ABSTRACT: A reliable and sensitive detection approach for SARS-CoV-2 is essential for timely infection diagnosis and transmission prevention. Here, a two-dimensional (2D) metal–organic framework (MOF)-based photoelectrochemical (PEC) aptasensor with high sensitivity and stability for SARS-CoV-2 spike glycoprotein (S protein) detection was developed. The PEC aptasensor was constructed by a plasmon-enhanced photoactive material (namely, Au NPs/Yb-TCPP) with a specific DNA aptamer against S protein. The Au NPs/Yb-TCPP fabricated by in situ growth of Au NPs on the surface of 2D Yb-TCPP nanosheets showed a high electron–hole (e− h) separation efficiency due to the enhancement effect of plasmon, resulting in excellent photoelectric performance. The modified DNA aptamer on the surface of Au NPs/Yb-TCPP can bind with S protein with high selectivity, thus decreasing the photocurrent of the system due to the high steric hindrance and low conductivity of the S protein. The established PEC aptasensor demonstrated a highly sensitive detection for S protein with a linear response range of 0.5–8 μg/mL with a detection limit of 72 ng/mL. This work presented a promising way for the detection of SARS-CoV-2, which may conducive to the impetus of clinic diagnostics.

KEYWORDS: photoelectrochemical, metal–organic framework, plasmon, aptasensor, SARS-CoV-2, spike glycoprotein

INTRODUCTION

The current coronavirus disease 2019 (COVID-19) pandemic around the world caused by SARS-CoV-2 began to spread at the end of 2019, which seriously endangered human health and lagged the global economy. At present, the worldwide spread of SARS-CoV-2 has not been effectively curbed. As of July 2021, more than 182 million cases of coronavirus infection had been reported, with over 3.9 million fatalities worldwide. Rapid and accurate diagnosis is the key to the current epidemic prevention and control. Currently, real-time reverse transcription polymerase chain reaction (RT-PCR) is the main method for early diagnosis of SARS-CoV-2, and it is also the gold standard for the diagnosis of SARS-CoV-2. Although RT-PCR has enough sensitivity to determine early infection, it is prone to false-negative results inconsistent with computed tomography (CT) imaging, which greatly affects the accuracy of diagnosis. To compensate for the deficiency of nucleic acid detection, many rapid quantitative detection methods of immunoglobulin M (IgM)/immunoglobulin G (IgG) antibodies in serum have been widely reported. Compared with RT-PCR, these detection methods indirectly detect SARS-CoV-2 through unified collection of serum, which have less stringent requirements for specimens, and have developed into useful supplements for nucleic acid detection. However, from the onset of symptoms, IgM was initially detected within 3–5 days, followed by IgG within 4–14 days. Compared with the direct detection of viral antigens in SARS-CoV-2 clinical samples, the detection of IgM/IgG antibody was slightly delayed.

The SARS-CoV-2 spike glycoprotein (S protein), located on the surface of virus, is necessary to infect host cells and has high immunogenicity. It is considered as a common target for neutralizing antibody and vaccine development. The unique structural protein characteristics make it become a candidate antigen protein for SARS-CoV-2 diagnosis. For example, Seo et al. developed a field-effect transistor (FET)-based biosensing device for the detection of SARS-CoV-2 in clinical samples on the basis of antibody specificity to S protein. Lin et al. developed a portable microfluidic immunoassay system, which can simultaneously detect S protein and IgG/IgM within 15 min. Fabiani et al. established an electrochemical immunoassay platform for S protein and nucleocapsid protein. However, these methods were mainly based on...
the antigen–antibody immunoassay, and the very high production cost of antibody will increase the detection cost to a certain extent, which is not conducive to large-scale batch detection. Although antibodies have been widely used in clinical treatment and diagnostic intervention, aptamers have the advantages of easy chemical modification, thermal stability, rapid synthesis, low cost, and specific target recognition, which make them better suitable for large-scale clinical diagnosis of various diseases.\textsuperscript{26,27} The aptamer targeting S protein was successfully screened by Yang’s group last year.\textsuperscript{28} However, the aptamer-assisted diagnostic strategy for SARS-CoV-2 has not been fully developed.\textsuperscript{29–31}

The photoelectrochemical (PEC) biosensing platform has attracted considerable attention due to the advantages of high sensitivity, rapid detection, low cost, and simple equipment.\textsuperscript{32–36} The essence of PEC sensors is to use photosensitive materials as sensing materials to convert light radiation into electrical signals. The development of photosensitive materials with a wide spectrum response is the key to improve the sensitivity of PEC sensors.\textsuperscript{36–38} Thus, significant effort has been made to improve the photoelectronic performance of photoelectric materials. For example, appropriate design, doping, and combining semiconductors with metals or other semiconductors to form heterojunctions have been applied to boost the photon-to-electricity conversion efficiency.\textsuperscript{37,39–44} Among them, the Schottky junctions formed by metal and semiconductor have been paid much attention to for improving the photovoltaic conversion performance due to the enhancement effect of plasmon.\textsuperscript{37,45–50} However, the developed PEC sensors still face some serious problems, such as relatively low photocurrent conversion efficiency and intolerance to photobleaching, which greatly limits their applications.\textsuperscript{36,42} Therefore, to meet the specific aims, it is necessary to develop proper photoactive materials with high photocurrent conversion efficiency and stable photocurrent.

In this work, a two-dimensional (2D) metal–organic framework (MOF)-based Schottky junction, namely, Au NPs/Yb-TCPP (Yb-TCPP, a 2D MOF reported in our previous work\textsuperscript{51,52}), was successfully fabricated by a simple \textit{in situ} synthesis strategy. The plasmon-enhanced effect of Au NPs, including large scattering cross section and locally amplified electric field, plasmon-induced resonance energy transfer (PIRET), and hot-electron transfer between Au NPs and 2D Yb-TCPP nanosheets, greatly improved the e− separation efficiency of 2D Yb-TCPP nanosheets, making the photoelectrochemical activity of Au NPs/Yb-TCPP approximately 16 times that of Au NPs and 2D Yb-TCPP nanosheets. The S protein could be captured by the modified aptamer on the surface of Au NPs/Yb-TCPP to block the photoelectron transfer, leading to the decrease of the photocurrent. Based on the photocurrent change against S protein concentration, a sensitive PEC aptasensor was developed to detect S protein, which can be considered as a useful supplement for nucleic acid detection, and even provide a potential strategy for direct detection of SARS-CoV-2.

\section*{EXPERIMENTAL SECTION}

\textbf{Materials and Reagents.} Yb(NO\textsubscript{3})\textsubscript{3}·5H\textsubscript{2}O, H\textsubscript{2}TCPP, NaBH\textsubscript{4}, tris(2-carboxyethyl)phosphine (TCIMP), bovine serum albumin (BSA), and acetic acid (AA) were purchased from Aladdin (Shanghai Aladdin Biochemical Technology Co., Ltd, China). Tetrakis(4-carboxyphenyl) porphyrin (H\textsubscript{2}TCPP) was obtained from Frontier Scientific (Logan, Utah). Ethanol, N,N-dimethylformamide (DMA), and anhydrous sodium sulfate (Na\textsubscript{2}SO\textsubscript{4}) were purchased from Chuandong Chemical Co., Ltd. (Chongqing, China). SARS-CoV-2 Spike S1 + S2 ECD-His recombinant protein (40589-V08B1) was purchased from Sino Biological, Inc. (China). The DNA aptamer was designed based on Yang’s group report,\textsuperscript{28} and the sequences (5′-SH-(A\textsubscript{15})CAGGACGCCACCTTGTGCCTTTGGAAGTTGTGGC-3′) were synthesized by Sangon Biotech with HPLC purification (Shanghai, China). All reagents were purchased from commercial suppliers and used as received without further purification. Milli-Q purified water (18.2 MΩ) was used in the whole study.

\textbf{Apparatus.} The household microwave oven (M1-L213B, Midea Co., Ltd., China) was used to prepare 2D Yb-TCPP nanosheets. Transmission electron microscopy (TEM) images were taken on an FEI Tecnai G2 F20 TEM instrument (FEI, America). Powder X-ray diffraction (PXRD) patterns were recorded on a D8 ADVANCE X-ray diffractometer (Bruker), using Cu K\textalpha\ radiation (\lambda = 1.5406 \textmu\text{m}). X-ray photoelectron spectroscopy (XPS) measurements were performed on a Thermo ESCALAB 250Xi (Thermo Fisher Scientific). Thermogravimetric analysis (TGA) was conducted on a Q600 (TA Instruments) thermogravimetric analyzer. Brunauer–Emmett–Teller (BET) surface areas were determined by N\textsubscript{2} adsorption–desorption isotherms obtained at 77 K on ASAP 2020. UV–vis absorption spectra and solid absorption spectra were recorded with a U-3010 spectrophotometer (Hitachi, Japan). All of the electrochemical measurements were carried out on a CHI 660E electrochemical workstation (CH Instruments, China). A CEL-PEX2000 Xenon lamp photoelectric test system with a 400 nm cutoff filter (Beijing China Education Au-Light Co., Ltd) was used for photocurrent test, and the power of the xenon lamp was 300 W.

\textbf{Preparation of 2D Yb-TCPP Nanosheets.} The 2D Yb-TCPP nanosheets were synthesized according to our previous report with some modifications.\textsuperscript{31,53} First, Yb(NO\textsubscript{3})\textsubscript{3}·5H\textsubscript{2}O (0.09 mmol, 40.4 mg) and H\textsubscript{2}TCPP (0.03 mmol, 23.7 mg) were dissolved in 9 mL of DMA, respectively. Then, 400 \textmu\text{L} of Yb(NO\textsubscript{3})\textsubscript{3} solution and 400 \textmu\text{L} of H\textsubscript{2}TCPP solution were added into a 3 mL Pyrex vial and the mixture was further diluted to 1 mL with DMA. After that, the capped vials were heated for 10 min under microwave irradiation in a household microwave oven with medium-low power (about 231 W). After cooling down to room temperature, the resulting nanosheets were washed twice with DMA and ethanol, respectively, and then collected by centrifugation at 15 000 rpm for 10 min. Finally, the obtained 2D Yb-TCPP nanosheets were redispersed in ethanol.

\textbf{Preparation of Au NPs/Yb-TCPP Composites.} First, a 1 mL ethanol dispersion of 2D Yb-TCPP nanosheets (1 mg/mL) was added into 9 mL of water. To obtain Au NPs/Yb-TCPP with different Au NP loadings, different volumes of HAuCl\textsubscript{4} aqueous solution (0.1 M) were added. For example, 20, 60, 100, 150, and 200 \textmu\text{L} of HAuCl\textsubscript{4} aqueous solutions were added, respectively, to obtain corresponding Au NPs/Yb-TCPP with different Au NP loadings. After stirring at room temperature for 5 min, freshly prepared NaBH\textsubscript{4} aqueous solution (0.1 M; 25, 70, 125, 187.5, and 250 \textmu\text{L} corresponding to different dosages of HAuCl\textsubscript{4}) was added. After further stirring for 5 min, Au NPs/Yb-TCPP with different Au NP loadings were obtained by centrifugation and washing three times, marked as Au NPs/Yb-TCPP–1, Au NPs/Yb-TCPP–2, Au NPs/Yb-TCPP–3, Au NPs/Yb-TCPP–4, and Au NPs/Yb-TCPP–5.

\textbf{Fabrication of the PEC Aptasensor.} First, the Tris-HCl buffer solution (pH 7.4, containing 137 mM NaCl, 2.7 mM KCl, 0.55 mM MgCl\textsubscript{2}) of a DNA aptamer was heated at 95 °C for 3 min and slowly cooled to 25 °C for 2 h. Then, TCEP (the concentration ratio of TCEP to DNA aptamer was 100:1) was added and incubated at 37 °C for 1 h to activate the –SH group. Then, \textmu\text{L} of Au NPs/Yb-TCPP–4 water dispersion was deposited on the clean glassy carbon electrode surface and dried completely at room temperature. After that, \textmu\text{L} of the activated DNA aptamer (2 \muM) was dropped onto the surface of the modified electrode and incubated for 12 h at 4 °C. Subsequently, to get rid of unlinked DNA aptamer, Tris-HCl buffer solution (pH 7.4) was used to swell the as-prepared modified electrode. To block the nonspecific adsorption, the resulting modified

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The electrode was incubated with 1% BSA for 1 h at 37 °C. Finally, the modified electrode was washed with Tris-HCl buffer solution (pH 7.4) to obtain the PEC aptasensor.

**Measurement Procedure.** A total of 7 μL of S protein solution with different concentrations was dropped onto the modified electrode and incubated at 37 °C for 70 min. Subsequently, the electrode was washed with Tris-HCl (pH 7.4) buffer solution and inserted into Tris-HCl buffer solution containing 0.1 M Na2SO4 and 0.15 M AA to carry out photocurrent measurements using a CEL-PECX2000 photoelectric test system. The light source was turned on and off every 20 s, and a constant potential of 0.1 V was applied.

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**RESULTS AND DISCUSSION**

**Characterization of Au NPs/Yb-TCPP Composites.** The Au NPs prepared by NaBH4 and HAuCl4 showed typical surface plasmon resonance (SPR) absorption at about 515 nm (Figure S1a), which overlapped well with the absorption spectrum of 2D Yb-TCPP nanosheets. The absorbance in the range of 500−800 nm increased with the increase of HAuCl4 concentration (Figure S1b), demonstrating that the loading of Au NPs can be easily controlled by changing the amount of HAuCl4. Besides, the solid diffuse reflectance spectra also manifested that the larger the loading of Au NPs, the larger the absorption cross section of the composite (Figure S2). That is, the Au NPs as plasmon can be used as energy-harvesting antennas to increase the light absorption cross sections of surrounding semiconductor materials.

Au NPs/Yb-TCPP-4 was taken as an example to characterize the structure and morphology. Scanning electron microscopy (SEM) and transmission electron microscopy (TEM) images showed that the in situ synthesized Au NPs with irregular shape and size were almost all deposited on the surface of 2D Yb-TCPP nanosheets (Figures 1b and S3), and the Au NPs/Yb-TCPP-4 kept the sheetlike 2D structure of the as-synthesized 2D Yb-TCPP nanosheets. The high-resolution TEM (HRTEM) image of the loaded Au NPs showed a lattice fringe with interplanar distances of 0.23 nm and 0.20 nm, which were attributed to the (111) and (200) planes of Au NPs, indicating the high crystallinity of Au NPs (Figure 1c). Four diffraction rings corresponding to Au(111), Au(200), Au(220), and Au(311) crystal planes could be observed in the selected area electron diffraction pattern (SAED), which further manifested that Au NPs on 2D Yb-TCPP nanosheets were highly crystalline (Figure 1d).

High-resolution X-ray photoelectron spectroscopy (XPS) of Au 4f showed two peaks at 83.95 and 87.58 eV, which corresponded to Au 4f5/2 and Au 4f7/2, suggesting the presence of Au in the form of Au0 valence state (Figures 1e and S4). The powder X-ray diffraction (PXRD) pattern of Au NPs/Yb-TCPP-4 showed that the main diffraction peaks were consistent with that of 2D Yb-TCPP nanosheets in the low angle range (3−20°), revealing no structural disruption by loading of Au NPs (Figure 1f). The strong diffraction peaks at around 38.1, 44.4, 64.7, and 77.5° corresponded to the diffractions from Au(111), Au(200), Au(220), and Au(311) lattice planes, demonstrating that the Au NPs existed in the crystalline state. Besides, according to thermogravimetric analysis, the burning residual amounts were 39.77 and 61.06% for 2D Yb-TCPP nanosheets and Au NPs/Yb-TCPP-4, respectively, and the loading of Au NPs was calculated to be 21.29% (Figure S5). Furthermore, the Brunauer−Emmett−Teller (BET) surface areas of the as-prepared 2D Yb-TCPP nanosheets and Au NPs/Yb-TCPP-4 were calculated to be 392 and 32 m2/g, respectively, and the pore size distribution has no obvious change (Figure S6), indicating that the Au NPs were deposited on the surface of 2D Yb-TCPP nanosheets with high loading. All of the above results verified that the Au NPs have been successfully introduced onto the surface of 2D Yb-TCPP nanosheets.
**Plasmon-Enhanced Photocurrent Response and Mechanism.** To investigate the e−h separation efficiency of Au NPs/Yb-TCPP composite with different loadings of Au NPs, the photocurrent responses were performed (Figure 2a).

The solitary Au NPs and 2D Yb-TCPP nanosheets were activated under visible light excitation, showing weak photocurrent responses of 1.25 μA and 1.32 μA. The photocurrent increased gradually with increasing Au NPs loading, wherein Au NPs/Yb-TCPP-4 exhibited a high photocurrent close to that of Au NPs/Yb-TCPP-5 without significant change. The photocurrent response of Au NPs/Yb-TCPP-4 was approximately 16 times that of solitary Au NPs and 2D Yb-TCPP nanosheets. That is, the coupling of Au NPs greatly improved the photoelectric conversion efficiency of 2D Yb-TCPP nanosheets. On the one hand, the Au NPs as plasmon can be used as energy-harvesting antennas to increase light absorption cross sections and effective optical path length of surrounding semiconductor materials due to the large scattering cross section and locally amplified electric field.49,53−56 On the other hand, since the SPR absorption spectrum of Au NPs overlapped well with the absorption spectrum of 2D Yb-TCPP nanosheets, the PIRET can occur between Au NPs and 2D Yb-TCPP nanosheets, thereby improving the e−h formation rate and separation efficiency of 2D Yb-TCPP nanosheets.55,59−63

The enhanced e−h separation effect also could be verified by electrochemical impedance spectroscopy (EIS). As expected, with the increase of Au NP loading on the surface of 2D Yb-TCPP nanosheets, the radius of the Nyquist curve decreased gradually, indicating that the charge-transfer resistance (Rct) decreased gradually, which could accelerate the photoelectron transfer and increase the photocurrent (Figure 2b). Furthermore, the time-dependent photocurrent response test showed that the PEC intensity was very stable with a relative standard deviation (RSD) of 1.69% under 90 times on/off irradiation cycles for 3600 s, indicating the high stability and photobleaching resistance (Figure S7). All of the above results demonstrated that the Au NPs as plasmon greatly boosted the photoactivity of 2D Yb-TCPP nanosheets, leading to a high and stable photocurrent response, which made the Au NPs/Yb-TCPP composite a promising candidate for the construction of a PEC sensor.

**Construction of the PEC Aptsensor for S Protein Detection.** The design principle of S protein detection was that after the DNA aptamer captured S protein, due to its low conductivity and large steric hindrance, the path through which the electrons transfer between the electrode and electrolyte was blocked, resulting in a decrease of photocurrent (Scheme 1). To verify the successful assembly of Au NPs/Yb-TCPP-4 and aptamer on the electrodes as expected, EIS examinations of different modified electrodes were carried out (Figure 4a). The Au NPs/Yb-TCPP-4/GC electrode showed a small radius of Nyquist curve a, indicating the high electroconductivity. With the aptamer assembled on the Au NPs/Yb-TCPP-4/GC electrode (Apt/Au NPs/Yb-TCPP-4/GC), Rct increased obviously (curve b) due to the insulativity of aptamer.

**Scheme 1. Schematic Illustration of the PEC Aptsensor for SARS-CoV-2 S Protein Detection**

![Scheme 1](https://doi.org/10.1021/acsami.1c17574)
implying that the DNA aptamer was successfully modified on the surface of Au NPs/Yb-TCPP-4. After blocking the nonspecific sites by BSA, the $R_d$ value was further increased due to its high steric hindrance and low conductivity (curve c, BSA/Apt/Au NPs/Yb-TCPP-4/GC electrode). Subsequently, after incubation with S protein (curve d), the $R_d$ value of S protein/BSA/Apt/Au NPs/Yb-TCPP-4/GC electrode increased sharply due to the high insulation and steric hindrance of S protein, manifesting that the S protein was successfully captured on the electrode surface by its DNA aptamer. Meanwhile, the photocurrent responses of different modified electrodes were recorded (Figure 4b). The Au NPs/Yb-TCPP-4/GC electrode exhibited a high photocurrent of 20.5 $\mu A$ (curve a). However, the stepwise assembly of DNA aptamer and BSA increased the steric hindrance of the electrode interface, resulting in a low photocurrent response (curves b and c). After the aptamer specifically reacts with S protein, the photocurrent (curve d) drastically decreased due to the nonconductive property and steric hindrance of the large protein. All of these results confirmed the feasibility of the proposed PEC aptasensor for S protein detection.

**Performance of the Aptasensor.** To obtain the best sensing performance of the developed PEC aptasensor, it was essential to optimize the important parameters, including the concentrations of Au NPs/Yb-TCPP-4 and AA and incubation time (Figure S8). Under the optimal assay conditions, the photocurrent response of the PEC aptasensor was directly related to the concentration of S protein. The time–photocurrent curves of the PEC aptasensor toward S protein showed that the PEC signal intensity gradually decreased with the increase of S protein concentration (Figure 5). The relative change of photocurrent intensity $\Delta I$ ($\Delta I = I_0 - I$, where $I_0$ is the photocurrent intensity without S protein and $I$ is the photocurrent intensity of S protein at different concentrations) showed a good linear relationship with S protein concentration in the range of 0.5–8 $\mu g/mL$. The linear equation was: $\Delta I = 1.84c - 0.12$, with a correlation coefficient of $R^2 = 0.998$, and the detection limit was 72 ng/mL ($S/N = 3$). The proposed PEC aptasensor exhibited a comparable or even lower detection limit versus other sensor for S protein detection (Table S1).

**Interferences and Application in Real Samples.** For biological extracts, such as pharynx swabs and nose swabs, their composition and proportion are very complex, which is a major challenge for the actual sample determination. Therefore, in this work, the pharyngeal swab extracts of healthy people were used to evaluate the anti-interference performance of the PEC aptasensor. Compared with the control group of water, the extract of throat swabs of healthy people did not significantly change the photocurrent signal, indicating that the PEC aptasensor had sufficient anti-interference ability to meet the detection of S protein by pharynx swabs (Figure S9). To further verify the feasibility of this method in the detection of actual samples, the recovery rates of S protein in the pharynx swabs extracts of healthy people were evaluated by the standard addition method. As expected, the recovery rates of three different samples were in the range of 104.0–106.0% with the RSD lower than 2.8% (Table S2), suggesting that the proposed PEC aptasensor had good accuracy and reliability in the detection of S protein, and it had potential application value in the practical detection of SARS-CoV 2.
CONCLUSIONS

In summary, we have developed an efficient plasmon-enhanced PEC aptasensor for S protein detection by employing Au NPs/Yb-TCPP as photothermal materials and an aptamer as a recognition element. The loaded Au NPs provided a strong SPR effect, resulting in an approximately 16 times increase of photocurrent response, which was beneficial to construct a high-sensitivity PEC biosensor. The S protein-binding aptamer immobilized on the surface of Au NPs/Yb-TCPP can specifically capture the S protein, resulting in the decrease of photocurrent intensity due to the high steric hindrance and low conductivity. The developed PEC aptasensor displayed excellent sensitivity, good stability, and anti-interference performance toward S protein detection. This contribution not only provided a promising photothermal material for PEC sensing but also offered a potential strategy for the detection of SARS-CoV-2.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsami.1c17574.

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Notes

The authors declare no competing financial interest.

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