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The electrochemical applications of quantum dots

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As newly developed inorganic materials, semiconductor nanocrystals (NCs), or quantum dots (QDs), have received considerable attention because of their unique nano-related properties including high quantum yield, simultaneous excitation with multiple fluorescence colors, and electrochemical properties. This review presents a general description of the electrochemical properties of QDs with their electrochemical applications including indirect and direct effects. The fields of inorganic substance analysis, organic analysis, immunoanalysis, DNA analysis and aptamer analysis are discussed in detail.

1 Introduction

QDs are nanostructured materials which mainly comprise the elements from the periodic groups II–VI, III–V and IV–VI; they are also known as zero-dimensional materials.[1] They are defined as semiconductor structures with physical dimensions that are smaller than the excitation Bohr radius (an excitation is an electron–hole pair).[2] Originating from their size confinement and anisotropic geometry, QDs not only inherit the excellent properties of bulk semiconductor metal oxides, but also exhibit novel piezoelectric,[3] optoelectric,[4] photochemical,[5] magnetic,[6] and catalytic properties,[7] *etc*. These excellent properties endow QDs with attractive applications in various fields like photochemical reagents,[8] solar cells,[9] light emitting diodes,[10] and catalysis.[11] In 1998, Alivisatos's[12] and Nie's[13] groups simultaneously demonstrated that the water-soluble and biocompatible QDs could be prepared by appropriate surface modification, which opened a new field for the QD biosensing applications.[14] Since then, research on the synthesis and applications of QDs has received considerable attention.

However, most of the traditional QDs are made of heavy metal ions (*e.g.*, Cd^{2+}), which may result in potential toxicity that hampers their practical applications. Therefore, systematic cytotoxicity research of QDs is of critical importance for their practical biological and biomedical applications, and a large number of studies have been carried out for this purpose.[15–17] During the synthesis process, the synthetic methods and surface modifications of quantum dots will greatly affect their biotoxicity. QDs prepared *via* the organometallic route and aqueous route have quite different surface properties. In contrast to the presence of hydrophobic ligand molecules on the surface of organic QDs, the surface of aqueous QDs is covered with a large amount of hydrophilic molecules.[17] This difference in surface properties could induce distinct cytotoxicity and *in vivo* behaviors. The surface modifications of

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quantum dots could also greatly affect their interaction with the cellular membrane and the subsequent uptake into the cells. Taking CdSe as an example, a common surface modification to reduce the cytotoxicity of the core material is coating with a ZnS shell. On the one hand, the additional shell semiconductor layer could increase the QDs' photoluminescence. On the other hand, the ZnS shell protects the core CdSe from oxidation and other environmental factors that contribute to cadmium release. Besides, ligands with terminal carboxylic acid, hydroxyl, or amine groups have been used as charged surface coatings for the QD protection, which could effectively prevent the core oxidation, cell death, and inflammatory responses.

Another important problem, concerning the clearance of these nanoparticles from the body, has attracted more and more attention. When employing a living mouse for the *in vivo* imaging study by QD injection, Ballou *et al.*[18] found that methoxy-terminated poly(ethylene glycol) amine QDs (mPEG-QDs) remained for at least one month in the liver, lymph nodes, and bone marrow. Therefore, the use of QDs *in vivo* must be critically examined.

Considering these biotoxicities, various new kinds of QDs have emerged in recent years such as silicon QDs,[19] carbon dots,[20] and graphene QDs.[21] Owing to their special cadmium free property, excellent biocompatibility and environmental friendliness, these novel nanomaterials have gained significant consideration after being successfully prepared.

Our group has reviewed the preparation of QDs, their electrochemiluminescent behaviors,[22] fluorescent behaviors, cytotoxicity, and their biosensing and bio-imaging applications.[23] The aim of this review is focused on the electrochemical properties of QDs with the electrochemical applications in inorganic substance analysis, organic analysis, immunoassay, aptasensing assay, and solar cells. Different techniques utilized by different groups are discussed in detail.

2 The electrochemical behavior of QDs

The electrochemical behavior of QDs revealed quantized electronic behavior as well as decomposition reactions upon reduction and oxidation. In 2001, Bard *et al.* fully investigated the direct correlation between the electrochemical band gap and the electronic spectra of CdS QDs in *N*,*N*′-dimethylformamide (DMF).[24] Their research revealed that CdS QDs could act as multi electron donors or acceptors at a given potential due to trapping of holes and electrons within the particle. On the other hand, the surface structure of QDs also plays a key role in determining the properties of the particles. Unpassivated surface atoms can form electronic traps for electrons and holes. Later, Bard's group studied the differential pulse voltammetric (DPV) behavior of trioctylphosphine oxide (TOPO)-capped CdTe QDs in dichloromethane and a mixture of benzene and acetonitrile (Fig. 1).[25] The DPV of TOPO-capped CdTe NPs had the band gap of about 2.1 eV and two discrete anodic peaks which resulted from diffusion of NPs in solution. One large anodic peak at 0.7 V was attributed to a multielectron reaction, and the other anodic peak appeared because of the oxidation of reduced species. Gao *et al.*[26] and Greene *et al.*[27] reported the

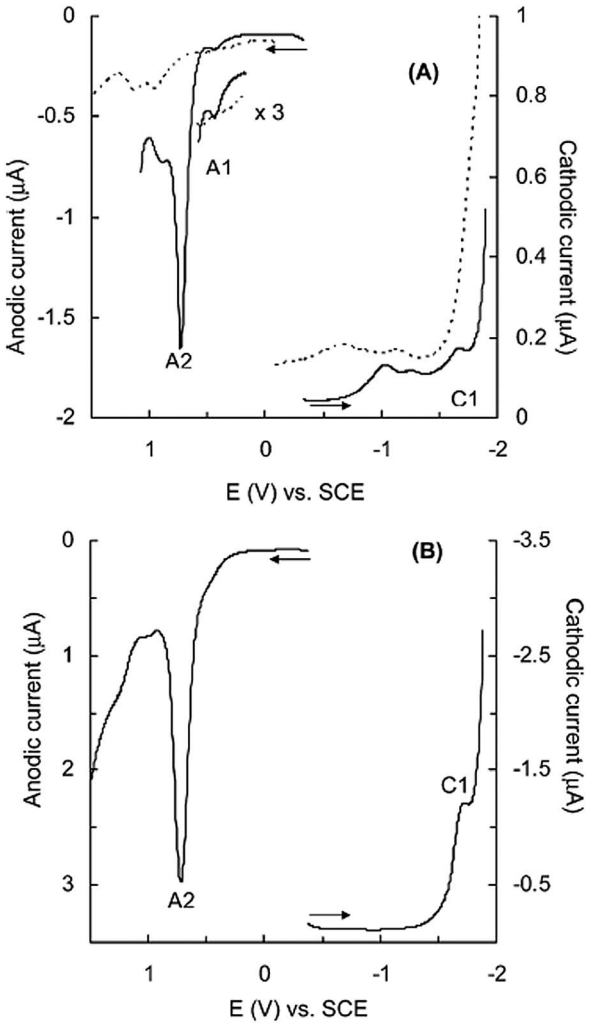

Fig. 1 DPV of two different batches of CdTe NPs at a 0.06 cm^2 Pt working electrode with scan toward positive or negative potentials. (A) 9.6 μM CdTe NPs in 5 : 1 (v/v) benzene/acetonitrile containing 0.1 M TBAP. (B) 32 μM CdTe NPs in CH_2–Cl_2 containing 0.1 M $TBAPF_6$. Reproduced with permission from ref. 25. Copyright 2004, American Chemical Society.

voltammetric current peaks of QDs in an aqueous solution and concluded that the electrochemical band gap was located at potentials inside the valence band edge, which was explained by hole injection into the surface traps of the particles.

To deeply understand the QDs' electrochemical properties, a full investigation into the effects of different parameters on the QDs' electrochemical response was needed, which included the QDs' size, the capping stabilizer, the value of pH, and the coexisting chemicals. Given the fact that cyclic voltammetry (CV) is very sensitive to the nanocrystalline surface state and could provide complementary information for a better understanding of the special size-dependent properties of semiconductor QDs, the size effect on the reduction and oxidation potentials was studied *via* CV in an aqueous buffer solution with the thiol-capped CdTe QDs as the subject.[28] CV studies of CdTe in an aqueous solution demonstrated that the size effect on the reduction and oxidation potentials could be attributed to the energetic band positions owing to the quantum size effect. In

contrast to a prediction based on the quantum size effect, the oxidation peak moves to a more negative potential as the nanocrystalline size decreases.

By using the mercaptopropionic acid (MPA) capped CdTe QDs as the object, the effects of the capping stabilizer, the value of pH, and coexisting chemicals on the electrochemical responses of QDs were investigated in detail *via* DPV.[29] Three DPV peaks (A1 at 0.36, A2 at 0.68 and A3 at 0.84 V) could be observed in the MPA-capped CdTe QD solution, which indicated that three electrochemical processes existed in the single scan. And the conclusions could be presented as follows:

• Different stabilizers showed little effects on the existence of A1.

• The value of pH showed an important effect on the DPV response of the MPA-capped CdTe QDs. A1 only existed in a pH range from 5.2 to 8.0 with the maximum response at pH 6.0. A2 and A3 merged with each other simultaneously at pH 6.6, and became one peak completely with a pH value higher than 7.0.

• Coexisting chemicals showed different effects on the DPV response of the MPA-capped CdTe QDs. Electroinactive chemicals, like chlorobenzene, showed little effect on DPV response. ECL coreactants, such as oxalic acid, hydrogen peroxide and persulfate, also showed little effect on the A1 process. Magnesium nitrate could dramatically suppress all the processes (A1, A2 and A3), while potassium nitrate had little effect on A1.

Recently, Amelia *et al.*[30] systemically summarized the electrochemical properties of CdSe and CdTe QDs. By using the most common electrochemical methods such as voltammetric methods and spectroelectrochemistry, they fully investigated the electrochemical studies of core and core–shell semiconductor nanocrystals of spherical shape. Representative studies were carried out taking CdSe and CdTe as examples. Different techniques by different groups were compared in order to attempt an interpretation of sometimes contradictory results.

As a new type of QDs, graphene QDs have been widely studied. In 2004, Compton and co-workers[31] fully investigated the electrochemical characteristics of highly ordered pyrolytic graphite (HOPG) and found that the edge plane sites/defects of the HOPG were the predominant electrochemically active sites. Later, Daniel's group and Robert's group studied the electrochemical behavior of monolayer graphene sheets, respectively, and the results were both published in ACS Nano sequentially. Daniel's[32] group first performed electrochemical studies of individual monolayer graphene sheets derived from both mechanically exfoliated graphene and CVD graphene. They concluded that the electron transfer rates of graphene electrodes are more than 10-fold faster than the basal plane of bulk graphite, which could be attributed to the presence of corrugations in the graphene sheets. By investigating the electrochemical properties of CVD-grown graphene electrodes in FcMeOH electrolyte at different scan rates, they found that the effective surface area of the graphene electrode was less than the geometric area of this electrode, indicating that the redox reactions occurred predominantly on a clean graphene surface. The kinetic parameter of ΔE_p (after appropriate resistance correction) ranged from 68.6 to 72.6 mV and increased at a higher scan rate, indicative of quasi-reversible kinetics in the system, which was directly proportional to the reciprocal of the square root of the scan rate, $\nu^{-1/2}$ (Fig. 2).

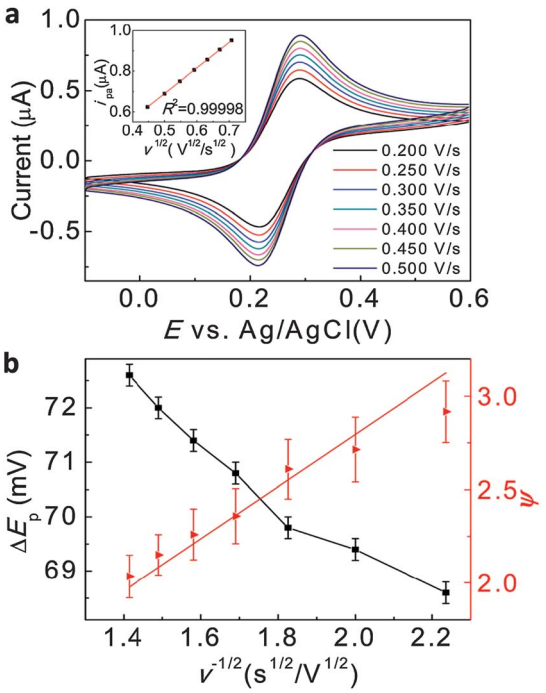

Fig. 2 Electrochemistry at a CVD graphene electrode. (a) Cyclic voltammograms of FcMeOH (1 mM) in H_2O/0.1 M KCl measured at a CVD graphene electrode at different potential scan rates. Inset: plot of the anodic peak current (i_p) *versus* the square root of the potential scan rate ($v^{1/2}$). (b) Peak separation ΔE_p and Nicholson's kinetic parameter ψ *versus* the reciprocal of the square root of the potential scan rate ($v^{-1/2}$). A linear fit is used to determine the standard heterogeneous charge transfer rate constant (k^0). Reproduced with permission from ref. 32. Copyright 2004, American Chemical Society.

Afterwards, Robert's group[33] researched the electrochemical properties of the exfoliated single and multilayer graphene flakes to measure the rate constant for electron transfer. Mechanically exfoliated graphene flakes were deposited on silicon/silicon oxide wafers to make the masked graphene/graphite samples as the working electrode. They found that both multilayer and monolayer graphene microelectrodes showed quasi-reversible behavior during voltammetric measurements in potassium ferricyanide. More detailed descriptions about the electrochemical behavior of graphene are beyond the scope of this review, and interested readers may refer to ref. 34.

3 Indirect applications in bioanalysis

Owing to their inherent electrochemical properties and their miniaturization, low cost, low power requirements, as well as excellent biocompatibility, QDs could be used as active labels for electrochemical biosensors.[35–40] By immobilizing hemoglobin (Hb) in a water-soluble CdSe–ZnS QD film on a glassy carbon electrode, the direct electrochemistry of Hb could be obtained.[35] Hb immobilized in the QD film retained its biological activity and gave sensitive electrochemical reduction signals involving reactions with NO and H_2O_2. The reduction

peak potential of NO located at 20.80 V exhibited a linear relationship with the NO concentration in the range of 0.18–4.32 μM ($R = 0.998$). The same result was obtained for H_2O_2 in the range of 6.3–35.28 μM ($R = 0.995$).

Similarly, Li's group[41] constructed an organized multicomponent hybrid material of mesoporous cellular foam silicate (MCFs) and quantum dots (QDs). The MCF material was firstly functionalized with a high density of amino groups by a post-synthesis method. Thioglycolic acid-stabilized CdTe QDs could then assemble in the mesopores of amino-functionalized MCFs. When the prepared composite was used as the matrix to immobilize myoglobin (Mb), it showed satisfactory biocompatibility and a large surface area, thereby enabling the immobilized Mb with good bioactivity without denaturation. The QD-MCFs provided a biocompatible microenvironment for the entrapped Mb to achieve direct electron transfer. The high surface to volume ratio and the corresponding high surface energy of CdTe QDs could result in a strong interaction between Mb and QDs, which probably allow the protein to obtain a more favorable orientation. When the system was used for H_2O_2 detection, the linear range of 2.5–60 μM was achieved with a detection limit of 0.7 μM ($S/N = 3$) (Fig. 3).

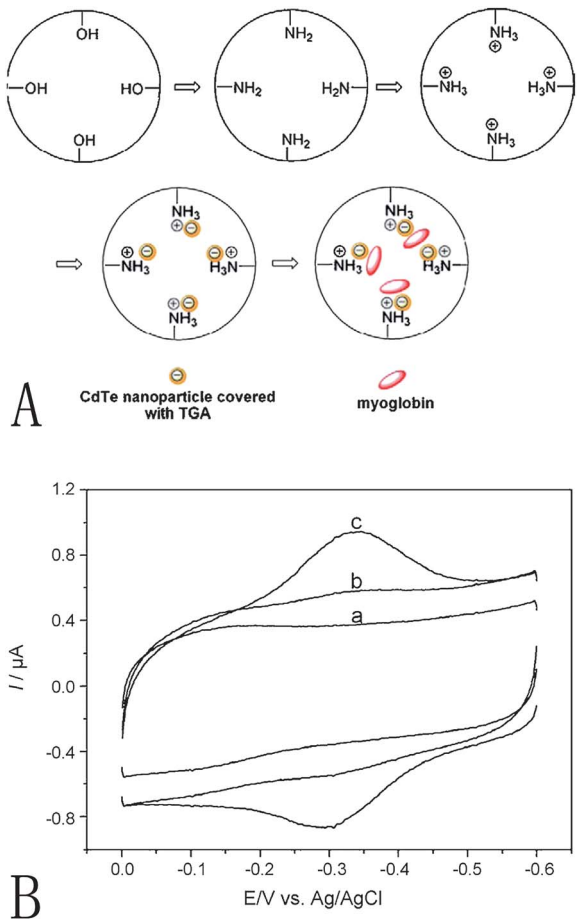

Fig. 3 (A) Process of fabricating Mb–QD–MCF hybrid material. (B) CV of MCF/GC (a), Mb–MCF/GC (b) and Mb–QD–MCF/GC (c) electrodes in a 0.1 M PBS solution (pH 7.0). Reproduced with permission from ref. 41. Copyright 2011, American Chemical Society.

Other enzymes like glucose oxidase (GOD) and acetylcholinesterase (AChE) were also employed to investigate the electrochemical properties of QDs. GOD adsorbed on CdS QDs maintained its bioactivity and structure, and could catalyze the reduction of dissolved oxygen, which resulted in a great increase in the reduction peak current.[36] By effectively entrapping GOD into the Nafion–CdTe–CNTs composite matrix, the direct electron transfer of GOD can be obtained and the immobilized GOD retained its bioactivity.[37]

Since gold nanoparticles (GNPs) have shown widespread use particularly for constructing electrochemical biosensors through their high electron-transfer ability, Du *et al.*[38] constructed a novel acetylcholinesterase (AChE) biosensor by modifying a glassy carbon electrode with CdTe QDs and GNPs through chitosan microspheres to immobilize AChE. The combined AChE retained its bioactivity and exhibited high affinity to its substrate of monocrotophos. The combination of CdTe QDs and GNPs not only favored the interface enzymatic hydrolysis reaction to form an electroactive substance, which increased the sensitivity and facilitated the amperometric response of the biosensor, but also prevented enzyme molecules from leaking out of the electrode through covalent binding of Schiff bases. The synergistic effect between the CdTe QDs and GNPs promoted electron transfer and catalyzed the electro-oxidation of thiocholine. This novel biosensing platform based on the CdTe QD–GNP composite responded even more sensitively than that on CdTe QDs or GNPs alone. The inhibition of monocrotophos was proportional to its concentration in two ranges, from 1 to 1000 ng mL^{-1} and from 2 to 15 μg mL^{-1}, respectively, with a detection limit of 0.3 ng mL^{-1}.

In recent years, graphene as a new class of two-dimensional nanomaterial has attracted considerable attention. The excellent electronic transfer rate, single-layered structure and good biocompatibility endow graphene with great potential applications in the field of electro-catalytic bio-devices.[42–44] Wang's group[45] reported on the utilization of a graphene–CdS nanocomposite as a novel immobilization matrix for the immobilization of GOD. The nanocomposite could provide a unique microenvironment for the direct electrochemistry of GOD, and the immobilized GOD on the modified electrode possessed its native structure and electrocatalytic activities. In comparison with the graphene sheets and CdS nanocrystals, the graphene–CdS nanocomposites exhibited excellent electron transfer properties for GOD with a rate constant (k_s) of 5.9 s^{-1} due to the synergistic effect of graphene sheets and CdS nanocrystals. Based on the electrocatalytic response of the reduced form of GOD to dissolved oxygen, the obtained glucose biosensor displays a satisfactory analytical performance over an acceptable linear range from 2.0 to 16 mM with a detection limit of 0.7 mM.

In our group, a series of graphene QDs (GQDs) and their nanocomposites were synthesized and used in electrochemical applications. Different from the route of traditional nanolithography and the chemical breakdown of graphene oxide (GO), we produced GQDs with different size distributions in scalable amounts with acidic exfoliation and etching of carbon fibers.[46] The stacked graphitic submicrometer domains of the

fibers could be easily broken down during the acid treatment and chemical exfoliation of traditional pitch-based carbon fibers. The size of the as-prepared GQDs varies with the reaction temperature, and the emission color and the bandgap of GQDs can be controlled accordingly. Owing to its good biocompatibility, high water solubility and low toxicity, GQD and its composite were employed to fabricate different kinds of biosensors. In 2012, graphene–CdS (GR–CdS) nanocomposites were prepared in a one-step synthesis in an aqueous solution. GO was simultaneously reduced to GR during the deposition of CdS. The heteronanostructure of the as-prepared GR–CdS nanocomposite films could facilitate the spatial separation of the charge carriers, which endows the nanomaterial with excellent electron transport properties. When used for the fabrication of an advanced photoelectrochemical cytosensor, the GR–CdS nanocomposite based biosensor showed a good photoelectronic effect and cell-capture ability, and had a wide linear range and low detection limit for Hela cells.[47] Later, another composite of anatase TiO_2–graphene (ATG) nanocomposites was synthesized *via* a one-step approach using titanium(III) ions as the reductant and titanium source in an aqueous solution.[48] The high surface area, excellent conductivity and sufficiently functional groups enable the ATG nanocomposites to be favourable for fabricating biosensors. When used for hemoglobin (Hb) immobilization, it could realize the enhanced direct electron transfer (DET) of Hb, and the Hb–ATG nanohybrid exhibited good electrocatalytic activity toward the reduction of H_2O_2.

4 Direct applications in bioanalysis

The metal components of the QDs could yield well-resolved and highly sensitive stripping voltammetric signals for the corresponding targets. Given the fact that their concentrations were low in the solvent, it is difficult for QDs themselves to obtain good electrochemical behavior.[25] Most applications are based on the traditional electrochemical techniques of the square wave anodic stripping voltammetric technique (SWASV) and differential pulse voltammetry (DPV), *etc*. Compared to cyclic voltammetry (CV), SWASV and DPV could ignore the background charging current and obtain the better resolved voltammograms from NPs with a small current scale. QDs such as ZnS,[49] PbS,[50] and CdS[51,52] are particularly attractive for such bioassays in view of the stripping behavior of their metal ion components.

4.1 Small molecule analysis

Inorganic small molecules, especially metal ions, are widely detected *via* square wave voltammetry. Here, we take the lead detection as an example for the description of QD-based electrochemical detection. Based on the fact that the DNAzymes can catalyze many chemical and biological reactions and the catalytic activities of the DNAzymes can be regulated by specific metal ion co-factors, Yuan *et al.*[53] designed a highly sensitive DNAzyme-based sensor for electrochemical monitoring of lead. With layer-by-layer assembled PbS QDs as signal amplification labels, the fabricated sensor could release numerous ions upon acid dissolution and dramatically enhance the current response, leading to subnanomolar sensitivity for Pb^{2+}. A dynamic range from 1 to 1000 nM with a detection limit of 0.6 nM was obtained under the optimal conditions. In order to further improve the sensitivity, Zhang[54] introduced the rolling circle amplification (RCA) process as a signal amplification tool. In this strategy, the DNAzyme catalytic strands were firstly immobilized onto the surface of magnetic beads and then hybridized with substrate strands. In the presence of Pb^{2+}, the DNAzyme could be activated to cleave the substrate strand into two DNA fragments. After the RCA reaction, a long ssDNA product with repeating sequences was obtained. Subsequently, CdS QD modified ssDNA (CdSQD-ssDNA) was used as a signaling probe to hybridize with the long ssDNA product. Due to the dramatic signal amplification by the numerous QDs and the low background signal by magnetic separation, an ultra-low level (7.8 pM) of Pb^{2+} could be detected.

Besides the traditional analytical assays, a multi-channel screen-printed carbon electrochemical array was employed in a QD-based electrochemical biosensor. By using CdSe/ZnS QD labeled biotin as the probe, García's group[55] designed a sensitive electrochemical biosensor for biotin determination. Individual screen-printed carbon electrodes (SPCEs) and 8-channel screen-printed carbon electrochemical arrays (8xSPCEs) were modified with streptavidin and used for incubation with QD labeled biotin (biotin-QD). After the biological reaction, Cd^{2+} ions released from the dissolution of the QDs were determined *in situ* by voltammetric stripping. A linear range of 1×10^{-9}–1.2×10^{-8} M and a limit of detection of 3×10^{-10} M (in terms of QD) were obtained (8.5% RSD, $n = 3$) for 8xSPCEs. The use of screen-printed carbon electrodes with the *in situ* detection of quantum dots provides an excellent platform for the development of electrochemical biosensors. This simple and fast procedure allows us to perform simultaneous multi-analysis and to get a large amount of data in a short time (Fig. 4).

In 2003, Wang *et al.* firstly employed the multi-target electrochemical biosensor *via* the utilization of different QD codes for DNA detection, which will be discussed in detail later. Based on this strategy, Tang's group[56] designed a novel multiplexed stripping voltammetric immunoassay protocol for the simultaneous detection of multiple biomarkers. With polyamidoamine dendrimer-metal sulfide QD nanolabels as distinguishable signal tags and trifunctionalized magnetic beads as immunosensing probes, CdS, ZnS and PbS QDs were utilized for the labeling of polyclonal rabbit anti-CA 125, anti-CA 15-3 and anti-CA 19-9 detection antibodies, respectively. A sandwich-type immunoassay format was adopted for the simultaneous determination of target biomarkers in a low-binding microtiter plate. Experimental results indicated that the multiplexed immunoassay enabled the simultaneous detection of three cancer biomarkers in a single run with wide dynamic ranges of 0.01–50 U mL^{-1} and a limit of detection (LOD) of 0.005 U mL^{-1}.

4.2 Immunoanalysis

By using the bio-immunological reaction between the antigen and antibody for analytical purposes, immunoassays have been

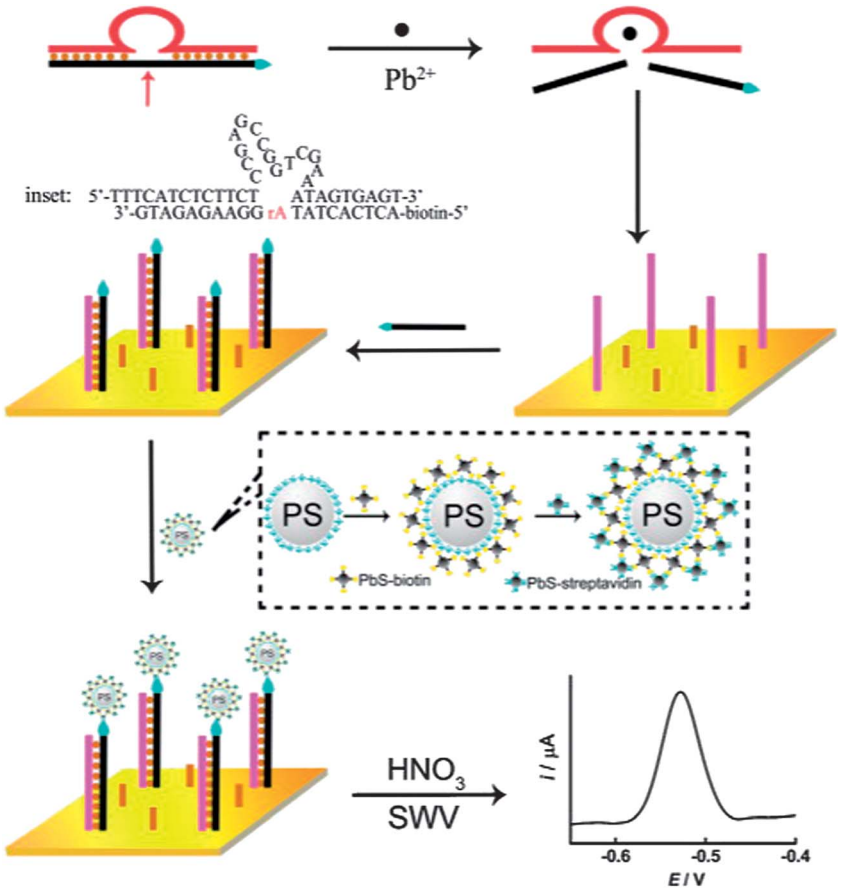

Fig. 4 The structure of Pb^{2+}-specific-DNAzyme ("8–17" DNAzyme) and principle of the DNAzyme-based assay for Pb^{2+} detection. Reproduced with permission from ref. 53. Copyright 2011, Elsevier.

successfully applied in many fields ranging from food safety,[57] environmental protection[58] to clinical treatment.[59,60] Combined with the excellent merits of high sensitivity, fast response and low detection limit, electrochemical immunosensors have received considerable attention. A series of sandwich-type immunosensors were fabricated with the electrochemical signal of labeled QDs as readout.[61] The typical scheme could be illustrated as follows: the first antibodies (Ab1) were immobilized on the substrate, followed by the immunoreaction of the antigen (Ag) with Ab1. Lastly, QD labeled Ab2 (the second antibodies) was reacted with the combined Ag. The concentration of the target antigen was detected indirectly by the electrochemical signal response to the labeled QDs.

With CdS@ZnS QDs as labels for the immunodetection of human IgG (HIgG),[62] the captured QD labels in the test zone could be determined by the highly sensitive stripping voltammetric measurements of the dissolved metallic component (cadmium) with a disposable screen-printed electrode, which is embedded in the membrane on the test zone. It opens a new door to the application of highly sensitive electrochemical immunosensors and immunoassays. Latterly, our group[63] constructed a sandwich-type immunosensor using CdTe quantum dots as electrochemical labels for the sensitive detection of HIgG. With gold nanoparticles as a signal amplifier and the SWASV signal of the dissolved cadmium ions as signal readout, the linear range of this immunosensor was 0.005–100 ng mL^{-1} with a detection limit of about 1.5 pg mL^{-1}. What's more, the immunosensor showed good precision, high sensitivity, and acceptable stability, and could be used for the detection of real samples with consistent results in comparison with those obtained by the ELISA (enzyme-linked immunosorbent assay) method (Fig. 5).

Other types of cadmium compound QDs, like CdSe[64] and CdTe,[65] are also widely used as labels in the immunosensor field. With CdSe QDs bonded to the secondary antibody and with microtiter plates as a readout platform,[64] the Cd^{2+} concentration of the labeled QDs could be measured, which could indirectly potentiometrically bioanalyse the target proteins in a microtiter plate format with a detection limit lower than <10 fmol. This provided a new route to further reduce the final detection volume and lower the detection limit of such potentiometric bioassays in terms of total analyte mass to an even larger extent.

By employing the core–shell structural QDs of CdSe/ZnS as the protein biomarker, the electrochemical biosensors for phosphorylated bovine serum albumin (BSA-OP)[66] and interleukin-1α (IL-1α)[67] were fabricated by Lin's group successively. In the BSA-OP detection, the QDs were used as labels for amplifying electrochemical signals and were conjugated with a secondary anti-phosphoserine antibody in a heterogeneous

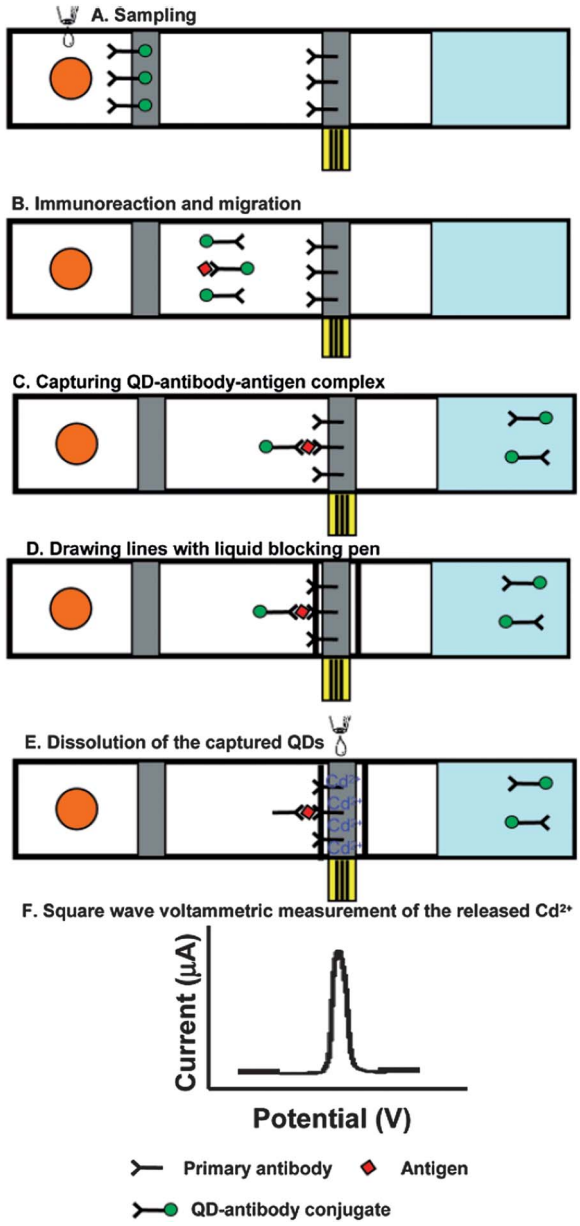

Fig. 5 Measurement principle of the disposable electrochemical immunosensor diagnosis device (DEIDD). Reproduced with permission from ref. 62. Copyright 2007, American Chemical Society.

sandwich immunoassay. After the bound QD was dissolved in an acid dissolution step, its concentration was detected by electrochemical stripping analysis, and the measured current responses were proportional to the concentration of BSA-OP. Under optimal conditions, a voltammetric linear response to BSA-OP over the range of 0.5–500 ng mL^{-1} was achieved with a detection limit of 0.5 ng mL^{-1}.

4.3 DNA analysis

DNA analysis is associated tightly with tissue matching, genetic diseases and forensic applications in molecular diagnostics.[68,69] Sensitive detection of specific nucleic acid sequences on the basis of the hybridization reaction is the key point for various applications including clinical diagnosis, environmental control, and forensic analysis.[70] Given the fact that the QDs have excellent biocompatibility, they play an important role in DNA analysis.[71]

In order to fully investigate the interaction between the QDs and the DNA, an electroactive dsDNA indicator of $Co(phen)_3^{3+/2+}$ (phen = 1,10-phenanthroline) was used to measure the dissociation behavior of double stranded DNA (dsDNA) *via* the electrochemical technique.[72] It was found that $Co(phen)_3^{3+/2+}$ was more easily dissociated from a dsDNA modified gold electrode in the presence of CdTe QDs. In relatively low ionic strength, the dissociation coefficient constant of $Co(phen)_3^{3+/2+}$ in the presence of CdTe QDs was 3.1 times higher than that in the absence of CdTe QDs. This value reduced to 1.32 times in relatively high ionic strength. This indicated that the binding site of CdTe QDs on dsDNA was probably at the major groove of dsDNA. This demonstration offers a new approach to illustrate the QDs' cytotoxicity mechanism. Based on this research, Jiao *et al.*[73] developed electrochemical biosensing for dsDNA damage induced by PbSe QDs under UV irradiation. In this research, the damage of dsDNA was fulfilled by immersing the sensing membrane electrode in PbSe QD suspensions and illuminating it with a UV lamp. Cyclic voltammetry was utilized to detect dsDNA damage with $Co(phen)_3^{3+}$ as the electroactive probe. The synergistic effect among the UV irradiation, Pb^{2+} ions liberated from the PbSe QDs under the UV irradiation and the reactive oxygen species (ROS) generated in the presence of the PbSe QDs dramatically enhanced the damage of dsDNA. This electrochemical sensor provided a simple method for detecting DNA damage, and may be used for investigating the DNA damage induced by other QDs.

Using CdSe/ZnS as a label, a relatively simple, time-saving and multi-approach biosensor for the DNA detection was fabricated in our group.[74] By detecting the cadmium content in the bonded QDs, the target DNA could be indirectly detected through the SWASV assay. Based on the hairpin probe and site-specific DNA cleavage of restriction endonuclease, Chen *et al.*[75] fabricated an electrochemical DNA biosensor. This biosensor was used to detect DNA species related to cymbidium mosaic virus. The stripping voltammetric measurements of the dissolved Cd^{2+} were successfully performed to indirectly determine the sequence-selective discrimination between perfectly matched and mismatched target DNA including a single-base mismatched target DNA, and the limit detection could reach as low as 3.3×10^{-14} M for complementary target DNA. Given the simplicity in the design of the proposed electrochemical sensor, it is fairly easy to generalize this strategy to detect a spectrum of targets and might have a promising future for the investigation of DNA hybridization, and could also play a predominant role in the diagnosis of virus or diseases (Fig. 6).

What's more, based on the fact that different metal components of different QD nanocrystal tracers yield different well resolved highly sensitive stripping voltammetric signals, the multi-target electrochemical biosensor could be fabricated *via* the utilization of different QD codes. This new multi-electrochemical coding technology opens new opportunities for DNA diagnostics and for bioanalysis.

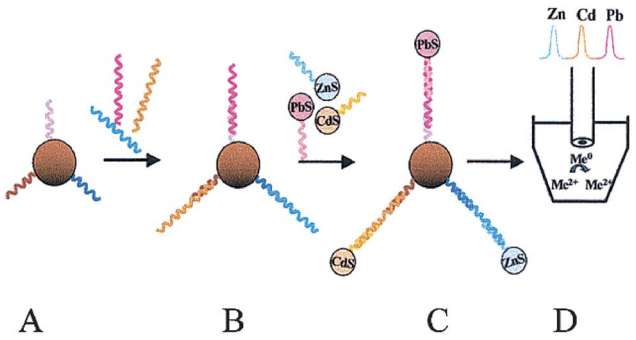

Fig. 6 Multi-target electrical DNA detection protocol based on different inorganic colloid nanocrystal tracers. (A) Introduction of probe-modified magnetic beads. (B) Hybridization with the DNA targets. (C) Second hybridization with the QD-labeled probes. (D) Dissolution of QDs and electrochemical detection. Reproduced with permission from ref. 76. Copyright 2003, American Chemical Society.

In 2003, Wang *et al.*[76] first employed this strategy for the simultaneous detection of multiple DNA targets based on QD tags with diverse redox potentials. Such encoding QDs offered a voltammetric signature with distinct electrical hybridization signals for the corresponding DNA targets. By using different inorganic-colloid QD nanocrystal tracers, whose metal components yield well-resolved highly sensitive stripping voltammetric signals for the corresponding targets, three encoding QDs (ZnS, CdS, and PbS) have thus been used to differentiate the signals of three DNA targets in connection with a sandwich hybridization assay and stripping voltammetry of the corresponding heavy metals. The new multi-target electrical detection scheme incorporates the high sensitivity and selectivity advantages of QD-based electrical assays.

4.4 Aptamer analysis

As a new class of single-stranded DNA/RNA molecules, aptamers have received a great deal of attention and attracted much interest in recent years. Aptamers are selected from synthetic nucleic acid libraries *via* the selection procedure called SELEX (systematic evolution of ligands by exponential enrichment).[77,78] Aptamers have the ability to form defined tertiary structures upon specific target binding. Since their first discovery in the 1990s, many aptamers have been selected for combination with the corresponding targets ranging from metal ions, organic molecules, biomolecules, to entire organisms and even whole cells.[79–83] Compared with natural receptors such as antibodies and enzymes, aptamers could be simply and reproducibly synthesized and easily labeled.[84,85] Besides, aptamers have high flexibility and could be modified with certain functional groups in biosensor design. Because of these important features, more and more attention is attracted to developing aptamer-based biosensors (aptasensors).[86–90]

With QDs coupled with different analytes, different targets could be detected *via* DPV and SWASV by fabricating the aptasensor, such as ATP,[91] thrombin,[92] and cocaine.[93] In our group, the three-dimensionally ordered macroporous (3DOM) gold film was used, instead of the classical bare flat Au electrode, to fabricate a sensitive electrochemical aptasensor for the detection of ATP.[91] The 3DOM gold film endowed the active surface area of the electrode up to 9.52 times larger than that of a classical bare flat one. The reaction was monitored by the electrochemical stripping analysis of dissolved QDs which were bound to the residual cDNA through a biotin–streptavidin system. The decrease of peak current was proportional to the amount of ATP. The unique interconnected structure of the 3DOM gold film along with the "built-in" preconcentration remarkably improved the sensitivity down to 0.01 nM. This promised a novel model for the detection of small molecules with higher sensitivity.

The multi-component analysis could not only be used in the DNA analysis, but could also be employed in the field of aptasensors. In 2006, based on their multi-electrochemical coding technology for the simultaneous detection of multiple DNA targets, Wang and others described a simple method for preparing a QD/aptamer-based ultrasensitive multianalyte electrochemical biosensor with subpicomolar (attomolar) detection limits.[94] The main strategy is accomplished using a simple single-step displacement assay, which involved the

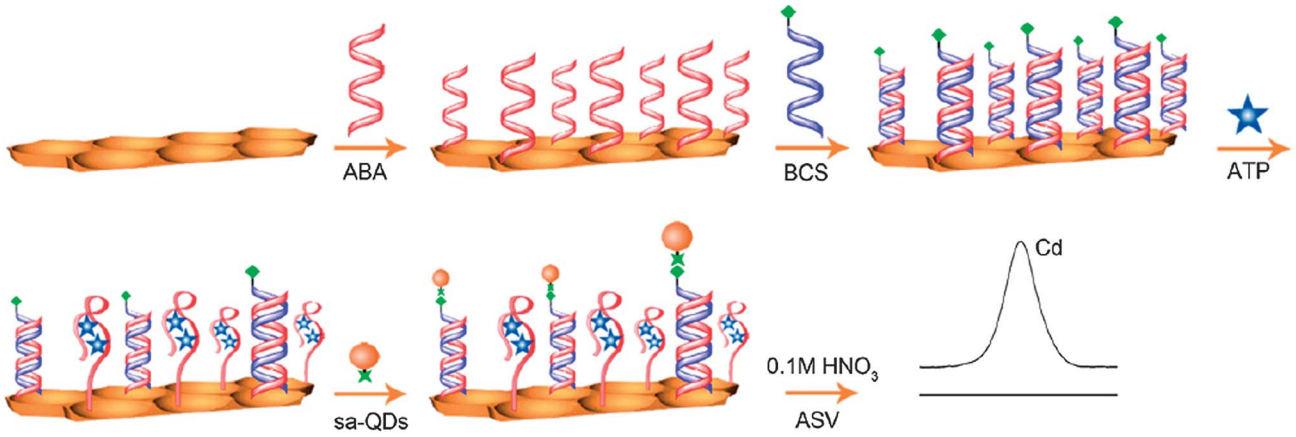

Fig. 7 Schematic illustration of the QD (CdSe/ZnS) electrochemical aptasensor based on a 3DOM gold film. Reproduced with permission from ref. 91. Copyright 2010, Elsevier.

coimmobilization of several thiolated aptamers, along with the binding of the corresponding QD-tagged proteins on a gold surface. After the addition of the protein sample without QD label, monitoring the displacement through electrochemical detection of the remaining QDs could be achieved. Such electronic transduction of aptamer–protein interactions is extremely attractive for meeting the low power, size, and cost requirements of decentralized diagnostic systems. What's more, unlike two-step sandwich assays, the new aptamer biosensor protocol relies on a single-step displacement protocol (Fig. 7).

Most recently, Yuan's group[93] developed a "signal on" and sensitive biosensor for one-spot simultaneous detection of multiple small molecular analytes based on electrochemically encoded barcode QD tags. In this route, the target analytes of adenosine triphosphate (ATP) and cocaine are respectively sandwiched between the corresponding set of surface-correimmobilized primary binding aptamers and the secondary binding aptamer/QD bioconjugates. The captured QDs (CdS and PbS) yield distinct electrochemical signals after acid dissolution. Due to the inherent amplification feature of the QD labels and the "signal on" detection scheme, as well as the sensitive monitoring of the metal ions released upon acid dissolution of the QD labels, low detection limits of 30 nM and 50 nM were obtained for ATP and cocaine, respectively, in this assay. The high specificity to target analytes and the promising applicability to a complex sample matrix made the proposed assay protocol an attractive route for screening of small molecules in clinical diagnosis.

5 Applications in solar cells

Due to the quantum confinement effect, the optical properties and the band gap of QD can be adjusted by changing the size of the QDs. Based on this size-dependent band gap, QDs like CdS,[95] CdSe[96] and CdTe[97] could provide light energy in the visible and infrared spectra, and could be used to fabricate highly efficient, low cost photovoltaics, also called quantum dot sensitized solar cells.[98] In 1996, Könenkamp *et al.*[99] fully studied the interaction between PbS QDs and the porous nanocrystalline TiO_2 anatase films. They found that the structurally stable, loosely packed nanocrystalline films could be prepared from colloidal solutions, which maintained many of the interesting properties of the clusters. After the PbS QDs were adsorbed on the internal surface of the TiO_2 films, the prepared composite films could be doped, and the injecting or blocking of electrical contacts could be established. This opens a new way for the preparation of a number of all-solid-state devices.

In order to improve the penetration of the reacting solution and the assembling of the QDs onto the substrate film, Chang and Lee[100] used a chemical bath deposition process for the *in situ* synthesis of CdS QDs onto mesoporous TiO_2 films. By employing alcohol instead of water as the solvent, a well-covered CdS on the surface of mesopores was achieved, which showed a higher amount of CdS incorporated. After the construction of the QD-sensitized solar cell, the efficiency reached as high as 1.84% under the illumination of one sun (AM1.5, 100 mW cm^{-2}). Afterwards, Lei *et al.*[101] decorated CdSe QDs onto the ZnO nanorod coated vertically aligned carbon nanotube (VACNT) arrays. When using the prepared VACNTs/ZnO/CdSe as the photoanode, a power conversion efficiency of 1.46% is achieved under an illumination of one sun.

In the above mentioned solar cell, the iodine compounds of I^-/I_3^- were used as the electrolyte, which endows the cell with high efficiency. However, the interaction between the QDs and iodine compounds, which was known as "photocorrosion",[102] may result in the unstable performance of the solar cells. To obtain a solar cell with more stable photovoltaic performance, Kang *et al.*[103] utilized CdS QD-sensitized nanospheroidal TiO_2 films. Due to both better interconnectivity among spheroidal particles and the larger mesopores of the TiO_2 layer, the spheroidal treated electrode resulted in improved performance, which was promising for developing QD-sensitized TiO_2 solar cells at lower cost with broader applicability. Latterly, Lee and co-workers[104] employed mesocellular carbon foams (MSU-F-Cs) with a high surface area (911 m^2 g^{-1}) and large pores ($\sim$25 nm) as counter electrodes for CdS/CdSe QD sensitized solar cells. Using polysulfide as the electrolyte, the MSU-F-C countered cell showed a maximum energy conversion efficiency of 1.75% under 1 sun illumination, which was much higher than that of those employing conventional Pt (1.22%) or commercial carbon (0.94%) counter electrodes.

In order to further suppress the photocorrosion effect, another type of QD, ZnS QD, was used in the field of solar cells. As compared with the traditional TiO_2 electrode, ZnS could block the back electron transfer from TiO_2 to the oxidant in the electrolyte solution.[105,106] Also, the ZnS could bind the non-bonding surface S3p orbital with the Zn valence orbital.[107]

6 Conclusions

Since the first report on the formation of metal-chalcogen bonds by the reaction of metal alkyls with silyl chalcogenides, both the fundamental and applied research of QDs has rapidly developed over the past several years. Large numbers of papers have been published on topics ranging from the synthesis, the optical and electrochemical study, to the bio-related applications of QDs. QDs have high quantum yield and stability and efficient and stable electrochemical properties. *Via* the surface functional modification, QDs could be used safely for bioconjugation with inorganic small molecules, proteins, enzymes, *etc*. Based on these bioconjugation properties, QD sensors could be fabricated for the detection ranging from inorganic analysis, organic analysis, immuno-analysis to DNA/aptamer analysis *via* the electrochemical assay. Together with the development of new synthesis routes, research into novel doped QDs and their electrochemical properties, QDs will continue to be a powerful nanomaterial in developing novel electrochemical based biosensors and other applications.

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