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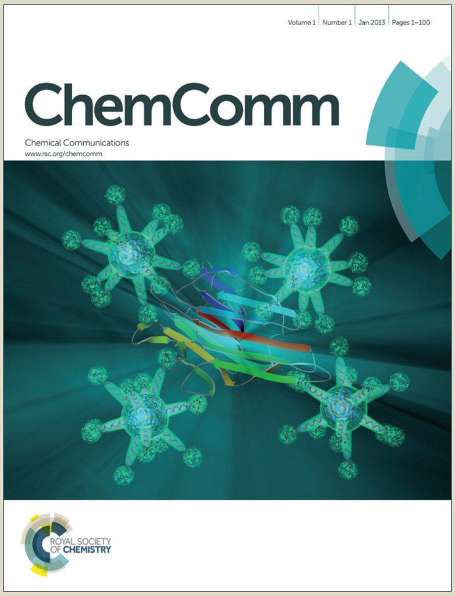

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FEATURE ARTICLE

Selective molecular recognition on calixarene-functionalized 3D surfaces

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Host-guest recognition plays an important role in biological analysis and biosensing. Accordingly, great efforts have been devoted to the development of sensors using versatile 3D surface materials. These functionalized nanomaterials possess the advantages of high selectivity and visual signals, enabling the selective detection of ions, amino acids, proteins, and other biological molecules. Therefore, in this feature article, we present some significant and representative examples of molecular recognition on calixarene functionalized 3D surface nanomaterials. By virtue of host-guest interactions, the functional interfaces displaying high selectivity and featuring a reversible switch response towards the environmental stimuli with various signal output (electrochemical and optical signals) are herein introduced. Furthermore, various 3D surface materials with unique signal amplification in molecular recognition are presented, including quantum dots (QDs), metal nanoparticles (NPs), nanotubes, and mesoporous silica. These excellent properties enable calixarene-functionalized 3D materials to become an outstanding platform for molecular recognition, offering convenient approaches for sensing and separation.

Introduction

Three-dimensional (3D) surface nanomaterials, including quantum dots (QDs), metal nanoparticles (NPs), nanotubes (NTs) and mesoporous silica with their unique size-dependent photophysical and electrochemical properties have been extensively exploited in photonic devices, catalysis, energy harvesting and storage, adsorption, biological probes, biosensors, etc.[1-7] Owing to the relatively large specific surface area and associated nano-confinement effect, 3D nanomaterials exhibit excellent signal amplification and transduction, which has triggered substantial interest in molecular recognition.[8-10] It should also be noted that nanomaterial-based optical detection has emerged as one of the most robust methods in bioanalysis and bioassays due to its high efficiency, simplicity, and ultrasensitivity.[11-14] The fascinating mechanical and tuneable optical features make these materials indispensable in many fields of application, particularly in sensing. Nonetheless, the realization of a recognition system for a specific target molecule with high selectivity and sensitivity remains a challenging task.

To fully exploit the aforementioned excellent properties of versatile systems with high selectivity and specific recognition ability, surface functionalization is vital and critical. Generally, the foremost factors taken into account when modifying the surface are the preservation of the original photophysical properties of the parent nanomaterials and the realization of flexible chemical properties of receptors. Thus, host-guest systems are promising candidates in the development of selective molecular recognition and surface functionalization due to remarkably specific and reversible non-covalent interactions and self-assembly.[15-17] In particular, calixarenes, being one of the best-known hosts with unique cavities and molecular skeleton, have been extensively employed in the field of molecular recognition.[18-23] Owing to their availability and easy functionalization at either the upper and/or lower rim, functional calixarenes can selectively bind specific guest molecules through multiple non-covalent interactions, such as hydrogen bonding, van der Waals forces, π-π stacking interactions, hydrophobic interactions, electrostatic effects, and others.[24-26] Therefore, grafting the host-guest chemistry on the 3D surface can be a reliable and convenient strategy to realize specific molecular recognition with macro scale visual signals.

So far, a myriad of studies in molecular recognition utilising calixarene-based 3D surfaces have been achieved, and our group has been working on it for a long time. The reported functionalized interfaces can selectively and sensitively detect ions, amino acids, proteins and other biological molecules with distinctive optical and electrochemical properties. As a result, these merits rendered calixarene-functionalized 3D materials into a versatile and robust platform for molecular recognition,

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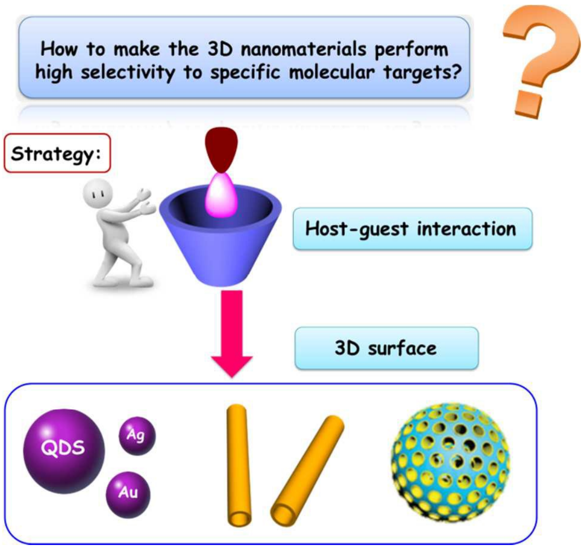

Fig. 1 Schematic illustration of the design and fabrication of highly selective molecular recognition systems for specific molecular targets.

offering convenient approaches for analysis and sensing applications.

Herein, we outline some recent progress in molecular recognition on calixarene-functionalized 3D surfaces and provide new insights into molecular recognition using functional nanomaterials (Fig. 1). The review is mainly composed of 3 sections where different 3D surface materials with unique signal amplification mechanisms for molecular recognition are presented. Moreover, an overview of both molecular recognition and sensing behaviour of different nanomaterials are also introduced herein. Overall, we provide a general focus on the preparation, formation, structure, and applications of functional 3D surface materials for molecular recognition and promote the advent of new methods and novel strategies.

1. Calixarene-functionalized nanoparticles for molecular recognition

The development of innovative nanoparticles with superb optical and electrochemical properties and attractive surface properties paves new avenues for molecular recognition and sensing, as well as fluorescent labelling in cells, tissues, and organisms.[27-30] These nanoparticles, including quantum dots (QDs), noble metals (Au, Ag, Pt) nanoparticles and magnetic nanoparticles (Fe_3O_4) routinely display excellent mechanical properties, tuneable shape and size, multi-functional surface properties, flexible physical and chemical properties, etc. These outstanding properties guarantee these materials as superior and indispensable platforms for molecular recognition in many areas of human activity and bioanalysis.[31-34] Notably, to fully harness these properties, functionalizing the nanoparticle surface is considerably critical. In this section, calixarene derivatives as organic ligands attached to versatile nanoparticles surfaces for molecular recognition are summarized.

1.1 Calixarene-functionalized QDs for molecular recognition

Quantum dots (QDs) are one of the most well-known luminescent colloidal nanocrystals, generally composed of semiconductor cores and various shells, such as CdS, PbSe, HgTe, GaAs QDs and CdSe/ZnS core/shell QDs. The diameter of QDs ranges from 2 to 10 nm, which is small enough for them to display quantum-mechanical properties such as the quantum-size effect, macroscopic quantum tunnelling effect, and surface effect, etc. These quantum effects invalidate macroscopic rules and result in outstanding optical or electrochemical molecular recognition properties. Due to their excitons being restricted in a confined three-dimensional space, the electrons are quantized to certain energy levels, similarly to the case of organic molecules, resulting in superb optical properties (such as tuneable narrow emission bands and wide-range excitation wavelength), completely different form bulk materials.[35] Generally, through well-developed synthetic methods, size-tuneable QDs can be readily prepared from a variety of materials, which are capable of good photostability and high fluorescence quantum yields.[36-38] Therefore, on account of their unique size-dependent physical and photoluminescence properties, QDs have been extensively employed in fluorescence assays and imaging in biological and medical research.

In order to acquire swift and sensitive analysis, numerous endeavours have been devoted into exploiting new approaches to prepare functional quantum dots capable of molecular recognition. Among them, calixarene derivatives have been intensively utilised as surface functionalization agents. For instance, Kinjo et al.[39] have reported amphiphilic *p*-sulfonatocalix[4]arene **1** assembled water-soluble CdSe/ZnS QDs for determination of the neurotransmitter acetylcholine (ACh) (Fig. 2). In this particular system, calix[4]arene grappling on the CdSe/ZnS QDs surface formed a bilayer structure with trioctylphosphine oxide (TOPO) molecules by virtue of hydrophobic interactions. Such design improved the solubility and stability in aqueous media of the functional CdSe/ZnS QDs. The optical properties of QDs can also be tuned by using different sized calixarene-based oligomers for the surface coating layer, which does not change the particle size. In addition, owing to the electron rich cavity, the *p*-sulfonatocalix[4]arene can selectively bind ammonium based cationic compounds by host-guest interactions. Thus, when ACh interacts with the functional QDs surface, it enters into the cavity of the calixarene, resulting in a drastic fluorescence quenching effect as the core electron hole recombination is reduced. The fluorescence emission of the QDs can be selectively quenched by acetylcholine in presence of other anionic and neutral neurotransmitters (L-glutamic acid and GABA). These functional QDs with sensitive optical properties will result in a variety of applications based on molecular recognition and biological analysis.

Using a similar strategy, Valcarcel et al. reported a fluorescent sensor for detection of fullerene-C_{60} in aqueous solutions (Fig. 3).[40] It is well understood that calixarenes with different size are excellent acceptors for π-system- containing

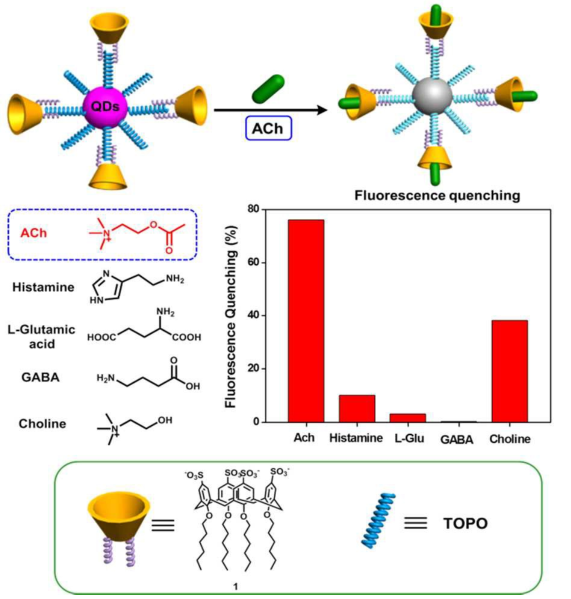

Fig. 2 Schematic representation of *p*-sulfonatocalix[4]arene modified CdSe/ZnS QDs for selective recognition of acetylcholine (ACh). (Reproduced with permission from ref. 39)

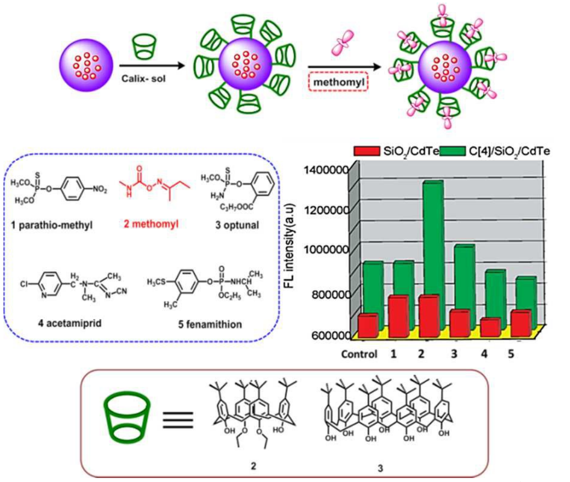

Fig. 4 Schematic representation of calix[4]arene **2**-functionalized CdTe/SiO$_2$ QDs for selective recognition of methomyl. (Reproduced with permission from ref. 41)

molecules, such as C_{60} and C_{70}. Among the various calixarenes, *p-tert*-butylcalix[8]arene, having a 3 Å deep cavity and a diameter of 11.7 Å, which is suited to accommodate fullerene-C_{60}. Thus, in the studied system, the hydrophobic *p-tert*-butylcalix[8]arene is attached to the QDs surface by the interaction with the aliphatic chains of the TOPO. This method maintains the fluorescence intensity of the quantum dots and their unique size, and meanwhile the immobilized calix[8]arenes preserve the capability of specific molecular recognition. When fullerene-C_{60} is added to the system, it quenched the original fluorescence emission of calix[8]-QDs through a typical electron transfer (ET) process. The calix[8]arene includes the fullerene-C_{60} within a 1:1 complex. As a result, the functional nanomaterial as a simple and rapid analytical method is capable of detecting C_{60} in river water with a lower limit value of 5µg/L. It is undoubtedly that this highly efficient strategy opens up a new avenue for developing sensors for toxicological and environmental applications. And it also provided a potential application to separate fullerene-C_{60} and fullerene-C_{70} by the difference of specific binding and solubility.

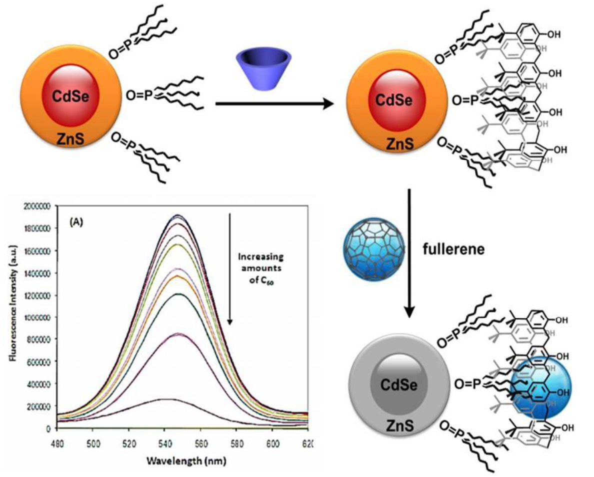

Fig. 3 Schematic representation of calix[8]arene assembled CdSe/ZnS QDs as an optical sensor for fullerene-C_{60}. (Reproduced with permission from ref. 40)

As pesticide residue has been a serious environmental and food safety problem, it is of great significance to develop highly efficient and sensitive sensors to detect trace amounts of these pesticides. Therefore, Li and Qu reported that diethoxy-calix[4]arene **2** anchored CdTe/SiO$_2$ QDs act as a highly sensitive luminescent probe for methomyl recognition (Fig. 4).[41] Initially, using the well-known Stober method,[42] the SiO$_2$/CdTe QDs were obtained *via* a sol-gel technique. Then calix[4]arene was introduced onto the QDs by grafting the calix[4]arene sol to the surface of the silica sphere. The functional nanocomposites were characterized by transmission electron microscopy (TEM), photon correlation spectroscopy (PCS), FT-IR, UV-vis and fluorescence spectroscopy. Owing to the host-guest interactions of calix[4]arene **2** with methomyl, the CA[4]/SiO$_2$/CdTe QDs show high selectivity for methomyl over other pesticides, which is accompanied with significant fluorescence enhancement. This phenomenon can be ascribed to the methomyl intercalation restricting the distortion of the calixarene cavity, which induces a uniform arrangement and enhances the conformational rigidity of the surface substituents. The drastic change of fluorescence intensity enables a detect limit of methomyl down to 0.08 µM, which can thus be used as a selective and sensitive fluorescent probe for pesticides analysis.

Subsequently, the author further utilized calix[4]arene **2** and calix[7]arene **3** grafted CdTe /SiO$_2$ quantum dots serving as selective fluorescent sensors for the determination of polycyclic aromatic hydrocarbons (PAHs).[43] In the system, the fluorescence intensity of QDs was varied by using different sizes of calixarene oligomers as the surface coating layer. As a result, two functional QDs can respond to anthracene and pyrene with different fluorescence increases. The calix[4]arene **2** functionalized QDs proved to be sensitive to anthracene, having a detection limit value of 2.45 × 10^{-8} M. At the same time, the calix[7]arene-coated QDs also showed sensitive fluorescence response toward pyrene with a low detection limit value of 2.94 × 10^{-8} M.

1.2 Other metal nanoparticles functionalized by calixarene for molecular recognition

Metal nanoparticles (AuNPs, AgNPs, CuNPs, PtNPs) have attracted considerable interest as viable biomedical sensors due to their ease of preparation, inherent optoelectronic properties and good biocompatibility.[44] Their superior photophysical properties and surface plasmon resonance absorption can be used for signal generation in different recognition processes. Generally, the majority of synthetic procedures for obtaining colloidal metal nanoparticles involves chemical reduction, using of a precursor salt with an reducing agent, such as sodium citrate or sodium borohydride.[45] The surface modification of the nanoparticles can be achieved through diverse covalent and non-covalent linking, such as Au–S, Au–N, Ag–C≡H bonds and electrostatic interactions. Thus, metal nanoparticles can be simply prepared and their surfaces can be easily functionalized. For this reason, calixarene-modified metal NPs have been the subject of interesting research. For convenient and rapid molecular recognition, functional nanoparticles offer versatile and powerful platforms for a myriad of applications in the areas of nanotechnology, sensors, biomedical applications, bioimaging, and drug delivery. Based on the thiol-Au interaction, Paul et al. have reported gold nanoparticles functionalized with calixarene **4** as a colorimetric sensor for various metal ions (Fig. 5).[46] In the system, biisopropyl substituted-1,3-alternate-calix[4]arene was selected as the ionophore anchored on the AuNPs surface. It shows that out of a large number of metal ions, Au@calixarene **4** performs with high selectivity to Cu^{2+} and Pb^{2+}, which exhibit distinct color changes from dark brown to green and blue, respectively. In addition, UV-Vis spectra, dynamic light scattering (DLS), HR-TEM and surface plasmon resonance (SPR) experiments were conducted to confirm the aggregation process in presence of Cu^{2+} and Pb^{2+}. The clear colorimetric response of the calixarene functionalized gold nanoparticles can be detectable by naked eye, which can enable practical application for in-field environmental analyses.

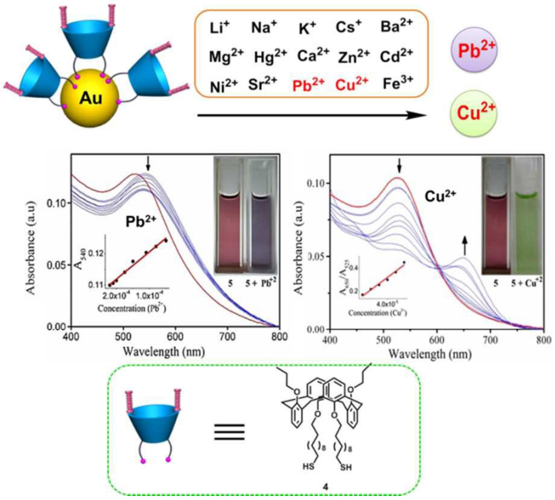

Fig. 5 Schematic representation of calix[4]arene functionalized gold nanoparticles for colorimetric detection of Cu^{2+} and Pb^{2+} ions. (Reproduced with permission from ref. 46)

Likewise, by incorporating a dithiocarbamate unit, calixarene **5** was prepared and fixed on the surface of AuNPs, which can serve as a Co (II) sensor, using colorimetric and electrochemical methods.[47] The modification process is driven by the formation of Au-S bonds. In the system, Au@calixarene **5** exhibits a sharp naked eye detectable colour change from pink to blue upon the addition of Co(II). Furthermore it performed with negligible interference from other metal ions. The colour change accompanied by the emergence of a new surface plasmon resonance (SPR) band are ascribed to the nanoparticles aggregation, which was further confirmed by TEM and dynamic light scattering (DLS) studies. This colorimetric method for Co(II) detection was found to have a detection limit of 10^{-9} M. In addition, due to the versatile properties of gold nanoparticles, Au@calixarene **5** exhibits a highly sensitive electrochemical response toward Co(II) in aqueous solution with a detection limit of 10^{-12} M.

1,3-alternate-*p*-sulphonatocalix[4]arene **6** functionalized AuNPs acting as a visible sensor for anion detection was also reported by Paul and co-workers.[48] Upon the addition of different anions, only iodide (I^-) caused a clear change in the SPR. This result shows that the intensity of the SPR peak was substantially weakened at 524 nm and meanwhile a new peak appeared at 660 nm. Additionally, owing to the selective binding of I^-, the morphology and size of nanoparticles undergoes a clear change, thus the sensor can easily report iodide with a sharp colour variation from pink to blue detectable by naked eye. The limit of detection (LOD) for iodide in the presence of periodate ion is 80 nM. The detection system can be used in the determination of I^- in water and iodized edible salt.

In another study, Pochini and co-workers have introduced a simple route to preparing a 1,3-dialkoxycalix[4]arene derivative **7** functionalized, monolayer protected gold cluster (MPC), which exhibits a remarkable binding ability towards quaternary ammonium salts in a homogeneous solution.[49,50] By using the Brust–Schiffrin method, the host can be immobilized on the AuNPs surface with dodecanethiol MPC by partial or complete exchange reactions, thus obtaining functional gold MPCs with a core diameter of approximately 2 nm. The delicate design retained the molecular recognition properties of calixarene in aqueous environment and selected the MPCs as readily detectable markers for the specific recognition process. As a consequence, the nanoparticles exhibit cation binding properties in aqueous media and are easily detectable with the naked eye thanks to the glaring red colour of the gold nanoparticles. The demonstrated opportunity to convert completely water-insoluble recognition systems into to aqueous solutions is simple and attractive, thus making colour-based diagnostic tests easily implementable to other selective analytes and could enable bioanalytical applications.

Menon *et al.* reported the recognition of amino acids by *p*-sulfonatocalix[4]arene functionalized nanoparticles (Fig. 6).[51] In the system, the *p*-sulfonatocalix[4]arene **8** easily assembled onto the gold nanocluster surface through the Au-S interaction. Upon the addition of eleven different amino acids, lysine, arginine and histidine induced an obvious color change from red to purple. Additionally, the maximum UV-Vis absorption wavelength also shifted from 524 to 550nm and was accompanied with the appearance of a broad SPR band. These changes were mainly attributed to particle aggregation via electrostatic interactions when calixarenes captured these basic amino acids. In addition, the authors also tested the stability of the functionalized AuNPs in different pH ranges. It was demonstrated that the calixarene-functionalized gold nanoparticles are very stable in pH range of pH 6 to pH 10 up to several months. Therefore, calixarene capped AuNPs provide a convenient means for the colorimetric detection of Lys, Arg and His in water.

In addition, Li and co-workers reported on a colorimetric sensor for probing histidine in water, based on calixarene **9**-modified silver nanoparticles.[52] The highly selective method allows a rapid quantitative detection of His up to a concentration of 5×10^{-6} M, which provides a new tool for immediate quantitation assays of this amino acid.

2. Calixarene-functionalized nanotubes for molecular recognition

Nanotubes (NTs) are remarkable 3D nanomaterials with unique mechanical stability, geometrical regularity, electrical conductivity, and physical/chemical properties and have received wide applications in electrochemical analysis and detection. Notable examples include carbon nanotubes (CNTs) and metal oxide nanotubes (e.g. TiO_2NTs, MnO_2NTs, ZnONTs). These architectures are leading candidates for chemiresistor materials due to their advantage of active surfaces and electrical properties.[53] Typical methods to obtain various nanotubes include template-based synthesis, filling processes, sol-gel processes, self-assembly methods, and more.[54-56] These nanotubes greatly boost the electrochemical signals and improve the signal/noise ratio (S/N), thus leading to a high sensitivity.[57] In the past decade, functional nanotubes have found applications in detecting chemical and biological analytes with exemplary sensitivity. The organic/inorganic nanocomposite provides great flexibility in its design and synthesis, thus enabling the combination of various recognition units and enhancing selectivity and sensitivity.

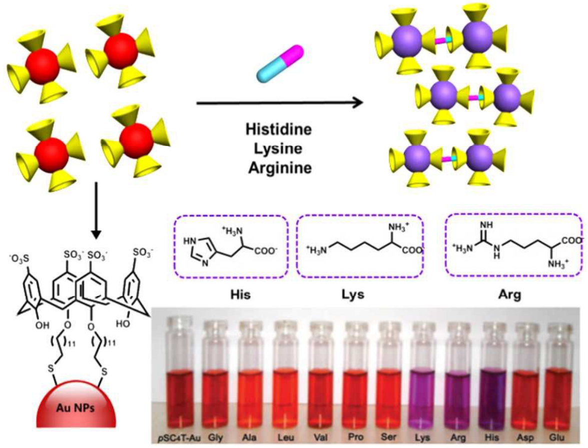

Fig. 6 *p*-Sulfonatocalix[4]arene thiol functionalized gold nanoparticles for the selective recognition of amino acids. (Reproduced with permission from ref. 51)

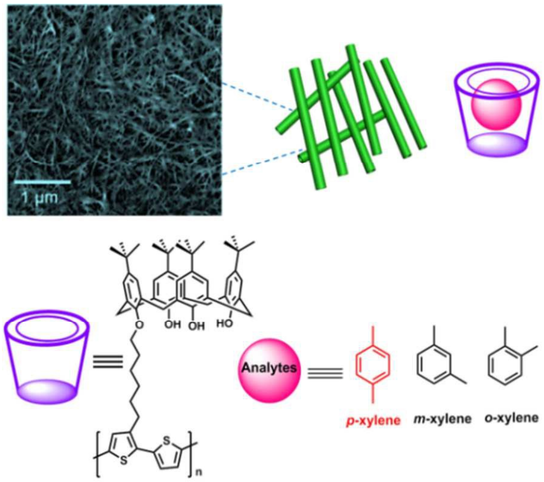

Fig. 7 Preparation of SWCNT/calix[4]arene sensor for selective recognition of *p*-xylene. (Reproduced with permission from ref. 58)

Distinguishing stereoisomers is always a challenging task in chemical analysis to achieve enantiomeric resolution, particularly important in the biopharmaceutical industry as well as useful in the field of environmental protection. Therefore, based on host-guest recognition, Swager prepared a resistance sensor based on single-walled carbon nanotubes (SWCNTs) coated with polythiophene grafted calix[4]arene **10** capable of distinguishing different xylene isomers (Fig. 7).[58] By virtue of the inherent cone conformation and the unique hydrophobic cavity of the calixarene, *p*-*tert*-butylcalix[4]arene was selected as an excellent receptor to differentiate *p*-xylene, *m*-xylene and *o*-xylene. The sensor exhibits high sensitivity to *p*-xylene with a rapid conductance response, which was also confirmed by a quartz crystal microbalance (QCM) experiment. The result shows that SWCNT/calixarene composited film adsorbed more *p*-xylene than the other two isomers (*m*-xylene and *o*- xylene). Additionally, the adsorption phenomena were also verified by fluorescence spectroscopy. Indeed, the fluorescence observed from the composited film continuously increased, which revealed that the polymer was subjected to swelling and related conformational changes, and thus verifying more *p*-xylene was adsorbed by the composited film. It was reported that these calixarene-functionalized SWCNTs with high selectivity for xylene isomers are promising candidates to develop highly efficient, low-cost and real-time sensors.

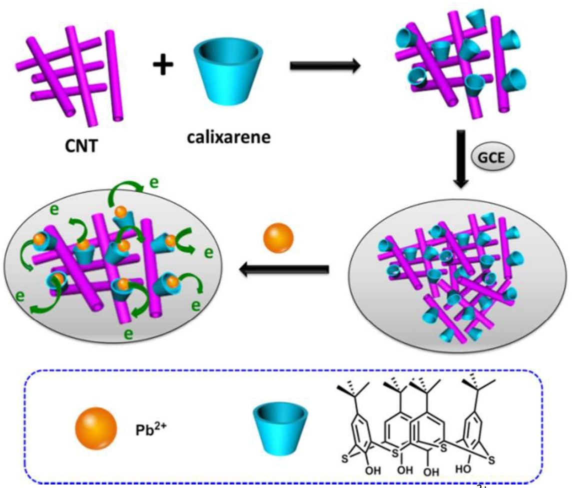

Fig. 8 Design and fabrication of TCA/MWCNT for detection of Pb^{2+}. (Reproduced with permission from ref. 59)

In order to improve the dispersion and selectivity of CNTs, much effort has been invested into preparing nanocomposites that incorporate a high surface area and demonstrate excellent conductivity originating from the carbon nanotubes decorated with various functional organic or inorganic compounds. For example, the Ding group reported a new type of multi-walled carbon nanotubes covalently functionalized with thiacalixarene **11** (TCA-MWCNTs). This material coated on an electrode can serve as a good sensor for the detection of ultratrace Pb^{2+} ions by a sensitive voltammetric method (Fig. 8).[59] Such design, endowing MWCNT with high selectivity and sensitivity permits convenient quantative detection of Pb^{2+} down to the sub microgram/liter level. The results demonstrate that the system shows a linearly response to Pb^{2+} ($R = 0.999$) in the concentration range of 2×10^{-10} to 1×10^{-8} M, and the limit of detection was found to be 4×10^{-11}M. Upon the addition of equal amounts of interfering Sn^{2+} ions, the determination of Pb^{2+} (10^{-7}M) still yielded well-separated signals.

Additionally, TiO_2 nanotubes represent another promising platform for fabricating photo electrochemical sensors due to their large surface area, photochemical stability, and high photocatalytic efficiency. Williams and co-workers reported a visible light actuated profenofos (PFF) sensor, achieved by calixarene **12** grafted on highly ordered and vertically aligned TiO_2 nanotubes (Fig. 9). [60] In the system, *p-tert*-butyl calix[4]arene (CA) was employed as the recognition unit attached to the TiO_2NTs surface by forming coordination covalent bonds between phenolic hydroxyls of calix[4]arene and Ti atoms. Such a design enabled the construction of a visible light actuated photo electrochemical sensor and improved the stability of sensor. By virtue of proper hydrophobicity and the complementary size of calix[4]arene, CA@TiO_2NTs can selective recognize profenofos over other pesticides signalled by a photocurrent change. It displays excellent selectivity towards profenofos with a low concentration limit of 1 nM (S/N = 3), and almost negligible changes in presence of other excess interferences. Moreover, the sensor can be applied to the detection of profenofos in spiked samples of lake water together with other pesticides, which also shows satisfying results. This study paves the way for designing highly selective photo electrochemical sensors for environmental monitoring purposes.

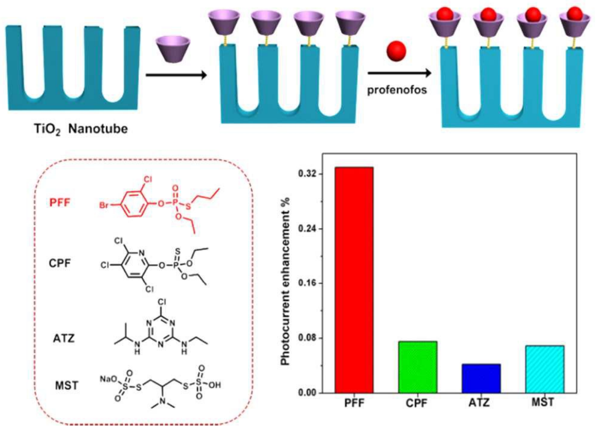

Fig. 9 Schematic of the fabrication of CA@TiO_2NTs and selective recognition of profenofos. (Reproduced with permission from ref. 60)

3. Calixarene-functionalized mesoporous silica for molecular recognition

Mesoporous silica nanoparticles (MSNs) are a type of classic solid silica materials possessing periodic mesopores with hexagonal, cubic or lamellar structures with sizes ranging from 2 to 50 nm.[61] These materials, with large surface areas and large pore volumes in the inorganic matrix have been developed to be promising tools for catalysis, sensing, adsorption as well as separation.[62-64] When combined with a host-guest systems, porous materials generally display high selectivity to specific guests confined in well-defined pores. These organically modified silica porous materials normally exhibit different hydrophobic and hydrophilic properties, and have been employed to a variety of applications.

As the detection of detrimental substances has been the focus in environmental protection, Valeur and co-workers have reported a calixarene grafted mesoporous silica material for selective mercury (II) ion recognition in water with optical changes.[65] In the system, in order to keep the behaviour of mesoporous silica binding to Hg^{2+}, long aliphatic chains were chosen to control the surface-grafting properties of the multifunctional molecule. The organic-inorganic hybrid material has been characterized by X-ray diffraction (XRD), thermo gravimetric analysis (TGA) and NMR spectroscopy analysis, which shows that the grafted fluoroionophore and the mesoscopic arrangement of the host solid are not affected by the modification process. This functional material exhibits a specific response towards Hg^{2+} over interfering cations with a detection limit of 3.3 x 10^{-7} M. It also exhibits noticable fluorescence quenching in the course of a few seconds. The work utilized the mesoporous silica as a robust inorganic supporter for purpose of grafting a fluoroionophore and opens

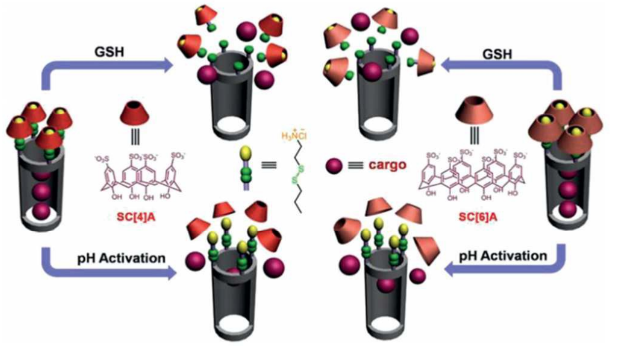

Fig. 10 Preparation of stimuli-responsive supramolecular nanovalves for releasing of cargo on host-guest interaction regulated mesoporous silica. (Reprinted with permission from ref. 67)

new opportunities to achieve efficient optical sensors for heavy metals in water.

In addition to the specific recognition properties of mesoporous silica based host-guest systems, these scaffolds can be further applied for drug-delivery or separation.[66] For instance, Yang and co-workers have exploited novel drug-releasing systems based on biocompatible sulfonato-calix[4,6]arenes (SC[4]A and SC[6]A) and alkylammonium functionalized mesoporous silica nanoparticles (MSNs). The systems can encapsulate and release cargos when exposed to L-glutathione (GSH) or pH changes (Fig 10).[67] Based on the host-guest interaction between alkylammonium and SC[4]A/SC[6]A, the cargo can be sealed into the pore orifices of MSNs. The disulphide bonds of the alkylammonium bearing molecule can readily be snipped with increased concentrations of GSH. At the same time, host-guest interaction between SC[4]A/SC[6]A and alkylammonium cations can be attenuated at lower pH. Thus, in the presence of either of these two stimuli the loaded cargo can diffuse out. Owing to the excellent biocompatibility and the sensitive dual-stimuli responsiveness, the functionalized mesoporous silica can easily be implementated to drug delivery in solid tumours featuring an acidic microenvironment as well as high concentrations of GSH. This example of dually responsive mechanized MSNs with excellent response performance can be a promising candidate for diagnosis and treatment of cancers.

A final highlight of a recent development in literature was motivated by the fact that the supramolecular host has a high selectivity of for acetylcholine (ACh). In this work a novel therapeutic method was demonstrated consisting of calixarene and pillarene functionalized mesoporous silica nanoparticles.[68] The two supramolecular-based systems presented diverse cargo release efficiencies as a result of differential binding constants to these cargos. This system may be employed to treat and ameliorate dystonic, dyskinetic, and choreiform behaviors, with ACh serving as a competitive agent to regulate calixarene or pillarene-based supramolecular switches, which holds great promises for *in vivo* applications of *in situ* diseases treatments for related diseases such as Parkinson's disease.

Conclusions

In this feature article, we briefly summarized calixarene-functionalized 3D surfaces serving as smart nanomaterials for specific molecular recognition. The careful design permits the highly selective binding of specific molecular targets, including ions, amino acids, pesticides and biomolecules. Importantly, by virtue of host-guest interactions, calixarene assembled 3D surfaces are a quite simple, rapid and efficient way to exploit versatile sensors for analysis application. The fundamental and general insights coming from our analysis are given as follows: (i) The functionalization process and surface selectivity can be achieved by a synergistic combination of covalent and non-covalent interactions, such as hydrophobic interaction, charge, cavity inclusion, hydrogen bonding and stereostructure (ii) Harnessing the merits of the 3D surface and the calixarene, the functionalized systems can produce unique signal amplifications of optical and electronic properties indicating molecular recognition. (iii) The development of 3D surfaces via host-guest interaction facilitates the design of biosensing devices and can mimic sophisticated biological processes such as drug release. Additionally, based on the versatile interfacial properties of nanomaterials and the selective molecular recognition of calixarenes, more potential applications are likely to be developed by using the calixarene assembled 3D surface nanomaterials. Such as mesoporous silica nanoparticles, we especially foresee applications in the field of environmental adsorption and separation.

These examples considerably extend the horizon of host-guest chemistry within the area of interfacial science, and provide a variety of excellent and straightforward routes to fabricate multifunctional nanomaterials for molecular recognition, drug release and separation. We anticipate that the engineering principles of these materials will vastly expand the application of molecular recognition.

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