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Original article

Development of a triple channel detection probe for hydrogen peroxide

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ABSTRACT

The rapid and reliable measurement of hydrogen peroxide (H_2O_2) is imperative for many areas of technology, including pharmaceutical, clinical, food industry and environmental applications. In this work, a novel multifunctional complex, $[Ru(bpy)_2(Luminol\text{-}bpy)](PF_6)_2$(bpy: 2,2′-bipyridine), was designed and synthesized by incorporating a Ru(II) complex with a luminal group. In the presence of horseradish peroxidase (HRP), reaction of $[Ru(bpy)_2(Luminol\text{-}bpy)]^{2+}$ with H_2O_2 can be monitored by three sensing channels including photoluminescence (PL), chemiluminiscence (CL) and eletrochemiluminiscence (ECL). The quantitative assays for H_2O_2 in aqueous solutions using $[Ru(bpy)_2(Luminal\text{-}bpy)](PF_6)_2$ as a probe were established with PL, ECL and CL signal output modes, respectively.

1. Introduction

Reactive oxygen species (ROS) are a class of radical or nonradical oxygen-containing molecules that show high reactivity to biomolecules [1]. Although generation of ROS is often simply regarded as representing oxidative stress, each ROS has unique chemical characteristics in terms of chemical reactivity and lifetime in aqueous solution and, therefore, may play a distinct role in biological systems [2]. Hydrogen peroxide (H_2O_2) exhibits relatively mild reactivity among ROS and has attracted intense interest in recent years. It appears to be involved in signal transduction by reversible oxidation of proteins, such as phosphatases and thioredoxins, in a tightly regulated manner. The fast and accurate detection of H_2O_2 has profound applications in pharmaceutical, clinical, food industry, environmental analysis and other fields [3,4]. Thus, numerous analytical methods have been applied for the detection of H_2O_2 such as fluorescence [5,6], chemiluminescence [7,8], and electrochemical methods [9–11].

Among these methods, the electrochemical technique is the most studied because of its simplicity, fast response for analysis, low detection limit, and low costs [12]. Sombers and co-workers have detected rapid H_2O_2 fluctuations at an uncoated carbon fiber microelectrode by fast scan cyclic voltammetry in vitro and in brain slices. Recently, several boronate-based fluorescence probes capable of detecting H_2O_2 have been reported, such as peroxyfluor-1, peroxyresorufin-1 and peroxyxanthone-1 [13–17]. These fluorescent probes are cell membrane-permeable, and able to monitor the intracellular H_2O_2 concentration changes in living cells. At the same time, chemiluminescence (CL)-based assays possess several advantages such as simplicity in instrumentation [18], high sensitivity, and wide linear range. Since no external light source is used for excitation in chemiluminescent approaches, nonspecific signals caused by external light excitation as often observed in fluorescence-based measurements can be minimized. Suzuki et al. has reported a luciferin-based long-wavelength chemiluminescent based probe, KEIO-BODIPY-imidazopyrazine, which exhibited the strong response toward H_2O_2.

Although various techniques in H_2O_2 sensing have been installed to enhance sensitivity, selectivity, and the dynamic working range, these approaches mainly follow the paradigm that is still dominating traditional probe design: one probe for one detection method. Therefore, the application of the probe will be significantly limited by the requirement of instrument and complicated samples containing the different interfering species. As an alternative strategy, here we reported a mutli-signaling probe, $Ru[(bpy)_2luminol\text{-}bpy](PF_6)_2$, that can detect H_2O_2 in three sensing channels including photoluminescence, chemiluminiscence and eletrochemiluminiscence.

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2. Experimental

2.1. Materials and instrumentation

5-Amino-2,3-dihydrophthalazine-1,4-dione, hydrogen peroxide, horseradish peroxidase (HRP) were purchased from Aladdin. 4-methyl-4′-methyl-2,2′-bipyridine were purchased from Sigma-Aldrich. $[Ru(bpy)_2(COOH\text{-}bpy)](PF_6)_2$ were synthesized by using the literature methods [19]. Unless otherwise stated, all chemical materials were purchased from commercial sources and used without further purification.

^1H NMR and ^{13}C NMR spectra were measured on a Bruker Avance spectrometer (400 MHz for ^1H NMR and 100 MHz for ^{13}C NMR). Mass spectra were recorded on a HP1100 LC/MSD MS spectrometer. Absorption spectra were measured on a Perkin-Elmer Lambda 35 UV–Vis spectrometer. Elemental analysis was carried out on a Vario-EL analyser. Photoluminescence spectra were measured on a Perkin-Elmer LS-50 luminescence spectrometer. All the ECL measurements were carried out on an ECL insECL cell at room temperature. All measurements of chemiluminiscence were carried out IFFM-D flow injection chemiluminescence analyzer and IFFS-A instrument system (Remex Electronics Instrument Co., Ltd.).

2.2. Synthesis of $[Ru(bpy)_2(Luminol\text{-}bpy)](PF_6)_2$

A solution of $[Ru(bpy)_2(COOH\text{-}bpy)](PF_6)_2$ (93.6 mg, 0.1 mmol) in 5 mL $SOCl_2$ was refluxed for 5 h under an argon atmosphere. After removing the excess $SOCl_2$ by distillation under reduced pressure, the residue was dried in vacuum for 2 h, and dissolved in 30 ml absolute CH_3CN. The solution was added to a mixture of luminal (17.5 mg, 0.1 mmol) and Et_3N (21 L, 0.15 mmol). The mixture was refluxed 12 h. The solvent was evaporated, and the residue was purified by silica gel column chromatography using CH_3CN–H_2O–KNO_3 (sat.) (100:20:1, v/v/v) as eluent. The fractions containing the target product were collected, and the solvent was evaporated. The resulting solid was dissolved in a small amount of CH_3CN–H_2O(1:1), and a saturated solution of NH_4PF_6 was added to give a red precipitate. The product was filtered and washed with small amount of water. Compound $[Ru(bpy)_2(Luminol\text{-}bpy)](PF_6)_2$ was obtained as a red powder (75.89 mg, 70.4% yield). ^1H NMR (400 MHz, CD_3CN): δ 2.54 (s, 3H), 7.27(m, 1H), 7.38–7.43(m, 4H), 7.57(m, 1H), 7.70(s, 1H), 7.74(m, 3H), 7.78(s, 1H), 7.81(m, 2H), 7.97(m, 1H), 8.04–8.09(m, 4H), 8.51(d, J(H,H) = 4 Hz, 5H), 8.97(s, 1H), 8.99(m, 1H). ^{13}C NMR (100 MHz, CD_3CN): δ 19.97, 117.04, 118.96, 121.24, 123.44, 124.00, 124.03, 124.08, 125.32, 127.29, 127.34, 127.37, 127.39, 128.59, 134.81, 137.70, 150.54, 150.59, 151.28, 151.47, 151.49, 152.63, 155.63, 156.51, 156.62, 156.73, 158.25, 161.52. ESI-MS (m/z): 932.0 ($[M\text{-}PF_6]^+$), 393.4 ($[M\text{-}2PF_6]^{2+}$). Elemental analysis (%) calcd. for $C_{40}H_{31}F_{12}N_9O_3P_2Ru{\cdot}2H_2O$: C 43.17, H 3.17, N 11.33; found (%): C 43.12, H 3.03, N, 11.13.

2.3. Chemiluminiscence measurements

A mixture of $[Ru(bpy)_2(Luminol\text{-}bpy)](PF_6)_2$ solution (1.0 μmol/L), HRP (1.0 μmol/L) and different concentrations of H_2O_2 (0.1 μmol/L, 1.0 μmol/L, 2.0 μmol/L, 4.0 μmol/L, 6.0 μmol/L, 8.0 μmol/L, 10 μmol/L, 12 μmol/L, 28 μmol/L, 40 μmol/L, 50 μmol/L, 60 μ mol/L, 70 μ mol/L) was injected into injection port, respectively. The rotate speed of main and vice-peristaltic pump were set as 20 and 15 r/min, respectively, and CL intensities of the solutions were determined on chemiluminescence analyzer.

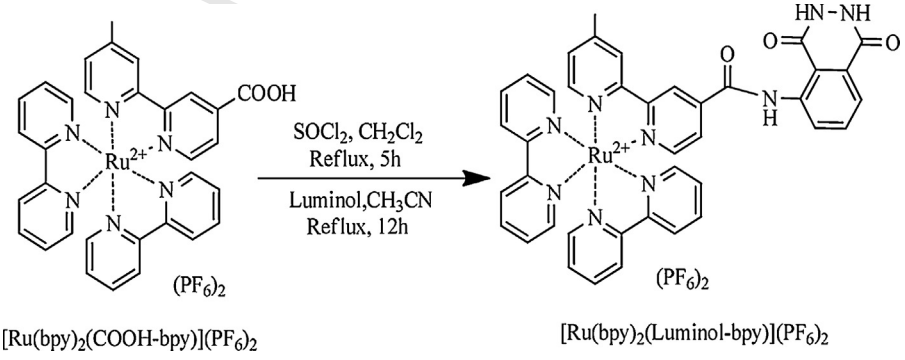
2.4. ECL measurements

$[Ru(bpy)_2(Luminol\text{-}bpy)](PF_6)_2$ (10 μmol/L) and HRP (1.0 μmol/L) was stirred with different concentrations of H_2O_2 (0 μmol/L, 5 μmol/L, 15 μmol/L, 20 μmol/L, 25 μmol/L) at room temperature for 30 min in the PBS buffer (25 mmol/L, pH 7.4), respectively. The glassy carbon (3.0 mm in diameter) electrode and KCl saturated Ag/AgCl electrode were used working electrode and reference electrode, respectively, and a platinum wire (0.3 mm in diameter) was used as the auxiliary electrode. Before measurements, the glassy carbon working electrode was soaked in 10% HNO_3 in an ultrasonic water bath for 1 min, then polished by an Al_2O_3 slurry, and thoroughly rinsed with deionized water for 1 min. The voltage of the photomultiplier tube was set at 900 V in the detection process while collecting the ECL signals.

3. Results and discussion

3.1. Design and synthesis of the mutli-signaling probe

A novel multi-signaling probe for H_2O_2, $Ru[(bpy)_2luminol\text{-}bpy](PF_6)_2$, was developed by conjugating luminal with a luminescent Ru(II) complex. The luminescent Ru(II)-polypyridyl complexes has attracted much attention due to their abundant photophysical, photochemical, and electrochemical properties, such as visible-light excitation and emission with large Stokes shifts, high photo- and chemical stabilities, low cytotoxicity, good water-solubility, and high PL and ECL response efficiency [20–23]. In addition, the output signals of Ru(II)-polypyridyl complexes can be modulated by appropriate modification of the pyridine moiety. At the same time, it is well known that luminal is a specifically reactive group for H_2O_2, and has been widely used for the development of chemiluminescent probe for H_2O_2 detection. $Ru[(bpy)_2luminol\text{-}bpy](PF_6)_2$ was successfully synthesized as shown in Scheme 1, and the structure of the probe was well confirmed by NMR spectroscopy, MS, and elementary analyses.



$[Ru(bpy)_2(COOH\text{-}bpy)](PF_6)_2$ $[Ru(bpy)_2(Luminol\text{-}bpy)](PF_6)_2$

Scheme 1. Synthesis of $Ru[(bpy)_2luminol\text{-}bpy](PF_6)_2$.

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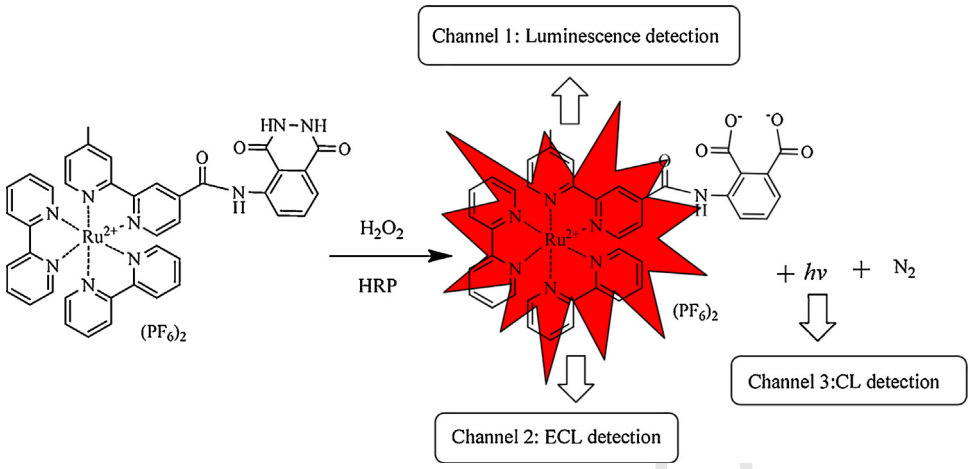

Fig. 1. Reaction of Ru[(bpy)$_2$luminol-bpy](PF$_6$)$_2$ with H_2O_2 in the presence of HRP.

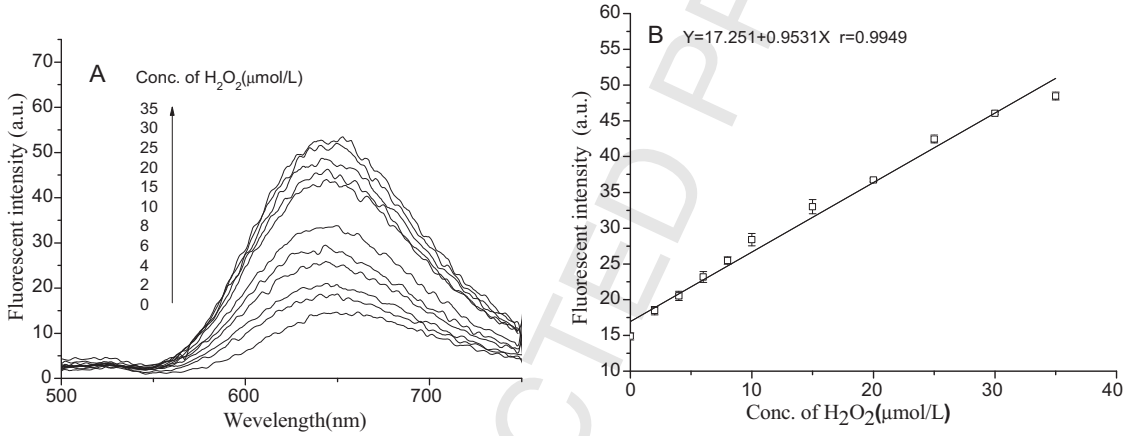

Fig. 2. A. Luminescence emission of [Ru(bpy)$_2$(Luminal-bpy)](PF$_6$)$_2$ (10 μmol/L) upon addition of H_2O_2 (0–35 μmol/L) and HRP (1 μmol/L) for 5 min at 25 °C in 25 mmol/L PBS buffer (pH = 12.0). λ_{ex} = 450 nm. B. The calibration curve for luminescence detection of H_2O_2.

3.2. Luminescence measurements H_2O_2

After conjugated with a luminal moiety, the metal-to-ligand charge transfer (MLCT) emission of the Ru(II) complex is effectively corrupted by the electron of N atoms via an intramolecular photoinduced electron transfer (PET) process. Ru[(bpy)$_2$luminol-bpy](PF$_6$)$_2$ exhibited weak luminescence at 645 nm. It is well known that the luminal moiety can react with ROS, which are generated by the reaction of H_2O_2 with HRP, to generate a high energy species that decomposes to give an excited molecule with loss of nitrogen molecule [24]. Therefore, after reacting with H_2O_2 in the presence of HRP to trigger the cleavage of the N atoms, the PET process is eliminated, so that the luminescence of the Ru(II) complex can be turned on (Fig. 1).

To investigate the luminescence response of the Ru(II) complex to H_2O_2, the emission spectra of [Ru(bpy)$_2$(Luminal-bpy)](PF$_6$)$_2$ (10 μmol/L) in the presence of HRP (1.0 μmol/L) and different concentrations of H_2O_2 were recorded in 25 mM PBS buffer of pH 12.0. As shown in Fig. 2A, the complex [Ru(bpy)$_2$(Luminal-bpy)](PF$_6$)$_2$ exhibited weak luminescence at 645 nm. Upon reaction with different concentrations of H_2O_2, the luminescence intensity of the complex was increased gradually. In addition, the dose-dependent luminescence enhancement showed a good linearity in the H_2O_2 concentration range of 0–40 μmol/L (Fig. 2B), suggesting [Ru(bpy)$_2$(Luminal-bpy)](PF$_6$)$_2$ can quantitatively detect H_2O_2 by using luminescence methods.

Furthermore, [Ru(bpy)$_2$(Luminal-bpy)](PF$_6$)$_2$ exhibited the good selectivity for H_2O_2. As shown in Fig. 3, the probe did not give any observable luminescence responses to the addition of other ROS/RNS, such as ClO^-, NO_3^-, ·OH, NO, NO_2^-, $ONOO^-$, $^1O_2$ and $O_2^{-\cdot}$, while the luminescence intensity was remarkably increased after [Ru(bpy)$_2$(Luminal-bpy)](PF$_6$)$_2$ was reacted with H_2O_2. These

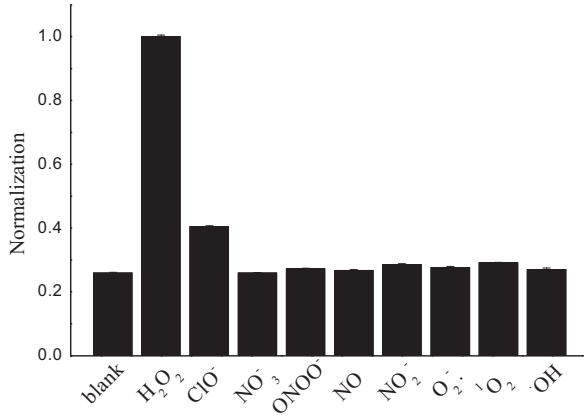

Fig. 3. PL intensities of Ru[(bpy)$_2$luminol-bpy](PF$_6$)$_2$ (10 μmol/L) upon reaction with various ROS/RNS (60 μmol/L) in 25 mmol/L PBS buffer with pH 12.0.

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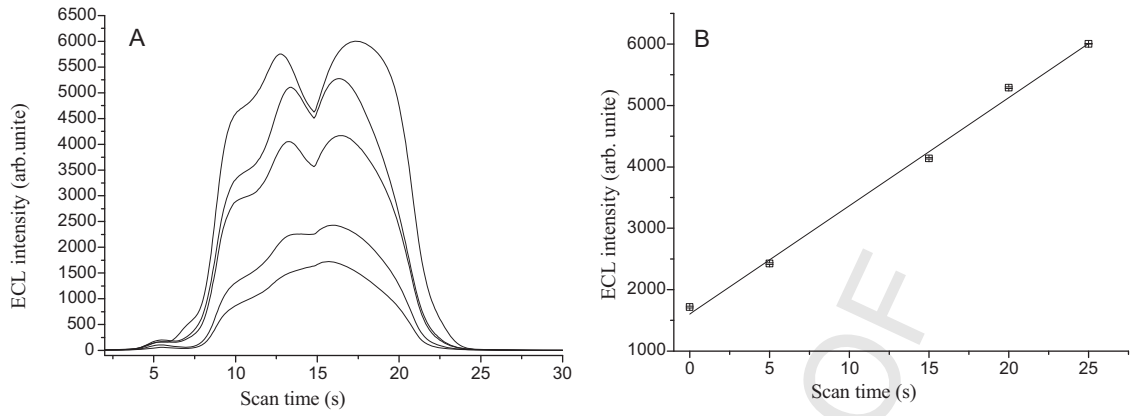

Fig. 4. A. ECL intensity responses of $[Ru(bpy)_2(Luminal\text{-}bpy)](PF_6)_2$ (10 μmol/L) upon addition of H_2O_2 (0–25 μmol/L) and HRP (1.0 μmol/L) at room temperature in 25 mmol/L PBS buffer (pH = 12.0) containing 10 mmol/L of TPrA. Photomultiplier tube voltage: 900 V; B. The calibration curve for the ECL detection of H_2O_2.

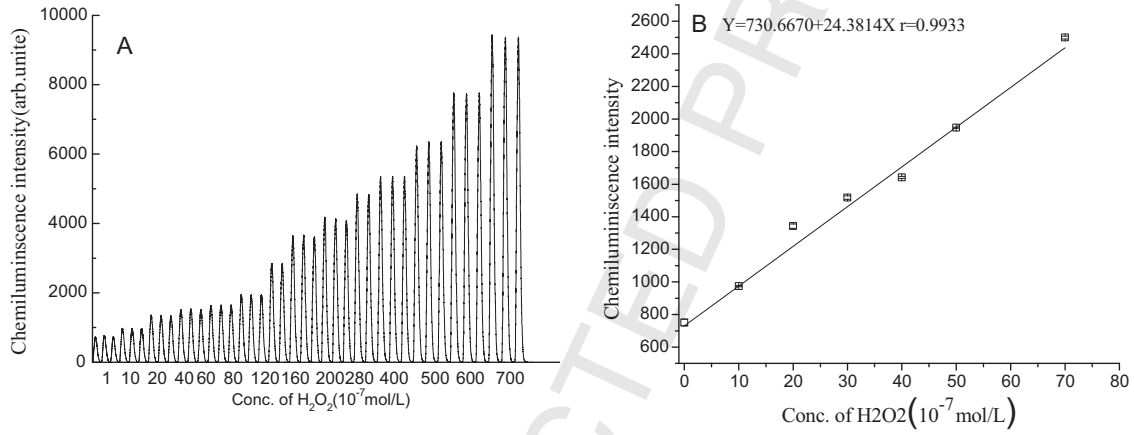

Fig. 5. A. Chemilunminescence spectra of $Ru[(bpy)_2luminol\text{-}bpy](PF_6)_2$ (1.0 μmol/L) upon addition of H_2O_2 (0.1–70 μmol/L) and HRP (1.0 μmol/L) in 25 mmol/L PBS buffer (pH = 12.0); B. The calibration curve for the chemiluminescence detection of H_2O_2.

results demonstrate that the response of the probe to H_2O_2 is highly specific by using luminescence methods.

3.3. ECL measurements for H_2O_2

In the ECL case, the similar phenomenon might also occur since the excited-state electron can be also withdrawn by the electron acceptor group to retain the complex in the ECL-off state, while its ECL behavior should be turned on after the cleavage reaction induced by H_2O_2 and HRP. The ECL intensity of $[Ru(bpy)_2(luminol\text{-}bpy)][PF_6]_2$ was investigated upon addition of different concentration of H_2O_2 in 25 mmol/L PBS buffer (pH = 12.0) containing 10 mmol/L of TPrA. As shown in Fig. 4A, when the cyclic potential was scanned from 0.2 V to 1.8 V and then backed from 1.8 V to 0.2 V, a typical ECL emission from the excited-state of the Ru(II) complex appeared at ~1.27 V, which was increased followed by the increase of H_2O_2 concentration. By plotting the ECL intensity versus the H_2O_2 concentration, a good linear calibration curve with a dynamic range of 0–25 μmol/L was obtained (Fig. 4B). This result indicates that $[Ru(bpy)_2(luminol\text{-}bpy)][PF_6]_2$ can be also used as a ECL probe for the quantitative detection of H_2O_2.

3.4. Chemiluminiscence measurements for H_2O_2

A unique advantage of chemiluminescence detection technique is that can effectively lower the signal-to-noise ratio and improve the sensitivity due to an excitation source is not needed for chemiluminescence detection, and the signal interferences from the background fluorescence that is triggered by an external excitation source can be avoided. The most widely used chemiluminescence system is a luminol/hydrogen peroxide reaction catalyzed by horseradish peroxidase. Here a Ru(II) complex containing a luminal moiety, $Ru[(bpy)_2luminol\text{-}bpy](PF_6)_2$, was evaluated for the chemiluminescence detection of H_2O_2. The chemiluminescence spectra of $Ru[(bpy)_2luminol\text{-}bpy](PF_6)_2$ (1.0 μmol/L) was recorded in the presence of H_2O_2 (0.1–70 μmol/L) and HRP (1.0 μmol/L) in 25 mmol/L PBS buffer (pH = 12.0). As shown in Fig. 5A, upon addition of H_2O_2, chemiluminescence intensity of $Ru[(bpy)_2luminol\text{-}bpy](PF_6)_2$ was clearly increased. The dose-dependent luminescence enhancement followed a good linear relationship with H_2O_2 concentrations in a range of 0–7.0 μmol/L, and a detection limit of 0.6 μmol/L was obtained (Fig. 5B). This result indicates that $Ru[(bpy)_2luminol\text{-}bpy](PF_6)_2$ can be also used as a chemiluminescence probe for the quantitative detection of H_2O_2 at a low micromolar concentration level.

4. Conclusion

In conclusion, a multifunction Ru(II) complex, $[Ru(bpy)_2(Luminal\text{-}bpy)](PF_6)_2$, has been developed as a probe for H_2O_2 by using triple-channel detection. Based on a luminal mioety/hydrogen peroxide reaction catalyzed by horseradish peroxidase, the novel probe can detect H_2O_2 in the three sensing channels including

photoluminescence, chemiluminiscence and eletrochemiluminiscence. The quantitative assays for H_2O_2 in aqueous solutions using $[Ru(bpy)_2(Luminal\text{-}bpy)](PF_6)_2$ were preliminarily established with PL, ECL and CL signal output modes, respectively and its feasibility of practical application was studied on. We believe that the present approach could provide a useful strategy to design and synthesize multifunctional probes for biomolecules.

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