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Molecular Assembly of Schiff Base Interactions: Construction and Application

Yi Jia and Junbai Li*

Beijing National Laboratory for Molecular Sciences, CAS Key Lab of Colloid, Interface and Chemical Thermodynamics, Institute of Chemistry, Chinese Academy of Sciences, Beijing, 100190, China

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1. INTRODUCTION

Controlled fabrication of nanosystems is essential in current science and technology.[1] One of the most successful strategies for constructing such nanosystems is preparation of controlled functional thin films on certain substrates.[2−11] In the past decades, several techniques have been developed to design thin films at the molecular level, such as the self-assembled monolayer (SAM) method,[12,13] Langmuir−Blodgett (LB) techniques,[14,15] and layer-by-layer (LbL) assembly.[16−18] Among these thin film preparation methods, the layer-by-layer (LbL) assembly method introduced by Decher et al. could be the most flexible and versatile technique,[19,20] which allows an unprecedented variety of materials to be assembled into nanoscale films using simple, controllable, inexpensive procedures.[18,21−28] The principle of LbL assembly relies on sequential adsorption of assembly components with an intervening rinsing step following each deposition. Electrostatic interaction is the original and conventional driving force for LbL assembly. With the increment of assembly components' diversity, the driving forces used in LbL assembly have also been extended from electrostatic interaction to hydrogen bonding,[29,30] covalent bonding,[31,32] charge transfer,[33,34] metal coordination,[35,36] and specific recognition.[37,38] The wide range of interactions available for performing the LbL assembly process has resulted in specific architectures and an incredibly wide variety of systems. Yet, most of the films obtained through electrostatic interaction, hydrogen bonding, and other noncovalent bonding offer poor stability under harsh conditions and therefore typically require a post-treatment process such as cross-linking with chemical agents or thermal treatment to enhance the stability of the films.[39−41] Compared to noncovalent bonding, introduction of covalent bonding to the LbL assembly could significantly improve the multilayer film's robustness,

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which is highly advantageous for practical application. Bergbreiter, Crooks, and co-workers performed the first example of covalent LbL assembly of polymers using poly(maleic anhydride)-*c*-poly(methyl vinyl ether) cross-linked with ethylenediamine through amide bonds.[42] Since then an amide bond has been used frequently for covalent assembly because of its desirable stability and ready availability of the reagents.[43−45] Blanchard reported on the covalent LbL multilayers of diphenylmethane derivatives through a urea moiety.[31] The advantage of the urea moiety involved in interlayer linking is its ability to form hydrogen-bonded networks parallel to the substrate. Caruso and co-workers first introduced click chemistry for LbL assembly.[32] It was performed by alternately immersing the substrates in the solutions of poly(acrylic acid) with either alkyne or azide groups in the presence of sodium ascorbate and Cu(I), finally obtaining covalently bonded thin films and capsules.[32] The high reactivity and selectivity of click chemistry under ambient conditions brought it rapid popularity in covalent LbL assembly. Recently, pioneering research on electrochemically catalyzed click chemistry for LbL assembly was reported by Rydzek et al., and one-pot film buildup was achieved.[46,47] As an evolution, Li and co-workers introduced a new concept of molecular coupling to LbL assembly technology in their invention of electrochemical-coupling LbL (ECC-LbL) assembly.[2,48] Considering the independence between reaction site and functional groups, this method could apply to various compounds and would be a powerful method for constructing well-designed and robust multilayered thin films in optoelectronic devices. Apart from these examples, many other strategies (oxyme chemistry, azlactone chemistry, carbodiimide chemistry, imine chemistry, photochemical cross-linking, and sol−gel reaction, etc.) have also been employed in covalent LbL assembly; more details could be referred to recent reviews or papers.[7,17,18,21,41,43,49−51] In this review, we will specifically focus on covalent molecular assembly with the LbL method through Schiff base interactions, including (i) the properties and advantages of Schiff base interactions, (ii) the micro- and nanostructures fabricated through Schiff base interactions, and (iii) the biomedical applications of the products fabricated through Schiff base interactions.

2. ADVANTAGES OF MOLECULAR ASSEMBLY VIA SCHIFF BASE INTERACTIONS

The Schiff base reaction was proposed in 1864 by the German chemist Hugo Schiff.[52,53] It refers to the reaction between a class of compounds containing aldehydes (or ketones) and amino groups, resulting in imine groups (−C═N−) (Figure 1). Schiff

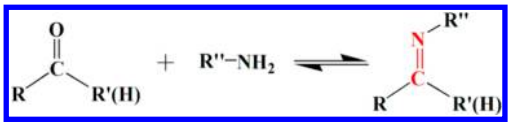

Figure 1. Schematic illustration of Schiff base reaction.

base reactions are widely used in chemistry due to their mild reaction conditions and high reaction rates. Recently, Schiff base complexes have drawn attention in biochemistry and biomedicine because of their unique properties.[54,55]

For applications that require multifunctional robust thin films, covalent LbL assembly through Schiff base interactions possess common advantages of covalent bonding compared to the noncovalent interactions. First, Schiff base bonding endows the thin film with high stability, allowing it to withstand harsh conditions. Second, in situ Schiff base formation avoids the extra post-treatment processes to improve the stability of the multilayer. Third, Schiff base reactions can be conducted both in aqueous and in organic solutions. This allows for incorporating materials that only dissolve or only can be used in nonaqueous solutions. Fourth, Schiff base reaction leaves behind excess reactive groups (aldehydes and amino) inside the multilayer films that can further react with other substances to tailor the properties of the product for diverse applications. Besides these excellent properties, the Schiff base interaction still has some pretty unique features.[43,52] (i) The Schiff base reaction proceeds under ambient conditions without activation and involves only water as a byproduct (contamination of the LbL multilayer films by impurities was avoided), which is essential for fabrication of certain sensors and reactors. (ii) Formation of a Schiff base bond enables composites with autofluorescence, attributing to the $n-\pi^*$ transition of the C═N bonds.[56−58] The autofluorescent property would be beneficial in monitoring the safety and efficacy of drug carriers in vivo while avoiding the use of external fluorochromes for biological tracing. (iii) The Schiff base bond is a dynamic covalent bond.[59−61] Compared to other covalent linkers such as click chemistry, the Schiff base structure provides extraordinary reversibility with changing pH values and the stability of these bonds decreases as the pH decreases.[54,55,60] This feature is highly preferable for specific pH-triggered drug release. All these merits make Schiff base interactions attractive in multilayer assembly with the LbL method, especially for those applied in biomedicine.

3. MICRO- AND NANOSTRUCTURES FABRICATED THROUGH SCHIFF BASE INTERACTIONS

3.1. Glutaraldehyde-Mediated Schiff Base Interactions

As mentioned above, it requires aldehydes and amino groups to form a Schiff base bond. Among the cross-linking agents used in biomedical applications, glutaraldehyde (GA, Figure 2) is by far the most widely used due to its high solubility in aqueous solution, bifunctionality, easy availability, and low price.[62,63]

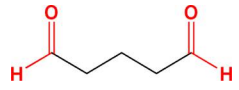

Figure 2. Molecular formula of glutaraldehyde.

3.1.1. Planar Films. In the past few years, GA has been widely used in the preparation of stable multilayer films on the surface of flat solid substrates by means of the LbL method through a Schiff base reaction, especially for fabrication of ordered monolayer or multilayer enzyme films. Since most enzymes are proteins that consist of abundant amino groups, they can easily react with GA through a Schiff base reaction. Typically, the solid substrate surface was first functionalized with primary amino groups. Next, the amino groups reacted with the aldehyde groups of GA through a Schiff base reaction. Then the excess aldehyde groups reacted with the amino groups of the enzymes, as illustrated in Figure 3. This procedure is also applicable to aldehyde-functionalized surface. Yang and coworkers immobilized horseradish peroxidase (HRP) on amino-modified carbon electrode using this strategy.[64] The multilayer enzyme immobilized on carbon electrode retained its catalytic activity and responded rapidly to low hydrogen peroxide (H_2O_2) concentration. Increasing the number of HRP layers can improve

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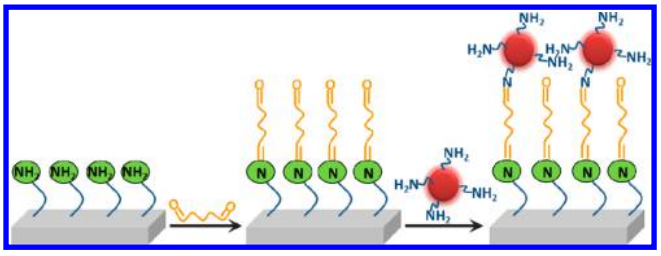

Figure 3. Preparation of multilayer films on flat solid substrate through GA-mediated Schiff base reaction.

the sensitivity of the biosensor. Similarly, glucose oxidase (GOD),[65,66] laccase,[67] lipase,[68] and galactose oxidase[69] attached to the surface of composite films or electrode have also been used. In order to improve the performance of the multilayer enzymes films, silica,[70] dendrimer,[71] chitosan, and/or carbon nanotubes[72,73] were coimmobilized on solid substrate surfaces to obtain multilayer composite films with high mechanical strength, large surface area, excellent membrane-forming ability, good adhesion, and good biocompatibility. Besides enzymes, other proteins,[74] DNA,[75] antigen,[76] and antibody[77] were also attached to the solid surfaces through GA-mediated Schiff base interactions for construction of different biosensors.

It is noteworthy that GA is a biocide, which is toxic to living organisms. For in vivo applications (tissue engineering or drug delivery), this toxicity of multilayer films fabricated through GA cross-linking must be considered. To reduce the toxicity of the multilayer films without compromising its stability, a lower concentration of GA or post-treatment with GA after LbL assembly was recommended. Ji and co-workers fabricated an ultrathin enzymatically degradable multilayer film through LbL assembly of poly-L-lysine (PLL) and DNA.[78] After post-treatment with GA, the stability of the PLL/DNA film was greatly improved. The cross-linking density of the film can be easily controlled by manipulating the incubation time with GA. Moreover, the GA cross-linking procedure effectively slowed down the enzymatic degradation of the film and led to various DNA release profiles. Therefore, the PLL/DNA films have great potential in gene therapy for DNA delivery. In a similar way, GA cross-linked heparin/collagen (HEP/COL) multilayer were also fabricated.[79] Multilayer coatings with slight GA cross-linking presented good stability both in static incubation and in flushing conditions as well as good hemocompatibility and cytocompatibility. Sukhishvili and co-workers reported single-component poly(allylamine hydrochloride) (PAH) hydrogel films obtained through electrostatic assembly of PAH and poly(methacrylic acid) (PMAA) followed by GA cross-linking and pH-triggered removal of PMAA (Figure 4).[80] Enzyme dispersin B (DspB) was subsequently loaded into the PAH hydrogel film for prevention of biofilm formation. These films showed nontoxicity and high biocompatibility with human osteoblast cell line. Combined with conventional antibiotics, it is promising to design highly efficient antibiofilm coatings for biomedical implants.

3.1.2. Nanotubes. Compared to flat and nonporous templates, use of porous planar templates for LbL assembly through GA-mediated Schiff base interactions allows preparation of stable and well-defined three-dimensional structures, i.e., nanotubes. In this way, GOD, hemoglobin (Hb), and cytochrome *c* (cyto-C) nanotubes were prepared.[81,82] Preparation of cross-linked protein nanotubes involved alternate immersion of the porous anode alumina oxide (AAO) membrane in solutions of protein and GA followed by removal of the surface

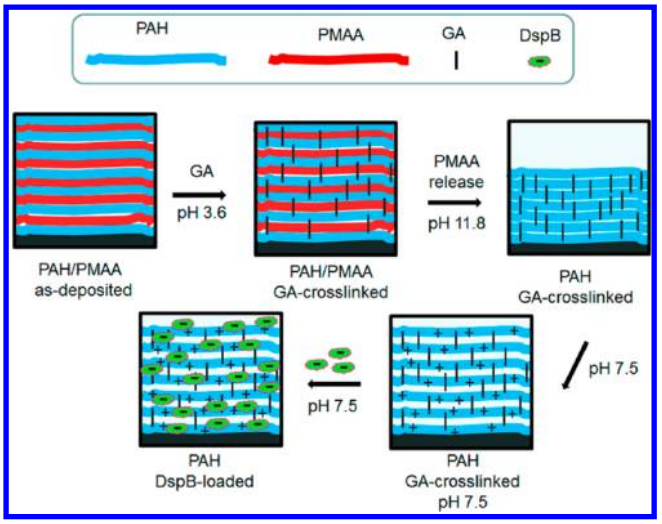

Figure 4. Preparation of DspB-loaded PAH hydrogel films. Reprinted with permission from ref 80. Copyright 2012 American Chemical Society.

material and the template (Figure 5).[82] It has been demonstrated that the GA cross-linked protein nanotubes were stable.

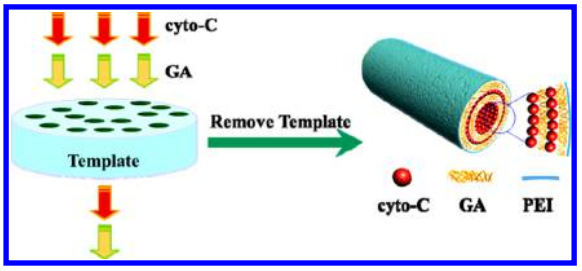

Figure 5. Schematic representation for fabrication of cyto-C/GA nanotubes via GA-mediated Schiff base interactions. Reprinted with permission from ref 82. Copyright 2006 American Chemical Society.

Moreover, the activity of cross-linked protein in nanotubes was retained and increased as the wall thickness increased.

3.1.3. Spheres. Multilayers through GA cross-linking were also prepared on spherical particles for fabrication of functional spheres. Liu and co-workers covalently immobilized bovine serum albumin (BSA) on amino-silane-modified magnetic silica supports by GA-mediated Schiff base interactions.[83] The BSA-functionalized magnetic nanospheres have great potential in affinity separation, especially for antibody purification, cell isolation, and immunoassay. Gao and co-workers prepared collagen-modified polylactide (PLA) microspheres using GA cross-linking for cell culture and injectable cell carriers.[84] Recently, Li and co-workers alternately assembled Hb and GOD on mesoporous silica nanoparticles (MSNs) using GA as cross-linker (Figure 6).[85] The resulting nanoparticles are glucose sensitive with autofluorescence properties due to formation of Schiff base bonds between proteins and GA. This makes these composite nanomaterials good candidates for biosensors and drug carriers.

3.1.4. Capsules. If the above-mentioned spherical particles templates are decomposable, hollow capsules can be obtained by template removal after multilayer formation. Initially, hollow capsules were mainly constructed through electrostatics or hydrogen bonding, which are comparatively unstable and not suitable for certain applications. Several approaches (photo-

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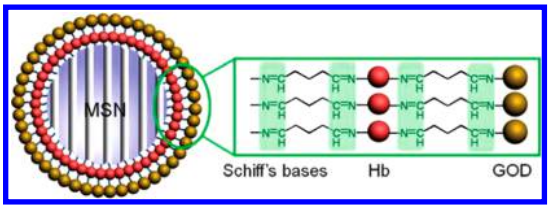

Figure 6. Hb (red) and GOD (yellow) immobilized on the surface of MSN with GA as a cross-linker. Reprinted with permission from ref 85. Copyright 2011 Royal Society of Chemistry.

chemical cross-linking, heat treatment, etc.) were introduced to solve this problem. Among them, GA cross-linking has always been considered to be the best and simplest solution to enhance the stability of these capsules. Gao and co-workers fabricated a series of capsules through electrostatic interactions between oppositely charged polyelectrolytes and then post-treated the capsules with GA via Schiff base reaction.[86−88] Thus, the stability of these capsules was improved. A number of single-component capsules (PAH capsules, poly(ethylenimine)(PEI) capsules and BSA capsules) were also prepared by Gao and co-workers through Schiff base reaction between the aldehyde groups of GA and amino groups in the component.[89−91] Similar approaches were also used to fabricated Hb capsules and chitosan (CHI) capsules by other groups.[63,92] A more simple and versatile strategy was proposed by Caruso and co-workers through infiltrating the solid core/mesoporous shell silica particles (SC/MS) with polyelectrolytes or polymer−drug complex, followed by GA cross-linking and removal of the templates (Figure 7).[93]

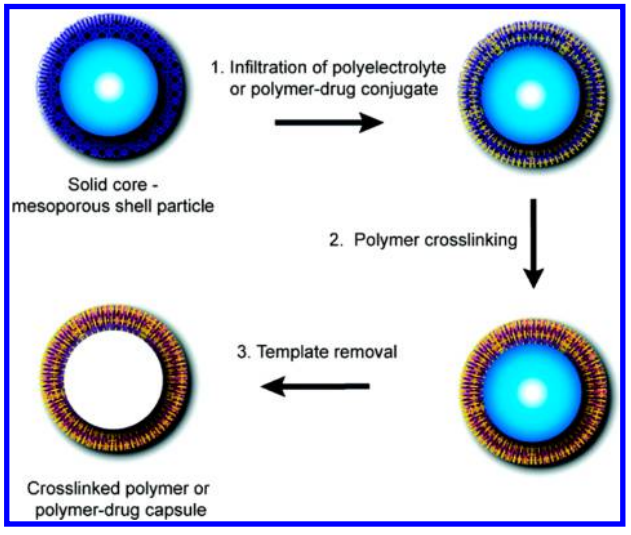

Figure 7. Preparation of single-component capsules through infiltration and cross-linking. Reprinted with permission from ref 93. Copyright 2008 American Chemical Society.

This method demonstrated its versatility in preparing thick-walled, single-component capsules consisting of polyamines by GA cross-linking. Compared to the conventional alternate deposition of polyelectrolytes, this method is highly advantageous in the fabrication procedure that only requiring two steps, infiltration and cross-linking.

All these demonstrate that GA-mediated Schiff base interactions were applied to a wide range of amino-containing compounds and widely used in fabrication of stable composite films, nanotubes, spherical particles, and microcapsules for various applications.

3.2. Aldehyde Polysaccharides-Mediated Schiff Base Interactions

The above-mentioned micro- and nanostructures fabricated through Schiff base interactions were all cross-linked with GA. It has been reported that GA is associated with calcification in certain applications and involved in local cytotoxicity.[62] These drawbacks have motivated the search for alternative cross-linking agents. Recently, polysaccharides oxidized by periodate (aldehyde polysaccharides, Figure 8) have drawn some attention

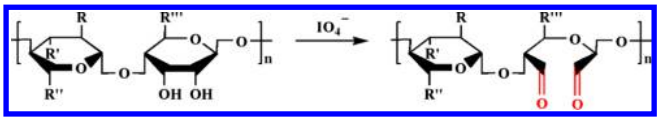

Figure 8. Oxidation of polysaccharide with periodate.

due to their low toxicity, biocompatibility, and biodegradability.[94,95] They have been employed both as a component and as a cross-linker in covalent LbL assembly through Schiff base interaction.

3.2.1. Planar Films. Periodate can specifically cleave vicinal diols to form aldehydes and ketones. Initially, this was used in the investigation of the polysaccharide structure.[96] Nowadays, low and mild periodate oxidations are used to confer the polysaccharide chain with aldehyde functionalities, which have a highly reactive nature toward amines and been used for immobilization of amino-containing compounds (enzymes, antigen, peptide, etc.) on various substrates. Massia and co-workers oxidized dextran to generate aldehyde groups via standard periodate methods and presented a novel method to covalently attach dextran on aminated glass surfaces through Schiff base interactions.[97] These dextran coatings greatly reduced cell adhesion and proved its ability in modification of a cell-resistant surface. Subsequently, they grafted cell adhesion peptides on cell-resistant dextran monolayer surfaces. The peptide-grafted substrates effectively promoted biospecific interactions and reduced nonspecific interactions. Compared to poly(ethylene glycol) (PEG), oxidized dextran not only has similar antifouling properties to PEG but also has the potential for high-density immobilization of biomolecules. The same strategy was adopted by Li and co-workers to modified PDMS microfluidic enzyme-linked immunosorbent assay (ELISA) devices,[98] as illustrated in Figure 9. In this work, the PDMS microfluidic device was functionalized with the aldehyde dextran through a simple and fast flow-through process, followed by covalent immobilization of proteins on the PDMS microchannel surface through Schiff base reaction. The device was then used in colorimetric detection of proteins and showed excellent sensitivity.

Apart from aldehyde−dextran, dialdehyde starch (DAS), dialdehyde cellulose (DAC), and other polysaccharides oxidized by periodate have also been employed as cross-linkers in covalent molecular assemblies.[99,100] Presumably, using this approach, any aminated surfaces of substrates can easily be activated with functional aldehyde polysaccharides and then immobilized bioactive molecules via Schiff base reactions. However, for certain applications, some probe molecules (for example, DNA probes) immobilized on the substrate surface are not very adequate for hybridization, resulting in a very low specific hybridization and a large nonspecific adsorption. To solve this problem, Fernández-Lafuente and co-workers tailormade heterofunctional aldehyde−aspartic−dextran with anionic and

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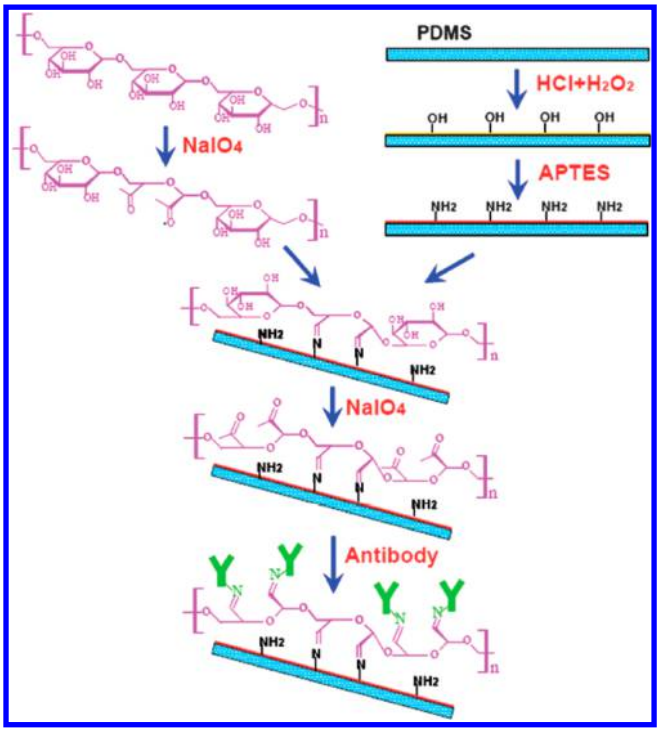

Figure 9. Schematic illustration of aldehyde−dextran-modified PDMS microchannel. Reprinted with permission from ref 98. Copyright 2009 Royal Society of Chemistry.

aldehyde groups (Figure 10).[101] Instead of aldehyde−dextran, the aldehyde−aspartic−dextran complex in conjunction with the

Figure 10. Immobilization of DNA through polyaldehyde−aspartic−dextran. Reprinted with permission from ref 101. Copyright 2004 American Chemical Society.

chemical blocking agents could completely eliminate the nonspecific adsorption of DNA on the substrate surface. Moreover, this also permitted high-density immobilization of DNA probes and facilitated hybridization due to the long spacer arms.

3.2.2. Capsules. Alginate (ALG) and chitosan (CHI) are the anionic and cationic polysaccharides used most commonly in biomedicine. Assemblies using these two polysaccharides were mainly fabricated through electrostatic interaction. They were not stable enough for some applications. Recently, Li and co-workers synthesized alginate dialdehyde (ADA) by oxidizing ALG with sodium periodate.[58] The aldehyde groups of ADA could react with the amino groups of CHI through Schiff base reaction (Figure 11). After alternate deposition of CHI/ADA

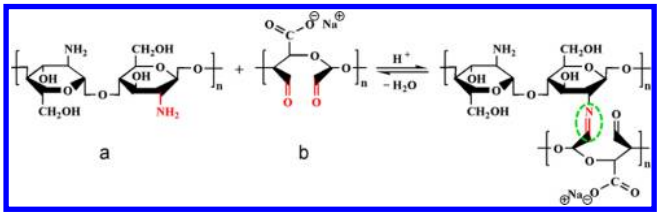

Figure 11. Schiff base reaction between (a) CHI and (b) ADA.

multilayers and removal of the templates, covalently assembled hollow microcapsules were obtained. It could be seen from Figure 12 that the obtained microcapsules possess autofluor-

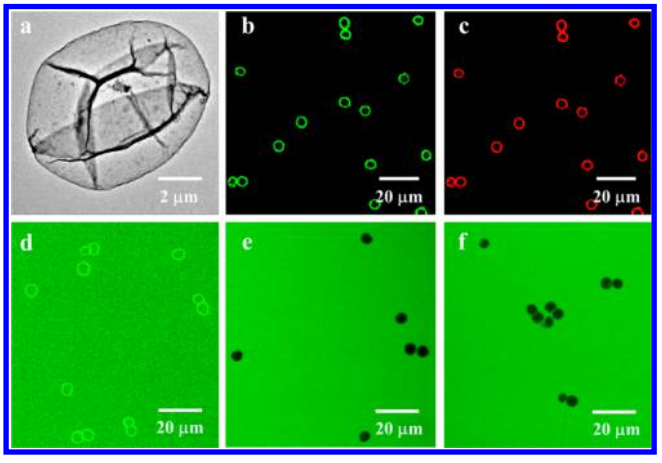

Figure 12. (a) TEM image and (b and c) CLSM images of $(CHI/ADA)_5$/CHI microcapsules, (d−f) CLSM images of $(CHI/ADA)_5$/CHI microcapsules in different pH media with FITC−dextran (20 kDa) as a probe molecule: pH 5, 7, and 9 (from left to right). Reprinted with permission from ref 58. Copyright 2011 Royal Society of Chemistry.

escent properties. This phenomenon is due to the $n-\pi^*$ transition of the C═N bonds in the Schiff bases formed between CHI and ADA.[56] The autofluorescence would be beneficial in tracing and monitoring the microcapsules in vivo, avoiding the use of extra fluorochromes. In addition, formation of a Schiff base bond also makes the microcapsules pH sensitive. Figure 12d−f demonstrates that the microcapsule wall was permeable for FITC-dextran when incubated at pH 5 while impermeable at pH 7 and 9. The distinct permeability of the microcapsules is ascribed to the dynamic property of the Schiff base bond with different pH values. Compared to pH 7 and 9, the Schiff base bond hydrolyzed faster at pH 5, making the cross-linked multilayer structures loosen and allowing FITC-dextran to diffuse through the shells. Besides, CHI assembled in the shells was charged at pH 5; therefore, the electrostatic repulsion may also contribute to the enhanced permeability. With the permeability only in low pH, such microcapsules may be used for controlled drug release, for instance, cancer therapy.

As most of the polysaccharides have *cis*-diol groups in their structure, Li and co-workers also synthesized other aldehyde polysaccharides, such as dialdehyde heparin (DHP) and dialdehyde starch (DAS), and then cross-linked them with

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CHI for preparation of microcapsules. Successful preparation of $(CHI/DHP)_5/CHI$ and $(CHI/DAS)_5/CHI$ microcapsules confirmed that this approach is also applied to other polysaccharides and their derivatives.

3.2.3. Nanotubes. Nanotubes have also been prepared with the LbL method through aldehyde polysaccharide-mediated Schiff base interactions, as demonstrated by Li and co-workers.[102] To this end, DHP was synthesized and chosen both as a wall component and as a cross-linker. Making use of the Schiff base reaction between the aldehyde groups of DHP and the amino groups of CHI, anticoagulant DHP/CHI nanotubes were obtained after assembly of DHP/CHI multilayers on the inner wall of the polycarbonate pores following removal of the template. Heparin (HEP)/CHI nanotubes bonded through electrostatic interactions were also prepared. Compared to HEP/CHI nanotubes, the stability of the DHP/CHI complex nanotubes was substantially improved due to formation of a Schiff base bond. As in the case of microcapsules, DHP/CHI nanotubes stabilized by a Schiff base bond also showed autofluorescence, which the HEP/CHI nanotubes did not have. Since DHP is a derivative of HEP, which has strong intrinsic anticoagulant activity, the anticoagulant activities of the assembled nanotubes were evaluated. The results demonstrate that the $(DHP/CHI)_8$ nanotubes had lower anticoagulation activity compared to that of $(HEP/CHI)_8$ nanotubes. Lower anticoagulation activity may be desired because it might cause severe bleeding complications. In this case, $(DHP/CHI)_8$ nanotubes have advantages over $(HEP/CHI)_8$ nanotubes as anticoagulant materials.

3.3. Aldehyde Proteins-Mediated Schiff Base Interactions

Many experimental approaches in biochemistry and applications in diagnosis or drug research require proteins immobilized on substrates.[103−105] A reliable and popular method for covalently attaching proteins to substrate surfaces involves formation of Schiff base bonds between the aldehyde and the amine groups. However, most biological molecules do not contain carbonyl aldehydes or ketones in their native state. It might be useful to create such groups on proteins,[106] especially for direct immobilization of enzymes or antibody on substrates.[107−110] In the past decade, a number of tools have been developed to incorporate aldehydes and ketones into proteins.[111,112] Here, we only discuss the glycoproteins, which usually contain sugar residues that have hydroxyls on adjacent carbon atoms. These *cis*-diols can be oxidized with sodium periodate, analogous to the above-mentioned polysaccharides, to create aldehyde proteins as a biocompatible cross-linker for covalent assembly (Figure 13). On this basis, Kim and co-workers constructed a thickness tunable enzyme multilayer film on the Au electrode surface

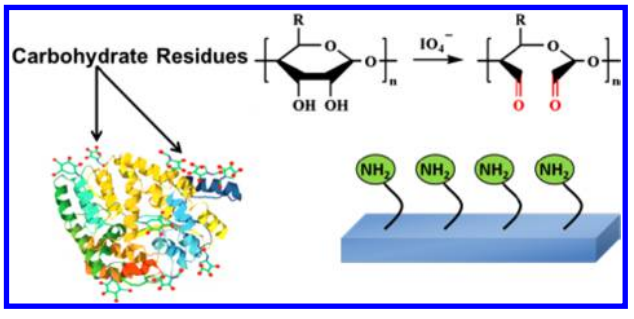

Figure 13. Preparation of multilayer films on flat solid substrate through aldehyde proteins-mediated Schiff base reaction.

through aldehyde proteins-mediated Schiff base interactions.[108,113] The basic mechanism of this covalent approach is that periodate first oxidizes the GOD to convert the numerous hydroxyl groups on its surface into aldehyde groups. In the first layer, the aldehyde groups of GOD reacted with amine groups on the Au electrode surface via a Schiff base reaction. Then excess aldehyde groups of GOD reacted with amino groups on G4 poly(amidoamine) dendrimers or ferrocenyl-tethered dendrimers. Covalent assembly between dendrimers and aldehyde−enzyme can be repeated until the number of desired bilayers is achieved. The result demonstrated that the enzyme/dendrimer multilayer forms a well-ordered and stable film on the Au electrode surface. Moreover, the sensitivity of the electrode was shown to be increased with multilayer growth. It therefore presented a simple and versatile approach for construction of multienzymes as well as single-enzyme biosensors with tunable thickness and sensitivity. A similar approach was adopted to enhance the electrode sensitivity by covalent assembly of Au nanoparticles,[114,115] carbon nanotubes,[116] and polymers[117] into multilayer films.

Besides GOD, other glycoproteins (enzymes or antibodies) can also be oxidized by periodate to form aldehyde proteins and then achieve covalent assembly.[109,118] For example, Atanassov's group and De Lacey's group exploited the fact that laccase, another glycoprotein that oxidized using sodium periodate, can covalently couple to form a Schiff base with the amine group-modified Au substrate.[109,118] This allows for one-step immobilization of proteins under mild conditions. Thus, periodate-oxidized proteins open up a new way for simple, rapid, and direct immobilization of proteins on aminated surfaces of substrates under mild conditions without using extra coupling agents.

3.4. Other Aldehyde Compound-Mediated Schiff Base Interactions

In addition to GA and aldehyde polysaccharides, many other aldehyde compounds have also been used in LbL assembly for fabrication of various micro- and nanostructures through Schiff base interactions.

3.4.1. Planar Films. Formaldehyde (FA) is probably the most commonly used cross-linking fixative in histology and cytology, owing to its small molecular weight which allows it to penetrate tissues and cells rapidly. It has a single aldehyde-containing carbon, exists as a gas, and is commercially available in solution ("formalin"). Since ssDNA and BSA can be covalently cross-linked with FA, a stable and biocompatible ssDNA/BSA multilayered film was assembled by Li and co-workers.[119] The ssDNA/BSA multilayered film was shown to be degradable through incubation with proteinase K, followed by release of ssDNA. Thus, the BSA assembled in this film could be employed as a trigger for controlled release of DNA (Figure 14). With this approach it is possible to fabricate thin film-based gene therapy systems, which have great potential in certain disease treatment. However, it should be mentioned that FA is less effective than GA as a cross-linking agent; for this reason it is rarely used in LbL assembly of multilayered films.

In sections 3.1 and 3.2, GA and aldehyde polysaccharides were involved in the activation of aminated surfaces to create aldehyde groups, which then reacted with the amine groups of biomolecules for covalent immobilization of biomolecules. The process needs multiple treatments to anchor biomolecules on substrate surface, which is time consuming and introduces unstable reagents such as cross-linkers that may intervene in some applications. For glycoprotein introduced in section 3.3,

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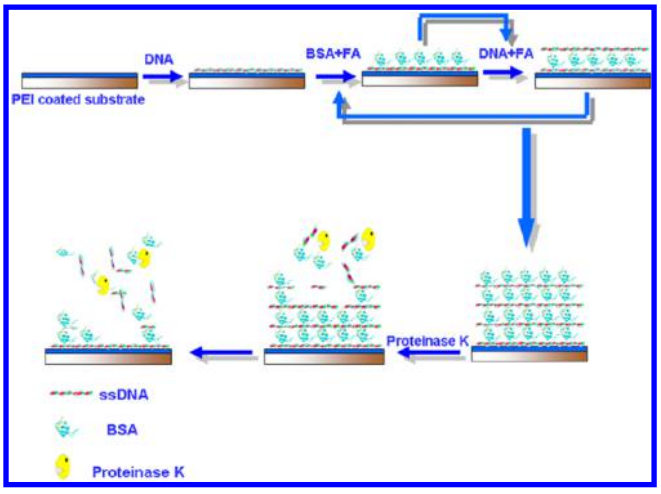

Figure 14. Construction and degradation of covalently linked ssDNA/BSA multilayered film. Reprinted with permission from ref 119. Copyright 2007 Elsevier.

the carbohydrate moieties on its surface can be partially oxidized by periodate to form aldehyde proteins, which could directly react with the amine group on a solid surface through Schiff base reaction, allowing for one-step immobilization of proteins on solid substrate. However, many biomolecules do not contain carbonyl aldehydes or ketones in their native state, and introduction of aldehydes or ketones into biomolecules is complicated and may also influence their biological activities.[120] An alternative to this procedure is the use of aldehyde-modified solid surfaces, which could directly anchor amino-containing biomolecules through Schiff base reaction.[105,121−127] Zare and co-workers realized a one-step attachment of trypsin to aldehyde-modified monolith surface via Schiff base reaction, in which an alkoxysilane reagent with an aldehyde functional group was employed as a cross-linker (Figure 15).[122] The immobilized

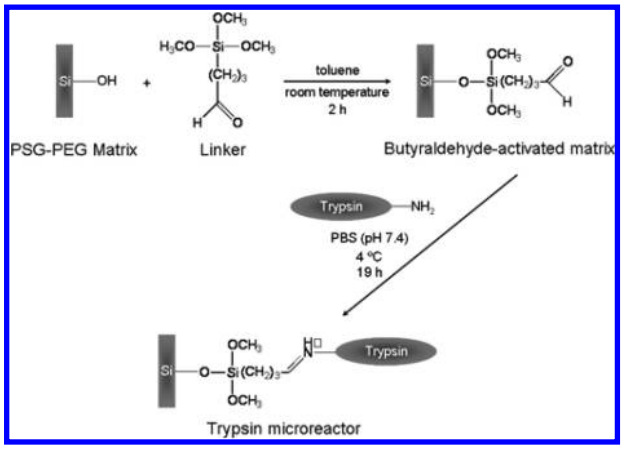

Figure 15. Direct attachment of trypsin to a trimethoxysilylbutyraldehyde-activated monolith. Reprinted with permission from ref 122. Copyright 2005 American Chemical Society.

trypsin exhibited long-term stability and enhanced bioactivity compared with those in solution. Besides, protein IgG and DNA/RNA have also been reported to be directly anchored on 3-aldehydepropyltrimethoxysilane- and trimethoxysilylalkylaldehyde-functionalized solid surface, respectively,[123,125] further confirming the versatility and broad applicability of the method.

In general, solid surfaces (glass, Si, SiO_2, etc.) can easily be modified by aldehyde alkoxysilane to introduce aldehyde groups on their surfaces. However, on certain metals alkanethiols with an aldehyde functional group may be more effective and the best choice. Myles and co-workers demonstrated the construction of aldehyde-terminated self-assembled monolayers (SAMs) on Au surfaces with an open-chain aldehyde-terminated alkanethiols isomer of 2-hydroxypentamethylene sulfide (HPMS).[128] The aldehyde-terminated Au surfaces could directly anchor amino compounds through Schiff base reaction without the help of extra coupling agents. This makes the procedure well suited for immobilizing enzymes and other receptor onto Au surfaces to construct biosensor. However, in some cases, it is demonstrated that the enzyme linked to short thiolate spacers may easily deactivate due to the interaction of the protein with bare Au domains. To avoid this, thiolate layers with long spacers on electrode supports were used. Smith and co-workers exploited the aldehyde-terminated alkanethiols with 11-carbon alkane chains to create aldehyde functionalities on Au surfaces.[129] Fabrication of DNA arrays and subsequent hybridization is illustrated in Figure 16. Compared to the shorter 5-carbon alkane

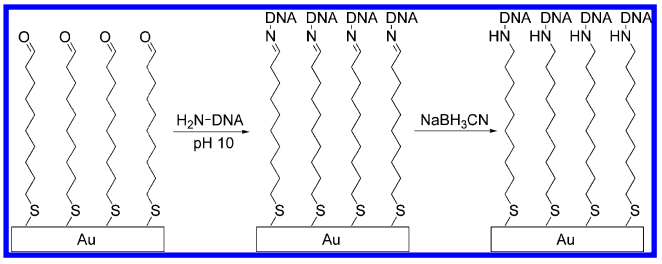

Figure 16. Immobilization of DNA on aldehyde alkanethiol-modified Au surface. Reprinted with permission from ref 129. Copyright 2005 American Chemical Society.

chains (HPMS), a more ordered monolayer and improved stability were obtained using long alkane chain. Since dynamic Schiff base linkage is undesirable for efficient recognition in a biosensor, it was reduced with $NaBH_4$ or $NaBH_3CN$ to generate a stable secondary amine.

The above-mentioned aldehyde cross-linking agents involved in LbL assembly through Schiff base reactions are all flexible aliphatic aldehydes. However, many reports have indicated that the alkyl SAMs easily interact with another substance (e.g., biomolecules, nanoparticles, etc.) and result in severe disorder within the film.[130−132] This issue can be resolved by replacing alkyl compounds with aryl compounds, which have strong intermolecular $\pi-\pi$ interactions in the SAMs that may reduce the disorder and enhance the stability of the film. Moreover, these SAMs assembled with aryl compounds possess intriguing optical and electrical properties, which may have great potential in optoelectronic devices.[132,133] Jen and co-workers demonstrated the use of (10-mercaptomethyl-9-anthryl)-(4-aldehydephenyl)acetylene (MMAPA) molecule, an aldehyde-terminated arylthiol, to introduce aldehyde groups on the Au surface.[132,134−136] Then the aldehyde-terminated SAM was employed to anchor specific polypeptides or proteins through Schiff base reactions and subsequent assembly of Au nanoparticles (AuNPs), quantum dots, or cells. For example, their group reported the patterning of polypeptides (gold-binding protein, GBP-1) on MMAPA-modified Au surfaces by microcontact printing (μCP). Schiff base reaction between GBP-1 and MMAPA occurs only in the areas where a patterned PDMS

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stamp is contacted. An atomic force microscopy (AFM) image shows that the GBP-1/MMAPA hybrid assemblies are well-ordered and homogeneous. The as-prepared patterned GBP-1 was then functioned as a template for assembly of Au nanoparticles. In comparison with physically adsorption of GBP-1, covalently grafted GBP-1 on the SAMs of MMAPA molecules is more powerful as a coupling reagent in capturing Au nanoparticles. In a similar way, quantum dot arrays and cell arrays have also been constructed by this group.[134,136] A noteworthy advancement made by this group was arrays of single AuNPs. In this work, MMAPA was used to backfill the nanoholes produced by lithography of 11-mercaptoundecanoic acid (MUA) on Au substrate and then reacted with 5-amino-2-mercaptobenzoimidazole (MBIZ) through Schiff base reaction, leaving free thiol groups for subsequent covalent bonding with AuNPs, as illustrated in Figure 17.[132] Covalent attachment of single

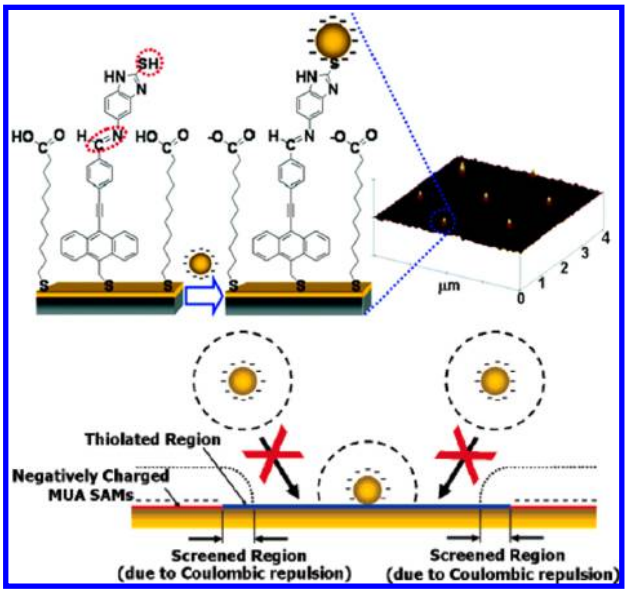

Figure 17. Covalent attachment of single AuNPs and the proposed mechanism. Reprinted with permission from ref 132. Copyright 2006 American Chemical Society.

AuNPs was achieved by exploiting a synergistic effect of electrostatic interactions (electrostatic repulsions between AuNPs themselves and MUA SAMs) and short-range covalent bonding. Covalent bonding of AuNPs onto a functional interface is very important to many disciplines and has a profound influence on construction of 2-D hybrid architectures.

Apart from the MMAPA, other aromatic aldehydes, such as terephthaldialdehyde (Figure 18a),[137−140] salicylaldehyde (Figure 18b),[141,142] 2-perfluorohexylethyl-4-formylthiobenzoate (Figure 18c),[143] and 5-formaldehyde-2,2′:5′,2″-terthiophene (Figure 18d),[144] have also been used in molecular assembly for fabrication of multilayer films through Schiff base interactions. For instance, terephthaldialdehyde is employed as a cross-linker for covalent assembly of phenyl-amine-functionalized single-walled carbon nanotubes (PA-SWCNT) and metal tetra-amino phthalocyanine (MTAPc) on phenyl-amino-functionalized gold electrode.[139] The choice of using terephthaldialdehyde as a cross-linker enables extension of the electronic delocalization between PA-SWCNT and MTAPc complexes. This extension of electronic delocalization promotes the conductivity of the hybrid systems, lowers the reduction potential, and increases the electrocatalytic activity. The electrochemical sensing of H_2O_2

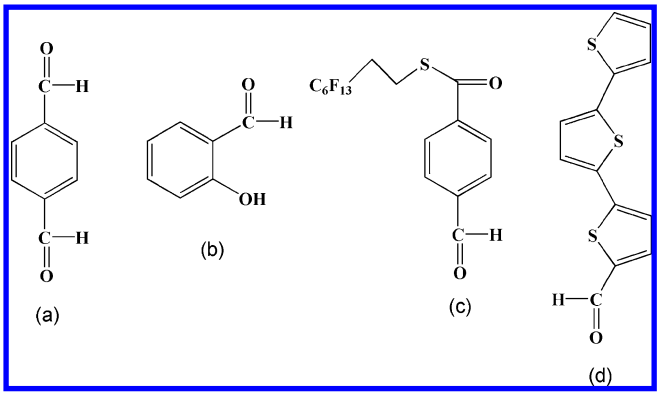

Figure 18. Series of aromatic aldehyde involved in molecular assembly of multilayer films.

was successfully conducted with the hybrid systems, showing excellent electrocatalytic activity. Besides, terephthaldialdehyde has also been used for fabrication of robust multilayer films in biomedicine applications, like cell patterning,[138] cell culture,[140] etc. Since the Schiff bases of salicylaldehyde and its derivatives could coordinate with some metal ions, especially for copper, salicylaldehyde assembled on an electrode surface through Schiff base reaction could be used as a copper ion sensor and its relevant applications, for example, for electrocatalysis of *p*-benzoquinone.[142]

In addition to the above-mentioned small molecular aldehyde cross-linkers, Kataoka and co-workers synthesized heterotelechelic PEG/PLA block copolymer bearing an acetal group and a methacryloyl group at each end (acetal-PEG/PLA-methacryloyl). The heterotelechelic acetal-PEG/PLA-methacryloyl block copolymers assemble spontaneously into spherical core−shell-type nanomicelles. In an acid environment, the acetal groups on the surface of the nanomicelles easily convert into reactive aldehyde groups.[145] These aldehyde-bearing micelles with densely packed PEG brushes on the surface were demonstrated as a robust reagent for surface modification of aminated substrates through Schiff base reaction.[146] In particular, this surface modification procedure was applied further for multilayer structure construction via alternate coating with polyallylamine and nanomicelles.[146−148] The resulting multilayer film is a thickness-tunable hydrogel structure with nonfouling surfaces. It can be used as a permselective membrane or a reservoir for hydrophobic reagents, which may exhibit high performance in medical devices for tissue engineering and drug delivery systems.[149,150]

Another kind of macromolecular aldehyde cross-linkers are aldehyde dendrimers, developed by Majoral and co-workers.[151−154] Aldehyde dendrimers possess some advantages over linear or partly branched aldehyde compounds, e.g., homogeneous structure, controllable composition, internal porosity, comparable size to biomolecules, and multiple homogeneous aldehyde groups available for coupling reactions.[113] With these unique features, aldehyde dendrimers are widely used in surface modification and subsequently for construction of functional multilayer films. Majoral and co-workers first modified the solid substrate (quartz or glass) with γ-aminopropyltriethoxysilane (APTS) and then reacted with aldehyde dendrimers through Schiff base reaction. Compared to the untreated substrate, an obvious reduced wettability of the modified substrate is observed, showing the hydrophobic character of these dendrimers.[155] In view of excess aldehyde groups remaining on the surface of

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dendrimers, further covalent grafting of NH_2-teminated dendrimers, nanoparticles, or proteins could be easily conducted.[71,108] For instance, this method was applied for immobilization of biomolecules such as DNA to create biochips.[152−154] The glass slides functionalized with the spherical dendrimeric structures provide large surfaces for binding more DNA and are envisaged to improve the detection sensitivity compared to using small aldehyde molecules.

3.4.2. Capsules. Multifunctional polymeric microcapsules have been widely studied due to their potential applications in drug delivery and other biomedical fields. However, the polyelectrolyte hollow microcapsules obtained through noncovalent bonds would always give concern regarding disintegration or aggregation in solutions with extreme pH and high salt concentrations.[156,157] This seriously restricts their practical application in humans. It is well known that PEG has extraordinary antifouling ability, low toxicity, and low immunogenicity, making it a suitable material for surface modification to impart functionality, water solubility, low fouling property, and biocompatibility.[158] Liu and co-workers grafted PEG-CHO onto polyelectrolyte hybrid hollow microcapsules through Schiff base reaction between aldehyde groups of PEG-CHO and amino groups on the microcapsules surface.[157,159] Compared with those microcapsules without PEG modification, PEGylation treatment not only improves the biocompatibility of the microcapsules but also effectively prevents aggregation and fusion of the microcapsules in high-salt media. When employed as drug vehicles, PEGylation of the polyelectrolyte microcapsules also enhanced the drug-loading capacity and improved the sustained release performance, ensuring their potential in targeted drug delivery. Almost at the same time, Xie and co-workers reported that modification of alginate/chitosan/alginate microcapsules with methoxy poly(ethylene glycol) (MPEG-CHO) helps to reduce the nonspecific protein adsorption and improves the biocompatibility in vivo.[160] Besides, the influence of different grafting parameters of MPEG on protein repellency was systematically investigated. The results indicated that neutralizing with alginate, increasing membrane thickness, and in situ covalent grafting could effectively increase surface graft density of MPEG, enabling almost complete immunity to protein adsorption. This antifouling material is very promising to be applied in biomedicine, especially for transplantation in vivo.

Recently, Gao and co-workers fabricated novel fluorescent microcapsules through Schiff reaction between the $-NH_2$ groups of PAH and −CHO groups of 1-pyrenecarboxaldehyde (Py-CHO) on PAH-doped $CaCO_3$ templates. Removal of the $CaCO_3$ templates yielded hollow PAH-Py microcapsules, as shown in Figure 19.[161] Surprisingly, an intriguing phenomenon of protrusion of one-dimensional nanotubes (1D-NTs) from the PAH-Py microcapsules was observed when incubating in pH 0 solution. The 1D-NTs grew with the incubation time and eventually form a reticulate structure, accompanying with gradual disappearance of microcapsules (Figure 19c−e). The 1D-NTs consisting of only Py-CHO exhibit a helical structure and anisotropic property. Interestingly, when changing the pH from 0 to 2, short 1D nanorods (1D-NRs) instead of the long 1D-NTs were obtained. This phenomenon is mainly due to the different hydrolysis rate of the Schiff base at different pH values. The obtained microcapsules with protruding Py-CHO NRs on the surface show excellent fluorescence properties due to the intrinsic property of Py and are expected to function as advanced fluorescent devices. However, during the NRs protruding process, the microcapsules are not thermodynamically stable

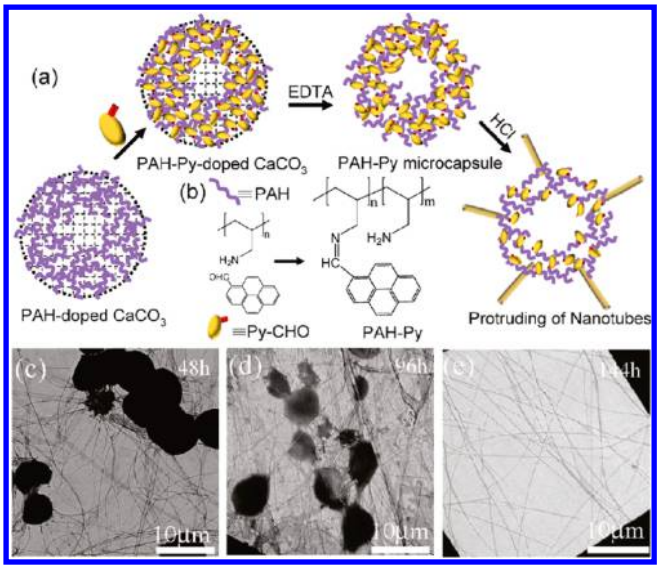

Figure 19. (a) Schematic illustration of PAH-Py microcapsule fabrication and 1D-NT protrusion. (b) Chemical structures of PAH, Py-CHO, and PAH-Py. (c, d, and e) TEM images showing the process of nanotube protruding from the PAH-Py microcapsules incubated in pH 0 HCl for 48, 96, and 144 h, respectively. Reprinted with permission from ref 161. Copyright 2011 American Chemical Society.

and eventually disappear owing to dissociation of the Py groups. Therefore, different measures have been adopted to obtain stable composite microcapsules-NRs in a controllable way. One attempt is cross-linking the PAH-Py microcapsules with GA before template removal.[162] After cross-linking, the microcapsules can remain stable even after 1D-NRs protrusion, and the fluorescence of Py on the surface of the microcapsules remains strong. The 1D-NRs could be repeatedly protruded by adjusting the reversible Schiff base formation and hydrolysis. Moreover, the length and coverage rate of 1D-NRs on the capsule surface can easily be adjusted in terms of the pH value of the incubation solution.

Another attempt is to assemble the Py-CHO NRs inside the microcapsules.[163] For this purpose, poly(sodium styrenesulfonate) (PSS) and PAH were alternately deposited on the surfaces of PAH-Py-doped $CaCO_3$ particles, obtaining the PAH-Py/$(PSS/PAH)_n$ microcapsules. When incubating in pH 2 solution, the 1D-NRs grow only within the $(PSS/PAH)_n$ microcapsules without protruding outside the microcapsules shells (Figure 20), demonstrating the restriction and protection effect of the polyelectrolyte multilayers under these conditions. In situ Py-CHO NRs formation inside the microcapsules offers a novel strategy for hybrid nanomaterials fabrication and demonstrates its application in smart nanodevices.

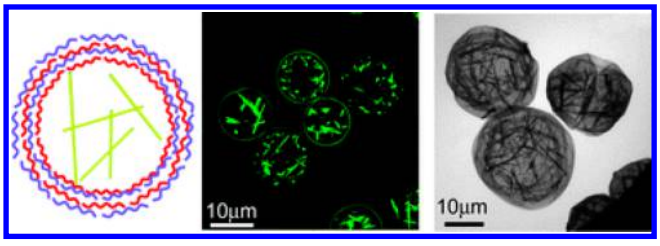

Figure 20. Formation of Py-CHO NRs inside the $(PSS/PAH)_n$ double-shell microcapsule and its CLSM and TEM images. Reprinted with permission from ref 163. Copyright 2012 Royal Society of Chemistry.

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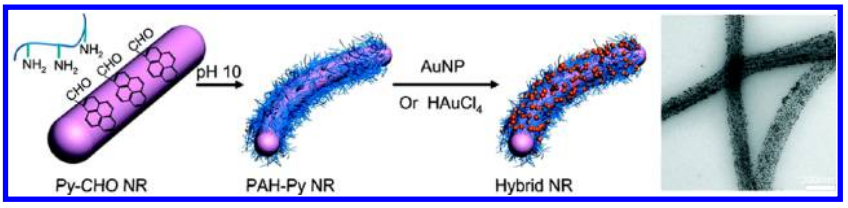

Figure 21. Fabrication of hybrid NRs from Py-CHO NRs, PAH, and metal nanoparticles. Reprinted with permission from ref 164. Copyright 2011 American Chemical Society.

3.4.3. Nanorods. Inspired by the above findings, Gao and co-workers further prepared multifunctional organic/inorganic hybrid NRs consisting of a Py-CHO NRs core and a PAH shell through Schiff base reaction, followed by Au or Pt nanoparticles decoration, as shown in Figure 21.[164] The PAH-Py NRs were annealed at 80 °C and showed good suspension stability in water. Considering the excess amino groups of PAH, Au or Pt nanoparticles can be either physically adsorbed or in situ reduced on the PAH-Py NRs surface. More importantly, the PAH layer modified on the surface of Py-CHO NRs plays a vital role in isolation of Py and the Au nanoparticles, preventing quenching of the fluorescence. Similarly, other hybrid organic/inorganic nanomaterials could be synthesized. This method presents a novel strategy in decorating organic surfaces with inorganic nanoparticles and offering them with multifunction.

3.4.4. Nanotubes. By applying the Schiff base chemistry, ingenious corking nano test tubes were developed by Martin and co-workers,[165] as illustrated in Figure 22. Silica nanotubes were

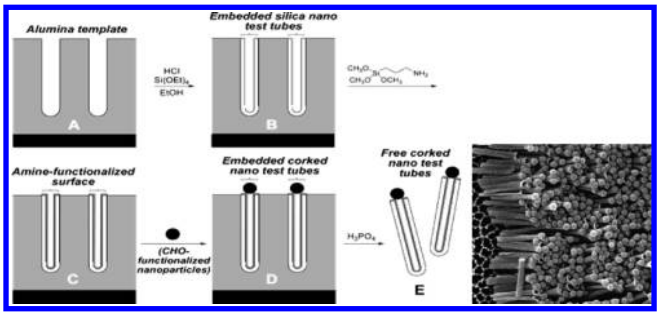

Figure 22. Schematic illustration of the synthesis and corking processes of the test tubes and their SEM image. Reprinted with permission from ref 165. Copyright 2006 American Chemical Society.

first synthesized within the nanopores of alumina films, followed by functionalization with aminosilane. Before removal of alumina template, the open ends of amino-functionalized silica nanotubes were spontaneously corked with aldehyde-terminated polystyrene nanoparticles via Schiff base linkage. With one open end that may be filled and subsequently capped, the nanotubes could be explored as drug carriers. Since the Schiff base is sensitive to pH, the cap could then be removed or biodegraded inside the cell, achieving controlled drug release. The open ends of the nanotubes could also be corked with other chemically reliable caps and used as different responsive carriers for universal drug delivery.

3.4.5. Spheres. Similar to the corking nano test tubes, Stoddart, Zink, and co-workers developed pH-manipulated nanopores on mesoporous silica nanoparticles for controlled drug release (Figure 23).[166] The mesoporous silica nanoparticles (MSNPs) were first modified with benzaldehyde derivatives to create aldehyde groups on its surface. Upon loading with rhodamine B molecules, the nanopores of MSNPs were capped

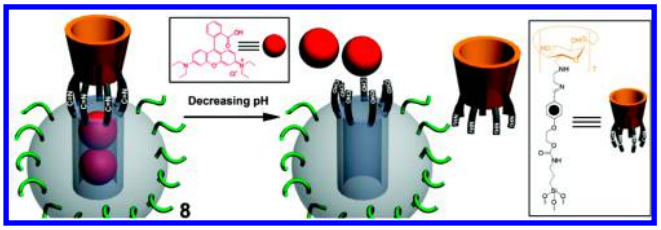

Figure 23. pH-manipulated nanopores prepared from diamino-β-CD derivative and the formyl-functionalized MSNPs in the presence of rhodamine B cargo through the Schiff base reaction. Reprinted with permission from ref 166. Copyright 2010 American Chemical Society.

with diamino-β-CD derivatives through a Schiff base bond. The rhodamine B molecule was chosen as cargo due to its suitable size so that it could not leak from the nanopores of MSNPs through the cavity of the β-CD ring. Thus, only when hydrolysis of the Schiff base bonds occurred under acidic conditions the rhodamine B cargo could be released from the nanopores owing to cleavage of the β-CD rings from the MSNPs surfaces. In another case, the Schiff base bond formed on MSNPs surfaces was reduced with $NaBH_4$ to generate C−N single bonds, and benzidine/rhodamine B conjugate was employed as nanopistons. These small benzidine/rhodamine B conjugates were loaded within MSNPs nanopores at neutral pH and released from β-CD cavities upon protonation at lower pH. With this technology it is possible to load drugs with different size and trigger release of both drugs using pH stimuli.

At the end of this section, it should be explained that molecular assembly through Schiff base reaction between ketones and amino groups was not presented in this review. This is because the reactivity of ketones is relatively low and not sufficient for LbL assembly.[167] Ketone has alkyl groups on either side of the carbonyl that not only contributes to steric hindrance in nucleophilic reactions but also stabilizes partial positive charge on the carbon atom of the carbonyl group. Therefore, studies rarely used ketones in molecular assembly.

4. MULTIRESPONSIVE ASSEMBLY FABRICATED THROUGH A SCHIFF BASE BOND

In previous sections, we introduced recent works on fabricating novel types of LbL-based micro- and nanostructures through Schiff base interactions. Formation of a Schiff base bond endows the micro- and nanostructures with stability, autofluorescence, and pH sensitivity. However, this is still not enough for the requirements in some practical applications. In this section, fabrication of a multiresponsive LbL-derived assembly through combination of the merits of Schiff base interactions with responsive materials is introduced.[168−177]

4.1. pH- and Glucose-Responsive Assembly

GOD is known to catalyze the oxidation and hydrolysis of glucose into gluconic acid and H_2O_2.[172,178] In view of the glucose sensitivity of GOD and pH sensitivity of a Schiff base bond, Li

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and co-workers fabricated a series of GOD-based capsules through GA-mediated Schiff base interactions, including GOD, GOD/Hb, and Cat/GOD capsules.[168−171] Take Cat/GOD capsules as an example: GOD can convert glucose into gluconic acid and H_2O_2, while Cat catalyzes the reduction of H_2O_2 into H_2O and O_2, and most of the O_2 produced is consumed again by GOD. Thus, two enzymatic reactions are coupled together (Figure 24a), making these capsules glucose sensitive.[171] It can

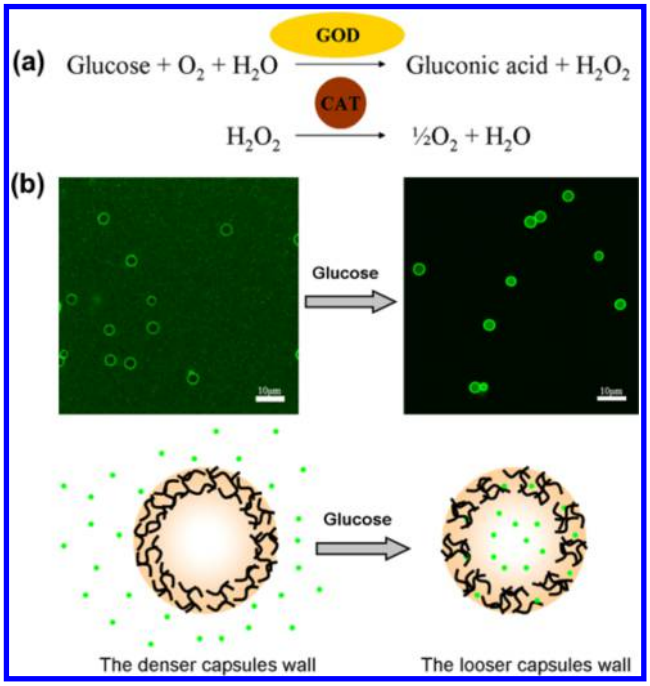

Figure 24. (a) Coupled enzymatic reaction between GOD and Cat on the capsule wall; (b) glucose-stimulated enhancement of the GOD/Cat capsules wall permeability. Reprinted with permission from ref 171. Copyright 2009 Elsevier.

be observed from Figure 24b that the presence of glucose enhanced the permeability of the capsule walls with FITC-dextran penetrating into capsules. This can be attributed to degradation of the Schiff base bond in acidic media caused by production of gluconic acid, thus loosening the multilayer structure and enhancing the wall permeability. This result is consistent with the results of pH-sensitivity tests of Cat/GOD capsules.[171] The pH- and glucose-responsive microcapsules are envisaged to have great potential in controlled release of hypoglycemic drugs (for example, insulin) in diabetes therapy.

4.2. pH- and Redox-Responsive Assembly

It is well known that disulfide or diselenide bonds could be reduced to single thiols or selenols in the presence of glutathione (GSH). The transition between oxidative and reductive states has been utilized to trigger decomposition of drug delivery systems after cellular uptake, promoting development of diverse redox-responsive carriers.[179] Following this basic route, Li and co-workers chose redox-responsive polymer−cystamine dihydrochloride (CM) as one of the wall components to cross-link with ADA through Schiff base interactions, expecting to obtain pH- and redox-responsive microcapsules through the LbL technique.[173] As in the microcapsules and nanotubes described above, the $(ADA/CM)_5$ microcapsules also exhibit autofluorescence with 405 nm as the best excitation wavelength. To examine the pH- and redox-responsive properties of $(ADA/CM)_5$ microcapsules, the permeability of microcapsules in different pH and redox solution was studied. The results showed that without dithiothreitol (DTT, a common reducing agent), the microcapsules were permeable to FITC-dextran at pH 5 while impermeable at pH 7.4. This confirms the pH sensitivity of $(ADA/CM)_5$ microcapsules due to the Schiff base bond formed in the microcapsules.[58] Adding 10 mM DTT to pH 7.4 while keeping the other parameters unchanged it is interesting to find that the microcapsules become permeable to FITC-dextran at pH 7.4. The improved permeability can be attributed to cleavage of disulfide within capsules walls at reducing conditions. This dual sensitivity may offer new opportunities for the capsules as efficient drug delivery carriers.

In addition to redox-responsive disulfide compounds, it has to be mentioned another fascinating class of redox-responsive materials, ferrocene and their derivatives, a series of organometallic compounds that is well known for their redox properties and stability. Gao and co-workers employed ferrocenecarboxaldehyde (Fc-CHO) as a cross-linker for fabrication of redox-responsive PAH-Fc microcapsules through Schiff base interactions.[174] The microcapsules have very thick shells that are stabilized by the hydrophobic aggregation of Fc moieties and the protection of PAH backbone. Due to the outstanding redox property of Fc, the PAH-Fc microcapsules exhibit reversible swelling and shrinking in response to oxidation and reduction, accompanied by reversible permeability changes. The reversible change in size and permeability of the microcapsules was exploited to controlled loading and release of dextran, as shown in Figure 25. The release rate could be easily controlled by the

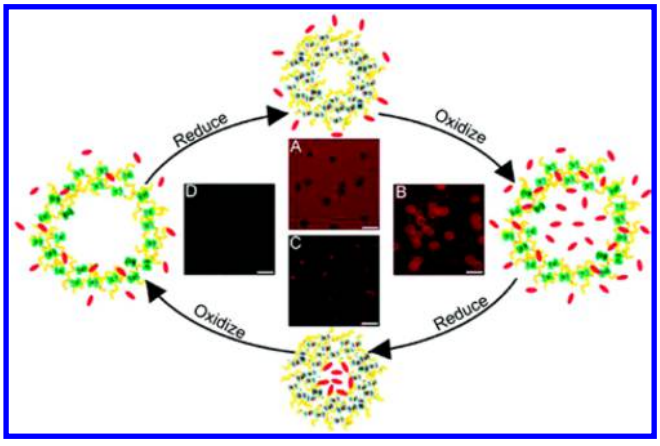

Figure 25. Redox-mediated loading and release of dextran. Reprinted with permission from ref 174. Copyright 2010 American Chemical Society.

stoichiometry of the Fc redox reaction. It should be mentioned that these microcapsules are not pH responsive since the Schiff base bond formed between Fc−CHO and PAH was reduced by excess $NaBH_4$. However, it can be envisaged that microcapsules obtained without reducing by $NaBH_4$ should be pH and redox responsive, which are good candidates for intracellular anticancer drug delivery.

4.3. pH- and Magnetic-Responsive Assembly

Magnetic nanoparticles are promising stimuli-sensitive drug carriers. An applied magnetic field can concentrate these nanoparticles at a desired site and then release the encapsulated drug, thereby reducing the drug-associated side effects due to nonspecific distribution.[180] Sun and co-workers grafted 6-

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hydroxy-chromone-3-carbaldehyde to the surfaces of PEG-dopamine (DPA) modified Fe_3O_4 nanoparticles via Schiff base chemistry (Figure 26).[176] The chromone coupled to PEG-DPA-

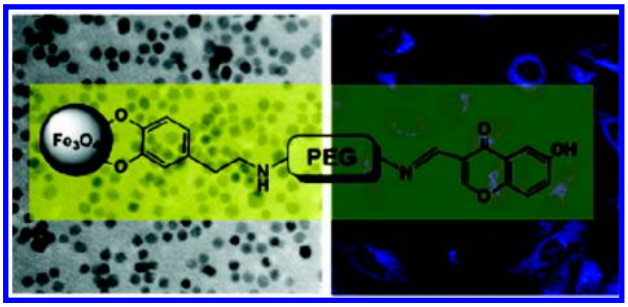

Figure 26. Coupling of chromone onto the surface of a Fe_3O_4 nanoparticle via Schiff base reaction, corresponding TEM image and CLSM image in HeLa cells. Reprinted with permission from ref 176. Copyright 2008 American Chemical Society.

Fe_3O_4 nanoparticles substantially increased the solubility of chromone from less than 2.5 to 633 $\mu g\ mL^{-1}$ in cell culture media, and the free chromone can be controlled released through hydrolysis of the Schiff base bond at low pH media. Therefore, plus the fluorescent chromone, the pH responsive Schiff base bond and superparamagnetic Fe_3O_4 nanoparticles render the hybrid nanoparticles a powerful multifunctional carrier for both diagnostics and therapeutics.

5. BIOMEDICAL APPLICATIONS OF THE PRODUCTS FABRICATED THROUGH SCHIFF BASE INTERACTIONS

5.1. Drug Delivery

One of the most important applications of the LbL assembly (flat membranes, capsules, or particles) is drug delivery.[21,181] These systems carry encapsulated drugs to predetermined sites and release them in a controlled manner. Controlled drug release could minimize unwanted side effects, protect drugs from enzymatic degradation, and allow stimulus-responsive release or targeted release.[16,182,183]

Among drug delivery systems, delivery of anticancer drugs has been extensively studied.[51,184] It is well known that the tissues around cancer cells have a lower pH compared to those of normal cells. Therefore, design of pH-sensitive drug delivery vehicles is favorable to improve therapy efficiency for tumor treatment.[185,186] Considering that the Schiff base bond hydrolyzed faster at low pH, assemblies fabricated through Schiff base interactions are well suited for delivery of anticancer drugs. Gao and co-workers loaded the antitumor drug doxorubicin (DOX) into GA cross-linked polysaccharides microcapsules.[187] The in vivo study showed that the encapsulated DOX had better therapy efficiency than that of the free drug during 4 week culture. To achieve targeted delivery, specific ligands (for example, folic acid) were conjugated to the surface of microcapsules.[188] These folic acid-functionalized microcapsules showed high selectivity to tumor cells, providing them with large opportunity to function as a targeted delivery vehicle for controlled release of anticancer drugs.

Considering the differences between the environment in the bloodstream (neutral pH and low concentration of GSH) and subcellular structures in tumor cells (low pH and high concentration of GSH),[189] pH- and redox-responsive $(ADA/CM)_5$ microcapsules through covalent assembly of the Schiff base bond and disulfide bond have been engineered by Li and co-worker for delivery of docetaxel (Figure 27).[173] As discussed

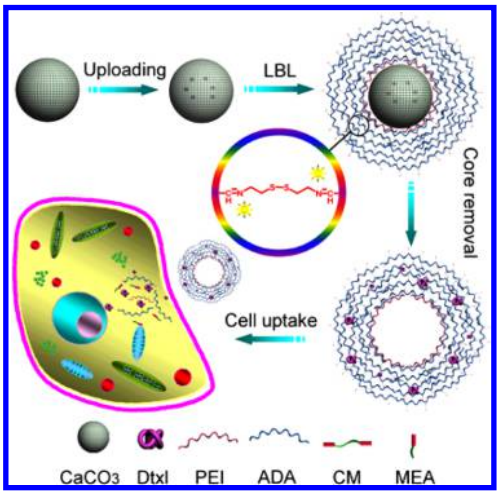

Figure 27. LbL assembly of pH- and redox-responsive microcapsules through Schiff base and disulfide bonds for controlled release of docetaxel. Reprinted with permission from ref 173. Copyright 2012 Wiley-VCH Verlag GmbH & Co. KGaA.

before, Schiff base- and disulfide-bonded capsules are stable under neutral and oxidizing conditions but readily degrade in acidic and reducing environments. Thus, docetaxel-loaded $(ADA/CM)_5$ capsules readily triggered drug release in tumor cells and prevented unwanted release in the bloodstream. As a proof-of-concept demonstration, a MTT cell viability assay was conducted to evaluate the cytotoxicity of docetaxel-loaded capsules in tumor cells. The results confirm that the docetaxel are successfully loaded in the microcapsules and could be controlled released in tumor cells through the carriers' response to intracellular low-pH and reduction conditions.

With the advances in understanding and manipulating genes, gene therapy has aroused increasing concerns in the field of disease treatment (mainly aimed at cancer and hereditary diseases), owing to its high therapy efficacy, specific selectivity, nontoxicity, and broad scope of application.[190,191] As introduced in the previous section, GA cross-linked DNA/PLL multilayered films have been fabricated for controlled DNA release,[78] and the kinetics of DNA release can be easily and finely modulated by the cross-linking density of GA. Compared with multilayered films, controlled release of DNA from microcapsules is considered to be a more promising method. Yang and co-workers prepared hollow DNA/PLL microcapsules through the LbL technique, followed by GA cross-linking.[192] Similar to the DNA/PLL multilayered films, the release profiles of DNA from DNA/PLL microcapsules could be easily and precisely regulated in terms of the cross-linking density of GA. Moreover, the hollow cavity of the capsule could be used to encapsulate other nongene drugs, thus achieving dual carriers for DNA and chemotherapeutics at the same time. This dual-carrier system is expected to induce higher efficiency on cancer therapy owing to the synergistic effect of DNA and nongene drug.

The rapid developments of gene therapy and concomitant DNA-recombinant techniques have led to the emergence of protein drugs as a very promising class of therapeutic reagents. Therefore, it is not surprising that microsphere-based therapy has been increasingly studied.[56] Ma and co-workers prepared Schiff base-bonded monodisperse microspheres of chitosan and/or a

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quaternized chitosan derivative *N*-(2-hydroxyl) propyl-3-trimethylammonium chitosan chloride (HTCC) through cross-linking with glutaraldehyde and/or *p*-phthaldehyde.[56] Microspheres with different structures accompanying with different drug loading capacity and release profiles were obtained (Figure 28). The diverse structures of microsphere enabled these

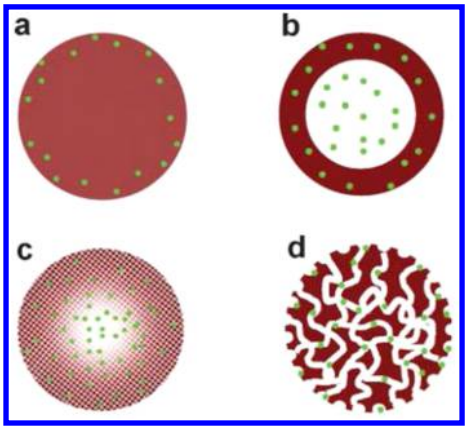

Figure 28. Loading patterns of BSA (green dots) in Schiff base-bonded microspheres prepared by different methods: chitosan (C) or HTCC (H) cross-link with glutaraldehyde (G) and/or *p*-phthaldehyde (P). (a) C-G microspheres, (b) C-PG microspheres, (c) CH-G microspheres, and (d) CH-PG microspheres. Reprinted with permission from ref 56. Copyright 2008 Wiley-VCH Verlag GmbH & Co. KGaA.

microspheres to cater to specific requirements for various drug vehicles. For example, CH-G microspheres with high porosity and large cavities (Figure 28c) showed a minimal initial burst and sustained release. They are desirable carriers for drugs (e.g., insulin, interferon) that require drugs being maintained at specific therapeutic concentrations.[193] In contrast, macroporous CH-PG microspheres with a strong initial burst (Figure 28d) are much better suited for pulsed therapy, such as cancer therapy.

In addition to chemotherapy and gene therapy, photodynamic therapy (PDT) with high selectivity and limited adverse effects is another promising method for treatment of cancer. The cytotoxicity is only induced at tissues exposed to the photosensitizers that are activated by light of an appropriate wavelength. However, this method is limited by the light accessibility since visible light cannot reach all sites of tissues. Therefore, a mobile light that can be delivered to tumors is highly desired. Very recently, Li and co-workers designed and fabricated a kind of bioluminescent microcapsules by covalent LbL assembly of ADA and luciferase (fLuc) on luciferin coprecipitated $CaCO_3$ microparticles.[194] In the presence of O_2, Mg^{2+}, and ATP, fLuc could catalyze oxidation of its substrate luciferin to produce light. This then could be used to activate photosensitizers for production of active oxygen ($^1O_2$), as shown in Figure 29. Cytotoxicity tests confirmed that photosensitizers in the capsules could be activated by excitation of bioluminescent microcapsules in the dark without external light and prevent cell proliferation. In addition, the as-prepared microcapsules also displayed autofluorescence due to the Schiff base bonds formed between fLuc and ADA. This dual-luminescent system has potential applications in simultaneous bioimaging and photodynamic therapy.

Apart from anticancer drug delivery, Schiff base-bonded particles have also been used for delivery of hypoglycemic drug, for example, insulin.[171,172] Li and co-workers salted out insulin particles with NaCl from insulin acid solution, followed by

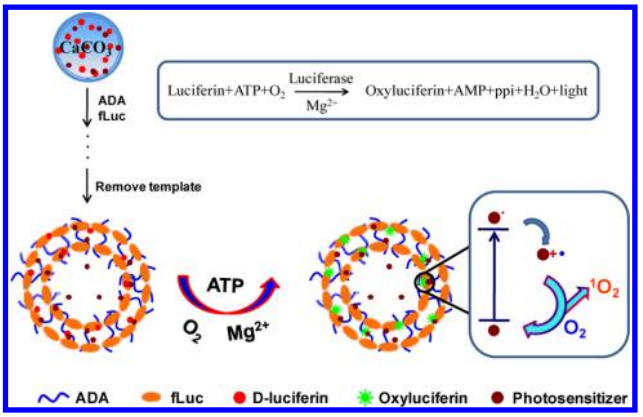

Figure 29. Fabrication and bioluminescent process of $(ADA/fLuc)_n$ microcapsules. Reprinted with permission from ref 194. Copyright 2013 Wiley-VCH Verlag GmbH & Co. KGaA.

deposition of multilayered Cat and GOD onto it through GA cross-linking. It is mentioned in section 4.1 that glucose could induce the enhanced permeability of Cat/GOD multilayers owing to production of gluconic acid. Together with the increased solubility of insulin at low pH, it is anticipated that insulin could be released from the Cat/GOD multilayers after adding glucose. As a proof-of-conjecture demonstration, release studies of insulin from the Cat/GOD microcapsules were conducted in glucose-free phosphate-buffered saline (PBS) and glucose solution. When incubating with glucose solution, about 40% of the insulin was released from the Cat/GOD multilayer shells within 3 h, and then the release gradually decreased. In contrast, little insulin was released in PBS. Therefore, the Cat/GOD multilayers assembled on the surfaces of insulin particles are glucose sensitive and can be exploited to tune the release of insulin in response to glucose. In another study, the same strategy was adopted to fabricate Cat/GOD multilayers on insulin-loaded MSNPs.[172] The MSNPs acted as insulin reservoir, and the enzyme multilayer cross-linked with GA acted as a glucose-responsive valve to manipulate release of insulin. Moreover, the influencing factors (such as the enzyme activity, glucose concentration, multilayers thickness) on the insulin release profiles were well demonstrated.

Besides conventional drug carriers, Li and co-workers recently exploited a new application of Schiff base-bonded LbL multilayer films for use as oxygen carriers, namely, blood substitutes.[57] It is well known that the Hb, a protein purified from red blood cells (RBCs), possesses the ability of delivering and releasing oxygen. However, stroma-free Hb is liable to dissociate into dimers, leading to severe renal toxicity.[195] Despite various strategies being proposed to solve these issues,[196] adverse effects still occurred owing to the difference in structure from RBCs.[197] Considering this, Li and co-workers proposed a novel route to fabricated $(Hb/DHP)_6$ capsules that mimic artificial RBCs through aldehyde polysaccharides-mediated Schiff base interactions (Figure 30),[57] expecting to solve the problems of molecular Hb. The Schiff base-bonded $(Hb/DHP)_6$ capsules were also found to be autofluorescent.[58] This is helpful to monitor the capsules in humans, avoiding the use of extra fluorochromes. Moreover, the Schiff base bond formed between Hb and the DHP offers the microcapsules good stability, preventing dissociation of the Hb tetramer into dimers and thus avoiding renal toxicity.[198] In vitro cell experiments demonstrated the nontoxicity, biodegradability, and biocompatibility of the microcapsules. It is worth mentioning that DHP was chosen both

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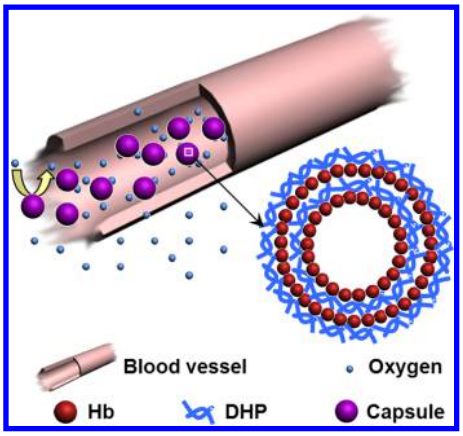

Figure 30. $(Hb/DHP)_6$ capsules fabricated through Schiff base interactions for use as blood substitutes. Reprinted with permission from ref 57. Copyright 2012 Wiley-VCH Verlag GmbH & Co. KGaA.

as one of the wall components and as a cross-linker not only because of its nontoxicity, biodegradability, and biocompatibility but also because of its "stealth" effect and hemocompatibility. When incubating the microcapsules with macrophage cells, a similar "stealth" effect compared to PEGylation was found, ensuring the long circulation time of these microcapsules in vivo.[199] In addition, the assembled DHP endows the capsules with lower anticoagulant properties than heparin, therefore preventing severe bleeding complications and exhibiting excellent hemocompatibility. More importantly, the Hb assembled in the microcapsules maintained its intrinsic bioactivity of reversibly binding and releasing oxygen. Therefore, the as-prepared $(Hb/DHP)_6$ microcapsules have great potential to function as blood substitutes.

To enhance the loading capacity, highly loaded Hb spheres were fabricated through coprecipitation Hb within porous $CaCO_3$, followed by GA cross-linking.[200] The density of Hb per $CaCO_3$ particle was up to 1.36 g cm^{-3}, which was much more suitable for artificial blood substitutes, particularly for an urgent need of large amounts.

5.2. Bioreactors

The contribution of enzymes as biocatalysts to the field of pharmaceutical chemistry, food industries, clinical analysis, or energy production is increasing.[201−203] Immobilization of enzymes is a prerequisite for their use as biocatalysts in most applications. As discussed, aldehyde groups can easily react with primary amino groups under mild conditions to form a Schiff base bond; this provides a versatile, simple, and convenient method for enzyme immobilization. Immobilization of enzymes through a Schiff base bond has been demonstrated to induce higher resistance to temperature, denaturants, and organic solvents[202,204] and successfully employed as bioreactor.[100,109,118,205,206] For example, Girelli and co-workers covalently immobilized tyrosinase with GA as cross-linking agent to aminopropyl-modified pore glass support for online HPLC application.[205] After immobilization, the enzyme selectivity toward D,L-3,4-dihydroxyphenylalanine was improved whereas the activity was the same as free enzyme. Moreover, the enzymatic activity of the immobilized enzyme reactor could be completely preserved for 6 months and after more than 3500 injections. The good selectivity, stability, catalytic activity, and reproducibility of the immobilized enzyme rendered this chromatographic reactor extremely useful for bioanalytical studies. In another study, trypsin immobilized directly on oxidized cellulose-coated glass fibers was inserted into the channel of a microchip and constituted a microfluidic proteolytic bioreactor.[100] The digestion time of hemoglobin or cytochrome *c* by the bioreactor was reduced to 10 s, which is comparable to 12 h digestion by tryptic solution, indicating the excellent performance of the novel enzymatic microreactor. The ease, simplicity, efficiency, and low cost of the proteolysis setup provide it great promise in automated analysis of large sets of proteins. Moreover, the core of the microchip bioreactor is changeable so that it can be easily regenerated by changing the enzymatic core than in the case of the conventional microchip bioreactors. In a similar way, laccase, a blue copper-containing oxidase, has also been immobilized on solid substrates through Schiff reaction and extensively used for electrocatalytic reduction of oxygen, phenolic substances, and dyes degradation.[109,118,206−209]

As support matrices, LbL multilayer capsules offer new opportunities for manipulation of more complicated reactions inside the capsules. Li and co-workers reconstituted the F_oF_1-ATPase in the outer shell of the lipid bilayer-coated GA/Hb microcapsules to mimic cell functions.[210] Covalently bonded GA/Hb microcapsules were robust enough to serve as support of the lipid bilayer incorporating with F_oF_1-ATPase. When adding glucose and GOD solution to the obtained capsules suspension, protons can be produced by GOD-catalyzed oxidation and hydrolysis of glucose. The generated proton gradient flowing across the membrane of the capsules provides the driving force for F_oF_1-ATPase rotation. Adenosine 5′-triphosphate (ATP) can thus be synthesized from adenosine 5′-diphosphate (ADP) and inorganic phosphate, as shown in Figure 31. The concentration

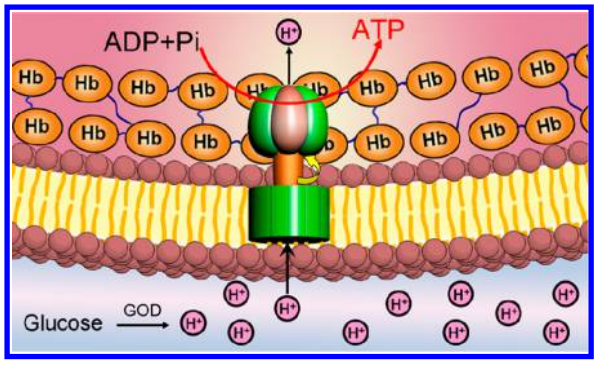

Figure 31. Reconstitution of F_oF_1-ATPase in lipid-coated GA/Hb microcapsules. Reprinted with permission from ref 210. Copyright 2008 Wiley-VCH Verlag GmbH & Co. KGaA.

of ATP continuously increased with reaction time, in particular after destroying the lipid bilayers on the capsules, demonstrating that a large proportion of ATP was synthesized and reserved inside the capsules.

Later, this group directly employed GOD as a building block to fabricate GA/GOD microcapsules through Schiff base interactions for ATP synthesis.[168] In comparison to the GA/Hb microcapsules, the protons can be produced only by adding glucose solution, which is more convenient and simple for ATP synthesis. Quantitative determination of ATP showed similar results to those of the GA/Hb microcapsules. These two types of protein-based capsules may act both as reactors and as containers for synthesis and storage of ATP as well as glucose-sensitive devices in biomedicine.

Inspired by the multicompartment structure of mitochondria, Jiang and co-workers prepared hybrid multicompartment

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microcapsules via the combination of LbL assembly and biomimetic mineralization.[211] Oxidized alginate and protamine were first alternatively deposited on $CaCO_3$ templates, followed by protamine-induced biomimetic silicification of a silicate precursor and biomimetic mineralization of a titanium precursor. After removal of the $CaCO_3$ template and silica template, multicompartment microcapsules with microscale lumen and nanoscale intermembrane space were obtained (Figure 32).

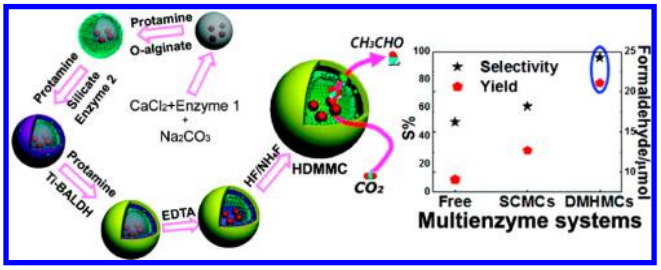

Figure 32. Fabrication of a multienzyme system via combination of LbL assembly and biomimetic mineralization, and the catalytic performance of three types of multienzyme systems. Reprinted with permission from ref 211. Copyright 2011 American Chemical Society.

Taking advantage of the LbL technique, the structure of the microcapsules, such as the size of lumen and the thickness of the intermembrane, etc., can be easily adjusted. As a demonstration, two types of enzymes (formate dehydrogenase and formaldehyde dehydrogenase) were encapsulated, respectively, in the lumen and the intermembrane space of the microcapsules for fabrication of a multienzyme system. Compared with a multienzyme system in a single compartment or solution, this multicompartment multienzyme system exhibited enhanced enzymatic activity, selectivity, and recycling stability in the conversion of CO_2 to formaldehyde. These multicompartment structures may have potential applications in biocatalysis, separation, and biosensors.

5.3. Biosensors

The LbL technique is one of the best methods to incorporate biological components into various devices. Therefore, sensor application is a promising subject for LbL assemblies. Recently, a convenient approach to construct stable biosensors was achieved by introducing a covalent Schiff base bond into the interlayers. Schiff base reaction between amino groups and aldehyde groups easily proceeds in a mild condition and involves only water as byproduct that avoids deactivation and contamination of the bioactive molecules. Therefore, this approach has proven to be an efficient and a simple strategy to construct biosensors with controlled performance.

5.3.1. Enzyme-Based Biosensor. Thin films of active enzyme structures immobilized on solid surfaces through Schiff base interactions can not only be used as bioreactors but also be frequently used as biosensors for determination of various biomolecules. Among the immobilized enzymes, GOD is undeniably one of the most commonly used enzymes widely applied in detection of glucose either in aqueous solution or in blood. Mansur and co-workers directly immobilized GOD on chemically functionalized solid substrates through GA as a bifunctional cross-linker, followed by coupling a layer of HRP to construct three-dimensional (3D) engineered glucose biosensors.[66] As a proof of concept, the bienzyme systems constructed on aminated microplate were employed in the analysis of commercially available drinks, as shown in Figure 33. The blue

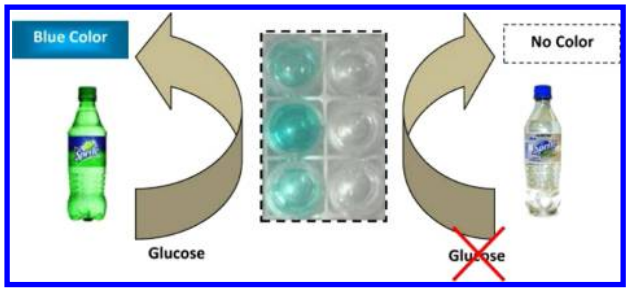

Figure 33. Analysis of commercially available drinks using GOD/HRP bienzymatic system. Reprinted with permission from ref 66. Copyright 2013 Elsevier.

color was clearly observed in the cavities of the microplate with the sugar-containing drink (Figure 33, left) while still transparent in the cavities with the sugar-free drink (Figure 33, right). This glucose biosensor may be used as a simple device for food and beverage analysis by diabetes patients and health-care professionals.

Since immobilization of enzymes (or other proteins) on electrode surfaces is a big trend, development of LbL-based electrochemical biosensors through Schiff base interactions has been studied extensively.[212] Sun and co-workers performed substantial investigations on LbL-based electrochemical glucose biosensors.[70,107,114−117,213,214] For example, this group constructed an amperometric glucose biosensor through GA cross-linking of GOD and aminated silica nanoparticles (ASNPs) on an Au electrode.[70] The ASNPs/GOD multilayer films functionalized gold electrodes demonstrated excellent electrocatalytical response to oxidation of glucose. In their study, the importance of silica nanoparticles is highlighted. First, the biocompatible ASNPs act as a protection layer that isolate the GOD and Au electrode, preventing inactivation of the enzyme. Second, the ASNPs provide a large surface area for immobilizing more enzymes. Finally, incorporation of ASNPs promotes electron transfer between enzyme and electrode surface, thus improving the performance of the biosensors compared to those GOD multilayer film electrodes without the ASNPs. The sensitivity of the $(ASNPs/GOD)_4$ biosensor is up to 5.11 $\mu A\ mM^{-1}\ cm^{-2}$ with a detection limit of 9 μM. Comparable to silica nanoparticles, biocompatible gold nanoparticles (AuNPs) also possess a large surface area and are expected to enhance the sensitivity of enzyme-based sensors.[215] Some researchers prepared the $(GOD/AuNPs)_n$ multilayer films on a Au electrode surface.[115,213] Different from previous studies, periodate-oxidized GOD (IO_4-GOD) was employed both as an active enzyme component and an aldehyde cross-linker in the LbL multilayer assembly, avoiding the use of extra cross-linker and at the same time simplifying the assembly process. To further facilitate electron transfer between enzyme and electrode, some redox mediators (or electroactive components) including ferrocene and its derivatives,[113,117] carbon nanotubes (NTs),[73,116] organic dye thionine[107] have been introduced to the enzyme-based system. For example, Kim and co-workers constructed a reagentless enzyme electrode by alternate depositions of ferrocenyl-tethered dendrimers (Fc-D) and IO_4-GOD on Au electrode surface.[113] The five bilayers of the IO_4-GOD/Fc-D assembly showed a sensitivity of 7.38 $\mu A\ mM^{-1}\ cm^{-2}$ and a detection limit as low as 1 μM. Later, Sun and co-workers chose poly(allylamine)ferrocene (PAA-Fc) as an assembly unit to construct IO_4-GOD/PAA-Fc multilayer films on Au electrode.[117] The sensitivity for eight bilayers of the IO_4-GOD/

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PAA-Fc assembly was up to 17.7 μA mM^{-1} cm^{-2}. Moreover, the activity of the assembly remained stable over 40 days.

The proposed enzyme biosensor fabricated through Schiff interactions not only can be used for immobilization of GOD but also be extended to other enzymes, such as immobilization of HRP, LAX, ChOx, or GalOD for detection of corresponding substrate H_2O_2, lactate, cholesterol, or galactose,[64,69,71,73,139,216] respectively.

5.3.2. Antibody-Based Biosensor. With the notable exception of the enzyme-based sensor, the vast majority of rapid detection systems exploit antibodies for recognition, identification, and quantitation of the target analytes.[217] Monoclonal antibodies, immunoglobulins (IgG), are the most frequently used receptors in immunosensors because of their strong binding ability to specific antigens. For instance, Abdelghani and co-workers immobilized antirabbit IgG on a silicon nitride/aminosilane/GA surface through Schiff base interaction.[77] The binding between antibody and antigen (rabbit IgG) could easily be detected by monitoring the variation of resistance, and a low detection limit of 50 ng mL^{-1} for IgG was obtained. In another study, Zhang and co-workers conjugated antihuman IgG onto magnetic beads through aldehyde dextran-mediated Schiff base reactions. They employed polyelectrolyte multilayers modified Au film as a sensing film and quantitated the antigen−antibody immunoreaction by surface plasmon resonance (SPR).[218] Though the sensitivity of this SPR sensor was no better than those obtained by other methods, it still has several advantages such as label-free detection, minimal dosage, and easy regeneration. To further simplify the detection process, Li and co-workers developed a dextran-functionalized PDMS microfluidic ELISA device and achieved colorimetric detection of proteins directly by eyes.[98] The detection limit of the microfluidic device is up to 100 pg mL^{-1}, which is strikingly better than those PDMS devices without treatment. Moreover, this microfluidic device could realize simultaneous detection of multiple biomarkers.

On the basis of the sensitive response between antigen and antibody, antibody-based biosensors have been widely used for disease diagnosis. Bojorge-Ramírez and co-workers covalently immobilized apyrase onto a graphite−epoxy surface to fabricate an immunosensor for detection of antibody antiapyrase in serum samples.[76] All the sera of schistosomiasis patients presented a high detection current with low background. This ensures application of this amperometric immunosensor in clinical diagnosis of schistosomiasis. Li and co-workers conjugated HRP and anti-HBsAg onto the surface of silica nanoparticle, and successfully achieved an ELISA detection of the hepatitis B surface antigen (HBsAg). The detection limit was three times lower than that of the commercially available ELISA kit.[219] Very recently, Jia and co-workers employed Ag@BSA microspheres as a sensing layer to cross-link RBP monoclonal antibody (RBPmAb) via GA for sensitive detection of retinol-binding protein (RBP).[220] The as-prepared immunosensor demonstrated high specificity for RBP and a remarkable low detection limit of 18 ng mL^{-1}. It thus presented a potential alternative method to ELISA for RBP detection in clinical diagnosis of renal tubular injury. Inspired by the pioneering investigation and as an extension, this group established an ultrasensitive electrochemical cytosensor by immobilizing monoclonal antibody of carcinoembryonic antigen (anti-CEA) onto the Au@BSA microspheres surfaces, as illustrated in Figure 34.[221] These Au@BSA microspheres showed good biocompatibility and offered a desirable platform for cell adhesion and proliferation.

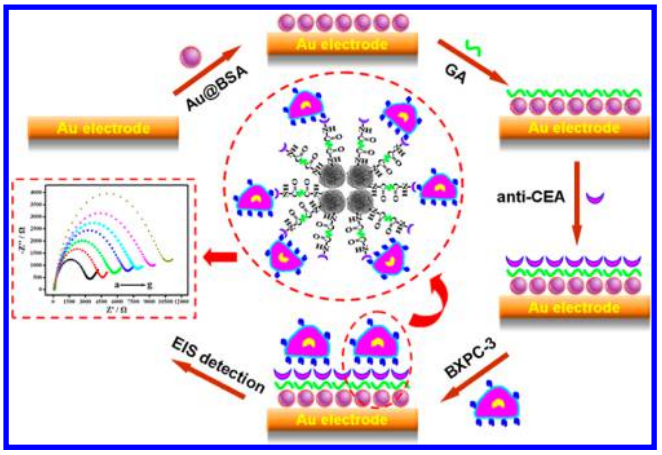

Figure 34. Fabrication of the Au@BSA-based cytosensor for cancer cell detection via EIS. Reprinted with permission from ref 221. Copyright 2013 American Chemical Society.

Electrochemical impedance spectroscopy (EIS) signals were demonstrated to respond rapidly and change linearly with the concentration of tumor cells, achieving a minimum detection level of 18 cells mL^{-1}. This enabled the electrochemical cytosensor as a promising technique for early cancer diagnosis.

As an innovative technique for constructing simple, low-cost, portable, and disposable analytical devices,a three-dimensional (3D) paper-based electrochemiluminescence (ECL) immunosensor was designed for multiplexed measurement of tumor markers by Yu and co-workers.[222] As shown in Figure 35, the 3D

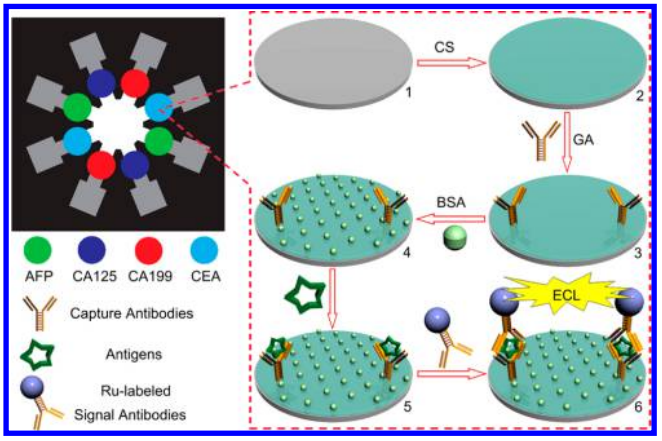

Figure 35. Fabrication and assay procedure of 3D paper-based ECL device. Reprinted with permission from ref 222. Copyright 2012 Elsevier.

paper-based ECL immunodevice was constructed by conjugating the corresponding capture antibodies onto chitosan-modified electrodes through GA cross-linking, followed by BSA blocking. With the aid of a simple homemade device holder, different tumor markers in serum samples were measured. The detection limit was found to be as low as 0.15 ng mL^{-1}, far below the threshold of these tumor markers in clinical diagnosis, thus confirming its validity in simple, low-cost, sensitive, and portable diagnosis of tumors and other diseases.

5.3.3. Aptamer-Based Biosensor. Aptamers are single-stranded structured nucleic acid ligands that can bind with high specificity and affinity to a broad range of target biomolecules. Compared with traditional recognition units such as antibodies,

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aptamers have many advantages including synthesis convenience, high stability, and nonimmunogenicity. In the past decades, numerous aptamer biosensors (aptasensors) have been designed and proven suitable for analytic and diagnostic applications. Yang and co-workers prepared a high-performance impedimetric aptasensor by immobilizing amino-functionalized thrombin aptamer (TBA) onto the Au/cysteamine/GA/dendrimer/GA electrode through Schiff base interactions.[223] The impedance results revealed a satisfactory linear relationship with the concentration of thrombin in the range of 1−50 nM and a detection limit as low as 0.01 nM. This aptasensor also showed high stability, selectivity, and good regeneration ability.

With the rapid development of graphene-based field effect transistors (FETs), Jang and co-workers ingeniously designed an ultrasensitive vascular endothelial growth factor (VEGF) aptasensor by integrating anti-VEGF RNA aptamer/hybrid graphene conjugate into a liquid-ion-gated FET structure (Figure 36).[224] Field-induced outstanding sensitivity was

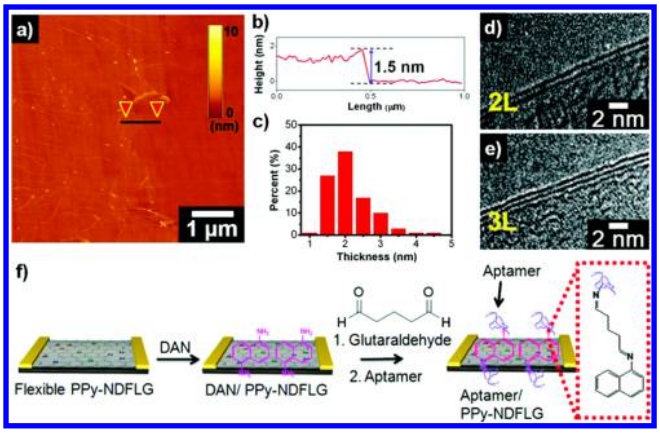

Figure 36. (a) High-magnification AFM image of hybrid graphene on a silicon substrate. (b) Scanning trace of the hybrid graphene. (c) Histogram of the average graphene thickness. (d and e) HR-TEM images of hybrid graphene. (f) Fabrication procedure of VEGF aptasensor. Reprinted with permission from ref 224. Copyright 2012 American Chemical Society.

observed for VEGF, with an unprecedented low concentration of 100 fM. The FET-based aptasensor also displayed a rapid response time (<1 s), excellent reusability, and mechanical flexibility. From the viewpoint of its unprecedented sensing performance, the method presented here may offer a wide range of applications in biomedical diagnosis and environmental monitoring.

5.3.4. DNA-Based Biosensor. DNA sensors, based on nucleic acid recognition processes, have been developed tremendously over the past few years for their broad application in clinical diagnosis, bioengineering, and environmental protection.[225] Like other biosensors introduced previously, DNA could also covalently bind onto aminated solid substrate through GA-mediated Schiff base reaction and be used as a sensor.[226] Despite the good accuracy obtained, the planar structure of these DNA sensors produced by the linear structure of the GA still limits the accessibility of the targets as well as the loading capacity. In this regard, Caminade and co-workers made use of aldehyde dendrimers in place of linear cross-linker GA for fabrication of DNA sensors (Figure 37).[152,154] Hybridization could easily be detected by the fluorescence of complementary DNA. Compared to commercially available aldehyde slides, the aldehyde dendrimers functionalized glass slides had higher DNA binding capacities and higher sensitivity with a detection threshold of 1 pM. Moreover, the dendrislides could be reused up to 10 times and were found to remain active over 3 months. All these features make dendrimer-modified slides ideal for manufacturing low-cost, high-performance DNA arrays applied in gene expression and mutations detection. Similar results were also obtained by Yang and co-workers.[227] Instead of replacing the cross-linker GA they incorporated amino-terminated dendrimers into the multilayer films on Au electrode surfaces, followed by attachment of DNA through GA cross-linking. The as-prepared assembly was then used as an electrochemical sensor for DNA hybridization analysis. The EIS results demonstrate high sensitivity and selectivity of this DNA sensor with a detection limit of 3.8×10^{-12} M. The DNA sensor also displayed high stability and favorable regeneration ability.

The heterofunctional aldehyde−aspartic−dextran designed by Fernández-Lafuente and co-workers is another alternative to dendrimers.[101] It can also permit attachment of many DNA probes onto the solid surfaces and facilitate hybridization due to the long spacer arms. Applying this cross-linker, high density DNA probes were covalently immobilized onto magnetic particles for sensitive DNA sensors construction.[228] The DNA sensor was subsequently combined with PCR amplification and achieved DNA determination via ELISA with an excellent detection limit of 10^{-18} or even 10^{-19} g mL^{-1}. This DNA sensor is promising for trace detection of target molecules. Combined with its outstanding stability, these DNA sensors have great potential as a molecular diagnostic tool.

Apart from the mentioned biosensors, aldehyde compounds were also applied in the detection of other molecular or ions.[142,144,229−232] For example, a biosensor with salicylaldehyde or L-lysine covalently linking to Au electrode through Schiff base reaction could be used for detection of Cu^{2+},[142,229] while a sensor with covalently bonded phosphotyrosine was employed for Ca^{2+} detection.[231]

A summary with respect to the main sensors fabricated through different aldehyde-mediated Schiff base reaction is presented in Table 1 to aid readers to get a more comprehensive understanding of this section. It should be mentioned that some GA cross-linked enzyme sensors in a sequential injection format are not included in this table because they were discussed already in another review.[233]

5.4. Microarrays

Array technology has rapidly developed into a fundamental tool for parallel analysis of biomolecules. Examples include DNA arrays for gene expression and mutation detection,[225] peptide or protein arrays for evaluation of protein−protein interactions,[242,243] and so on. A universal strategy for constructing microarrays is covalently attaching the interested biomolecule to a reactive group on the solid substrate surface. Since most of the biomolecules contain amino groups in their structure, aldehyde-mediated Schiff base reactions have widely been used in the preparation of microarrays.

5.4.1. DNA Arrays. In the past few years, a great effort has been devoted to development of DNA microarray technology, since it considerably accelerates genetic analysis by monitoring tens of thousands of gene expressions simultaneously on a single chip. DNA microarrays on patterned surfaces can be fabricated with methods similar to those used for DNA-based biosensors. For example, DNA microarrays could be prepared by directly printing DNA on aldehyde-activated surfaces[124,244] and then

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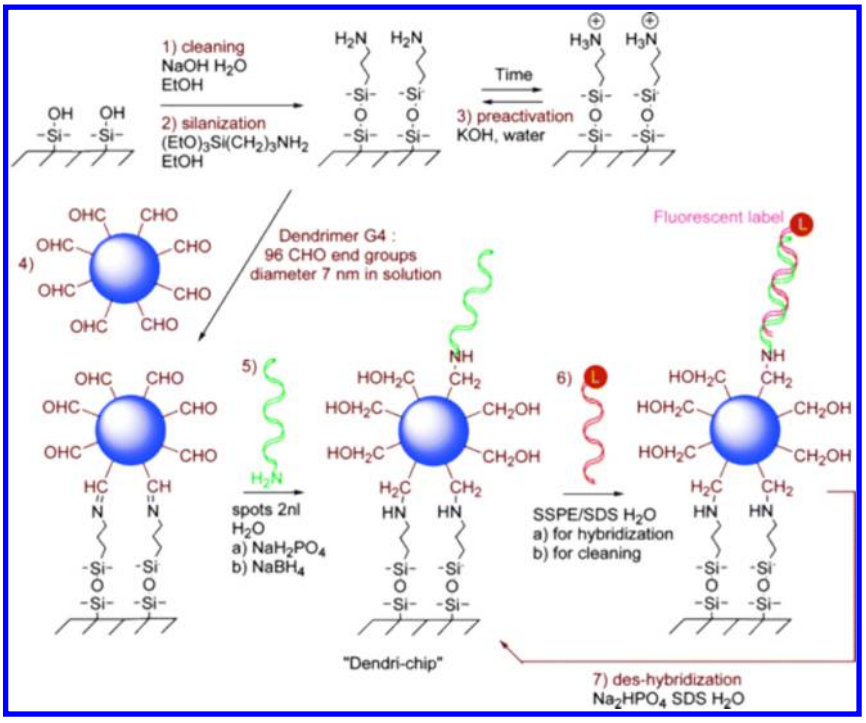

Figure 37. Fabrication of DNA sensor using aldehyde dendrimers and oligonucleotides. Reprinted with permission from ref 154. Copyright 2004 American Chemical Society.

employed in hybridization detection. In addition to aldehyde-activated surfaces, DNA also binds with good efficiency to other groups-activated surfaces. For comparison, covalent attachment of DNA onto amine- or carboxylic acid-activated glass surfaces was performed by Zammatteo and co-workers.[121] The results indicate that fixation of DNA to an aldehyde-modified surface is the best method for DNA microarrays constructions. The reason is that the Schiff base reaction proceeds without the help of other cross-linking agents and involves only water as a byproduct. It does not contaminate the surface of microarrays, thus avoiding nonspecific adsorption and allowing preparation of microarrays with high detection sensitivity.

Besides spotting the probe DNA molecules by a robot as used for most of the microarrays, an e-beam-based approach was also frequently utilized to create patterns of DNA.[245] First, a PEG-covered silicon wafer was patterned through e-beam to produce silanol groups, followed by an aldehyde-terminated self-assembled monolayer. Then, NH_2-terminated PAMAM dendrimers were covalently linked to the spots where the aldehyde groups were patterned. Finally, DNA was coupled to the PAMAM dendrimers in the e-beam-defined patterns via GA-mediated Schiff base reaction. Thus, a DNA microarray was obtained. As mentioned above, the dendrimer-activated surfaces allowed for immobilizing a high density of DNA and also enabled easier access of the target DNA.[246] Therefore, high detection sensitivity was achieved.

Another method for patterning applies stamps for micro-contact printing.[125] A stamp is inked with poly(propyleneimine) dendrimers, yielding a patterned positive charge on the stamp, which in turn can be used to bind negatively charged DNA or RNA molecules through LbL assembly. The grafting is then transferred by directly printing DNA or RNA onto aldehyde-terminated glass supports, affording the DNA microarray, as demonstrated in Figure 38. It shows that DNA or RNA is uniformly distributed within the patterned area and available for hybridization. Combined with contact printing robotic systems, this method was exploited to deposit various oligonucleotide spots and realized multiple probe printing.

5.4.2. Protein Arrays. Protein microarrays, also known as protein biochips, were developed owing to the limitations of DNA microarrays in proteomics. Protein biochip is a high-throughput method to evaluate protein−protein interactions and becoming an attractive tool in biomedicine for diagnostics and therapeutic purposes as well as for basic research.[247] Since protein microarrays are based on the technology developed for DNA microarrays, they are relatively easy to prepare. MacBeath and Schreiber reported the preparation of a protein microarray on aldehyde slides using a high-precision contact-printing robot, generating spots about 150−200 μm in diameter, and demonstrated its application in studying protein−protein interactions.[105] Later, Gordus and co-workers used this method to generate protein microarrays of Src homology 2 (SH2)/phosphotyrosine binding (PTB) for mapping a quantitative protein interaction network of epidermal growth factor receptor.[244]

With the development of ultrasmall biosensors and biochips, the motivation to not only fabricate arrays of proteins but also create patterns on a surface with feature sizes in the nanometer regime has spurred development of new fabrication strategies, for example, atomic force microscopy (AFM) based lithography consisting of dip-pen nanolithography (DPN), nanografting and nanoshaving, enzymatic lithography, and conductive AFM lithography.[248,249] Mirkin and co-workers first introduced dip-pen nanolithography and employed it to achieve direct-write proteins on aldehyde-modified SiO_2 substrates through Schiff base interactions (Figure 39).[123] The protein nanostructures could be produced on substrates while keeping their native structures intact. Besides, arrays of multiple proteins were also achieved in conjunction with multiple-pen AFM arrays.

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Table 1. Various Sensors Fabricated through Aldehyde-Mediated Schiff Base Reaction[a]

probe	cross-linker	analyte	detection technique	detection limit	ref
GOD	GA	glucose	CV	9×10^{-6} M	70
GOD	GA	glucose	CV	5×10^{-6} M	234
GOD	GA	glucose	CV	2.5×10^{-6} M	235
GOD	GA	glucose	CA	1×10^{-4} M	72
GOD	GA	glucose	CA		65
GOD and HRP	GA	glucose	UV		66
GOD and HRP	aldehyde-GOD	glucose	CV/CA	3.5×10^{-5} M	107
GOD	aldehyde-GOD	glucose	CV/CA	1.5×10^{-5} M	236
GOD	aldehyde-GOD	glucose	CV/CA	8×10^{-6} M	116
GOD	aldehyde-GOD	glucose	CV/CA	8×10^{-6} M	115
GOD	aldehyde-GOD	glucose	CV		108
GOD	aldehyde-GOD	glucose	CV	1×10^{-6} M	113
GOD	aldehyde-GOD	glucose	CV	3.8×10^{-6} M	214
GOD	aldehyde-GOD	glucose	CV		117
GOD	aldehyde-GOD	glucose	CV/CA	8.2×10^{-6} M	213
GOD	aldehyde-GOD	glucose	CA	2.3×10^{-5} M	114
GOD or LAX	GA	glucose or lactate	CV		216
GalOD	GA	galactose		2.5×10^{-7} M	69
ChOx or CE	GA	cholesterol	CV	3×10^{-6} M	73
thrombin aptamer	GA	thrombin	EIS	1×10^{-11} M	223
anti-VEGF RNA aptamer	GA	VEGF	CA	1×10^{-13} M	224
anti-CEA antibody	GA	CEA-positive tumor cells	EIS	18 cells mL^{-1}	221
(anti-B2M)	GA	β_2-rnicroglobulin (B2M)	CCD		237
IgG	GA	anti-IgG			238
anti-IgG	GA	IgG	EIS	50 ng mL^{-1}	77
anti-IgG	aldehyde dextran	IgG	SPR	0.078 μg mL^{-1}	218
anti-IgG	aldehyde dextran	IgG	ELISA	0.1 ng mL^{-1}	98
RBP mAb	GA	RBP	EIS/DPV	18 ng mL^{-1}	220
apyrase	GA	antiapyrase	CA		76
antibody	GA	antigen	ECL	0.15 ng mL^{-1} for AFP	222
anti-HBsAg IgG	aldehyde-HRP/aldehyde dextran	HBsAg	ELISA	0.06 ng mL^{-1}	219
anti-HSA	triethoxysilane aldehyde	HSA	EIS	1×10^{-14} M	239
laccase	GA	catechol	CA		67
ssDNA	GA	ssDNA	ECL	4.5×10^{-9} M	75
ssDNA	GA	ssDNA	EIS	3.8×10^{-12} M	227
ssDNA	GA	ssDNA	EIS		226
ssDNA	GA	ssDNA	CCD		240
ssDNA	aldehyde−aspartic−dextran	ssDNA	PCR-ELISA	10^{-19} g mL^{-1}	228
PNA	superaldehyde	ssDNA	SWV	4×10^{-16}	241
ssDNA	aldehyde dendrimers	ssDNA	FL	1×10^{-12} M	152
HRP	GA	H_2O_2	CA	2×10^{-6} M	71
HRP	GA	H_2O_2	CA	5×10^{-7} M	64
MTAPc	terephthaldialdehyde	H_2O_2	CV	10^{-7} M	139
2-aminoethyl dihydrogen phosphate	GA	UO_2^{2+}	EIS		230
phosphotyrosine	GA	Ca^{2+}	conductometry	1×10^{-7}	231
L-lysine	GA	Cu^{2+}	DPV	1.2×10^{-13} M	229
salicylaldehyde	salicylaldehyde	Cu^{2+}	EIS	8.3×10^{-12} M	142
salicylaldehyde	salicylaldehyde	Cu^{2+}	FL		141
DNA	aldehyde cellulose	Pb^{2+}	ECL	1×10^{-11} M	232
DNA	aldehyde cellulose	Hg^{2+}	ECL	2×10^{-10} M	232
3T	3T-CHO	HCHO	FL		144

[a]Abbreviations: GOD, glucose oxidase; LAX, lactate oxidase; ChOx, cholesterol oxidase; CE, cholesterol esterase; CEA, carcinoembryonic antigen; HRP, horseradish peroxidase; VEGF, vascular endothelial growth factor; AFP, r-fetoprotein; RBP, retinol-binding protein; RBPmAb, RBP monoclonal antibody; GalOD, galactose oxidase; HBsAg, hepatitis B surface antigen; anti-HBsAg IgG, monoclonal anti-HBsAg immunoglobulin G (IgG) antibody; PNA, peptide nucleic acid; 3T, 2,2′:5′,2″-terthiophene; 3T-CHO, 5-formaldehyde-2,2′:5′,2″-terthiophene; HSA, human serum albumin; MTAPc, metal tetra-amino phthalocyanine. CA, chronoamperometry; CCD, charge-coupled device; CV, cyclic voltammetry; DPV, differential pulse voltammetry; SWV, square wave voltammetry; EIS, electrochemical impedance spectroscopy; ECL, electrochemiluminescence; FL, fluorescence emission spectra; PCR-ELISA, polymerase chain reaction-enzyme-linked immunosorbent assay; SPR, surface plasmon resonance.

Another kind of AFM-based lithography, nanografting, was used by Liu and co-workers for fabricating nanometer-sized protein arrays on aldehyde-modified substrate surface through Schiff base interaction.[250] In their study an AFM tip was used as

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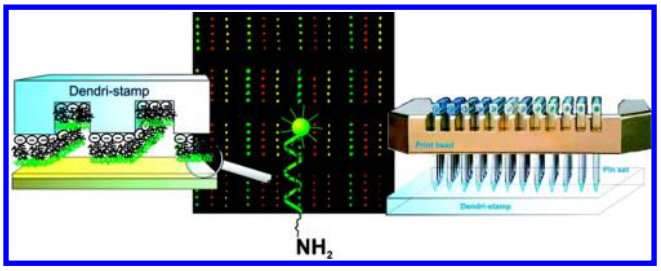

Figure 38. Microcontact printing of DNA with dendrimers stamp. Reprinted with permission from ref 125. Copyright 2007 American Chemical Society.

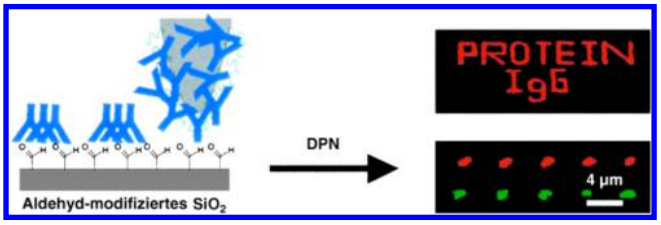

Figure 39. Construction of protein arrays on aldehyde-modified SiO_2 substrates through dip-pen nanolithography. Reprinted with permission from ref 123. Copyright 2003 Wiley-VCH Verlag GmbH & Co. KGaA.

"nanoshaver". It was operated on a matrix self-assembly monolayer immersed in a solution containing $HS(CH_2)_2CHO$ molecules. As the tip plowed through the matrix monolayer, the self-assembly monolayer molecules under contact were removed and replaced by the new $HS(CH_2)_2CHO$ molecules. After injection of lyzysome or IgG solutions, selective protein adsorption occurred on aldehyde-terminated areas within 5 min. To obtain higher resolution, the combination of DPN with nanografting was also engineered by Liu and co-workers,[251] called a "nanopen–reader–writer". It retained the advantages of each method and allowed precise positioning of proteins and monitoring the antibody–antigen recognition process.

5.4.3. Cell Arrays. Cell arrays, which are built on the foundation of protein arrays, are initiated by attachment of cell-adhesive proteins on surfaces at defined areas. For example, Reinhoudt and co-workers covalently immobilized cytophilic proteins by microcontact printing through Schiff base reaction. The remaining areas were blocked with amino-PEG, forming a layer that was resistant to cell adhesion. Therefore, cells selectively adhered to and spread on the protein patterns after seeding and incubating cells onto the patterned substrate, affording cell arrays, as shown in Figure 40.[138] It can be clearly seen that the cells only attached to the patterned areas with cytophilic proteins. They remained stable on the pattern even after repeatedly rinsing the substrate with PBS. The same strategy was adopted by Desai and co-workers for preparation of monolayered and multilayered pancreatic β-cell arrays by adjusting the cell seeding concentration and the adherent areas.[252] The technique not only provides a way to better understand the size-dependent behavior and function of pancreatic β-cells that have important implications for islet transplantation therapy but also demonstrates its potential applicability to other cell.

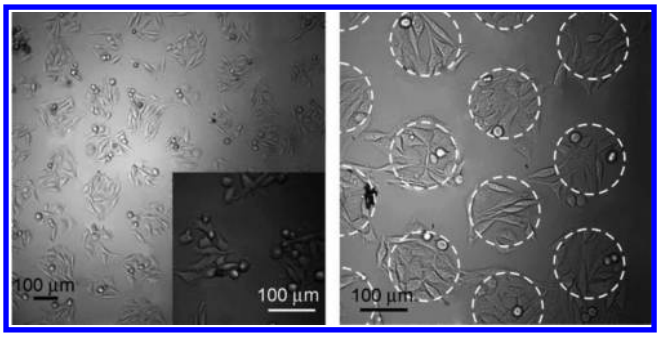

Figure 40. HeLa cells arrays generated on patterned cytophilic proteins by microcontact printing. Reprinted with permission from ref 138. Copyright 2006 Wiley-VCH Verlag GmbH & Co. KGaA.

In view of cell-to-cell differences, single-cell patterning is necessary in certain specific analytical applications. For this purpose, Jen and co-workers employed soft lithography to prepare adjustable micrometer-sized wells of different diameters and interstitial spacings. This was followed by sputtering gold, a MMAPA self-assembly monolayer, covalent immobilization of collagens in each microwell through Schiff base reactions, and then cell attachment.[134] By tuning the structural parameters, single-cell arrays were obtained in microwells with a diameter of 20 μm and an interstitial spacing of 250 μm. These single-cell arrays were then applied in the analysis of gangliosides and demonstrated their ability in analyzing cell-to-cell diversity. The proposed approach allows one to easily locate and image the cells at a fixed location and thus has great potential as cell-based sensors for high-throughput cell analysis and also other biomedicine applications.

In addition, quantum dot array,[136] Au nanoparticles array,[135] and single Au nanoparticles array[132] were also fabricated by this group using similar strategies, so the procedure will not be repeated. However, an interesting reversible patterned self-assembly monolayer constructed on Au and SiO_2 surfaces should be introduced. Similar to the assembly process used for other arrays, Reinhoudt and co-workers patterned monolayers of different aldehydes or lucifer yellow on amino-terminated Au and SiO_2 surfaces through Schiff base reaction.[137] These aldehyde or lucifer yellow monolayers could be removed by hydrolysis in acid solutions, and it could also be recycled by reacting with aldehyde or lucifer yellow again. Thus, repeated "printing" and "erasing" of a pattern on substrate surface via a reversible Schiff base reaction is realized. This work well demonstrated the unique advantage of dynamic Schiff base chemistry, which combines the merits of both covalent chemistry (i.e., stable immobilization and wide range of reactions) and noncovalent chemistry (i.e., "write and erase" under appropriate conditions).

5.4.4. Microcapsules Arrays. Microcapsules are one of the most successful examples for applying the LbL technique with potentially wide application in drug delivery, microreactor, and biosensors. Therefore, it is not surprising that microcapsule arrays also arouse extensive concern.[253−258] Gao and co-workers reported the fabrication of diverse $(PSS/PAH)_3$ microcapsule arrays.[255,256] In their study, GA cross-linked $(PSS/PAH)_3$ microcapsules were fabricated first through the LbL technique and then conjugated to the patterned PAH regions on the glass substrate via Schiff base reactions. Different PAH patterns created diverse microcapsule arrays, as demonstrated in Figure 41. The number of aggregated microcapsules in a pattern could be precisely controlled by tuning the diameter of the capsules and the patterned area. If the size of the patterned PAH region was smaller than that of the microcapsule, a single-microcapsule array could be obtained. Quite remarkably, these covalently attached microcapsule arrays exhibited good stability even in solutions of

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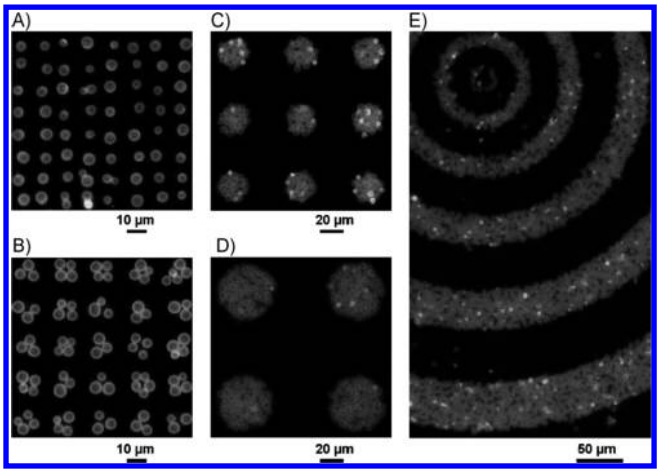

Figure 41. Fluorescence microscopy images of the microcapsule arrays fabricated on the patterned glass substrates: (A) single-microcapsule arrays, (B−D) microcapsule clusters arrays with different density, and (E) ring-like microcapsule clusters arrays. Reprinted with permission from ref 255. Copyright 2010 Wiley-VCH Verlag GmbH & Co. KGaA.

high salt concentration and extreme pH, therefore allowing for successive processing and downstream applications.

6. CONCLUSIONS AND PROSPECTIVE

We highlighted recent progress on fabricating novel types of LbL-based micro- and nanostructures through GA, aldehyde polysaccharide, aldehyde protein, and other aldehyde-mediated Schiff base interactions. Covalent LbL assembly through Schiff base interactions not only has advantages similar to other covalent LbL assembly methods but also has its unique superiority, such as mild reaction conditions, high reaction rates, autofluorescence, and pH sensitivity. Combining the merits of Schiff base interactions with responsive polymers, some dual-responsive assemblies through the LbL technique have been fabricated and successfully applied in drug delivery, bioreactors, biosensors, and microarrays. Beyond this it is assumed that this approach is not limited to the above but that it could be extended readily to the design of smart responsive and adaptive multifunctional interface or materials. For instance, it could (i) cooperate with an aromatic compound that may form a big conjugated system and endow the system ascendant photoelectric properties, such assembly may respond to specific stimulus and be applied in smart photoelectric devices, (ii) fuse with various available functionalities, with which to modulate interfacial properties in space and time, such as wettability, biological interactions, and so on, (iii) integrate with current technologies in different fields of application, in particular, integration with well-developed top−down nanofabrication. Overall, with particular designs, molecular assembly through Schiff base interactions may exert a huge impact on future science and technology.

AUTHOR INFORMATION

Corresponding Author

*E-mail: jbli@iccas.ac.cn.

Notes

The authors declare no competing financial interest.

Biographies

Yi Jia graduated from Liaoning University in 2009 and received her Ph.D. degree in Physical Chemistry in 2012 from the Institute of Chemistry, the Chinese Academy of Sciences. Then she joined Professor Li's group as an assistant professor. Her research interests include biomacromolecule assemblies, bioinspired stimuli-responsive microcapsules, and microspheres based on layer-by-layer assembly for biomedical application.

Junbai Li obtained his B.S., M.S., and Ph.D. degrees in Polymer Science from Jilin University. He then spent several years carrying out postdoctoral work and a joint research project at the interface department in the Max Planck Institute of Colloids and Interfaces in Germany. He is currently a Professor at the Institute of Chemistry in the Chinese Academy of Sciences. His research interests involve molecular biomimetics based on molecular assembly, molecular mechanisms, and structure in assembled biological systems, microcapsules, and nanostructured design.

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REFERENCES

(1) Ariga, K.; Hill, J. P.; Lee, M. V.; Vinu, A.; Charvet, R.; Acharya, S. *Sci. Technol. Adv. Mater.* **2008**, *9*, 014109.
(2) Li, M.; Ishihara, S.; Akada, M.; Liao, M.; Sang, L.; Hill, J. P.; Krishnan, V.; Ma, Y.; Ariga, K. *J. Am. Chem. Soc.* **2011**, *133*, 7348.
(3) He, Q.; Cui, Y.; Li, J. *Chem. Soc. Rev.* **2009**, *38*, 2292.

DOI: 10.1021/cr400559g
Chem. Rev. XXXX, XXX, XXX−XXX

(4) Tang, Z.; Wang, Y.; Podsiadlo, P.; Kotov, N. A. *Adv. Mater.* **2006**, *18*, 3203.
(5) Ho, P. K. H.; Kim, J.-S.; Burroughes, J. H.; Becker, H.; Li, S. F. Y.; Brown, T. M.; Cacialli, F.; Friend, R. H. *Nature* **2000**, *404*, 481.
(6) Ejima, H.; Richardson, J. J.; Liang, K.; Best, J. P.; van Koeverden, M. P.; Such, G. K.; Cui, J.; Caruso, F. *Science* **2013**, *341*, 154.
(7) Ariga, K.; Ji, Q.; Hill, J. P.; Bando, Y.; Aono, M. *NPG Asia Mater.* **2012**, *4*, e17.
(8) Park, S.; Vosguerichian, M.; Bao, Z. *Nanoscale* **2013**, *5*, 1727.
(9) Shaikhutdinov, S.; Freund, H.-J. *Adv. Mater.* **2013**, *25*, 49.
(10) Ariga, K.; Yamauchi, Y.; Mori, T.; Hill, J. P. *Adv. Mater.* **2013**, *25*, 6477.
(11) Innocenzi, P.; Malfatti, L. *Chem. Soc. Rev.* **2013**, *42*, 4198.
(12) Love, J. C.; Estroff, L. A.; Kriebel, J. K.; Nuzzo, R. G.; Whitesides, G. M. *Chem. Rev.* **2005**, *105*, 1103.
(13) Chinwangso, P.; Jamison, A. C.; Lee, T. R. *Acc. Chem. Res.* **2011**, *44*, 511.
(14) Talham, D. R. *Chem. Rev.* **2004**, *104*, 5479.
(15) Chen, X. D.; Lenhert, S.; Hirtz, M.; Lu, N.; Fuchs, H.; Chi, L. F. *Acc. Chem. Res.* **2007**, *40*, 393.
(16) Deshmukh, P. K.; Ramani, K. P.; Singh, S. S.; Tekade, A. R.; Chatap, V. K.; Patil, G. B.; Bari, S. B. *J. Controlled Release* **2013**, *166*, 294.
(17) Ariga, K.; Yamauchi, Y.; Rydzek, G.; Ji, Q.; Yonamine, Y.; Wu, K. C. W.; Hill, J. P. *Chem. Lett.* **2014**, *43*, 36.
(18) Tong, W.; Song, X.; Gao, C. *Chem. Soc. Rev.* **2012**, *41*, 6103.
(19) Decher, G.; Hong, J. D. *Makromol. Chem. Macromol. Symp.* **1991**, *46*, 321.
(20) Decher, G. *Science* **1997**, *277*, 1232.
(21) Ariga, K.; Lvov, Y. M.; Kawakami, K.; Ji, Q.; Hill, J. P. *Adv. Drug Delivery Rev.* **2011**, *63*, 762.
(22) Kreft, O.; Javier, A. M.; Sukhorukov, G. B.; Parak, W. J. *J. Mater. Chem.* **2007**, *17*, 4471.
(23) Vriezema, D. M.; Aragones, M. C.; Elemans, J.; Cornelissen, J.; Rowan, A. E.; Nolte, R. J. M. *Chem. Rev.* **2005**, *105*, 1445.
(24) Shiratori, S. S.; Rubner, M. F. *Macromolecules* **2000**, *33*, 4213.
(25) Lvov, Y.; Ariga, K.; Ichinose, I.; Kunitake, T. *J. Am. Chem. Soc.* **1995**, *117*, 6117.
(26) Berth, G.; Voigt, A.; Dautzenberg, H.; Donath, E.; Möhwald, H. *Biomacromolecules* **2002**, *3*, 579.
(27) Rouse, J. H.; Lillehei, P. T. *Nano Lett.* **2003**, *3*, 59.
(28) Ma, N.; Zhang, H. Y.; Song, B.; Wang, Z. Q.; Zhang, X. *Chem. Mater.* **2005**, *17*, 5065.
(29) Zelikin, A. N.; Li, Q.; Caruso, F. *Angew. Chem., Int. Ed.* **2006**, *45*, 7743.
(30) Schmidt, D. J.; Hammond, P. T. *Chem. Commun.* **2010**, *46*, 7358.
(31) Kohli, P.; Blanchard, G. J. *Langmuir* **2000**, *16*, 4655.
(32) Such, G. K.; Quinn, J. F.; Quinn, A.; Tjipto, E.; Caruso, F. *J. Am. Chem. Soc.* **2006**, *128*, 9318.
(33) Shimazaki, Y.; Mitsuishi, M.; Ito, S.; Yamamoto, M. *Langmuir* **1997**, *13*, 1385.
(34) Zhang, Y.; Cao, W. *Langmuir* **2001**, *17*, 5021.
(35) Xiong, H.; Cheng, M.; Zhou, Z.; Zhang, X.; Shen, J. *Adv. Mater.* **1998**, *10*, 529.
(36) Yang, H. C.; Aoki, K.; Hong, H. G.; Sackett, D. D.; Arendt, M. F.; Yau, S. L.; Bell, C. M.; Mallouk, T. E. *J. Am. Chem. Soc.* **1993**, *115*, 11855.
(37) Muller, W.; Ringsdorf, H.; Rump, E.; Wildburg, G.; Zhang, X.; Angermaier, L.; Knoll, W.; Liley, M.; Spinke, J. *Science* **1993**, *262*, 1706.
(38) Azzaroni, O.; Álvarez, M.; Abou-Kandil, A. I.; Yameen, B.; Knoll, W. *Adv. Funct. Mater.* **2008**, *18*, 3487.
(39) Richert, L.; Boulmedais, F.; Lavalle, P.; Mutterer, J.; Ferreux, E.; Decher, G.; Schaaf, P.; Voegel, J.-C.; Picart, C. *Biomacromolecules* **2003**, *5*, 284.
(40) Harris, J. J.; DeRose, P. M.; Bruening, M. L. *J. Am. Chem. Soc.* **1999**, *121*, 1978.
(41) Gribova, V.; Auzely-Velty, R.; Picart, C. *Chem. Mater.* **2012**, *24*, 854.
(42) Liu, Y.; Bruening, M. L.; Bergbreiter, D. E.; Crooks, R. M. *Angew. Chem., Int. Ed.* **1997**, *36*, 2114.
(43) Bergbreiter, D. E.; Liao, K.-S. *Soft Matter* **2009**, *5*, 23.
(44) Major, J. S.; Blanchard, G. J. *Chem. Mater.* **2002**, *14*, 2574.
(45) Quinn, J. F.; Johnston, A. P. R.; Such, G. K.; Zelikin, A. N.; Caruso, F. *Chem. Soc. Rev.* **2007**, *36*, 707.
(46) Rydzek, G.; Jierry, L.; Parat, A.; Thomann, J.-S.; Voegel, J.-C.; Senger, B.; Hemmerlé, J.; Ponche, A.; Frisch, B.; Schaaf, P.; Boulmedais, F. *Angew. Chem., Int. Ed.* **2011**, *50*, 4374.
(47) Rydzek, G.; Thomann, J.-S. b.; Ben Ameur, N.; Jierry, L. c.; Mésini, P.; Ponche, A.; Contal, C.; El Haitami, A. E.; Voegel, J.-C.; Senger, B.; Schaaf, P.; Frisch, B. t.; Boulmedais, F. *Langmuir* **2009**, *26*, 2816.
(48) Li, M.; Ishihara, S.; Ji, Q.; Ma, Y.; Hill, J. P.; Ariga, K. *Chem. Lett.* **2012**, *41*, 383.
(49) del Mercato, L. L.; Rivera-Gil, P.; Abbasi, A. Z.; Ochs, M.; Ganas, C.; Zins, I.; Soennichsen, C.; Parak, W. J. *Nanoscale* **2010**, *2*, 458.
(50) Ichinose, I.; Kawakami, T.; Kunitake, T. *Adv. Mater.* **1998**, *10*, 535.
(51) De Koker, S.; Hoogenboom, R.; De Geest, B. G. *Chem. Soc. Rev.* **2012**, *41*, 2867.
(52) Xin, Y.; Yuan, J. *Polym. Chem.* **2012**, *3*, 3045.
(53) Schiff, H. *Justus Liebigs Ann. Chem.* **1864**, *131*, 118.
(54) Kratz, F.; Beyer, U.; Schutte, M. T. *Crit. Rev. Ther. Drug* **1999**, *16*, 245.
(55) Saito, H.; Hoffman, A. S.; Ogawa, H. I. *J. Bioact. Compat. Polym.* **2007**, *22*, 589.
(56) Wei, W.; Yuan, L.; Hu, G.; Wang, L.-Y.; Wu, H.; Hu, X.; Su, Z.-G.; Ma, G.-H. *Adv. Mater.* **2008**, *20*, 2292.
(57) Jia, Y.; Cui, Y.; Fei, J. B.; Du, M. C.; Dai, L. R.; Li, J. B.; Yang, Y. *Adv. Funct. Mater.* **2012**, *22*, 1446.
(58) Jia, Y.; Fei, J.; Cui, Y.; Yang, Y.; Gao, L.; Li, J. *Chem. Commun.* **2011**, *47*, 1175.
(59) Lehn, J.-M.; Eliseev, A. V. *Science* **2001**, *291*, 2331.
(60) Tauk, L.; Schröder, A. P.; Decher, G.; Giuseppone, N. *Nat. Chem.* **2009**, *1*, 649.
(61) Rowan, S. J.; Cantrill, S. J.; Cousins, G. R. L.; Sanders, J. K. M.; Stoddart, J. F. *Angew. Chem., Int. Ed.* **2002**, *41*, 898.
(62) Jayakrishnan, A.; Jameela, S. R. *Biomaterials* **1996**, *17*, 471.
(63) Manna, U.; Dhar, J.; Nayak, R.; Patil, S. *Chem. Commun.* **2010**, *46*, 2250.
(64) Gao, Q.; Yang, F.; Ma, Y.; Yang, X. *Electroanalysis* **2004**, *16*, 730.
(65) Gade, V. K.; Shirale, D. J.; Gaikwad, P. D.; Savale, P. A.; Kakde, K. P.; Kharat, H. J.; Shirsat, M. D. *React. Funct. Polym.* **2006**, *66*, 1420.
(66) Marques, M. E.; Mansur, A. A. P.; Mansur, H. S. *Appl. Surf. Sci.* **2013**, *275*, 347.
(67) Gupta, G.; Rajendran, V.; Atanassov, P. *Electroanalysis* **2003**, *15*, 1577.
(68) Kuo, C.-H.; Chen, G.-J.; Twu, Y.-K.; Liu, Y.-C.; Shieh, C.-J. *Ind. Eng. Chem. Res.* **2012**, *51*, 5141.
(69) Tkac, J.; Whittaker, J. W.; Ruzgas, T. *Biosens. Bioelectron.* **2007**, *22*, 1820.
(70) Sun, Y.; Yan, F.; Yang, W.; Sun, C. *Biomaterials* **2006**, *27*, 4042.
(71) Liu, Z.-M.; Yang, Y.; Wang, H.; Liu, Y.-L.; Shen, G.-L.; Yu, R.-Q. *Sens. Actuators B: Chem.* **2005**, *106*, 394.
(72) Wan, D.; Yuan, S.; Li, G. L.; Neoh, K. G.; Kang, E. T. *ACS Appl. Mater. Interfaces* **2010**, *2*, 3083.
(73) Yang, M.; Yang, Y.; Yang, H.; Shen, G.; Yu, R. *Biomaterials* **2006**, *27*, 246.
(74) Gan, S.; Yang, P.; Yang, W. *Biomacromolecules* **2009**, *10*, 1238.
(75) Zhang, X.; Zhao, Y.; Zhou, H.; Qu, B. *Biosens. Bioelectron.* **2011**, *26*, 2737.
(76) Bojorge-Ramirez, N. I.; Salgado, A. M.; Valdman, B. *Assay Drug Dev. Technol.* **2007**, *5*, 673.
(77) Tlili, A.; Jarboui, M. A.; Abdelghani, A.; Fathallah, D. M.; Maaref, M. A. *Mater. Sci. Eng., C* **2005**, *25*, 490.
(78) Ren, K. F.; Ji, J.; Shen, J. C. *Bioconjugate Chem.* **2006**, *17*, 77.
(79) Lin, Q.; Ding, X.; Qiu, F.; Song, X.; Fu, G.; Ji, J. *Biomaterials* **2010**, *31*, 4017.
(80) Pavlukhina, S. V.; Kaplan, J. B.; Xu, L.; Chang, W.; Yu, X.; Madhyastha, S.; Yakandawala, N.; Mentbayeva, A.; Khan, B.; Sukhishvili, S. A. *ACS Appl. Mater. Interfaces* **2012**, *4*, 4708.
(81) Hou, S.; Wang, J.; Martin, C. R. *Nano Lett.* **2005**, *5*, 231.

DOI: 10.1021/cr400559g
Chem. Rev. XXXX, XXX, XXX−XXX

(82) Tian, Y.; He, Q.; Cui, Y.; Li, J. B. *Biomacromolecules* **2006**, *7*, 2539.
(83) Liu, X.; Xing, J.; Guan, Y.; Shan, G.; Liu, H. *Colloid Surf. A: Physicochem. Eng. Asp.* **2004**, *238*, 127.
(84) Hong, Y.; Gao, C.; Xie, Y.; Gong, Y.; Shen, J. *Biomaterials* **2005**, *26*, 6305.
(85) Yang, Y.; Jia, Y.; Gao, L.; Fei, J. B.; Dai, L. R.; Zhao, J.; Li, J. B. *Chem. Commun.* **2011**, *47*, 12167.
(86) Tong, W. J.; Gao, C. Y.; Möhwald, H. *Chem. Mater.* **2005**, *17*, 4610.
(87) Tong, W. J.; Gao, C. Y.; Möhwald, H. *Macromolecules* **2006**, *39*, 335.
(88) Zhao, Q.; Mao, Z.; Gao, C.; Shen, J. *J. Biomater. Sci. Polym. Ed.* **2006**, *17*, 997.
(89) Tong, W.; Gao, C.; Möhwald, H. *Macromol. Rapid Commun.* **2006**, *27*, 2078.
(90) Tong, W.; Gao, C.; Möhwald, H. *Polym. Adv. Technol.* **2008**, *19*, 817.
(91) Tong, W. J.; Gao, C. Y.; Möhwald, H. *Colloid Polym. Sci.* **2008**, *286*, 1103.
(92) Duan, L.; He, Q.; Yan, X.; Cui, Y.; Wang, K.; Li, J. *Biochem. Biophys. Res. Commun.* **2007**, *354*, 357.
(93) Wang, Y.; Bansal, V.; Zelikin, A. N.; Caruso, F. *Nano Lett.* **2008**, *8*, 1741.
(94) Bertoldo, M.; Zampano, G.; Suffner, L.; Liberati, E.; Ciardelli, F. *Polym. Chem.* **2013**, *4*, 653.
(95) Kristiansen, K. A.; Potthast, A.; Christensen, B. E. *Carbohydr. Res.* **2010**, *345*, 1264.
(96) Maia, J.; Carvalho, R. A.; Coelho, J. F. J.; Simões, P. N.; Gil, M. H. *Polymer* **2011**, *52*, 258.
(97) Massia, S. P.; Stark, J. *J. Biomed. Mater. Res.* **2001**, *56*, 390.
(98) Yu, L.; Li, C. M.; Liu, Y.; Gao, J.; Wang, W.; Gan, Y. *Lab Chip* **2009**, *9*, 1243.
(99) Hoffmann, B.; Volkmer, E.; Kokott, A.; Weber, M.; Hamisch, S.; Schieker, M.; Mutschler, W.; Ziegler, G. *J. Mater. Chem.* **2007**, *17*, 4028.
(100) Bao, H.; Liu, S.; Zhang, L.; Chen, G. *Microchim. Acta* **2012**, *179*, 291.
(101) Fuentes, M.; Mateo, C.; García, L.; Tercero, J. C.; Guisán, J. M.; Fernández-Lafuente, R. *Biomacromolecules* **2004**, *5*, 883.
(102) Cui, W.; Cui, Y.; Zhu, P.; Zhao, J.; Su, Y.; Yang, Y.; Li, J. *Chem.—Asian J.* **2012**, *7*, 127.
(103) Hodneland, C. D.; Lee, Y. S.; Min, D. H.; Mrksich, M. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 5048.
(104) Fields, S. *Science* **2001**, *291*, 1221.
(105) MacBeath, G.; Schreiber, S. L. *Science* **2000**, *289*, 1760.
(106) Alley, W. R.; Mann, B. F.; Novotny, M. V. *Chem. Rev.* **2013**, *113*, 2668.
(107) Sun, Y.; Bai, Y.; Yang, W.; Sun, C. *Electrochim. Acta* **2007**, *52*, 7352.
(108) Yoon, H. C.; Kim, H.-S. *Anal. Chem.* **2000**, *72*, 922.
(109) Gupta, G.; Rajendran, V.; Atanassov, P. *Electroanal* **2004**, *16*, 1182.
(110) Zhang, Y.; Kuang, M.; Zhang, L.; Yang, P.; Lu, H. *Anal. Chem.* **2013**, *85*, 5535.
(111) Rannes, J. B.; Ioannou, A.; Willies, S. C.; Grogan, G.; Behrens, C.; Flitsch, S. L.; Turner, N. J. *J. Am. Chem. Soc.* **2011**, *133*, 8436.
(112) Carrico, I. S.; Carlson, B. L.; Bertozzi, C. R. *Nat. Chem. Biol.* **2007**, *3*, 321.
(113) Yoon, H. C.; Hong, M.-Y.; Kim, H.-S. *Anal. Chem.* **2000**, *72*, 4420.
(114) Zhang, S.; Wang, N.; Niu, Y.; Sun, C. *Sens. Actuators B: Chem.* **2005**, *109*, 367.
(115) Yang, W.; Wang, J.; Zhao, S.; Sun, Y.; Sun, C. *Electrochem. Commun.* **2006**, *8*, 665.
(116) Sun, Y. Y.; Wang, H. Y.; Sun, C. Q. *Biosens. Bioelectron.* **2008**, *24*, 22.
(117) Zhang, S.; Yang, W.; Niu, Y.; Sun, C. *Sens. Actuators B: Chem.* **2004**, *101*, 387.
(118) Pita, M.; Gutierrez-Sanchez, C.; Olea, D.; Velez, M.; Garcia-Diego, C.; Shleev, S.; Fernandez, V. M.; De Lacey, A. L. *J. Phys. Chem. C* **2011**, *115*, 13420.
(119) Lu, Z.; Li, C. M.; Zhou, Q.; Bao, Q.-L.; Cui, X. *J. Colloid Interface Sci.* **2007**, *314*, 80.
(120) Henderson, G. E.; Isett, K. D.; Gerngross, T. U. *Bioconjugate Chem.* **2011**, *22*, 903.
(121) Zammatteo, N.; Jeanmart, L.; Hamels, S.; Courtois, S.; Louette, P.; Hevesi, L.; Remacle, J. *Anal. Biochem.* **2000**, *280*, 143.
(122) Dulay, M. T.; Baca, Q. J.; Zare, R. N. *Anal. Chem.* **2005**, *77*, 4604.
(123) Lim, J.-H.; Ginger, D. S.; Lee, K.-B.; Heo, J.; Nam, J.-M.; Mirkin, C. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 2309.
(124) Zhou, X.; Wu, L.; Zhou, J. *Langmuir* **2004**, *20*, 8877.
(125) Rozkiewicz, D. I.; Brugman, W.; Kerkhoven, R. M.; Ravoo, B. J.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **2007**, *129*, 11593.
(126) Chang, T.; Rozkiewicz, D. I.; Ravoo, B. J.; Meijer, E. W.; Reinhoudt, D. N. *Nano Lett.* **2007**, *7*, 978.
(127) Rogero, C.; Chaffey, B. T.; Mateo-Martí, E.; Sobrado, J. s. M.; Horrocks, B. R.; Houlton, A.; Lakey, J. H.; Briones, C.; Martín-Gago, J. A. *J. Phys. Chem. C* **2008**, *112*, 9308.
(128) Horton, R. C.; Herne, T. M.; Myles, D. C. *J. Am. Chem. Soc.* **1997**, *119*, 12980.
(129) Peelen, D.; Smith, L. M. *Langmuir* **2005**, *21*, 266.
(130) Hautman, J.; Klein, M. L. *Phys. Rev. Lett.* **1991**, *67*, 1763.
(131) Ong, T. H.; Ward, R. N.; Davies, P. B.; Bain, C. D. *J. Am. Chem. Soc.* **1992**, *114*, 6243.
(132) Zin, M. T.; Yip, H.-L.; Wong, N.-Y.; Ma, H.; Jen, A. K. Y. *Langmuir* **2006**, *22*, 6346.
(133) Kang, S. H.; Ma, H.; Kang, M.-S.; Kim, K.-S.; Jen, A. K. Y.; Zareie, M. H.; Sarikaya, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 1512.
(134) Leong, K.; Boardman, A. K.; Ma, H.; Jen, A. K. Y. *Langmuir* **2009**, *25*, 4615.
(135) Zin, M. T.; Ma, H.; Sarikaya, M.; Jen, A. K. Y. *Small* **2005**, *1*, 698.
(136) Zin, M. T.; Munro, A. M.; Gungormus, M.; Wong, N.-Y.; Ma, H.; Tamerler, C.; Ginger, D. S.; Sarikaya, M.; Jen, A. K. Y. *J. Mater. Chem.* **2007**, *17*, 866.
(137) Rozkiewicz, D. I.; Ravoo, B. J.; Reinhoudt, D. N. *Langmuir* **2005**, *21*, 6337.
(138) Rozkiewicz, D. I.; Kraan, Y.; Werten, M. W. T.; de Wolf, F. A.; Subramaniam, V.; Ravoo, B. J.; Reinhoudt, D. N. *Chem.—Eur. J.* **2006**, *12*, 6290.
(139) Mashazi, P.; Mugadza, T.; Sosibo, N.; Mdluli, P.; Vilakazi, S.; Nyokong, T. *Talanta* **2011**, *85*, 2202.
(140) Duan, J. J.; Hou, R. X.; Xiong, X. P.; Wang, Y. D.; Wang, Y.; Fu, J.; Yu, Z. J. *J. Mater. Chem. B* **2013**, *1*, 485.
(141) Zhang, H.; Zhang, P.; Ye, K.; Sun, Y.; Jiang, S.; Wang, Y.; Pang, W. *J. Lumin.* **2006**, *117*, 68.
(142) Shervedani, R. K.; Mozaffari, S. A. *Anal. Chem.* **2006**, *78*, 4957.
(143) Amigoni, S.; de Givenchy, E. T.; Dufay, M.; Guittard, F. *Langmuir* **2009**, *25*, 11073.
(144) Liu, T.; He, G.; Yang, M.; Fang, Y. *J. Photochem. Photobiol. A: Chem.* **2009**, *202*, 178.
(145) Nagasaki, Y.; Okada, T.; Scholz, C.; Iijima, M.; Kato, M.; Kataoka, K. *Macromolecules* **1998**, *31*, 1473.
(146) Emoto, K.; Nagasaki, Y.; Iijima, M.; Kato, M.; Kataoka, K. *Colloid Surf. B: Biointerfaces* **2000**, *18*, 337.
(147) Emoto, K.; Iijima, M.; Nagasaki, Y.; Kataoka, K. *J. Am. Chem. Soc.* **2000**, *122*, 2653.
(148) Emoto, K.; Nagasaki, Y.; Kataoka, K. *Langmuir* **2000**, *16*, 5738.
(149) Hirano, A.; Iijima, M.; Emoto, K.; Nagasaki, Y.; Kataoka, K. *Mater. Sci. Eng., C* **2004**, *24*, 761.
(150) Otsuka, H.; Nagasaki, Y.; Kataoka, K. *Adv. Drug Delivery Rev.* **2012**, *64*, 246.
(151) Slomkowski, S.; Miksa, B.; Chehimi, M. M.; Delamar, M.; Cabet-Deliry, E.; Majoral, J. P.; Caminade, A. M. *React. Funct. Polym.* **1999**, *41*, 45.
(152) Trevisiol, E.; Le Berre-Anton, V.; Leclaire, J.; Pratviel, G.; Caminade, A.-M.; Majoral, J.-P.; Francois, J. M.; Meunier, B. *New J. Chem.* **2003**, *27*, 1713.

DOI: 10.1021/cr400559g
Chem. Rev. XXXX, XXX, XXX−XXX

(153) Le Berre, V.; Trevisiol, E.; Dagkessamanskaia, A.; Sokol, S.; Caminade, A. M.; Majoral, J. P.; Meunier, B.; Francois, J. *Nucleic Acids Res.* **2003**, *31*, e88.
(154) Caminade, A.-M.; Majoral, J.-P. *Acc. Chem. Res.* **2004**, *37*, 341.
(155) Miksa, B.; Slomkowski, S.; Chehimi, M. M.; Delamar, M.; Majoral, J. P.; Caminade, A. M. *Colloid Polym. Sci.* **1999**, *277*, 58.
(156) Kharlampieva, E.; Sukhishvili, S. A. *Macromolecules* **2003**, *36*, 9950.
(157) Liu, P.; Li, X.; Mu, B.; Du, P.; Zhao, X.; Zhong, Z. *Ind. Eng. Chem. Res.* **2012**, *51*, 13875.
(158) Prencipe, G.; Tabakman, S. M.; Welsher, K.; Liu, Z.; Goodwin, A. P.; Zhang, L.; Henry, J.; Dai, H. J. *J. Am. Chem. Soc.* **2009**, *131*, 4783.
(159) Zhao, X.; Du, P.; Liu, P. *Mol. Pharmaceutics* **2012**, *9*, 3330.
(160) Zheng, J.; Xie, H.; Yu, W.; Tan, M.; Gong, F.; Liu, X.; Wang, F.; Lv, G.; Liu, W.; Zheng, G.; Yang, Y.; Xie, W.; Ma, X. *Langmuir* **2012**, *28*, 13261.
(161) Wang, Z.; Möhwald, H.; Gao, C. *ACS Nano* **2011**, *5*, 3930.
(162) Wang, Z.; Xie, Y.; Gao, C. *RSC Adv.* **2012**, *2*, 11354.
(163) Wang, Z.; Liu, M.; Xie, Y.; Gao, C. *J. Mater. Chem.* **2012**, *22*, 2855.
(164) Wang, Z.; Skirtach, A. G.; Xie, Y.; Liu, M.; Möhwald, H.; Gao, C. *Chem. Mater.* **2011**, *23*, 4741.
(165) Hillebrenner, H.; Buyukserin, F.; Kang, M.; Mota, M. O.; Stewart, J. D.; Martin, C. R. *J. Am. Chem. Soc.* **2006**, *128*, 4236.
(166) Zhao, Y.-L.; Li, Z.; Kabehie, S.; Botros, Y. Y.; Stoddart, J. F.; Zink, J. I. *J. Am. Chem. Soc.* **2010**, *132*, 13016.
(167) Lee, D. C.; Chang, B. J.; Morales, G. M.; Jang, Y. A.; Ng, M. K.; Heller, S. T.; Yu, L. P. *Macromolecules* **2004**, *37*, 1849.
(168) Duan, L.; Qi, W.; Yan, X. H.; He, Q.; Cui, Y.; Wang, K. W.; Li, D. X.; Li, J. B. *J. Phys. Chem. B* **2009**, *113*, 395.
(169) Qi, W.; Duan, L.; Li, J. B. *Soft Matter* **2011**, *7*, 1571.
(170) Qi, W.; Yan, X.; Juan, L.; Cui, Y.; Yang, Y.; Li, J. *Biomacromolecules* **2009**, *10*, 1212.
(171) Qi, W.; Yan, X.; Fei, J.; Wang, A.; Cui, Y.; Li, J. *Biomaterials* **2009**, *30*, 2799.
(172) Zhao, W.; Zhang, H.; He, Q.; Li, Y.; Gu, J.; Li, L.; Li, H.; Shi, J. *Chem. Commun.* **2011**, *47*, 9459.
(173) Gao, L.; Fei, J. B.; Zhao, J.; Cui, W.; Cui, Y.; Li, J. B. *Chem.—Eur. J.* **2012**, *18*, 3185.
(174) Wang, Z.; Möhwald, H.; Gao, C. *Langmuir* **2010**, *27*, 1286.
(175) Mu, B.; Lu, C. Y.; Liu, P. *Colloid Surf. B: Biointerfaces* **2011**, *82*, 385.
(176) Wang, B.; Xu, C.; Xie, J.; Yang, Z.; Sun, S. *J. Am. Chem. Soc.* **2008**, *130*, 14436.
(177) Liang, X.; Kozlovskaya, V.; Chen, Y.; Zavgorodnya, O.; Kharlampieva, E. *Chem. Mater.* **2012**, *24*, 3707.
(178) Zhang, K.; Wu, X. Y. *J. Controlled Release* **2002**, *80*, 169.
(179) Ma, N.; Li, Y.; Xu, H.; Wang, Z.; Zhang, X. *J. Am. Chem. Soc.* **2010**, *132*, 442.
(180) Reddy, L. H.; Arias, J. L.; Nicolas, J.; Couvreur, P. *Chem. Rev.* **2012**, *112*, 5818.
(181) de Villiers, M. M.; Otto, D. P.; Strydom, S. J.; Lvov, Y. M. *Adv. Drug Delivery Rev.* **2011**, *63*, 701.
(182) De Geest, B. G.; Sanders, N. N.; Sukhorukov, G. B.; Demeester, J.; De Smedt, S. C. *Chem. Soc. Rev.* **2007**, *36*, 636.
(183) Johnston, A. P. R.; Cortez, C.; Angelatos, A. S.; Caruso, F. *Curr. Opin. Colloid Interface Sci.* **2006**, *11*, 203.
(184) Vergaro, V.; Scarlino, F.; Bellomo, C.; Rinaldi, R.; Vergara, D.; Maffia, M.; Baldassarre, F.; Giannelli, G.; Zhang, X.; Lvov, Y. M.; Leporatti, S. *Adv. Drug Delivery Rev.* **2011**, *63*, 847.
(185) Zhang, J.; Xu, X.-D.; Liu, Y.; Liu, C.-W.; Chen, X.-H.; Li, C.; Zhuo, R.-X.; Zhang, X.-Z. *Adv. Funct. Mater.* **2012**, *22*, 1704.
(186) Li, C.; Luo, G. F.; Wang, H. Y.; Zhang, J.; Gong, Y. H.; Cheng, S. X.; Zhuo, R. X.; Zhang, X. Z. *J. Phys. Chem. C* **2011**, *115*, 17651.
(187) Zhao, Q.; Han, B.; Wang, Z.; Gao, C.; Peng, C.; Shen, J. *Nanomed.-Nanotechnol. Biol. Med.* **2007**, *3*, 63.
(188) Peng, C. Y.; Zhang, Y. Y.; Tong, W. J.; Gao, C. Y. *J. Appl. Polym. Sci.* **2011**, *121*, 3710.
(189) Dai, J.; Lin, S.; Cheng, D.; Zou, S.; Shuai, X. *Angew. Chem., Int. Ed.* **2011**, *50*, 9404.
(190) Agarwal, P.; Kudirka, R.; Albers, A. E.; Barfield, R. M.; de Hart, G. W.; Drake, P. M.; Jones, L. C.; Rabuka, D. *Bioconjugate Chem.* **2013**, *24*, 846.
(191) Mintzer, M. A.; Simanek, E. E. *Chem. Rev.* **2008**, *109*, 259.
(192) Wang, Z.; Qian, L.; Wang, X.; Zhu, H.; Yang, F.; Yang, X. *Colloids Surf. A: Physicochem. Eng. Aspects* **2009**, *332*, 164.
(193) Wei, W.; Ma, G.-H.; Wang, L.-Y.; Wu, J.; Su, Z.-G. *Acta Biomater.* **2010**, *6*, 205.
(194) Zhao, J.; Fei, J.; Gao, L.; Cui, W.; Yang, Y.; Wang, A.; Li, J. *Chem.—Eur. J.* **2013**, *19*, 4548.
(195) Keipert, P. E.; Gonzales, A.; Gomez, C. L.; Macdonald, V. W.; Hess, J. R.; Winslow, R. M. *Transfusion* **1993**, *33*, 701.
(196) Winslow, R. M. *Adv. Drug Delivery Rev.* **2000**, *40*, 131.
(197) Natanson, C.; Kern, S. J.; Lurie, P.; Banks, S. M.; Wolfe, S. M. *J. Am. Med. Assoc.* **2008**, *299*, 2304.
(198) Manning, L. R.; Morgan, S.; Beavis, R. C.; Chait, B. T.; Manning, J. M.; Hess, J. R.; Cross, M.; Currell, D. L.; Marini, M. A.; Winslow, R. M. *Proc. Natl. Acad. Sci. U.S.A.* **1991**, *88*, 3329.
(199) Sheng, Y.; Liu, C.; Yuan, Y.; Tao, X.; Yang, F.; Shan, X.; Zhou, H.; Xu, F. *Biomaterials* **2009**, *30*, 2340.
(200) Duan, L.; Yan, X. H.; Wang, A. H.; Jia, Y.; Li, J. B. *ACS Nano* **2012**, *6*, 6897.
(201) Sheldon, R. A.; van Pelt, S. *Chem. Soc. Rev.* **2013**, *42*, 6223.
(202) Rodrigues, R. C.; Ortiz, C.; Berenguer-Murcia, A.; Torres, R.; Fernandez-Lafuente, R. *Chem. Soc. Rev.* **2013**, *42*, 6290.
(203) Ariga, K.; Ji, Q.; Mori, T.; Naito, M.; Yamauchi, Y.; Abe, H.; Hill, J. P. *Chem. Soc. Rev.* **2013**, *42*, 6322.
(204) Hartmann, M.; Kostrov, X. *Chem. Soc. Rev.* **2013**, *42*, 6277.
(205) Girelli, A. M.; Mattei, E.; Messina, A. *Sens. Actuators B: Chem.* **2007**, *121*, 515.
(206) Zheng, X.; Wang, Q.; Jiang, Y.; Gao, J. *Ind. Eng. Chem. Res.* **2012**, *51*, 10140.
(207) Betancor, L.; Johnson, G. R.; Luckarift, H. R. *ChemCatChem* **2013**, *5*, 46.
(208) Karagoz, B.; Bayramoglu, G.; Altintas, B.; Bicak, N.; Yakup Arica, M. *Bioresour. Technol.* **2011**, *102*, 6783.
(209) Rekuć, A.; Bryjak, J.; Szymańska, K.; Jarzębski, A. B. *Bioresour. Technol.* **2010**, *101*, 2076.
(210) Qi, W.; Duan, L.; Wang, K. W.; Yan, X. H.; Citi, Y.; He, Q.; Li, J. B. *Adv. Mater.* **2008**, *20*, 601.
(211) Shi, J.; Zhang, L.; Jiang, Z. *ACS Appl. Mater. Interfaces* **2011**, *3*, 881.
(212) Ariga, K.; Ji, Q. M.; Hill, J. P. *Modern techniques for nano- and microreactors/-reactions*; Caruso, F., Ed.; Springer Berlin Heidelberg: Berlin, 2010; Vol. *229*; pp 51.
(213) Zhang, S.; Wang, N.; Yu, H.; Niu, Y.; Sun, C. *Bioelectrochemistry* **2005**, *67*, 15.
(214) Zhang, S.; Yang, W.; Niu, Y.; Sun, C. *Anal. Chim. Acta* **2004**, *523*, 209.
(215) Saha, K.; Agasti, S. S.; Kim, C.; Li, X.; Rotello, V. M. *Chem. Rev.* **2012**, *112*, 2739.
(216) Sirkar, K.; Revzin, A.; Pishko, M. V. *Anal. Chem.* **2000**, *72*, 2930.
(217) Chambers, J. P.; Arulanandam, B. P.; Matta, L. L.; Weis, A.; Valdes, J. J. *Curr. Issues Mol. Biol.* **2008**, *10*, 1.
(218) Sun, Y.; Song, D.; Bai, Y.; Wang, L.; Tian, Y.; Zhang, H. *Anal. Chim. Acta* **2008**, *624*, 294.
(219) Ke, R.; Yang, W.; Xia, X.; Xu, Y.; Li, Q. *Anal. Biochem.* **2010**, *406*, 8.
(220) Hu, C.; Yang, D.-P.; Xu, K.; Cao, H.; Wu, B.; Cui, D.; Jia, N. *Anal. Chem.* **2012**, *84*, 10324.
(221) Hu, C.; Yang, D.-P.; Wang, Z.; Yu, L.; Zhang, J.; Jia, N. *Anal. Chem.* **2013**, *85*, 5200.
(222) Ge, L.; Yan, J.; Song, X.; Yan, M.; Ge, S.; Yu, J. *Biomaterials* **2012**, *33*, 1024.
(223) Zhang, Z.; Yang, W.; Wang, J.; Yang, C.; Yang, F.; Yang, X. *Talanta* **2009**, *78*, 1240.

DOI: 10.1021/cr400559g
Chem. Rev. XXXX, XXX, XXX−XXX

(224) Kwon, O. S.; Park, S. J.; Hong, J.-Y.; Han, A. R.; Lee, J. S.; Lee, J. S.; Oh, J. H.; Jang, J. *ACS Nano* **2012**, *6*, 1486.
(225) Sassolas, A.; Leca-Bouvier, B. D.; Blum, L. J. *Chem. Rev.* **2007**, *108*, 109.
(226) Marquette, C. A.; Lawrence, I.; Polychronakos, C.; Lawrence, M. F. *Talanta* **2002**, *56*, 763.
(227) Li, A.; Yang, F.; Ma, Y.; Yang, X. *Biosens. Bioelectron.* **2007**, *22*, 1716.
(228) Fuentes, M.; Mateo, C.; Rodriguez, A.; Casqueiro, M.; Tercero, J. C.; Riese, H. H.; Fernández-Lafuente, R.; Guisán, J. M. *Biosens. Bioelectron.* **2006**, *21*, 1574.
(229) Shabani, R.; Mozaffari, S. A.; Husain, S. W.; Tehrani, M. S. *Iran. J. Sci. Technol. A* **2009**, *33*, 335.
(230) Shervedani, R. K.; Mozaffari, S. A. *Surf. Coat. Technol.* **2005**, *198*, 123.
(231) Bi, X.; Wong, W. L.; Ji, W.; Agarwal, A.; Balasubramanian, N.; Yang, K.-L. *Biosens. Bioelectron.* **2008**, *23*, 1442.
(232) Zhang, M.; Ge, L.; Ge, S.; Yan, M.; Yu, J.; Huang, J.; Liu, S. *Biosens. Bioelectron.* **2013**, *41*, 544.
(233) Silvestre, C. I. C.; Pinto, P.; Segundo, M. A.; Saraiva, M.; Lima, J. *Anal. Chim. Acta* **2011**, *689*, 160.
(234) Yang, M.; Jiang, J.; Yang, Y.; Chen, X.; Shen, G.; Yu, R. *Biosens. Bioelectron.* **2006**, *21*, 1791.
(235) Qiu, J.-D.; Xie, H.-Y.; Liang, R.-P. *Microchim. Acta* **2008**, *162*, 57.
(236) Bai, Y.; Yang, H.; Yang, W.; Li, Y.; Sun, C. *Sensors Actuators B: Chem.* **2007**, *124*, 179.
(237) Brynda, E.; Houska, M.; Brandenburg, A.; Wikerstal, A.; Škvor, J. *Biosens. Bioelectron.* **1999**, *14*, 363.
(238) Lee, L. M.; Heimark, R. L.; Baygents, J. C.; Zohar, Y. *Nanotechnology* **2006**, *17*, S29.
(239) Caballero, D.; Martinez, E.; Bausells, J.; Errachid, A.; Samitier, J. *Anal. Chim. Acta* **2012**, *720*, 43.
(240) Koçum, C.; Ülgen, Ş. D.; Çubukçu, E.; Pişkin, E. *Ultramicroscopy* **2006**, *106*, 326.
(241) Harding Lepage, P.; Peytavi, R.; Bergeron, M. G.; Leclerc, M. *Anal. Chem.* **2011**, *83*, 8086.
(242) Katz, C.; Levy-Beladev, L.; Rotem-Bamberger, S.; Rito, T.; Rudiger, S. G. D.; Friedler, A. *Chem. Soc. Rev.* **2011**, *40*, 2131.
(243) Cretich, M.; Damin, F.; Pirri, G.; Chiari, M. *Biomol. Eng.* **2006**, *23*, 77.
(244) Afanassiev, V.; Hanemann, V.; Wolfl, S. *Nucleic Acids Res.* **2000**, *28*, e66.
(245) Bhatnagar, P.; Mark, S. S.; Kim, I.; Chen, H.; Schmidt, B.; Lipson, M.; Batt, C. A. *Adv. Mater.* **2006**, *18*, 315.
(246) Caminade, A. M.; Turrin, C. O.; Majoral, J. P. *Chem.—Eur. J.* **2008**, *14*, 7422.
(247) Jonkheijm, P.; Weinrich, D.; Schroder, H.; Niemeyer, C. M.; Waldmann, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 9618.
(248) Wu, C. C.; Reinhoudt, D. N.; Otto, C.; Subramaniam, V.; Velders, A. H. *Small* **2011**, *7*, 989.
(249) Ginger, D. S.; Zhang, H.; Mirkin, C. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 30.
(250) Wadu-Mesthrige, K.; Xu, S.; Amro, N. A.; Liu, G. Y. *Langmuir* **1999**, *15*, 8580.
(251) Liu, G. Y.; Amro, N. A. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 5165.
(252) Mendelsohn, A. D.; Bernards, D. A.; Lowe, R. D.; Desai, T. A. *Langmuir* **2010**, *26*, 9943.
(253) Bhattacharya, A.; Balazs, A. C. *J. Mater. Chem.* **2010**, *20*, 10384.
(254) Erokhina, S.; Berzina, T.; Cristofolini, L.; Shchukin, D.; Sukhorukov, G.; Musa, L.; Erokhin, V.; Fontana, M. P. *J. Magn. Magn. Mater.* **2004**, *272−276* (Part 2), 1353.
(255) Yang, J.; Gao, C. *Macromol. Rapid Commun.* **2010**, *31*, 1065.
(256) Yang, J.; Gao, C. Y. *J. Zhejiang Univ. Sc. A* **2009**, *10*, 114.
(257) Yu, A.; Liang, Z. *J. Colloid Interface Sci.* **2009**, *330*, 144.
(258) Song, W.; Yang, Y.; Möhwald, H.; Li, J. *Soft Matter* **2011**, *7*, 359.

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Chem. Rev. XXXX, XXX, XXX−XXX