF core-shell heterostructures were reported which might be ascribed to a great challenge in the control of MOF growth to the core surface and shapes of core-shell structures.[80,81] As we know, ZnO with the richest morphologies of nanoscale is a very important semiconductor for applications in PEC. In Figure 10, a simple self-template strategy to fabricate ZnO@MOF core-shell heterostructures was proposed and the vertically freestanding ZnO@ZIF-8 was obtained.[82] The size and morphology of the heterostructure could be controlled by the template method, and ZnO nanorods afforded Zn^{2+} ions for the formation of ZIF-8 in addition to acting as the templates. Such ZnO@ZIF-8 nanorod arrays indeed exhibited selective PEC response towards different hole scavengers due to the limitation of the aperture of the ZIF-8 shell. Predictably, the as-prepared array could be applied in the H_2O_2 detection in the presence of serous buffer solution. Therefore, the above two examples including porphyrinic MOF and ZnO/MOF core-shell structure provide the potential applications of MOF-based materials in PEC sensors.

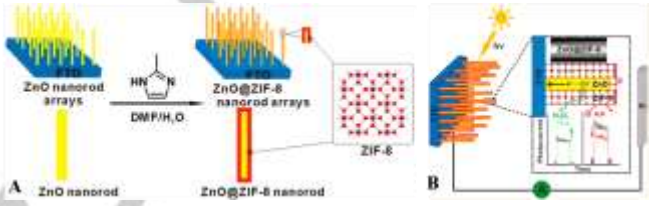

Figure 10. (A) Schematic illustration of ZnO@ZIF-8 nanorods synthesized via the self-template strategy; (B) Schematic diagram of the PEC sensor with selectivity to H_2O_2. Reproduced from Ref. [82]. Copyright 2013, American Chemical Society.

5.2. Electrochemiluminescence Sensors

Electrochemiluminescence (ECL) is an attractive electrochemical method due to its high sensitivity, low background signal and wide dynamic response range. Various luminophores, such as Ru complex, quantum dots, and luminol, have been used to determine many important analytes. However, the bottlenecks from the poor film formation ability or sophisticated immobilization process of luminophores still exist. The immobilization of luminophores on MOF materials was expected to supply some advantages including reusability, enhanced ECL signal, and simple operation process. Thus, a few of MOF-based ECL systems have been prepared and were used for the electrochemical analysis. For example, a redox-active MOF was prepared from Ru complex and Zn^{2+}, and further combined with GO, as illustrated in Figure 11.[83] The high ECL emission of Ru-MOF/GO modified electrode revealed the rapid electron transfer between the MOFs and co-reactants. That was because the distance between Ru-MOFs and GO was suitable for the energy tunneling of Förster resonance energy transfer. Consequently, GO mediated the oxidation of Ru-MOFs through electron tunneling, and the pore channel played an important role in the ECL process of MOFs. Thus, the MOF-based ECL sensor displayed quite higher sensitivity for cocaine detection on the basis of concentration-dependent ECL emission than that at Ru complex-modified electrode. Ru-MOF nanoflowers prepared by an one-step solvothermal method were

also used to construct an ECL "on-off" switch sensor with CdS quantum dots for the determination of tryptophan enantiomers based on the quenching effect.[84] Fu et al. investigated a Fe-MOF as the energy acceptor of perylene derivatives (3,4,9,10-perylenetetracarboxylic acid, PTCA), and a quenching effect on the ECL of PTCA with H_2O_2 was obtained via ECL-resonance energy transfer.[85] The "on-off" ECL sensor was designed to detect dopamine with a wide linear range. Additionally, Ma et al. exploited the composites of silver nanoparticles-doped Pb-MOF and β-cyclodextrins as a ECL probe for the label-free immunosensing towards prostate-specific antigen[86]. The β-cyclodextrins based MOF exhibited excellent ECL behavior and was superior to most previous proposed sensors for detection of prostate-specific antigen. The above applications confirm that MOF-based materials with ECL capability will be a good platform for the design of electrochemical systems.

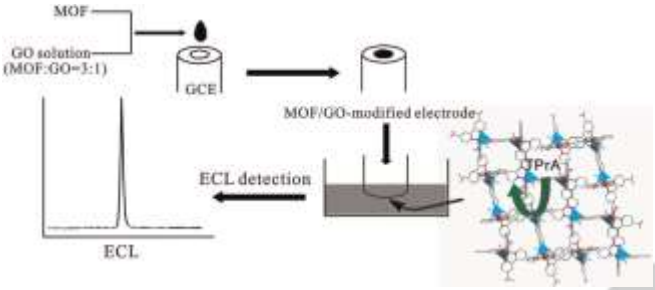

Figure 11. Preparation and test of Ru-MOF modified electrode. Reproduced from Ref. [83]. Copyright 2017, Elsevier.

5.3. Resistant Sensors

Electrochemical impedance spectroscopy (EIS) was performed to probe the interaction among biomolecules and the surface features of electrode surfaces during the modification steps. Based on the change of charge transfer resistance after the recognition of the target molecules, various electrochemical biosensors were investigated. Deep's group reported the sensing application of a Cd-MOF in the pesticide detection by the use of EIS.[87] The assembly of Cd-MOFs was firstly achieved through the amide linkage between free -COOH pendent groups (available on the Cd-MOF surface) and the amine-terminated electrode surface. Then the available pendent -COOH functional groups of the MOFs were conjugated with anti-parathion antibody. In the biosensing systems, MOFs with large surface areas provided a large amount of binding sites for the antibody molecules. Thus the proposed immunosensor showed highly sensitive and specific impedimetric detection of organophosphate pesticide. Considering this aspect, Fe-MOF-derived core-shell nanostructure and Al-MOF as biosensing platforms for immobilization of aptamer and antibody were used for the determination of high trace heavy metal ions and the assessment of food safety, respectively.[88,89] The gas detection was also performed based on the MOF-based resistant sensors. For example, γ-cyclodextrin-derived MOFs could react with gaseous CO_2 to form alkyl carbonate functions, which was designed as a resistant sensor with high sensitivity and high selectivity.[90] Additionally, surface-modified MOF materials were used as humidity sensors by impedance measurements.[91] These researches have demonstrated that MOFs have a promising future in sensing applications by EIS, which might be have higher sensitivity than current methods.[90]

5.4. Conductometric Sensors

In comparison to other competing nanomaterials, the use of MOFs as conductometric sensors has been a topic of interest because MOFs are less costly, easier to prepare, and more biocompatible.[91] Nevertheless, the poor electrical conductivity presents a hurdle to exploit them in the development of conductometric sensors. Dincă's group postulated that the overall electronic structure of the two-dimension (2D) sheets could be tuned through systematic variation of the metal center, which led to diverse properties and functionality.[92] They tried to replace the Ni sites in Ni-MOFs with Cu, which resulted in an isostructural material with high electrical conductivity due to the energy increase of the Fermi level. The Cu-MOFs had a dramatic effect on the conductometric response to ammonia vapor because the copper sites were critical for ammonia sensing. Thereby, the 2D framework-based sensor was capable of detecting sub-ppm levels of ammonia vapor with high selectivity. To distinguish between different types of molecules, a conductometric array was constructed from three conductive 2D MOFs with analogous structural and could reliably distinguish between five categories of volatile organic compounds based on functional groups.[93] Recently, the coordination with redox-active molecules or complex with conducting polymer enhanced the carrier mobility of MOFs.[94,95] Deep's group reported that tetracyanoquiondimethane (TCNQ) with charge transfer properties could be coordinated with Cu-MOF at opposite ends of the Cu(II) axis of the paddlewheel structure.[94] The insert of the TCNQ in the MOFs would improve electronic coupling and charge mobility, which introduced tunable electrical conductance. This conducting platform modified with antibodies was constructed as a conductometric immunosensor for the quantification of prostate cancer antigen. This group also reported the assembly of the silica-modified Cu-MOF film on a conducting substrate doped polyaniline.[95] The films were further conjugated with anitatrazine antibodies to fabricate a sensitive conductometric immunosensor. Hence, MOF-based devices demonstrate improved performances owing to the high surface areas and the combined effects with other conductive materials.

In addition, Eddaoudi's group studied on the fabrication of two rare-earth metal-based MOF thin films as advanced chemical capacitive sensors for the detection of ammonia and hydrogen sulfide, respectively.[96,97] A organic field effect transistor (OFET) sensor for sensing of the explosive analytes was prepared based on a composite of conductive polymers and MOFs as receptors and pre-concentrator sites.[98] In a word, these electrochemical signal-transduction methods, involving

PEC, ECL, resistance, conductance, capacitance, and OFET are necessary to be employed in order to expand the applicability of MOF materials.

6. Conclusions and Outlook

As a new kind of crystalline molecular material, MOFs are emerging as a very effective tool for electrochemical sensing applications, because of the excellent advantages such as ultrahigh porosity, large surface areas, large pore volume, tunable structure, thermal and chemical stability, and chemical functionality. These electrochemical sensors possess some merits, as illustrated in Table 1. Firstly, the MOFs modified on the electrodes could be used as electrochemical signal probes and large amounts of redox metal ions provide high signals. Secondly, the MOFs could act as catalysts to catalyze the electrochemistry of redox mediators and high catalytic activity is obtained because of the abundant active sites. Thirdly, the MOFs could be employed as an ideal loading platform to load recognition probes or signal probes due to the rationally ordered structure and stable micropores. The specific identification of targets by the MOFs may be ascribed to the interactions via hydrogen bonding, π-π interactions, open metal sites, and van der Waals interactions. The incorporation of the heterogeneous nanostructured materials in the MOFs promotes the development of applications for the MOF-based materials in the area of electrochemical sensing. The immobilization of biomolecules on the functionalized MOFs holds great promise for the design of electrochemical biosensors for the detection of a range of ions, organic molecules, and biomolecules. The electrochemical signal-transduction techniques including amperometric, potentiometric, resistant, conductometric, and photoelectrochemical methods are all suitable for MOF materials and also expand their applicability.

However, the above assays still exist some demerits (Table 1). Up to now, the MOF-based electrochemical assays are restricted under laboratory conditions and are far behind other fields because of the following limitations. (1) Most MOF materials are insulators or semiconductors, and thus the improvement in the conductivity of MOFs and the design of redox-active MOFs are the primary challenges for the application of MOF-based electrochemical assays. (2) In addition to above signal transduction, the weak strength of analytes binding to MOFs also influences the sensitivity due to the insufficient functional groups on the surface of MOFs. (3) Another limitation of these sensors is that they usually lack sufficient chemical selectivity despite the growing catalogue of MOF materials. (4) The stable and repetitive response is sometimes difficult to obtain owing to the difficulty of MOF synthesis with homogeneous and small enough dimensions. (5) The transport lead to a long response time because the big dimensions of MOFs could not ensure rapid analyte uptake and equilibration.

Table 1. Comparison of merits and demerits of MOF-based electrochemical sensors mentioned in this review.

Electrochemical Method	Merits	Demerits	Refs.
2. Electrochemical sandwich assays using MOFs as outer probes			
2.1 Electrochemically active MOFs as signal probes	High sensitivity, simplicity, no need for addition of redox molecules	Relatively few MOFs with electrochemical redox activity	[18-21]
2.2 Redox active species-modified MOFs as signal probes	High sensitivity, simplicity, no need for addition of redox molecules	Difficulty of the complex of redox active species with MOFs	[22-24]
2.3 MOFs as catalysts and carriers	High sensitivity, simplicity	Additional redox mediators	[25-28]
3. Electrochemical sensors based on the modification of MOFs on electrode surface			
3.1 MOFs with electrocatalytic activity	Simplicity	Relatively few MOFs with electrocatalytic activity	[29-35]
3.2 Composites of MOFs with carbon nanostructures	High electrocatalytic activity	Low reproducibility	[36-46]
3.3 Composites of MOFs with metal nanocrystals	High electrocatalytic activity	Low reproducibility	[47-59]
3.4 MOFs immobilized with biomolecules	High specificity, High electrocatalytic activity	Difficulty of synthesis of protein-encapsulated MOFs owing to the large size of protein molecules	[43,60-64]
4. MOF-modified electrodes for detection of electrochemically active metal ions	High sensitivity and selectivity due to the selective accumulation	Limitation of detection of electrochemically active metal ions	[66-76]
5. Other electrochemical assays based on the MOF-modified electrodes	High sensitivity	Nonspecific adsorption	[77-98]

The ultimate goal is the application of these MOF-based electrochemical sensors to routine biomedical, clinical and environment analysis, and ongoing intensive efforts should be made in future research work. (i) To enhance the sensitivity of the electrochemical sensors, it is necessary to enhance redox activity of MOF-based materials by the rational selection of multivalent ligands and metal nodes. (ii) To realize the selectivity for recognition of different species, it is desirable to design MOFs with a desired pores and active sites by control of the synthetic methods and conditions, dopant modification, and postsynthesis methods. (iii) A significant direction for MOF materials is to explore the assembly of nanoparticles and various functionalities, which endows the MOF-modified electrodes with excellent electrochemical properties and novel functions. (iv) A well-controlled immobilization method on the electrode surfaces such as a layer-by-layer technique, electrochemical deposition, and Langmuir-Blodgett method should be focused because of the requirement of well-organized structure for the stable electrochemical signals. (v) The solubility in water is very important in electrochemical biosensing, so functional groups should be modified on the MOFs by in situ synthesis, post modification and physical mixing. With the development of nanoscience and biotechnology, MOF-based materials will display very promising applications and offer a proof of concept in electrochemical sensing.

Acknowledgements

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Keywords:

Metal-organic frameworks • electrochemical sensors • analytical performances • redox activity • composites

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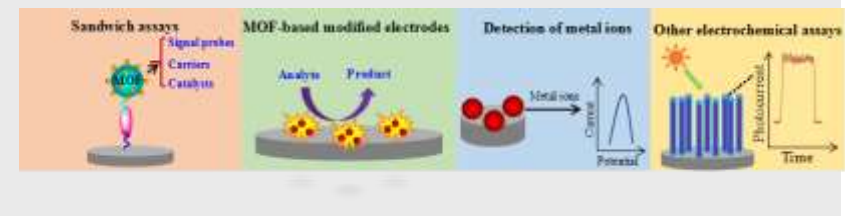
REVIEW



MOFs-based electrochemical sensors: Recent progress made in the development of techniques for electrochemical sensors based on MOFs materials are summarized. With the advancement of nanotechnology, MOF-based materials will display very promising applications and offer a proof of concept in electrochemical sensing.

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