

Review

Recent Advances in the Application of Metal–Organic Frameworks and Coordination Polymers in Electrochemical Biosensors

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Abstract: Electrochemical biosensors are critical in advancing biomedical and pharmaceutical therapies because of their adaptability and cost-effectiveness. Voltammetric and amperometric sensors are of particular interest. These sensors typically consist of a specialized tip or biorecognition element and a transducer that converts biological data into readable signals. Efficient biosensor materials are essential for addressing health emergencies, with coordination polymers (CPs) and metal–organic frameworks (MOFs) showing promise. Functionalization strategies are necessary to enhance the usability of pristine MOFs, owing to issues such as low conductivity. The integration of conductive polymers with MOFs has resulted in the development of highly efficient biosensors. Both enzymatic and nonenzymatic biosensors are used for analyte detection; nonenzymatic approaches are gaining popularity owing to their durability and accuracy. MOFs and CPs have been applied in sensitive electrochemical biosensors to detect fatal brain tumors such as glioblastomas (GBM). These biosensors demonstrate enhanced selectivity and sensitivity, highlighting the potential of MOFs and CPs in advancing electrochemical biosensor technology for both in vivo and in vitro applications.

Keywords: coordination chemistry; bioMOFs; coordination polymers; composite materials; electrochemical applications; biosensors; in vivo and in vitro biosensing



Citation: Kidanemariam, A.; Cho, S. Recent Advances in the Application of Metal–Organic Frameworks and Coordination Polymers in Electrochemical Biosensors.

Chemosensors **2024**, *12*, 135.

<https://doi.org/10.3390/chemosensors12070135>

Received: 29 May 2024

Revised: 2 July 2024

Accepted: 5 July 2024

Published: 9 July 2024



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1. Introduction

Electrochemical biosensor materials are crucial for the advancement of biomedicine and pharmaceutical therapies [1]. Electrochemical biosensors are extensively recognized for their adaptability and low cost compared to traditional methods such as atomic emission spectroscopy (AES), chromatography, and inductively coupled plasma mass spectroscopy (ICP-MS) [2]. Electrochemical sensors can be classified into five types: conductive, potentiometric, impedimetric, amperometric, and voltammetric [3,4]. Of the five classes of electrochemical sensors, voltammetric and amperometric sensors are considered acceptable [5]. A biosensor typically comprises a specialized tip or biorecognition element that is sensitive to a specific analyte, along with a transducer [6]. This biorecognition element, which can include molecules such as enzymes, antibodies, nucleic acids, carbohydrates, and cellular structures, interacts with specific analytes, leading to biological or chemical alterations [7]. The transducer then converts the data from the biological element and converts them into colorimetric, electrical, or other readable signals [8]. Efficient biosensor materials are critical for addressing health emergencies where rapid response is essential. Consequently, the synergy of a biosensor material plays a vital role in its practical effectiveness. Researchers are actively investigating the development of efficient biosensor materials for clinical applications [9–11]. Various organic and inorganic materials have been studied

for their potential applications in biosensing [12,13]. Recently, different materials such as macromolecules, polymers, nanoparticles, and hydrogels have been recognized for their practical application in the field of biosensing [14,15]. Coordination polymers (CPs) and metal–organic frameworks (MOFs) have been studied for use in biomedicine. MOFs and CPs are both coordination compounds with distinct characteristics. MOFs are known for their highly porous, crystalline structures composed of metal ions or clusters coordinated with organic ligands [16]. Similarly, CPs are formed from organic ligands coordinated with metal centers [17]. However, in contrast to MOFs, CPs are typically non-crystalline and exhibit little to no porosity [18].

The inherent versatility of MOFs, such as tailorable pore size, high surface-area-to-volume ratio, and ample active sites, make MOFs candidates for various applications, such as sensors, energy storage, catalysis, and drug delivery [19,20]. MOFs are excellent choices for electrochemical biosensors because of their unique structural and chemical characteristics [21,22]. Their exceptional porosity and specific surface area facilitate enhanced analyte mass transfer, resulting in moderate electric signal amplification and increased detection sensitivity [23]. Moreover, the ability to adjust pore sizes within MOFs enhances selectivity by enabling size-based screening and the exclusion of targeted analytes [24]. In addition, the abundance of unsaturated metal sites in MOFs provides opportunities for versatile functionalization with various materials, thereby broadening their applicability. Through deliberate functionalization and precise construction, MOFs can be tailored to develop highly efficient biosensors with enhanced selectivity and sensing capabilities across a wide spectrum of analyte concentrations [25]. Unmodified MOFs typically display low conductivity and are susceptible to chemical exposure and humidity, which currently restrict their practical application in electrochemical biosensors. Thus, developing effective strategies to modify these MOFs could significantly advance the field of electrochemical sensors [26]. This strategic approach holds promise for the development of robust biocompatible electrochemical biosensors capable of detecting diverse small biotic and abiotic molecules, including H_2O_2 , glucose, and heavy metals [27].

Furthermore, CPs have found widespread applications in both electrochemical and biomedical fields [28]. These CPs, comprising metal elements and organic ligands, offer versatility in composite formation with diverse materials, leading to enhanced electrochemical biosensing capabilities of the final product [29]. CPs have been extensively researched for applications in gas separation, catalysis, and drug delivery. Recently, there has been a growing interest in exploring CPs for electrochemical biosensors, especially when combined with other organic and inorganic materials. This integrated approach holds significant promise for advancing biosensing applications, suitable for both *in vitro* and *in vivo* therapeutic environments [30]. Typically, in the development of biocompatible and redox-active CP-based biosensors, biological ligands such as amino acids are complexed with transition metals [31]. Furthermore, CPs have been investigated for their capability to improve electrochemical biosensing efficacy by integrating lanthanide ions as coordination centers and leveraging their unique optical nature, high coordination number, and electronic and photoluminescence properties [32]. To create effective electrochemical biosensors, nanoscale materials, including noble metals, oxides, carbon, and composites, have been extensively explored as substrate supports.

Cutting-edge research has recently focused on enhancing electrochemical biosensor materials through the strategic integration of conductive polymers with MOFs [33]. This advanced approach combines the inherent advantages of both materials. Because of their exceptional electrical properties, a variety of conducting polymers have been chosen to improve the electrical sensitivity of MOFs, thereby enhancing their effectiveness in electrochemical sensing applications [34]. For instance, polyaniline (PANI), one of the most promising conducting polymers, holds significant promise when composited with MOFs, offering a synergistic effect conducive to the development of highly efficient electrochemical biosensors. Recently, Wang et al. reported that MOFs functionalized with PANI; specifically, PANI deposited on UiO-66- NH_2 surfaces exhibited remarkable electrochemical perfor-

mances for the identification of cadmium ions in an aqueous medium [35]. It is imperative to meticulously identify optimal methodologies for integrating conductive polymers and MOFs to push forward the development of advanced electrochemical biosensor technology.

Two main types of electrochemical biosensors used for detecting analytes are enzymatic and nonenzymatic sensors [36]. Enzymatic biosensors offer benefits like biocompatibility, specificity, and versatility; however, they are limited by issues such as instability, sensitivity to temperature and pH changes, and high costs, which hinder their practical application. On the other hand, nonenzymatic biosensors are known for their durability, versatility across a wide operating range, and cost-effectiveness, making them suitable for various practical applications [37]. Therefore, MOFs and CPs have been studied for their practical applications using enzymatic and nonenzymatic approaches. For instance, Sun et al. reported a sensitive and label-free electrochemical biosensor, Zr-MOF, for the detection of the most fatal brain tumor, glioblastoma (GBM), in practical applications [38]. Detection was performed based on the interaction of GBM-derived exosomes and Zr^{4+} ions on the Zr-MOF surface. Since methylene blue was incorporated into the electrode surface to generate strong electrochemical signals, the concentration of exosomes was quantified without extra amplification elements. The synergy between the electrode and analyte is critical for improving the precise detection of GBM in human serum, thereby enhancing both selectivity and sensitivity in practical applications.

This review provides a thorough analysis of MOFs and CPs, focusing on their electrochemical biosensing capabilities for the detection of biomolecules such as deoxyribonucleic acid (DNA), glucose, amino acids, and uric acid. This review summarizes recent advancements in the last three years and explores the production of composite biosensors using materials such as graphene oxide (GO), carbon nanotubes (CNTs), metal oxide nanoparticles, and carbon paste electrodes (CPEs). It also evaluates the electrochemical performance of these biosensors, both pristine and in a composite form.

2. Synthesis, Properties, and Application of MOFs and CPs

The reaction parameters (such as temperature, concentration, pH, and reaction time) in MOFs and CPs are essential for achieving precise control over the properties and performance of these materials, which will enable their application in electrochemical biosensors. By adjusting reaction parameters, researchers can tailor the pore size, distribution, specific surface area, phase purity, structural diversity, and the functional characteristics of MOFs and CPs. This adaptability enables these materials to be widely utilized across various fields such as catalysis, sensors, separation technologies, gas storage, batteries, and adsorption processes [39]. Hence, the type of metal center plays an important role in the final morphology of MOFs or CPs. In particular, MOFs' structural shapes are highly susceptible to the metal nodes; hence, distinct metal ions have different coordination numbers and geometries, such as square planar, square pyramidal, bipyramidal, octahedral, tetrahedral, and trigonal prismatic [40]. There are different synthetic strategies for developing MOFs and CPs, as shown in Figure 1. It is worth noting that depending on the final product, it is possible to make an informed decision regarding these synthesis routes. The assembly of the organic linker at the metal center must be considered in advance to meet the specific application requirements.

The characteristics of MOFs and CPs depend significantly on how they are synthesized and the specific reaction conditions used, tailored to meet the diverse requirements of different fields [41]. To achieve optimal performance, a thorough understanding of appropriate synthesis methods, material properties, and targeted applications is essential.

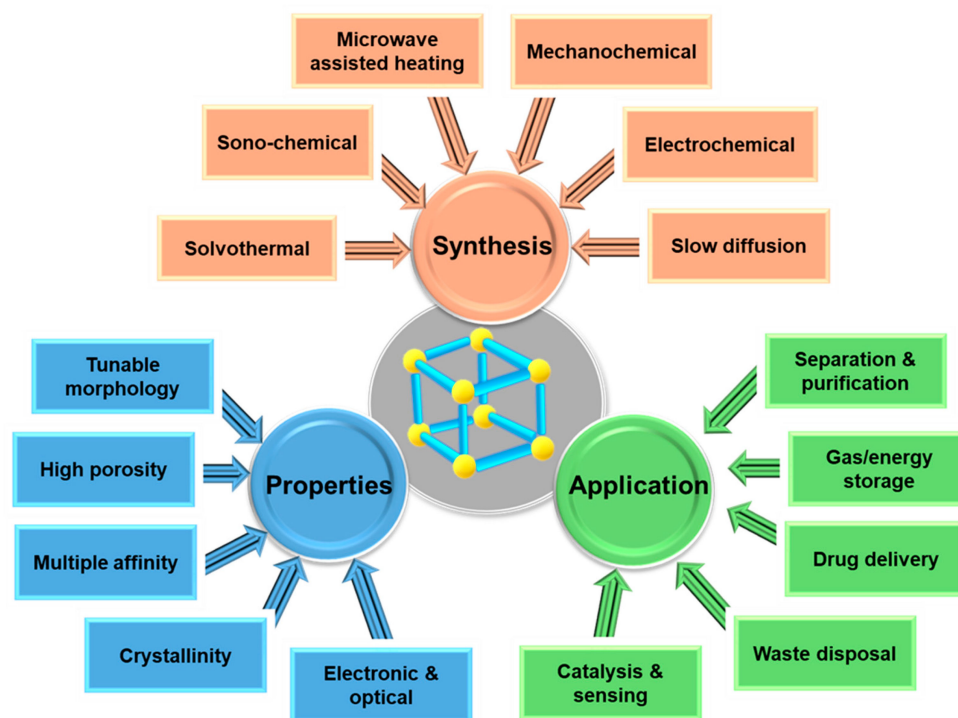


Figure 1. Synthesis properties and applications of MOFs.

2.1. Solvothermal Synthesis

Solvothermal synthesis, a common technique for preparing MOF and CP, involves mixing metal ions or clusters with organic ligands in a suitable solvent and heating them under controlled conditions in a sealed vessel [42]. This method provides benefits such as precise control over the particle characteristics, enhanced crystallinity, and access to diverse MOF structures [43]. However, achieving the desired outcomes requires careful optimization of the reaction parameters, including the temperature, pressure, solvent composition, and reaction duration. Lozano et al. reported the production of UiO-66 from Zr^{4+} and benzene dicarboxylic acid (BDC), which was heated in an acetone solvent for 6–72 h at 40–160 °C [44]. The solvothermal synthesis was carried out by varying the molar ratios of the metal node and organic linker, along with the reaction solvent, at various reaction times and temperatures. The results suggested that a molar ratio of 1:1:1622 of Zr: BDC:acetone at 80 °C, for 24 h, yields better UiO-66 properties. The as-prepared UiO-66 has higher crystallinity (150 nm size crystals) and a surface area of $1299 \text{ m}^2 \text{ g}^{-1}$. Therefore, the controlled production of UiO-66 provides insight into the alteration of the material properties, and the as-prepared MOF exhibits an excellent CO_2 adsorption capacity. Researchers have been investigating green chemistry for the fabrication of MOFs, in which water is used as a solvent. Recently, hydrothermal synthetic routes for MOFs have been investigated. MOF MIL-91(Ti) was produced by refluxing Ti^{4+} metal ions and N,N'-piperazine-bis (methylenephosphonic acid) in water for 68 h. The as-prepared MIL-91(Ti) exhibited a BET surface area of $360 \text{ m}^2 \text{ g}^{-1}$ and a pore volume of $0.138 \text{ cm}^3 \text{ g}^{-1}$ [45]. Additionally, solvothermal methods were practical in the fabrication of CPs, Liang et al. proposed the fabrication of CPs from AgNO_3 and 5-phenyl-1H-tetrazole (Hptz) ligands in the presence of four types of polyoxometalates. This synthesis strategy facilitates Ag- π interactions, making it suitable for photoluminescent applications [46].

2.2. Sono-Chemical Synthesis

The sonochemical synthesis of MOFs and CPs involves the use of ultrasound waves to aid the structural assembly [47]. In this process, metal salts and organic ligands are mixed in a solvent and exposed to ultrasonic irradiation. High-frequency ultrasound waves

generate acoustic cavitation within a solution, creating localized areas of high pressure and temperature. Recently, extended 3D-supramolecular CPs were fabricated using ultrasonic irradiation from cobalt and ethyl isonicotinate (EIN). The framework and network were achieved via H-bonding [48]. These conditions facilitate rapid and efficient mixing of the reactants, leading to the formation and growth of MOF crystals. Sonochemical synthesis is valued for its ability to produce MOFs with controlled characteristics such as morphology, particle size, and crystallinity within a shorter timeframe than traditional methods. In addition, it offers advantages such as scalability and operability under mild reaction conditions. MOF-177 has been synthesized from Zn^{2+} and 4,4',4''-benzene-1,3,5-triyl-tribenzoic acid through a sonochemical route under the 1-methyl-2-pyrrolidone solvent; the as-prepared material had a BET surface area of $4898 \text{ m}^2 \text{ g}^{-1}$ [49]. The as-prepared MOF-177 was suitable for the adsorption of CO_2 .

2.3. Microwave-Assisted Heating

Microwave-assisted MOF and CP synthesis involves the use of microwave irradiation to accelerate chemical reactions. This method rapidly heats the reaction mixture, leading to faster synthesis than conventional heating methods. Furthermore, microwave irradiation enhances reactant diffusion, promotes the coordination between metal ions and organic ligands, and improves crystallinity, all of which contribute to the efficient formation of MOF crystals. MOF-177 was produced by microwave synthesis methods; the metal node and organic linker were mixed in a 1-methyl-2-pyrrolidone solvent and heated in the microwave for 35 min at 100°C . In addition to the faster synthesis strategy of this microwave-assisted synthesis, it results in a high specific surface area of MOF-177 with $4197 \text{ m}^2 \text{ g}^{-1}$ [49]. In another study, MOFs and covalent organic framework composites (IRMOF₃-TzDa) were synthesized via the microwave synthesis procedure, in which $\text{Zn}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$ and 2-aminoterephthalic acid were mixed in a DMF solvent and heated for 30 min (120°C , 150 W, 5 MPa). The cube-shaped IRMOF₃-TzDa exhibits fluorescence sensing and a selective Cu^{2+} ion adsorption of up to 86 mg g^{-1} ; the morphology plays an important role in accommodating the heavy metal on its porous surface (Figure 2) [50]. Moreover, MOF-907 was synthesized via microwave-assisted radical polymerization within a short reaction time (30 min) [51]. As shown in Figure 2, microwave-based MOF-907 synthesis provides an opportunity for the precise control of the topology. This synthesis approach has been adopted for the fabrication of three-dimensional CPs from Pb(II) metal ion and 2,5-bis(4-pyridyl)-3,4-diaza-2,4-hexadiene ligand, which were used for the loading and unloading of guest molecules [52]. Overall, in addition to the fast reaction, microwave-assisted MOF and CP synthesis provide a well-structured assembly of the organic linker at the metal center and better electrochemical properties.

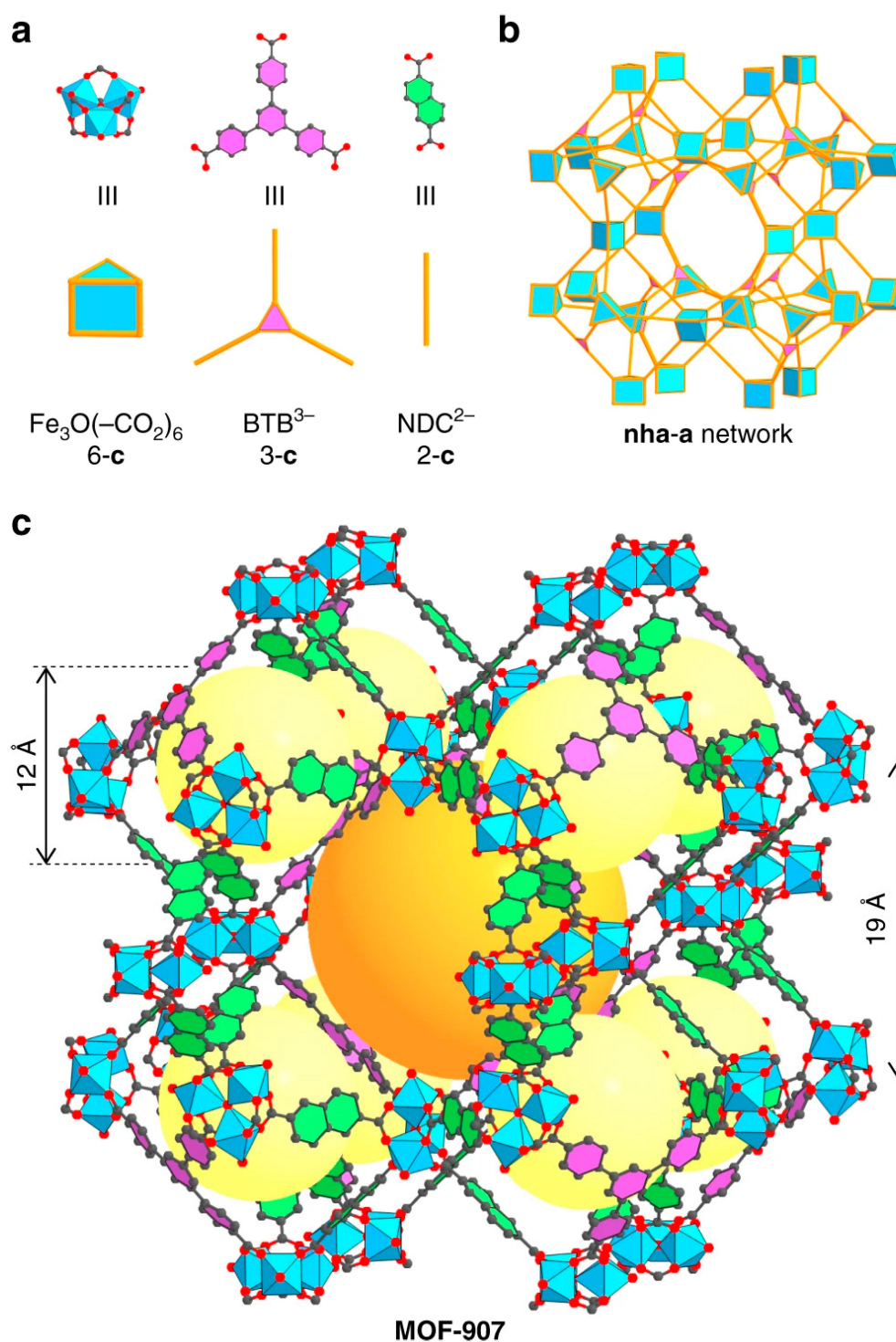


Figure 2. Structural representation of MOF-907. (a,b) Trigonal prismatic $\text{Fe}_3\text{O}(-\text{CO}_2)_6$ clusters linked together by triangular 4,4',4''-benzene-1,3,5-triyl-tris(benzoate) (BTB^{3-}) and linear 2,6-naphthalenedicarboxylate (NDC^{2-}) linkers. (c) The single crystal structure of MOF-907. Atom colors: Fe: blue polyhedral, C: black, and O: red. All H atoms are omitted for clarity. The yellow and orange spheres indicate the free space in the cages. Reproduced with permission [51]. Copyright 2018 Nature.

2.4. Mechanochemical Synthesis

During mechanochemical MOF synthesis, solid ingredients are mixed while being ground, sometimes with a small quantity of liquid or solvent, in a ball mill or similar

device [53]. The mechanical force produced during grinding helps break existing chemical bonds and aids in the creation of new bonds between metal ions and organic linkers. This approach presents numerous benefits over traditional solution-based synthesis methods, such as faster reaction times, increased yields, and the capability to generate crystalline MOFs without requiring elevated temperatures or severe reaction environments. Bhat-tacharyya et al. reported the solvent-free mechanochemical synthesis of a PQD@MOF composite for photovoltaic applications, which was mediated by heavy metal exchange (Figure 3). The as-prepared composite material exhibited a simple synthesis route, environmental friendliness, and efficient photovoltaic properties [53].

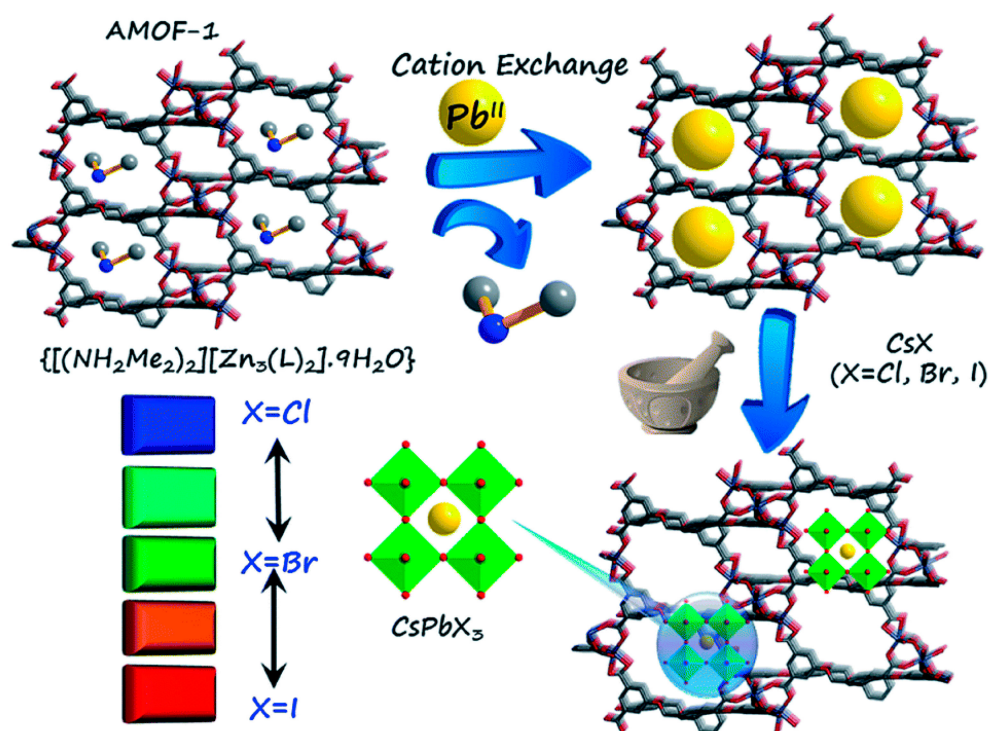


Figure 3. Mechanochemical synthesis of PQD@MOF composites mediated by Pb(II) exchanged AMOF-1. Reproduced with permission [53]. Copyright 2019 ACS.

A kinetically stable polymorph-based CP was developed using the mechanochemical techniques, obtained by grinding the Pb(II) metal center and 4,4'-bipyridine organic ligand. The resulting CP polymorph exhibits enhanced thermal stability [54].

2.5. Electrochemical Synthesis

The electrochemical synthesis of MOFs and CPs involves the use of electrical energy to facilitate the crosslinking of organic linkers to metal nodes [55]. This method offers distinct advantages, including precise control over the reaction conditions such as potential, current, and pH. Typically, in a given electrochemical cell, CPs and MOFs can be synthesized by containing metal ions and organic ligands in the solution or on the electrode. Zhang et al. reported the development of CP material for the removal of inorganic arsenic using an electrochemical route by loading a Fe(II) metal ion and 1,3,5-benzenetricarboxylic acid within the electrochemical cell [56]. This method employs scrap iron from wastewater as the metal ion source, making the process both cost-effective and environmentally sustainable. Furthermore, this synthesis method has been utilized in the development of MOFs for a wide range of applications. Recently, Liu et al. reported the electrochemical synthesis of 2D MOF films using a copper anode and a 2,3,6,7,10,11-hexydroxytriphenylene (HHTP) solution [57]. An organic ligand was deposited on the Cu^{2+} ions generated by the anode, as shown in Figure 4. The metal ions carried to the cathode electrode of these parameters

significantly influenced the morphology, size, and composition of the resulting MOF. Additionally, this approach allows for the direct growth of MOFs on conductive substrates, facilitating the production of thin films and coatings suitable for various professional applications such as catalysis and sensing.

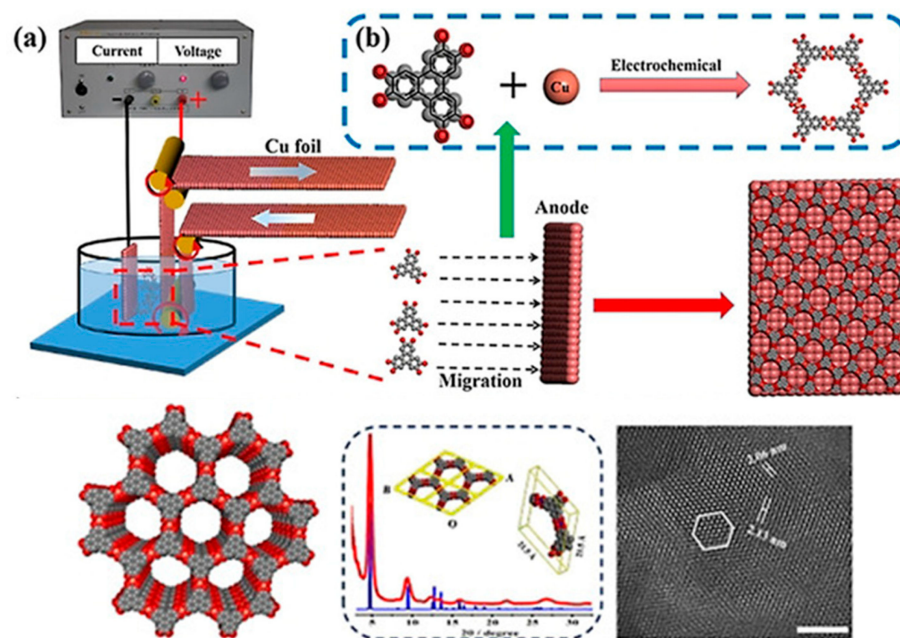


Figure 4. (a) Electrochemical reaction cell for the preparation of a $\text{Cu}_3(\text{HHTP})_2$ film on Cu foil. (b) Schematic diagram of the coordination reaction between Cu^{2+} and the HHTP ion. Reproduced with permission [57]. Copyright 2022 Wiley.

2.6. Slow Diffusion

The controlled synthesis of MOFs via slow diffusion entails the gradual diffusion of reactants within a solution, thus fostering the methodological growth of MOF crystals [58]. Typically, this procedure involves the amalgamation of metal ions or clusters with organic linkers in a solvent, followed by the gradual introduction of a secondary reactant such as a modulator or solvent into the solution [59]. The deliberate diffusion of this secondary reactant facilitates the gradual nucleation and development of MOF crystals under controlled conditions, resulting in the formation of well-defined structures with tailored properties. This approach has also been utilized to fashion CPs in various structures. For example, the Co(II) ion slowly diffuses in methanol in *trans*-1,2-bis(4-pyridyl)ethylene in chloroform, resulting in an infinite ladder-structured topology [60]. By alternating the solvents used for the metal ion and the organic ligand, the structure of the resulting CPs can be modified through a slow diffusion process. This approach offers notable advantages, including precise control over the crystal size, morphology, and composition, making it particularly suitable for applications in catalysis and sensing.

3. Applications for the Electrochemical Biosensor

Recently, MOFs and CPs have been used in biocatalysis and biosensing [61]. Their structural and chemical flexibility makes MOFs particularly useful for immobilizing and preserving enzymes. One approach involves loading enzymes into MOFs after synthesis by utilizing the porous nature of MOFs. However, this method faces challenges, such as limited enzyme loading due to poor attachment or adsorption, absorption difficulties, and pore size limitations [62]. To address these issues, innovative methods have been developed, such as the co-precipitation technique, in which the MOF forms around the enzyme in a biomimetic manner, providing enhanced protection. Moreover, the application of MOFs in practical electrochemical biosensing has been hampered by their low electrochemical

stability, limited electrical conductivity, limited mass transport, low compatibility with electrode materials, low scalability, and high cost [63]. Therefore, for the application of MOFs and CPs in practical clinical biosensing and therapeutic applications, there should be a mechanism that addresses these issues. Researchers are working to improve the electrochemical performance of MOFs and CPs by employing material engineering, surface modification techniques, and synthesis process optimization to achieve the utilization of MOFs for electrochemical biosensing applications [64]. Therefore, an effective strategy is required to realize MOF applications in electrochemical biosensors.

3.1. MOF-Based Biosensor

Diverse methodologies have been investigated to deploy MOF-based biosensors, whether utilized individually or in a composite form. These biosensors can be employed using various techniques, including ratiometric, enzymatic, nonenzymatic, optical, and electrochemical techniques [64,65]. In comparison to traditional nanomaterials used in electrochemical biosensing, MOFs demonstrate superior performance owing to their inherent properties (Table 1) [66–71]. While materials such as carbon nanotubes and metal nanoparticles offer robustness and reliable electron transfer, achieving an optimal balance between these attributes is critical for the effective development of biosensors [72].

Table 1. Comparison of MOFs and conventional nanomaterials in electrochemical biosensors for biosensing applications.

Criteria	MOFs	Traditional Nanomaterials (e.g., CNTs, Nanoparticles)
Surface Area	High surface area, enhancing sensitivity and detection limit	Generally high but often lower than MOFs
Functionalization	Easy functionalization with various organic and inorganic groups	Functionalization is possible but can be complex and less versatile
Porosity	Highly porous, allowing for efficient molecule capture and transport	Variable porosity, often less tunable than MOFs
Stability	Can be less stable under certain conditions (e.g., moisture, pH)	Typically more stable and robust under various conditions
Toxicity	Generally low toxicity, though dependent on metal and organic linkers used	Potential for higher toxicity, depending on the material (e.g., CNTs can be cytotoxic)
Service Life	Potentially shorter due to sensitivity to environmental conditions	Generally longer service life due to robustness

Combining MOFs with carbon and other nanomaterials in composite formations has proven to be a significant development in maximizing their potentiality in biosensors [73]. Recently, Zhang et al. reported a bimetallic-based MOF composite electrode, Nafion/Co/MnO@HC/GCE, as an excellent in vitro nonenzymatic electrochemical biosensor for glucose detection [42]. The as-prepared electrode had a wide range of electrocatalytic activity of 50–900 μM with a sensitivity of 233.8 $\mu\text{A mM}^{-1} \text{cm}^{-2}$. The electrode achieved a detection limit of 1.31 μM . When tested with actual serum samples, this composite electrode displayed exceptional reproducibility, interference resistance, and stability. The effective detection of glucose in alkaline environments is credited to the combined influence of the bimetallic component’s synergy with high surface area and multiple active sites. Notably, the heat treatment of MOFs enhances the physicochemical properties of biosensor materials during composite material development. Recently, a novel copper oxide-based composite biosensor was developed (CuOx@mC/GCE) as an electrochemical sensor for the enhanced nonenzymatic detection of pesticides (glyphosate) [74]. HKUST-1 cells were loaded onto glassy carbon electrodes (GCE). The composite pyrolyzed form of the MOF, CuOx@mC, showed an enhanced electrochemical response compared to the parent HKUST-1 material.

The CuOx@mC/GCE exhibits superior electrochemical performance with an ultralow detection limit of 7.69×10^{-16} M toward glyphosate over a linear range of 1.0×10^{-15} to 1.0×10^{-4} M. Such ultrasensitive sensors have been realized following the thermal treatment of HKUST-1, which is believed to enhance the mesoporous structure and electrical conductivity; thus, the overall electrochemical sensitivity is improved.

Advanced manufacturing methods and composite techniques have led to the creation of composite materials with dual functionalities for both analysis and sensing. Xue et al. showcased a method utilizing Cu-MOFs to enhance the electrochemical biosensing of miRNA through CHA-HCR dual-amplification (Figure 5) [75]. This approach involves immobilizing Cu-MOFs on electrodes to boost signals, with CHA and HCR amplifying input signals. These composite biosensors allow for the sensitive detection of miRNA across a wide linear range (0.1 fM to 100 pM) and with a low detection limit (0.02 fM).

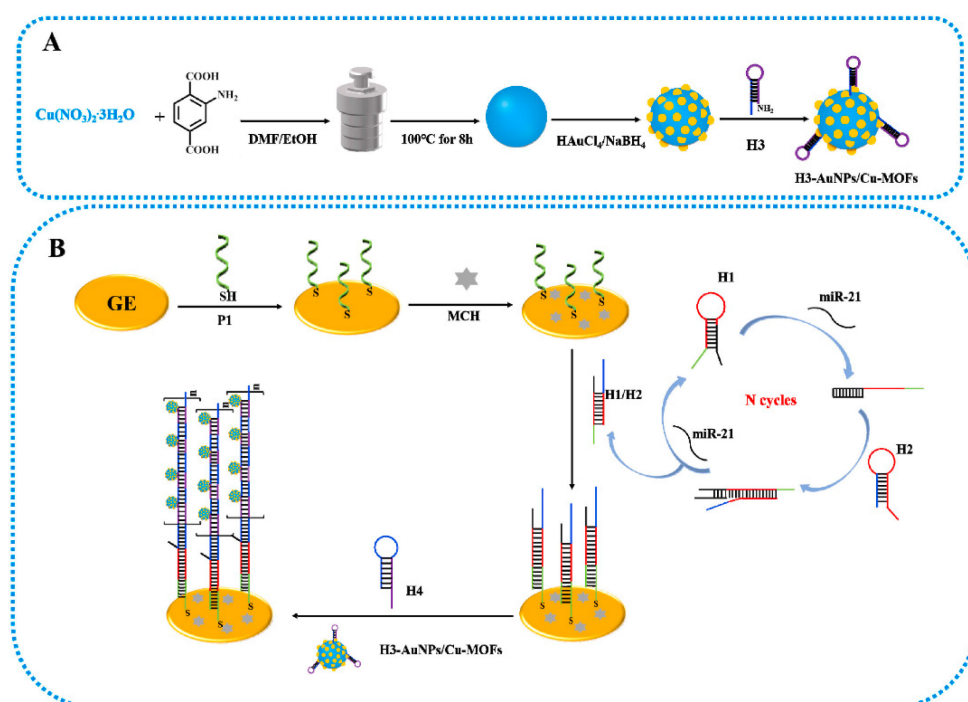


Figure 5. Schematic illustration of the production procedures of H3-AuNPs/Cu-MOFs (A) and an electrochemical biosensor for the detection of miRNA(miR-21) (B). Reproduced with permission [75]. Copyright 2022 Elsevier.

Moreover, the biofunctionalization of MOFs is vital for biosensing as it enhances sensor selectivity and sensitivity by integrating specific biological molecules [76]. Enhancing MOF stability and biocompatibility enables their versatility in interacting with various biomolecules. Integrating DNA into MOFs is critical for applications like targeted biomolecular sensing, biocatalysis, bioimaging, and theranostics. Through DNA programming, MOFs can selectively attach to biomolecules or cell receptors, thereby enhancing the precision of biosensing [77]. Additionally, DNA-functionalized MOFs serve as adaptable platforms for biosensing, aiding the identification of pathogens, and disease indicators [78]. Incorporating enzymes into MOFs through DNA hybridization boosts biocatalytic processes across a range of applications. Furthermore, by incorporating fluorescent or luminescent markers into the DNA-modified MOFs, their bioimaging capabilities can be enhanced, offering valuable insights into their biological functions. Liu et al. presented a pioneering methodology involving the integration of DNA-functionalized MOFs to enhance detection sensitivity through T7 exonuclease-aided recycling amplification. This innovative approach was used to detect immobilization-free carcinoembryonic antigen (CEA) via in vitro photoelectrochemical (PEC) detection [77]. In their study, UiO-66-NH₂

acted as a nanocarrier for electron donors, while a tailored hairpin probe detected CEA through a conformational change, initiating T7 exonuclease-mediated amplification. This process released electron donors, significantly increasing the photocurrent. With high sensitivity and selectivity, the biosensor detected CEA with a limit of 0.36 fg mL^{-1} and a range from 1.0 fg mL^{-1} to 10 ng mL^{-1} , showing promise for early disease diagnosis in human serum analysis. In another study, MOFs were adapted with various proteins for detection. Trino et al. developed a label-free electrochemical biosensor using ZIF-8 to monitor protein–protein interactions [79]. This biosensor, hosting Trx-1, effectively detected interactions with ADAM17cyto, showing superior sensitivity compared to conventional assays. The approach offers a rapid, label-free, and cost-effective strategy for detecting in vitro PPIs, showcasing the potential of protein-functionalized MOFs in biomedical applications.

3.2. CPs-Based Biosensor

CPs are a compelling candidate for biosensing applications because of their inherent characteristics [80,81]. In addition to their remarkable topological properties and inherent stability, their structural responsiveness to target binding enables precise and reliable signal transduction, and their stability and biocompatibility underscore their suitability in diverse biomedical contexts, including multiplexed detection and in vivo sensing. Moreover, the utilization of two-dimensional (2D) CPs in biosensors offers notable advantages. Their flat geometry provides an expansive surface area, facilitating efficient biomolecule immobilization, thereby enhancing binding capacity and sensitivity [82,83]. Additionally, their ability to be customized, including adjusting pore size and surface chemistry, allows for precise optimization for specific analytes, ensuring accurate detection. These polymers are stable under physiological conditions, consistently delivering reliable performance. Furthermore, their structural integrity enables the simultaneous detection of multiple analytes, making them highly valuable for applications in medical diagnostics and environmental control [84]. Overall, two-dimensional coordination polymers represent a promising platform for the development of highly sensitive, selective, and stable biosensors with diverse applications. Fu et al. described the creation of a hydrogen-bonded 2D coordination polymer (CP1) for nonenzymatic glucose sensing, which is crucial for effective diabetes management [85]. The nonenzymatic electrochemical glucose biosensor was synthesized from melamine (Mel), biphenyl-4,4'-dicarboxylate (BPDC^{2-}) co-ligands, and Zn(II) metal nodes and was denoted as CP1 for the 2D layered glucose sensor. The layers are interconnected through hydrogen bonding interactions among the melamine molecules. The CP1/GCE in the vitro-based sensor displayed accurate clinical performance, with a broad linear sensing range from $5.6 \text{ }\mu\text{M}$ to 5.56 mM ($R^2 = 0.9852$) and a high sensitivity of $517.36 \text{ }\mu\text{A mM}^{-1} \text{ cm}^{-2}$. The as-prepared biosensor exhibited enhanced CV conductivity, as shown in Figure 6. The low detection limit of the as-prepared CP1 is $80 \text{ }\mu\text{g}$ ($8 \text{ }\mu\text{L}$, 10 mg mL^{-1}). The stability of CP1/GCE in weakly acidic and weakly basic media supports its application in aqueous solution sensing.

Blending inorganic metals with CPs enhances the performance of electrochemical biosensors by improving sensitivity, selectivity, biocompatibility, stability, functionality, and fabrication flexibility [86]. This combination exploits the distinct properties of both materials to create adaptable sensors capable of detecting various analytes in complex samples [87]. Recently, ferrocene (Fc)-based polymers have gained recognition as essential redox agents in glucose biosensors [88]. Poly-L-lysine (PLL), known for its cationic nature and desirable characteristics like biocompatibility, biodegradability, and water solubility, underwent modification with ferrocene carboxylate. The resultant redox mediator (Fc-PLL), in conjunction with glucose oxidase (GOx) enzyme, displayed improved oxidation current in the presence of glucose in PBS (pH 7.4), as observed through cyclic voltammetry. Amperometry revealed a linear detection range from 0 to 10 mM , with a detection limit of $23 \text{ }\mu\text{M}$ and a sensitivity of $6.55 \text{ }\mu\text{A cm}^{-2} \text{ mM}$, along with strong selectivity. Scanning electrochemical microscopy confirmed the significant activity of Fc-PLL/GOx on the electrode

surface, establishing Fc-PLL redox polymer as a valuable material for glucose biosensing, and facilitating electron transfer between the redox polymer and GOx.

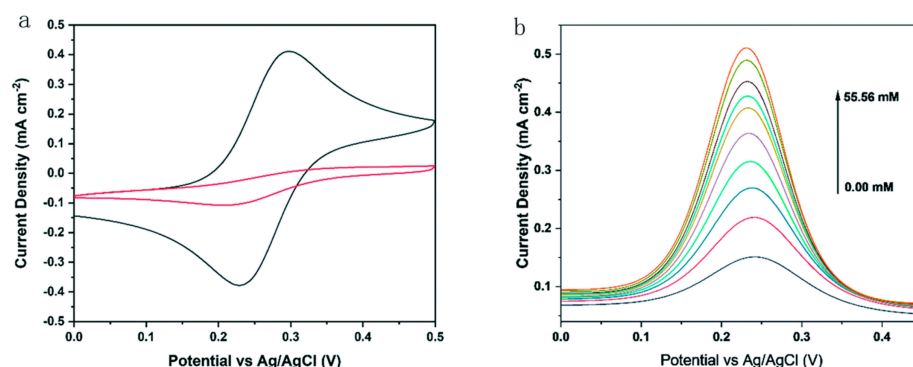


Figure 6. (a) CV characterization of the CP1 modified electrode in a $K_3[Fe(CN)_6]/K_4[Fe(CN)_6]$ solution containing 0.5 mM KCl at pH 7: bare electrode (i, black), CP1/GC (ii, red), scan rate 100 mV s^{-1} ; (b) DPV performance of a CP1 modified electrode from 0–55.56 mM in a $K_3[Fe(CN)_6]/K_4[Fe(CN)_6]$ solution containing 0.5 mM KCl at pH 7.5 for glucose detection. Reproduced with permission [85]. Copyright 2022 ACS.

Zahed et al. developed a sophisticated electrochemical biosensor capable of detecting glucose and pH levels in human sweat [89]. The sensor utilizes a flexible and conductive base made from PEDOT anchored to a porous graphene network and includes Pt and Pd nanoparticles to improve its electrocatalytic activity for detecting glucose. The biosensor showed a wide detection range, high sensitivity, and low detection limit. Testing with sweat samples validated its effectiveness for biosensing applications.

Polymeric materials can be deposited onto inorganic nanomaterials to create effective electrochemical biosensors. Bai et al. employed metal-free visible light-induced atom transfer radical polymerization (MVL ATRP) to fabricate IgG-imprinted polymers designed for biosensors [90]. These polymers were deposited onto a nano-Au/nano-Ni-modified Au electrode (Figure 7). The resulting biosensor exhibited a wide linear range and low detection limit for IgG detection using differential pulse voltammetry (DPV), offering a convenient and nontoxic method for IgG determination.

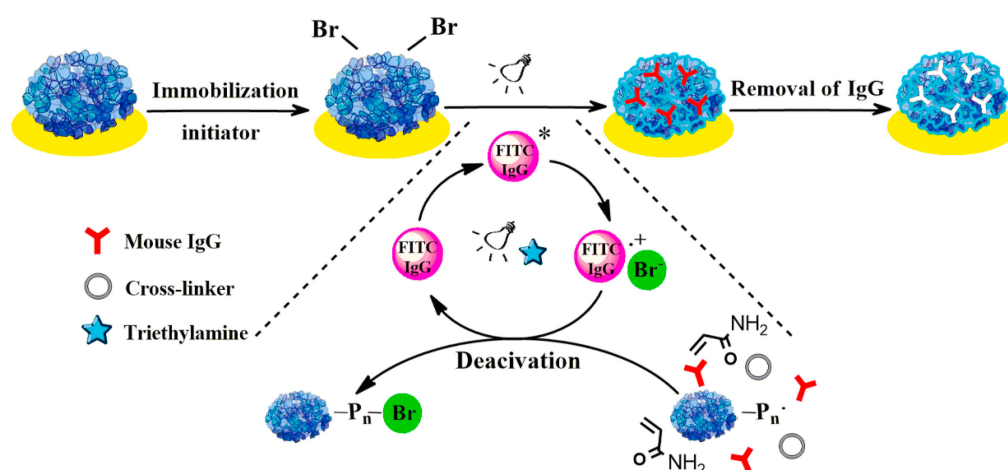


Figure 7. The schematic preparation process of IgGIPs/AuNCs/NiNCs/Au via MVL ATRP. Reproduced with permission [90]. Copyright 2021 Elsevier.

Furthermore, a widely recognized semiconductor material, titanium dioxide (TiO_2), has been employed as a composite material to achieve superior electrochemical biosensor

performance. Yang et al. demonstrated the impressive electrochemical biosensing capabilities of a composite material based on CP and TiO_2 [84]. They synthesized a composite biosensor by combining TiO_2 and a conducting polymer (CP) using Cu(I), chloride ions, and 4-mercaptobenzoic acid (MBA), termed CuClx(MBA)_y . This enabled the development of a sensitive photoelectrochemical (PEC) biosensor for miRNA detection. The biosensor showed a low detection limit of 0.29 fM ($S/N = 3$), excellent selectivity, and reproducibility. It has been successfully employed clinically to monitor miRNAs in cancer cells with promising results.

The investigation of conducting polymers has resulted in a fascinating turn in the production of effective biofouling-free biosensors. Han et al. have introduced an innovative strategy to address biofouling challenges in the direct detection of circulating tumor cells (CTCs) in human blood [91]. Their electrochemical biosensor integrates a multifunctional peptide and electrodeposited conducting polymer, poly(3,4-ethylene diox-ythiophene) (PEDOT). The peptide possesses antifouling properties and specific recognition capabilities for capturing MCF-7 breast cancer cells, while PEDOT enhances electron transfer at the sensing interface to improve sensitivity. Together, these components enable the biosensor to operate directly with blood samples without the need for complex purification or separation steps. It has demonstrated a wide detection range and low limit of detection (LOD), even in the presence of 25% human blood (in vitro), indicating strong resistance to biofouling. This study marks a significant advancement in analyzing circulating tumor cells (CTCs) directly in human blood, potentially transforming liquid biopsy procedures in cancer diagnostics.

Organic materials have been used as composite materials with polymer matrices to develop effective electrochemical biosensors. Popov et al. conducted research on developing an amperometric glucose biosensor utilizing a nanocomposite composed of reduced graphene oxide (rGO) and polyaniline nanofibers [92]. The precise monitoring of glucose concentration holds paramount importance in clinical diagnostics and the food industry, thus prompting the exploration of electrochemical biosensors integrating rGO and conducting polymers. The biosensors were fabricated by combining rGO with PANI, Nafion, and GOx on a graphite rod electrode. The as-prepared glucose biosensor possesses a wider linear range, excellent selectivity, and reproducibility. Consequently, it was deemed suitable for precise glucose determination in human serum. This study highlights the potential of PANI nanostructures and rGO dispersions in advancing the development of electrochemical glucose biosensors.

Furthermore, current research is directed towards the integration of conductive polymers into controlled synthetic environments within the field of CPs. Yang et al. conducted a study on the application of PEDOT as a dopant for crosslinking conductive polymer hydrogels (CPHs), with a focus on potential applications in bioelectronics [93]. The proposed method involves using PEDOT to crosslink various conductive polymers, such as polyaniline (PAni), polypyrrole (PPy), and polyaminoindole (PIn- X-NH_2 , $\text{X} = 4, 5, 6, 7$). The synthesis mechanism relies on electrostatic interactions between the negatively charged SO_3^- groups in PEDOT and the positively charged polymer chains. Compared to PA-crosslinked CPHs, those crosslinked with PEDOT demonstrated significantly improved conductivity and enhanced biocompatibility, essential characteristics for bioelectronic applications. PEDOT CPHs show candidacy for in vivo electrochemical sensing of dopamine and H_2O_2 . Moreover, Fedorenko et al. explored CP functionalization for enhancing biosensor efficiency, they investigated PDA-functionalized Zinc oxide (ZnO) for in vitro glucose biosensing applications [94]. ZnO nanostructures, commonly used in optics and biosensors, were coated with the biocompatible polymer polydopamine (PDA) to enhance their photoelectrochemical sensing capabilities. ZnO nanorods were grown on indium tin oxide (ITO)-modified glass substrates and subsequently layered with PDA. GOx was immobilized on the ZnO-PDA surface to develop a biosensing platform for detecting glucose in aqueous environments. This study underscored the enhanced performance of PDA-modified ZnO nanorods for photoelectrochemical sensing.

4. Enhancing Strategies for Electrochemical Biosensors Based on MOFs and CPs

Electrode sensitivity is pivotal for advancing materials for electrochemical biosensing applications. Various techniques have been investigated to enhance the performance of electrochemical biosensors based on MOFs and CPs [95]. These methods include nanoscale fabrication, surface modification, host–guest interactions, signal transduction, amplification, and stabilization. By refining the selectivity and electroactive areas of MOFs and CPs, it is possible to develop efficient and sensitive electrochemical biosensors tailored to specific analytes and biomarkers. Such improvements necessitate the identification of optimal routes and mechanisms for implementing meticulously designed synthetic strategies [95]. This strategic approach maximizes the potential of MOFs and their derivatives for practical application in electrochemical biosensors.

4.1. Hierarchical Porous Synthesis

Hierarchical porous MOF synthesis involves the creation of MOF structures with multiple porosity [96]. This can be achieved through the controlled assembly of the organic linker and metal clusters during the formation of the crystalline MOF structure [97]. These pores can be utilized for efficient electrochemical biosensing with high molecular mobility. Recently, $\text{MnCo}_2\text{O}_{4.5}$ and MnNi_6O_8 nanoparticles have been hierarchically synthesized using CP templating for electrochemical capacitor electrode applications [98]. These materials demonstrate high power density and excellent cycling life, attributed to their cage-like cluster structures that offer a large accessible surface area, thereby enhancing the electrode's electrical kinetics. Different approaches can be used to develop effective biosensors using hierarchical methods.

4.2. Post-Synthetic Modification

Post-synthetic modification (PSM) involves altering or adding functionalities to the MOF and CP structures after their synthesis to suit the specific application. PSM can be achieved through various chemical reactions, such as coordination, covalent, and physical adsorption [99]. Coordination chemistry involves the exchange of ligands within the MOF with new ligands to introduce the desired functionalities. Covalent chemistry involves the introduction of new functional groups through reactions with existing functional groups within the MOF and CP structures, whereas physical adsorption involves the incorporation of guest molecules into the host pores. Recently, Wu et al. reported three-step PSM-based MOFs (Ag-Eu-MOF-808-EDTA) for ratiometric fluorescent probe detection of creatinine [100]. The synthesis process involved the introduction of ethylenediaminetetraacetic acid (EDTA), Ag^+ , and Eu^{3+} into the MOF-808 framework through a three-step PSM, as shown in Figure 8. The as-prepared biosensor had a wide linear range and low detection limits towards the analytes.

Ma et al. developed a mixed Cd/Cu-based MOF for the electrocatalytic oxidation of uric acid (UA) using post-synthetic metal exchange [101]. They started with a Cd/macrocyclic-based MOF ($[\text{Cd}_5\text{O}(\text{L})(\text{H}_2\text{O})_4] \cdot 4\text{DMF} \cdot 5\text{H}_2\text{O}$, Cd-L) (L^{8-} = calix[4]resorcinarene-based carboxylate ion and DMF) and replaced the Cd(II) ions with Cu(II) ions, resulting in $[\text{Cd}_4\text{OCu}(\text{L})(\text{H}_2\text{O})_4] \cdot \text{DMF} \cdot 7\text{H}_2\text{O}$ (CdCu-L) (Figure 9). This substitution tripled the conductivity. The CdCu-L electrode effectively detected UA in real samples, with a detection range from 10 to 500 μM and a detection limit of 2.67 μM . The electrode also showed excellent selectivity, reproducibility, and stability.

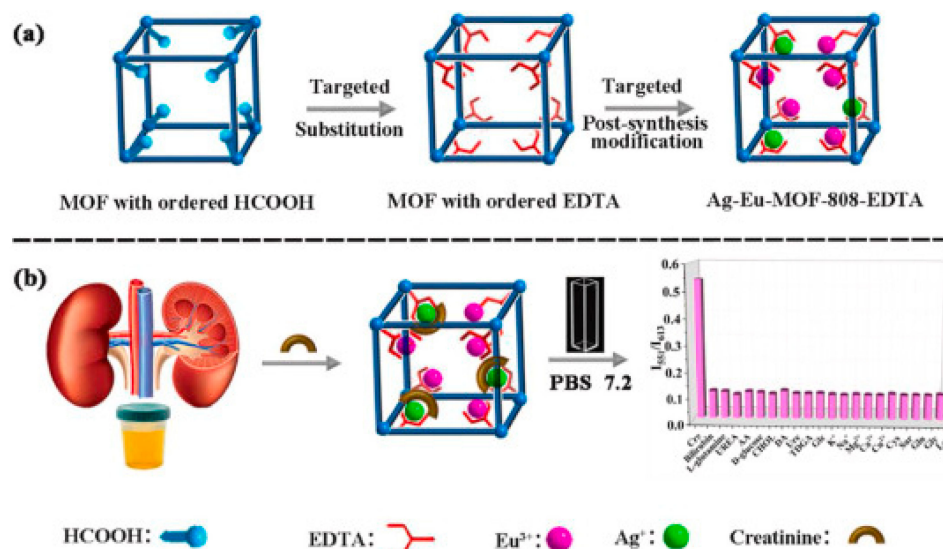


Figure 8. (a) Schematic illustration of the three-step Ag-Eu-MOF-808-EDTA synthesis; (b) Probe detection of creatinine in human urine and serum sample. Reproduced with permission [100]. Copyright 2022 Elsevier.

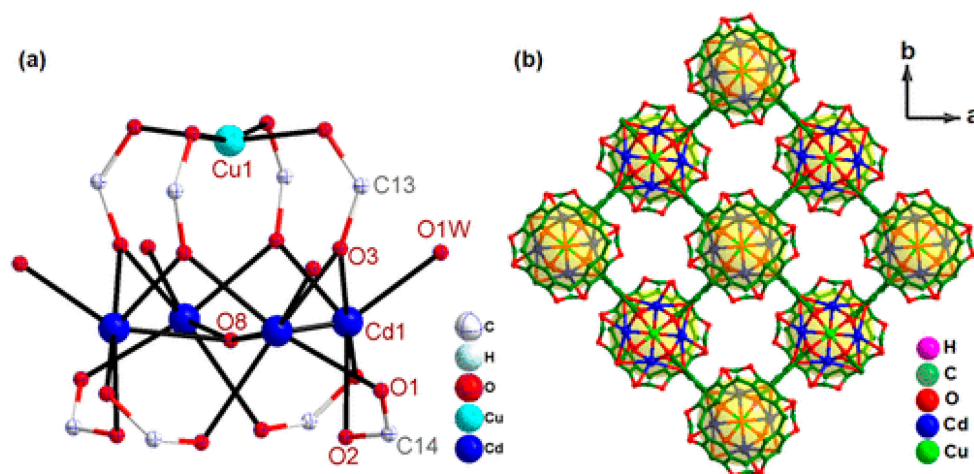


Figure 9. (a) Pentanuclear Cd-O cluster in Cd-L. (b) View of the 2D layer for Cd-L along the ab plane. Reproduced with permission [101]. Copyright 2022 ACS.

CPs have also been developed using covalent-PSM from the Fe(II) and amino-1,2,4-triazole ligands; the as-prepared material was used for the selective chemo-sensor for different volatile organic compounds (VOCs) [102]. This sensor method is straightforward and affordable, with detection signaled by distinct color changes upon exposure to hazardous VOC vapor (Figure 10).

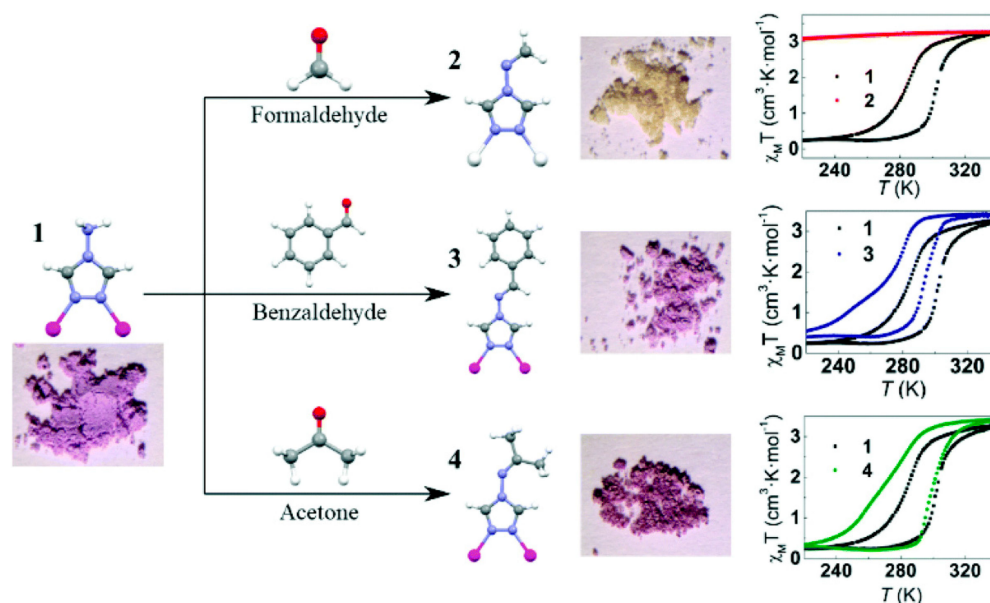


Figure 10. Possible illustration of the PSMs' behavior of $[\text{Fe}(\text{NH}_2\text{triazole})_3](\text{OTs})_2$ (1, in black are the magnetic curves), including the color and magnetic behavior of the starting (1) and final (2–4) compounds. Reproduced with permission [102]. Copyright 2020 RSC.

4.3. Template-Assisted Synthesis

Template-assisted MOF and CP synthesis employs external templates such as organic molecules or polymers to regulate the nucleation and growth of MOFs during their creation, which enables precise control over the MOF morphology and properties [103]. Recently, mesoporous ZIF-8 was assembled to immobilize cytochrome c (Cyt c) using a sacrificial template method [104]. The as-fabricated templated sensor, Cyt c@mesoZIF-8/SPE, was used for the efficient electrochemical detection of H_2O_2 . CPs have also been studied for the template-assisted synthesis of biosensors. Sapountzi et al. studied the synthesis of polyacrylonitrile/polypyrrole core-shell nanofibers and their application in glucose biosensors [105]. They developed a two-step method involving electrospinning and vapor-phase polymerization to deposit conductive polypyrrole layers on gold electrodes coated with polyacrylonitrile (PAN) nanofiber mats. PAN fibers were electrospun from a 12 wt% PAN solution and impregnated with Fe(III)tosylate. This matrix was then used to grow a conductive polymer layer through the copolymerization of pyrrole (Py) and pyrrole-3-carboxylic acid (Py3COOH) vapors in a nitrogen atmosphere. Incorporating carboxyl groups into the polypyrrole coatings enabled the covalent binding of glucose oxidase. Under optimal conditions (20 wt% FeTos, 30 min polymerization, 1:2 Py/Py3COOH), the biosensor showed a linear response to glucose concentrations (20 nM–2 μM) and selectivity for ascorbic and uric acids, with a low detection limit (2 nM), allowing precise glucose measurement in diluted human serum within the normal range (3.6–6.1 mM).

4.4. Mixed-Linker Synthesis

Mixed-linker synthesis of MOFs and CPs represents a sophisticated design approach in which two or more organic linkers are integrated concurrently during the production process [106]. This method enables the creation of MOFs with finely tuned properties and augmented functionalities, surpassing the limitations of single-linker systems [107]. Through the meticulous selection and combination of diverse linkers, researchers can precisely engineer the structure, pore characteristics, and surface chemistry of the resultant MOFs, thereby broadening their utility across applications in sensing.

Tan et al. introduced a one-step process to create an aluminum-based MOF using a combination of linkers, improving its ability to adsorb water vapor [108]. In a separate study, Fan et al. used a solvothermal method to produce CPs, $\text{Cu}(\text{tptr})_{0.5}(\text{phen})_n$ and

$[\text{Cd}(\text{tptc})_{0.5}(\text{phen})]_n$, demonstrating strong electrochemical features and dual sensing capabilities for metal ions and organic substances [109]. Through meticulous control, the mixed-linker synthesis approach offers a cost-effective way to develop a suitable structure of MOFs and CPs for electrochemical applications.

4.5. Self-Assembly of Building Units

The self-assembly procedure usually involves combining metal ions or clusters with organic ligands in environments with appropriate temperature, solvent choice, and pH level. Subsequently, these components spontaneously organize into a specific crystal lattice pattern determined by the coordination preferences of the metal ions and connectivity of the organic ligands. Key factors driving self-assembly in the synthesis of MOFs comprise coordination chemistry, hydrogen bonding, π - π stacking interactions, and van der Waals forces. Therefore, controlling the reaction parameters plays a significant role in determining the properties and performance of MOFs for specific applications. Recently, Afzalnia et al. reported a novel La(III)-MOF and silver nanoparticles in a sandwich-type fluorescence resonance-based energy transfer (FRET)-hybridized oligonucleotide for rapid and highly selective biosensor applications, with a higher sensitivity for detecting miRNA as a cancer biomarker [110]. The MOF and Ag NPs acted as energy donor-acceptor pairs during fluorescence quenching through the FRET process. This synthesis protocol enables the development of a highly sensitive biosensor tailored for clinical applications using real serum samples. Chang et al. reported a homogeneous electrochemical biosensor using UiO-66-NH₂ and dsDNA [111]. UiO-66-NH₂ was employed to take advantage of its highly porous surface area as a nanocontainer of dsDNA, which is an electroactive dye used as a gatekeeper to cap MOFs. MB@UIO and TMB@UIO MOFs were synthesized and used to simultaneously detect let-7a and miRNA, both crucial tumor biomarkers for cancer diagnosis and therapy. Moreover, ultrasensitive and selective label-free nonenzymatic homogeneous electrochemical detection has been developed for the early detection of tumor biomarkers.

4.6. Core-Shell Structure

A core-shell structure within MOFs denotes a configuration in which one component constitutes the core, often a metal cluster or another MOF, whereas another component forms the shell, typically an organic ligand or a distinct MOF [112]. This structural design yields advantageous properties such as enhanced stability, customizable functionality, and versatility. Different studies have been conducted to exploit the excellent physicochemical properties of the core-shell structure assembly. Yu et al. reported that CuO/Cu₂O@CuO/Cu₂O core-shell nanowire arrays (NWAs) were first synthesized by the calcination of the famous HKUST-1 MOF for application in nonenzymatic glucose sensing (Figure 11) [113]. This configuration has been proven to improve the traditional prevalent aggregation of MOF particles when used in a particle manner, and this route provides ample diffusion sites in which the ions can actively interact with the sensor, which, in turn, boosts the biosensor performance of the as-prepared material. The NWAs demonstrate enhanced sensitivity, selectivity, a low detection limit, and a wide linear range for glucose sensing.

In addition to MOFs, CP-based biosensors can be fashioned using core-shell architectural configurations. Sun et al. devised Au NPs@GMP-Tb ICPs, a core-shell nanocomposite integrating gold nanoparticles within fluorescent GMP-Tb³⁺ polymers. This composite functions as a dual-channel sensor for detecting ATP-related phosphates and monitoring ATP hydrolysis [114]. The interaction between Tb³⁺ and P-O bonds modulates the response of Au NPs@GMP-Tb ICPs to various phosphates, thereby regulating both fluorescence intensity and UV-vis absorbance. These sensors offer interference resistance and enhanced analyte detection, advancing “lab-on-a-nanoparticle” systems for precise chemical reaction monitoring.

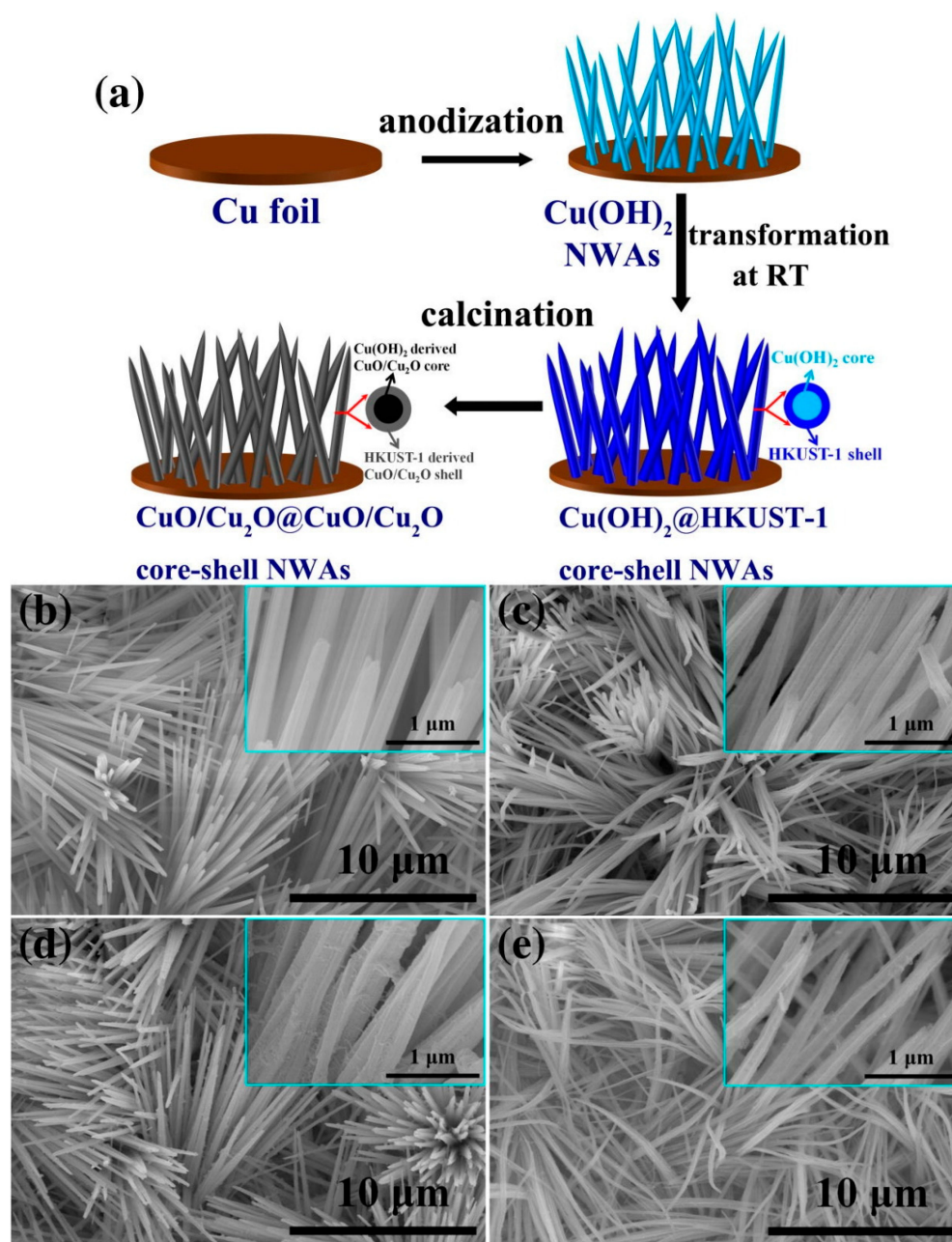


Figure 11. (a) Schematic illustration of the production process of CuO/Cu₂O@CuO/Cu₂O core-shell NWAs on Cu foil, FESEM images of (b) Cu(OH)₂ NWAs, (c) Cu(OH)₂ derived CuO/Cu₂O NWAs, (d) Cu(OH)₂@HKUST-1(8) core-shell NWAs, and (e) Cu(OH)₂@HKUST-1(8)-derived CuO/Cu₂O@CuO/Cu₂O(8) core-shell NWAs (insets show the corresponding FESEM images with high magnification). Reproduced with permission [113]. Copyright 2018 Elsevier.

4.7. Defect Design

Defect engineering offers researchers an opportunity to tailor the properties of MOFs and CPs for specific applications [115]. These defects can arise from various sources, such as the absence of linkers or metal ions, voids within the framework, or the inclusion of guest molecules during synthesis [116]. Additionally, defects may result from flaws in the synthesis process or postsynthetic treatments.

Recently, Luo et al. introduced a novel approach to develop a conductive 2D MOF tailored for use in electrochemical sensors for H₂O₂ [117]. The produced Cu-BHT MOF was synthesized by employing a straightforward and versatile defect engineering methodology

aimed at regulating metal vacancies within metal benzenehexathiolato (BHT) coordination polymer films. With a focus on sensor applications for ensuring food safety, the synthesized MOF leverages defects to effectively structure and integrate materials. Precise control of atomic defect engineering yields an abundance of Cu^{2+} vacancies, which serve as active sites for both H_2O_2 adsorption and reduction. In addition, the study highlighted that manipulating vacancies in the electronic structure enhanced the adsorption energy and electron transfer mechanisms during H_2O_2 reduction. MOFs synthesized with these deliberate defects exhibited excellent performance as electrochemical sensors, featuring superior sensing abilities, long-lasting stability, and resilience against interference.

4.8. Composite Material-Based Electrochemical Sensor

In recent decades, considerable research has been conducted on composite MOFs and CPs for their potential application in electrochemical biosensors [118]. This interest in these materials stems from their beneficial features, such as their large surface area, ability to adjust pore sizes, and chemical versatility. These qualities enable effective immobilization of biomolecules, thereby improving sensor performance [119,120]. Additionally, by incorporating compositing materials such as conductive polymers or metal nanoparticles, these composite structures exhibit notable synergistic electrochemical properties, thereby enhancing sensitivity and stability [121]. A variety of methodologies have been employed to synthesize composite materials consisting of MOFs and CPs, thereby offering diverse opportunities for the development of efficient biosensors.

4.8.1. Metal-Nanoparticle-Based Composites

Metal-based nanoparticles have been incorporated into MOFs and CPs to enhance electrical conductivity and electrochemical performance for biomolecule detection. Zha et al. presented a highly effective biosensor capable of dual electrochemical and photo-electrochemical sensing, as shown in Figure 12 [122]. This biosensor utilized Nd-MOF nanosheets modified with an ionic liquid and gold nanoparticles (Au NPs) and was specifically designed to detect circulating DNA (ctDNA) associated with triple-negative breast cancer. The biosensor utilized Au NPs for dual functionality, both as photoactive agents generating signals and as substrates for biorecognition elements. This biosensor enabled early-stage ctDNA detection with high selectivity, accuracy, stability, and reproducibility, facilitated by composite material synergies.

Moreover, AuNPs were integrated into the MOF to create an efficient biosensor. Liang et al. detailed the development of Au/Cu-MOF/SWNH nanomaterials, wherein a sensitive dual-signal sandwich-type electrochemical immunosensor was devised to detect Neutrophil Gelatinase-Associated Lipocalin (NGAL) in early-stage acute kidney injury (AKI) [123]. This material demonstrated an optimal linear range of $0.00001\text{--}10\text{ ng mL}^{-1}$ and detection limits of 0.0074 pg mL^{-1} (SWV). The synthesized composite materials exhibited enhanced sensor activity, which was attributed to their elevated surface areas and electrical conductivities. The former quality stems from the Cu-MOF, whereas the latter results from the metal node and Au NPs. The electrochemical signal was derived from the electron transfer between Cu^{2+} and Cu^+ ions with the incorporation of Au NPs, further enhancing the electroconductivity of the biosensor. In another study, composite sensors were developed using Ni(II)-based CPs combined with reduced graphene oxide to create efficient electrodes [124]. These electrodes were designed for nonenzymatic electrochemical glucose detection in alkaline environments, demonstrating significant improvements in sensitivity, selectivity, and overall performance.

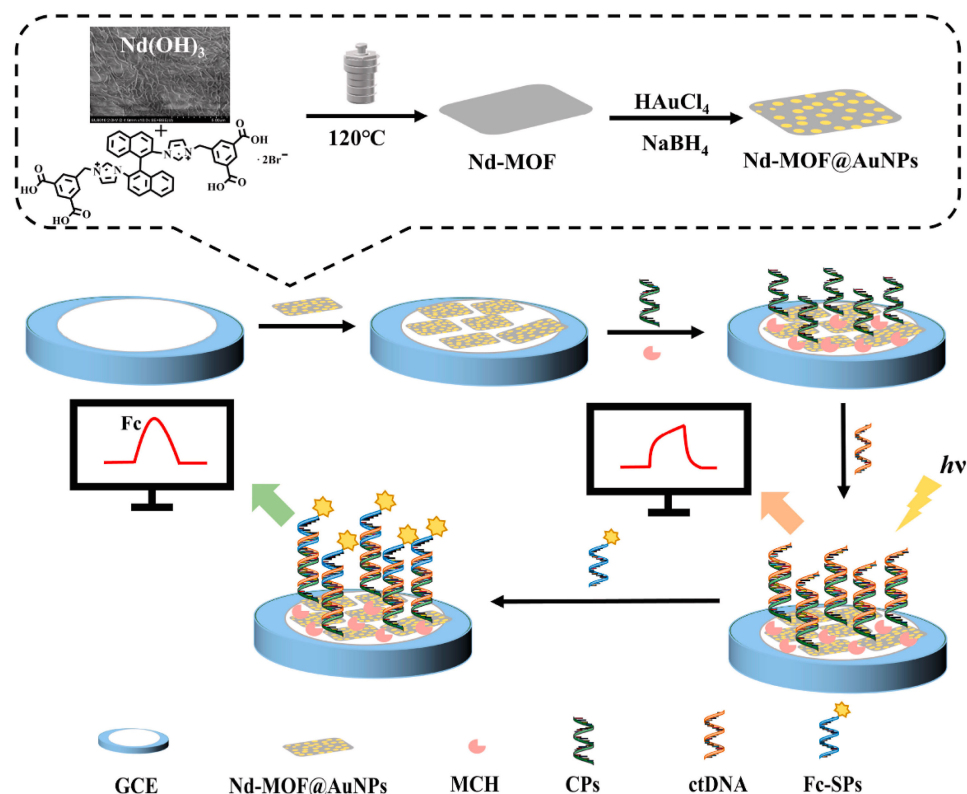


Figure 12. Schematics of the Nd-MOF@AuNPs nanocomposites synthesis and a PEC-EC dual-model ctDNA biosensor preparation. Reproduced with permission [122]. Copyright 2023 Elsevier.

4.8.2. Polymeric-Based Composites

The integration of polymeric materials with MOFs and CPs to form composite materials is a promising research topic. These composites exploit the combined properties of their constituent elements to yield enhanced electrochemical biosensor capabilities [125]. Recently, $\text{Ru}(\text{dcbpy})_3^{2+}$ -polyethyleneimine-L-lysine (Ru-PEI-L-lys)-immobilized ZIF-8 (Ru-PEI-L-lys-ZIF-8) was developed as an efficient electrochemiluminescent (ECL) indicator for thrombin detection [126]. PEI-L-lys was used as a co-reactant in the ECL biosensing process, and platinum nanoparticles (PtNPs) were incorporated to form a thin film on the composite MOF to increase the electron transfer and electrical conductivity of the composite materials, thus enhancing the ECL performance. The as-prepared biosensor had a linear thrombin concentration range of 1–10 pM, with a detection limit of 0.02 aM. Therefore, the incorporation of polymers into ZIF-8 yielded a composite material with enhanced ECL properties.

Moreover, Hira et al. developed a cost-effective and environmentally friendly technique to create electrochemical sensors using copolymer-grafted metal-organic frameworks, focusing on the detection of dopamine (DA) and H_2O_2 [127]. As-prepared $\text{UiO-66-NH}_2/\text{P}(\text{ANI-co-ANA})$ has a wide linear range of 25–500 μM and 10–110 μM for H_2O_2 and DA, respectively. The sensitivity and limited detection of DA in the human urine sample were 1110.2 $\mu\text{A } \mu\text{M}^{-1} \text{ cm}^{-2}$ and 0.3 μM , respectively. By compositing these two materials, more adsorption sites were obtained for UiO-66-NH₂, whereas polyaniline and poly(anthranilic acid) were used to enhance the electrical conductivity of the composite biosensor, as confirmed by the CV test (Figure 13).

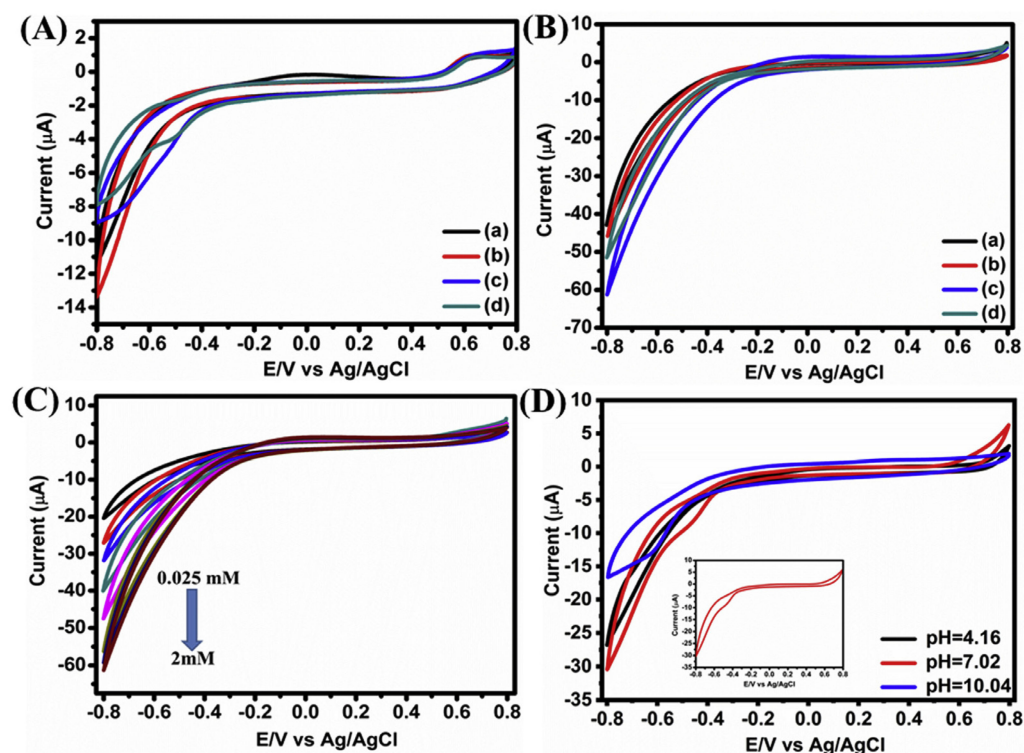


Figure 13. (A) CVs of the modified electrodes in 0.1 M PBS (pH = 7.02) solution in the absence of H_2O_2 at a scan rate of 50 mVs^{-1} , UiO-66- NH_2 (a), UiO-66- NO_2 (b), UiO-66- NH_2 @P(ANI-co-ANA) (c), and UiO-66- NO_2 @P(ANI-co-ANA) (d). (B) CVs of similar electrodes in 0.1 M PBS (pH = 7.02) solution containing 0.5 mM of H_2O_2 . (C) CVs of UiO-66- NH_2 @P(ANI-co-ANA)/GCE in 0.1 M PBS (pH = 7.02) at different concentrations of H_2O_2 (0.025 μM –2 mM). (D) CVs of UiO-66- NH_2 @P(ANI-co-ANA)/GCE in 0.5 mM H_2O_2 at various pHs. Reproduced with permission [127]. Copyright 2020 Elsevier.

In the realm of composite formulation, PEDOT has been investigated for the advancement of electrochemical biosensors. Due to its excellent conductivity, biocompatibility, flexibility, and transparency, incorporating this material into a MOF matrix is anticipated to yield biosensors of exceptional efficiency and effectiveness [128]. Recently, a ZIF-8@poly (3,4-ethylene dioxythiophene):poly (styrene sulfonate) (PEDOT: PSS) composite was synthesized and used for the electrochemical sensing of dichlorophenol [129]. The as-prepared ZIF-8@PEDOT:PSS composite material owned excellent electrochemical activities for dichlorophenol detections with a wide linear range response of $0.03\text{--}10.0 \mu\text{M}$ and a low limit of detection of $0.01 \mu\text{M}$. The composite material demonstrated strong electrical conductivity, effective electrocatalytic activity, and excellent stability, all attributed to its unique structural characteristics. This was attributed to the structural advantage of the composite materials; the matrix ZIF-8 provided an ample porous surface area for the enhanced adsorption of dichlorophenol and the PEDOT:PSS coating of ZIF-8 significantly improved both the material's conductivity and its catalytic efficiency.

4.8.3. Carbon Material-Based Composite

Carbon-based composite materials have significant potential in enhancing MOF and CP-based composite biosensors for biomedical applications. These materials offer a combination of biocompatibility, conductivity, surface area, stability, flexibility, and versatility, which is crucial for the development of sensitive, selective, and dependable biosensors for diverse healthcare applications [130]. Rong et al. reported an MB@MWCNTs/UiO-66- NH_2 composite material for the ratiometric electrochemical detection of the antitumor drug doxorubicin [131]. In this study, the inclusion of MWCNTs resulted in higher electrical

conductivity. The as-prepared biosensor has a wide linear detection range of 0.1–75 μM and a limit of detection of 0.051 μM . Compared to traditional electrocatalytic electrochemical methods, the as-prepared electrode ratiometric electrochemical sensor contributes to analyte signal amplification with high selectivity and stabilization. Lu et al. developed a three-dimensional infinite coordination polymer (ICP) nanocomposite incorporating SWCNTs for a biosensor designed to monitor in vivo glucose levels in guinea pig brains [132]. The ICP was synthesized using Tb^{3+} ions and β -nicotinamide adenine dinucleotide. This nanocomposite (ICP/SWCNTs) demonstrated superior selectivity and sensitivity towards glucose macromolecules compared to its pristine counterparts. The biosensor was designed for continuous glucose monitoring, simultaneously integrated with continuous-flow in vivo microdialysis.

4.8.4. Nanoparticle Formation

Nano-MOFs, which are synthesized at the nanoscale, possess distinctive characteristics owing to their size and configuration [133]. Nano-MOFs offer several benefits in biosensor applications. Nano-MOFs exhibit substantial potential for biosensor applications, offering distinct properties that can address fundamental biosensing challenges such as sensitivity, selectivity, stability, and integration [134]. Ongoing refinement and enhancement are expected to yield highly effective and adaptable biosensors that can be used in a broad spectrum of biomedical and environmental applications [135]. Hu et al. reported that Cr-MOF nanoparticles can be loaded onto a GCE to serve as an efficient electrochemical platform for detecting p-nitrophenol (p-NP) [136]. This sensor demonstrates a low detection limit of 0.7 μM for p-NP within a broad concentration range of 2–500 μM . Furthermore, these sensors exhibit strong performance even in the presence of competing analytes. Considering the benefits of their porous structure and straightforward synthesis strategy, Cr-MOFs were investigated for potential applications in the sensor field. The Cr-MOF nanoparticles displayed significant electrocatalytic activity towards p-NP, and the sensor was successfully validated for p-NP detection in river water, underscoring its practical utility. In another study, a nanocomposite-based CP was engineered using Pt ions and p-phenylenediamine incorporated into poly(N-vinyl-2-pyrrolidone)-graphene oxide [137]. This process resulted in the formation of metal coordination polymers within graphene nanosheets (MCPGNs). The resulting MCPGNs demonstrated exceptional efficiency in enzymatic immobilization for glucose oxidase, significantly enhancing the performance of glucose biosensors.

5. Conclusions and Outlook

To summarize the extensive exploration conducted in this review, it is evident that metal–organic frameworks (MOFs) and coordination polymers (CPs) are pivotal materials in the evolution of electrochemical biosensors. This review comprehensively explores the versatile applications of MOFs and CPs in biosensor technology, focusing on synthesis methodologies, property characterization, and diverse application areas. A thorough analysis of recent research highlights the increasing interest and rapid advancements in this field, showcasing innovative developments aimed at enhancing biosensor performance and functionality. MOFs and CPs are indispensable in the field of electrochemical biosensor development, primarily owing to their remarkable attributes such as high surface area, tunable surface chemistry, and robust stability. These attributes support efficient biomolecule binding, thereby enhancing biosensor performance. Their inherent or adjustable electrical conductivities enable rapid electron transfer, thereby accelerating electrochemical signal processing. In addition, their adaptable structures allow facile functionalization with diverse groups, enabling tailored properties that suit specific biosensing requirements. Consequently, MOFs and CPs serve as essential building blocks for elevating the sensitivity, selectivity, and reliability of electrochemical biosensors, thereby propelling advancements in fields ranging from healthcare to environmental monitoring.

Design is pivotal in the development and application of MOFs and CPs for electrochemical biosensors. In enzymatic biosensors, these materials offer a stable platform for enzyme immobilization, boosting sensitivity and selectivity in analyte detection. For enzyme-free biosensors, MOFs and CPs, when functionalized with metal nanoparticles or ions, catalyze electrochemical reactions directly, ensuring simplicity, stability, and cost-effectiveness. Moreover, MOF and CP-based electrochemical biosensors are employed both in vitro for accurate analyte detection in biological samples and in vivo for real-time monitoring of physiological parameters or drug levels in living organisms. Their versatility and precision greatly enhance biomedical research and clinical diagnostics.

One notable finding of this review is the superiority of composite biosensors over their standalone counterparts (Table 2). By integrating MOFs or CPs into biosensor architectures, researchers have effectively augmented sensing capabilities, achieving enhanced sensitivity, selectivity, and stability. This transformative synergy between materials science and biosensing underscores the pivotal role of interdisciplinary collaboration in driving innovation and addressing critical challenges in biosensor development.

Table 2. Comparison of different biosensor materials.

Methods/Sensor	Target Analyte	Detection Limit (μM)	Sensitivity ($\mu\text{Acm}^{-2} \text{mM}^{-1}$)	Recyclability	Ref.
GOD-GA-Ni/Cu-MOFs-FET	Glucose	0.51	26.05	-	[138]
PP/LIG	Glucose	3	247.3	5	[89]
Ru-PEI-L-lys-ZIF-8	Thrombin	2×10^{-14}	-	5	[126]
JUC-1000	TNP	3.46×10^{-17}	-	7	[139]
CuO/Cu ₂ O@CuO/Cu ₂ O	Glucose	0.48	10,090	6	[113]
CP1/GCE	Glucose	80×10^{-7}	517.36	3	[85]
Poly-L-lysine	Glucose oxidase	23	6.55	-	[88]
GR/PANI-AuNPs(6 nm)-GOx/GOx	Glucose oxidase	70	65.4	11	[140]
Ag@ZIF-67	Glucose	0.66	0.379	-	[141]
NiCo-MOF	Glucose	0.29	6844.0	10	[142]
Ni-MOF/CNTs	Glucose	0.82	1385.0	-	[143]
Cu-MOF-SWCNTs	Glucose	0.0017	573	-	[144]
HKUST ₃ -1/KSC800	Glucose	4.8	28.67	-	[145]
GOD/Cu-hemin MOFs	Glucose	2.73	22.77	-	[146]
Cu-MOF	Glucose	0.01	89	-	[147]
PdNP/PGaN	Glucose	1.0	353 and 116	5	[148]
MOCPs _{Cu} /Au	Glucose oxidase	0.194	59	-	[149]
MOF-71	Uric acid	15.61	0.4811	-	[150]
ZIF-67 HNPs	Glucose	0.96	445.7	-	[151]
3D N-Co-CNT@NG	Glucose	0.1	9.05	10	[152]

Although significant progress has been made in leveraging MOFs and CPs for in vitro biosensing applications, there is a foreseeable opportunity for expansion into the realm of in vivo biosensing. By addressing the existing barriers and harnessing the inherent properties of these materials, researchers can pave the way for the development of next-generation biosensors capable of real-time noninvasive monitoring in biological systems. As such, this review not only offers a comprehensive synthesis of the current knowledge but also serves as a catalyst for future research endeavors aimed at unlocking the full

potential of MOFs and coordination polymers in revolutionizing biosensing technologies and advancing biomedical science.

Author Contributions: Conceptualization, A.K. and S.C.; writing—original draft preparation, A.K.; writing—review and editing, A.K. and S.C.; visualization, A.K.; funding acquisition, S.C. All authors have read and agreed to the published version of the manuscript.

Funding: This research was supported by the National Research Foundation of Korea (NRF-2023R1A2C1003669, 020M3A9E4104385) and the Korea Environmental Industry & Technology Institute (KEITI) through “Technology Development Project for Biological Hazards Management in Indoor Air” Project, funded by Korea Ministry of Environment (MOE) (G232021010381).

Conflicts of Interest: The authors declares no conflicts of interest.

Abbreviations

PEC	photoelectrochemical
EC	electrochemical
ECL	electrochemiluminescent
FRET	fluorescence resonance-based energy transfer
PSM	post-synthetic modification
BET	Brunauer-Emmett-Teller
CV	cyclic voltammetry
SWV	square-wave voltammetry
GCE	glass carbon electrode
SPE	screen printed electrode
MOFs	metal–organic frameworks
CPs	coordination polymers
GO	graphene oxide
PANI	polyaniline
GBM	glioblastoma
BDC	benzene dicarboxylic acid
UiO-66	Universitetet i Oslo
MIL-91(Ti)	Materials of Institute Lavoisier-91 Titanium
MOF-177	Materials of Institute Lavoisier-177
ZIF-8	Zeolitic Imidazolate Framework-8
BTB	4,4',4''-benzene-1,3,5-triyl-tris(benzoate)
NDC	2,6-naphthalene dicarboxylate
PQDs	perovskite quantum dots
HHTP	2,3,6,7,10,11-hexahydroxytriphenylene
EDTA	ethylenediaminetetraacetic acid
PAN	polyacrylonitrile
H ₄ tptc	p-terphenyl-2,2'',5'',5'''-tetracarboxylic acid
phen	1,10-phenanthroline
Ru-PEI-L-lys	ru(dcbpy) ₃ ²⁺ -polyethyleneimine-L-lysine
DCN	2,6-dichloro-4-nitroaniline
p-NP	p-nitrophenol
PAni	polyaniline
PPy	polypyrrole
PEDOT	poly(3,4-ethylene dioxythiophene)
PEDOT:PSS	(3,4-ethylene dioxythiophene)-poly(styrene sulfonate)
MB	methylene blue
PBS	phosphate-buffered saline
ATP	adenosine triphosphate

NPs	nanoparticles
SWNH	single-walled nanotube
MWCNTs	multiwalled carbon nanotubes
SWCNTs	single-walled carbon nanotubes
LOW	low detection limit
MVL ATRP	metal-free visible-light-induced atom transfer radical polymerization
MBA	4-mercaptobenzoic acid
CTCs	circulating tumor cells

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