Applications of Carbon Quantum Dots in Electrogenerated Chemiluminescence Sensors

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Abstract

Carbon quantum dots (CQDs) are a new class of carbon nanomaterials with a size lower than 10 nm, and gain more and more attention since the discovery in 2004 due to the specific characteristics such as high solubility, robust chemical inertness, convenient for modification and high resistance to photobleaching. Compared with the traditional semiconductor quantum dots, CQDs have superior biological advantages such as low toxicity and good biocompatibility. Furthermore, CQDs have the excellent electronic properties to work as electron donors and acceptors, making this kind of material a kind of ideal emitters in the electrogenerated chemiluminescence process. In this review, we describe the recent progress in the field of electrogenerated chemiluminescence sensors using CQDs as emitters or enhancers, and in the applications of protein detection, cancer marker measurement and cell counting.

Keywords carbon quantum dots, electrogenerated chemiluminescence

1. Introduction

Carbon quantum dots (CQDs) are a new class of carbon based nanomaterials with a size below 10 nm. The discovery of this kind of material was reported in 2004 [1], during the purification of single-walled carbon nanotubes. Since then, CQDs have been paid more and more attention to from the researchers due to their outstanding characteristics such as facile synthesis, low cost, high solubility, convenient for modification and stability to photobleaching. In contrast to the semiconductor quantum dots, CQDs hold the excellent biological properties such as low toxicity and good biocompatibility, which expand them in the applications in bio-imaging, bio-sensors and drug delivery. Furthermore, CQDs can work as electron donors and acceptors due to their outstanding electronic properties, making them one class of emerging electrogenerated chemiluminescence (ECL) emitters.

Since the synthesis, properties, and applications in bio-imaging, luminescence, and catalysis of CQDs have already been systematically summarized in previous reviews [2-5], we will focus on the applications of CQDs in the electrogenerated chemiluminescence sensors in various applications. In this review, the recent progress of the development in the electrogenerated chemiluminescence sensors for protein detection, cancer marker measurement as well as cell counting using CQDs as emitters or enhancers will be described.

2. Mechanism of ECL from CQDs

The electrogenerated chemiluminescence (ECL), or also described as electrochemiluminescence, is a process in which electrochemically generated intermediates combine and undergo highly energetic electron transfer to produce excited state that emits light. The first reports on ECL emission were published in 1960s [6-8]. Since then, ECL has been quickly developed to be a powerful tool in various analytical chemistry related fields, such as medical diagnostics [9-11], food and water security [12-13], and biological related detection [14-15]. ECL has also been collaborated with various mature analytical methods such as high-performance liquid chromatography (HPLC) [16-17], electrophoresis [18-19] and flow-injection analysis [20-21] with improved analytical performances. The mechanism and applications of ECL have already been summarized in previous reviews [22-24].

There are two kinds of pathways of ECL emission: annihilation pathway and coreactant pathway. In the annihilation pathway, the emitters (e.g. 9.10-diphenylanthracene, DPA) are oxidized and reduced at the surface of the electrode to be the cation radical ($DPA^{\bullet+}$) and the anion radical ($DPA^{\bullet-}$), respectively. The recombination of the cation radical and the anion radical produces the ground state emitter (DPA) and the electronically excited emitter (DPA^{*}), which is not stable and emits photon signals to the ground state [7-8].

In the coreactant pathway of ECL emission, besides the emitter, a coreactant reagent is used in the system to produce the super-oxidative or super-reductive species, which accepts or donates electrons with the reduced or oxidized emitter, to generate the excited state luminophore. One typical example is the $Ru(bpy)_3^{2+}$-tripropylamine (TPA) based ECL [25]. Both $Ru(bpy)_3^{2+}$ and TPA are oxidized on the electrode surface to be $Ru(bpy)_3^{3+}$ and TPA^{+}, and the later undergoes a rapid deprotonation and generates a highly-reductive radical, which donates electron to $Ru(bpy)_3^{3+}$ to produce $Ru(bpy)_3^{2+*}$ with subsequent ECL emission.

The coreactant pathway of ECL emission is often used when the cation radical or the anion radical is not stable, or cannot be formed due to the narrow potential window of the solvent, e.g. in aqueous phase. Most of the ECL sensors for biological targets use the coreactant pathway and CQDs are no exception. The most widely used coreactant in CQDs based ECL is peroxydisulfate ($S_2O_8^{2-}$) [26], and the mechanism is described as follows:

$$CQDs + e^- \rightarrow CQDs^{\bullet-} \quad (1)$$

$$S_2O_8^{2-} + e^- \rightarrow SO_4^{2-} + SO_4^{\bullet-} \quad (2)$$

$$CQDs^{\bullet-} + SO_4^{\bullet-} \rightarrow CQDs^{*} + SO_4^{2-} \quad (3)$$

$$CQDs^{*} \rightarrow CQDs + h\upsilon \quad (4)$$

In step (1) and (2), the reduction of CQDs and coreactant produce the anion radical $CQDs^{\bullet-}$ and the super-oxidative

intermediate $SO_4^{\bullet-}$, and in step (3), the intermediate of the coreactant accepts electron from the anion radical to generate the excited state emitter $CQDs^*$, which in step (4) emit light by relaxation.

Recently Y. Dong *et al.* [27] reported the CQDs-sulfite based ECL emission, with a much more complicated mechanism, as shown in Fig. 1.

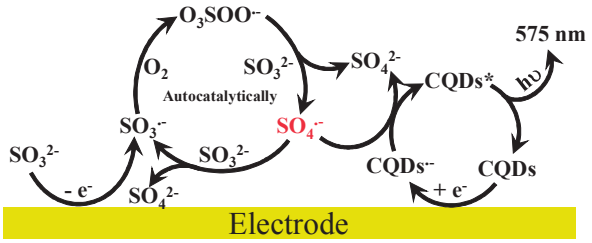

Fig. 1 Schematic diagram of the ECL reaction mechanism of $CQDs\text{-}SO_3^{2-}$ system.

According to the authors' description, in the CQDs-sulfite based ECL system, SO_3^{2-} is firstly electrochemically oxidized to be sulfur trioxide anion free radical ($SO_3^{\bullet-}$) in the anodic polarization process. Then the electrogenerated $SO_3^{\bullet-}$ is involved in a three-step auto-catalytic reaction in the presence of dissolved oxygen, producing sulfate radical ($SO_4^{\bullet-}$). In the subsequent cathodic polarization process, CQDs are electrochemically reduced to negatively charged $CQDs^{\bullet-}$. Finally the electrogenerated $CQDs^{\bullet-}$ species react with the $SO_4^{\bullet-}$ to form the excited state $CQDs^*$, emitting light (575 nm) when coming back to the ground state. Due to the fact that little attention has been paid to the ECL study of CQDs and especially few coreactants have been found to produce ECL signals with CQDs, the authors' study is a great contribution in understanding the reaction mechanisms of CQDs-based ECL.

3. ECL sensor based on CQDs working as label

The first detailed investigations of CQDs-based ECL were reported by L. Zheng *et al.* [28] and H. Zhu *et al.* [29] in 2009, and by Y. Dong *et al.* [26] in 2010. Although CQDs raised more and more attention from the researchers due to their outstanding characteristics, such as high solubility, convenient for modification, high resistance to photobleaching, low toxicity and good biocompatibility, there are limited reports in the applications of ECL sensors using CQDs as emitters [30-41] due to the short period (2010-2015). In this review, we would like to classify these reports in three aspects. The first one is to use the CQDs as labels in the ECL sensors [30-34], which benefits from the high sensitivity and facile in modification. The second type is to use the quenching effect in the ECL emission from the CQDs [35-39], which is extremely useful when the target can competitively react with the CQDs radical. The third type is to use the CQDs as the coreactant in the $Ru(bpy)_3^{2+}$-based ECL system [40-41], which can greatly improve the analytical performance.

W. Liu *et al.* [30] developed a sandwich type ECL sensor for the detection of the cancer antigen 125 (CA125), and the schematic diagram of the system is shown in Fig. 2. In order to increase the surface area of the working electrode, the authors deposited porous Ag onto the paper working electrode (PWE), and the first antibody was physically adsorbed onto the electrode surface. After blocking by BSA and reacting with the antigen, the labeled second antibody was dropped onto the paper working electrode for antibody-antigen reaction. In order to amplify the signal intensity, the amino-functionalized mesoporous silica nanoparticles (NH_2-MSN) were used as the carriers. The rich –COOH groups on the surface of the CQDs were firstly activated by the mixture of EDC/NHS, and then reacted with the $–NH_2$ groups on the NH_2-MSN surface to form the peptide binds. Through the same method, the second antibody was immobilized onto the CQDs surface.

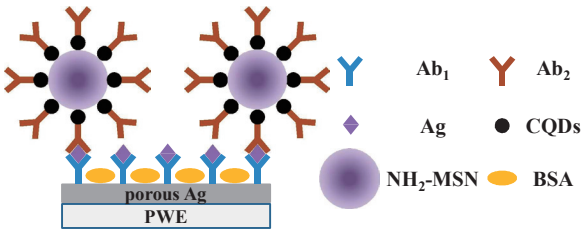

Fig. 2 Schematic diagram of the electrogenerated chemiluminescence sensor for the detection of cancer antigen 125 (CA125).

The ECL intensity was determined by the concentration of the antigen, and by using the NH_2-MSH of high volume-to-surface ratio, the detection limit of the authors' work was 0.0043 Unit/mL, which was much lower than the other reports of the same target (1.3~6.7 Unit/mL). For the human serum samples, the proposed CQDs-based ECL sensor showed a high recovery (97.6~106.2%), indicating the acceptable accuracy of the immunoassay for the detection of CA125 in the clinical samples.

L. Wu *et al.* [31] developed a dual-signal amplification ECL sensor for the detection of the prostate specific antigen (PSA) based on the CQDs working as label. The authors applied the three-dimensional (3D) graphene conjugated with gold nanoparticles (AuNPs) (3D-GR@AuNPs) to modify the glassy carbon electrode (GCE), which provided an effective matrix for antibody immobilization. The nanoporous silver (NPS) with controllable 3D structure could provide a proper platform for high loading of the carbon quantum dots (CQDs), which formed the NPS@CQDs composites as a good ECL label , as shown in Fig. 3.

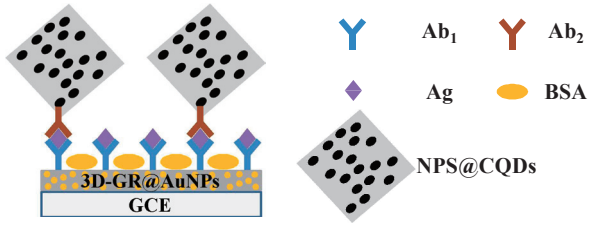

Fig. 3 Schematic representation of the electrogenerated chemiluminescence immunosensor for the detection of PSA.

The good electrical conductivity of 3D-GR@AuNPs and high loading of CQDs of NPS@CQDs composites provided the

significant advantage of the dual-signal amplification technique. The authors' work displayed excellent analytical performance for the detection of PSA in the linear range of 0.0001~50 ng/mL, with the detection limit of 0.0005 ng/mL, which was much lower than the other methods for the same target (0.00072~100 ng/mL). The authors also applied the proposed CQDs based ECL sensor in the detection of human serum samples. Compared with the results obtained from the conventional enzyme-linked immunosorbent assay (ELISA) method, there was no significant difference (relative deviation 2.47~4.03%).

Y. Zhang *et al.* [32] combined the CQDs based ECL with the flow-injection method to develop a multiplexed sandwich immunoassay for the detection of tumor markers (carcino embryonic antigen (CEA), prostate specific antigen (PSA) and α-fetoprotein (α-AFP)).

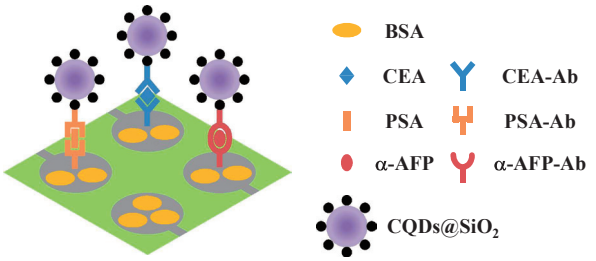

Fig. 4 Schematic diagram of the structure of the electrogenerated chemiluminescence sensor for the detection of CEA, PSA and α-AFP.

As shown in Fig. 4, the authors applied the four-electrode array on the indium tin oxide (ITO) glass, and the three kinds of first antibodies were immobilized onto the electrode by the photo immobilization method. After blocking by BSA, the mixture of the tumor markers was flowed through the electrode surface in a home-made flow cell, followed by the injection of the CQDs@SiO_2 labeled second antibodies. According to the authors, the proposed CQDs based ECL sensor showed a lower detection limit for the 3 targets, compared with the previous reports (CEA: 0.006 ng/mL, PSA: 0.003 ng/mL, α-AFP: 0.005 ng/mL), and the reproducibility and the stability of the sensor were acceptable.

Besides detecting the tumor marker, CQDs based ECL sensor has been applied for the detection of cancer cell. M. Su *et al.* [33] developed an ECL sensor for the ultrasensitive and selective detection of Michigan cancer foundation-7 (MCF-7) human breast cancer cells.

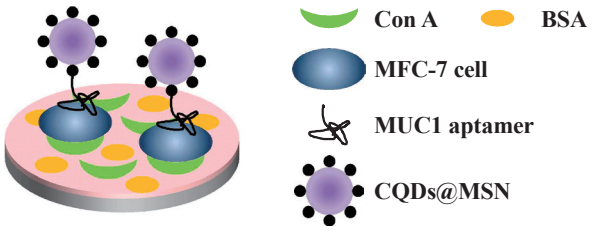

Fig. 5 Schematic drawing of the electrogenerated chemiluminescence sensor for the detection of MCF-7 cancer cell.

As Fig. 5 shows, the authors applied the three-dimensional macroporous graphene to carry gold nanoparticles (3D-GR@AuNPs) on a surface of glassy carbon electrode, and then a matrix of concanavalin A was used to capture the cancer cells due to the specific binding with the mannose oligosaccharides on the cell surface. The CQDs coated mesoporous silica nanoparticles (CQDs@MSN) were used as an excellent label and conjugated with mucin 1 aptamer to specifically bind mucin 1 aptamer on the cancer cells with high stability and bioactivity. The proposed method shows a good analytical performance for the detection of MCF-7 cells ranging within 500~$2*10^7$ cell/mL with a detection limit of 230 cell/mL.

M. Zhang *et al.* [34] developed a disposable ECL sensor for ultrasensitive and selective detection of leukemia cells. As Fig. 6 shows, the screen-printed carbon electrode (SPCE) was prepared on the PVC platform as the working electrode, and in order to increase the surface area, nano porous gold (NPG) was applied on the SPCE surface. The cancer cell was immobilized on the electrode surface by the specifically designed aptamer. A dual-signal amplification method was used to increase the sensitivity. First, the CQDs were immobilized on the surface of the amino-functionalized ZnO nanosphere, through peptide binding by using the EDC and NHS reagents. Second, the CQDs@ZnO was labeled with concanavalin A (con A), which could specifically react with the mannose oligosaccharides on the cancer cell surface. According to the authors, the detection limit of the proposed sensor was as low as 46 cell/mL, in the linear range of $1.0*10^2$ ~ $2.0*10^7$ cell/mL. And an acceptable recovery (91.5%~105.7%) was obtained in the cell detection of human blood samples. The sensor retained significant levels of activity after 10 cycles of regeneration for cell detection in human blood (92% of initial response), which showed a good stability.

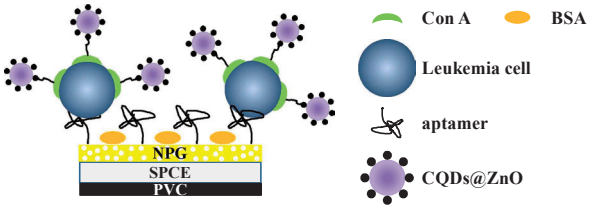

Fig. 6 Schematic diagram of the electrogenerated chemiluminescence sensor for the detection of leukemia cancer cell.

4. ECL sensor based on quenching effect from CQDs

Besides the papers introduced above which used the CQDs as the label benefiting from the low toxicity and good biocompatibility for the detection of tumor markers and cancer cells, some other researchers considered in an opposite direction, which focused on using the quenching effect to the ECL emission from the CQDs [35-39]. J. Li *et al.* [35] published the ECL detection of trace level pentachlorophenol (PCP) using the CQDs in a very simple process, as shown in Fig. 7.

As described in section 2, the recombination of $CQDs^{\bullet-}$ and $SO_4^{\bullet-}$ will produce the excited state $CQDs^*$ with subsequent

ECL emission. When a certain amount of PCP was added into the system, the $CQDs^{\bullet-}$ will also donate electrons to the PCP molecules, as shown in Fig. 7. Obviously, in the existence of PCP in the system, the $CQDs^{\bullet-}$ will be competitively consumed by the $SO_4^{\bullet-}$ and the PCP molecules, which causes quenching in the ECL emission compared with no PCP in the system. According to the authors, a detection limit of $1.3*10^{-12}$ g/L of PCP was obtained in the linear range of 10 pg/L ~ 1.0 μg/L.

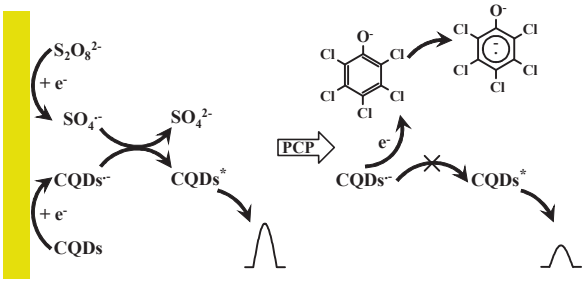

Fig. 7 Schematic showing of the ECL detection of PCP with CQDs in $S_2O_8^{2-}$ solution.

Another group of researchers S. Yang *et al.* [36] developed a similar ECL sensor for the same target, pentachlorophenol, as the indicator for chlorinated phenols in sludge and farmland soil. PCP of different concentrations was, respectively, spiked in real soil samples, including the sludge from a lake and the soil from the local farmland. The testing results of PCP in the sludge and the farmland soil by the proposed method were in good agreement with those achieved by GC/MS, indicating that the ECL sensor could be employed in the identification of the chlorinated phenols in the environment.

Besides the competitive consumption of $CQDs^{\bullet-}$, the antibody-antigen reaction on the surface of the electrode could also quench the ECL emission from the CQDs. T. Han *et al.* [37] synthesized a kind of nitrogen-doped carbon quantum dots (NCQDs). Compared with the pure CQDs, the NCQDs showed a higher and more stable ECL emission under the continuous cyclic voltammetry scan, which was due to that the doped nitrogen atoms on the NCQDs' surface increased the amount of surface traps and accelerated the electron transfer between the electrode and the NCQDs.

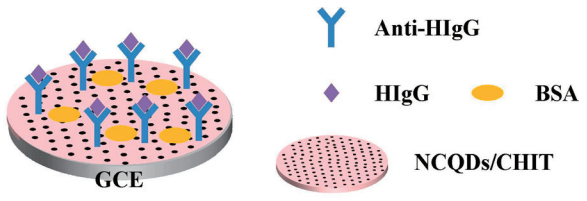

Fig. 8 Schematic illustration of the ECL immunosensor for the detection of HIgG based on NCQDs/CHIT film.

As Fig. 8 shows, the mixture of NCQDs and chitosan (CHIT) was poured onto the surface of glassy carbon electrode (GCE) to form the film to immobilize the NCQDs. Then EDC and NHS were used to activate the –COOH groups on the NCQDs' surface, followed by the formation of peptide binding with the addition of anti-human IgG (anti-HIgG) antibody. After blocking by BSA, the human IgG solution (HIgG) was dropped onto the electrode and incubated for 1 h. According to the authors, the assembled protein layers on the electrode surface could form a barrier for the electron transfer and hinder the diffusion of the ECL coreactant toward the electrode surface. The obtained detection limit of HIgG was 0.05 ng/mL, which was lower than the previous reports due to the good biocompatibility of the NCQDs resulting in improving the immobilization quantity of the antibody.

J. Zhou *et al.* [38] used an aminated graphene to quench the ECL emission from the CQDs to develop an ECL sensor for the detection of α-fetoprotein (α-AFP), as shown in Fig. 9. Similarly, the nitrogen-doped CQDs (NCQDs) and chitosan (CHIT) were used to form a film onto the electrode surface, and the first antibody was immobilized onto the film by using EDC/NHS to form the peptide binding. After blocking by BSA and incubating with the antigen, the animated graphene (NH_2-GR) labeled second antibody was dropped onto the electrode for incubation. Due to the ECL resonance energy transfer (ERET), the ECL emission from the NCQDs was quenched, which was determined by the concentration of the antigen. According to the authors, a good analytical performance was obtained from the proposed ECL sensor, which detection limit is 3.3 pg/mL in the linear range of 0.01~100 ng/mL. And the proposed sensor showed good stability, acceptable selectivity and reproducibility.

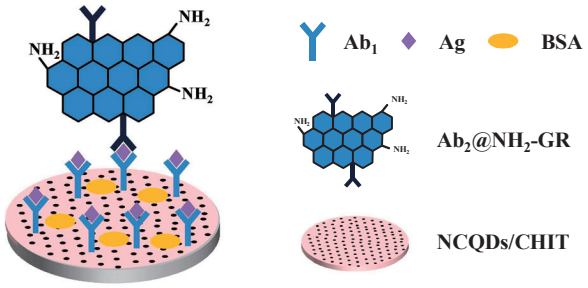

Fig. 9 Schematic illustration of the ECL sensor for the detection of α-AFP.

5. ECL sensor by using CQDs as coreactant

In the section 4 and 5, the CQDs are used as the emitter in the system, and peroxydisulfate ($S_2O_8^{2-}$) is used as the coreactant to produce the highly-oxidative intermediate ($SO_4^{\bullet-}$) to react with the CQDs radical ($CQDs^{\bullet-}$) to generate the excited state emitter ($CQDs^*$) with the subsequent ECL emission. On the other hand, the CQDs can also play the role of coreactant to assist the ECL emission from $Ru(bpy)_3^{2+}$ explained by the limited reports [42], and two groups of researchers developed the ECL sensor based on the $Ru(bpy)_3^{2+}$-CQDs system [40-41].

Z. Xu *et al.* [40] developed an ECL sensor for the detection of $Ru(bpy)_3^{2+}$ by using the CQDs as the coreactant in the system. According to the authors, the mechanism of the ECL emission can be expressed as follows:

$$Ru(bpy)_3^{2+} - e^- \rightarrow Ru(bpy)_3^{3+} \quad (5)$$

$$CQDs + e^- \rightarrow CQDs^{\bullet-} \quad (6)$$

$$Ru(bpy)_3^{3+} + CQDs^{\bullet-} \rightarrow Ru(bpy)_3^{2+*} + CQDs \quad (7)$$

$$Ru(bpy)_3^{2+*} \rightarrow Ru(bpy)_3^{2+} + h\upsilon \quad (8)$$

Where $Ru(bpy)_3^{2+}$ is oxidized on the working electrode to generate $Ru(bpy)_3^{3+}$, and the CQDs are reduced on the counter electrode to generate the $CQDs^{\bullet-}$. The recombination of $Ru(bpy)_3^{3+}$ and $CQDs^{\bullet-}$ will produce the excited state $Ru(bpy)_3^{2+*}$ with subsequent ECL emission. According to the authors, the detection limit of $Ru(bpy)_3^{2+}$ could be as low as 0.43 μM with a good stability.

L. Li *et al.* [41] focused on the $Ru(bpy)_3^{2+}$-CQDs based ECL emission to develop a sensor for the detection of bisphenol A (BPA). The authors suggested that the oxidized product of BPA, 2,2-bis(4-phenylquinone) propane, could react with the excited state $Ru(bpy)_3^{2+*}$ through electron transfer so that the ECL emission would be quenched if a certain concentration of BPA was added into the system, as shown in Fig. 10. The ratio between the ECL intensity to the initial ECL intensity was determined by the concentration of BPA in the system, and a linear relationship was obtained from 0.03 to 1.0 μM, with a detection limit of 10 nM. The analytical performance of the proposed ECL sensor was comparable to some recently developed sensors, but in comparison with the traditional chromatography (HPLC) or spectroscopy (FL, CL and SERS), the detection limit of the proposed system was not very low. The authors pointed out that the advantage of their work was that the system was relatively stable, time-saving and simple, which avoided complex preparation and modification process. The analytical performance could be expected to be improved by combining with traditional chromatography method such as HPLC or CE.

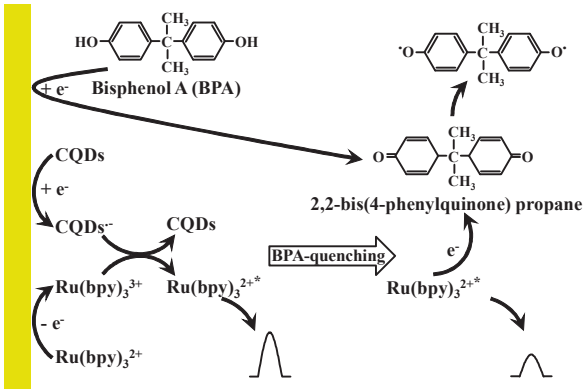

Fig. 10 The possible enhancement mechanism by NCQDs and the quenching mechanism by BPA in the $Ru(bpy)_3^{2+}$ based ECL system.

6. Conclusion

In this review, we summarized the applications of the carbon quantum dots (CQDs) in the electrogenerated chemiluminescence (ECL) sensor for the protein detection, cancer marker measurement, cell counting and so on. The CQDs have low toxicity and good biocompatibility, making this new carbon based nanomaterial a rising star in the biological related fields. The ECL sensor has become a power tool in the analytical chemistry, due to the high intensity, good controllability and avoided light scattering effect since no light source is needed in the system. The combination of CQDs and ECL has a broad prospect in the biochemical related fields, and it is certain that more and more attention will be focused on the CQDs-based ECL sensor.

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