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Supramolecular Chemistry at Interfaces: Host–Guest Interactions for Fabricating Multifunctional Biointerfaces

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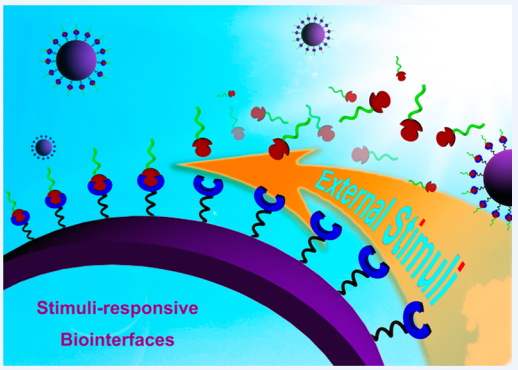
CONSPECTUS: Host–guest chemistry can greatly improve the selectivity of biomolecule–ligand binding on account of recognition-directed interactions. In addition, functional structures and the actuation of supramolecular assemblies in molecular systems can be controlled efficiently through various host–guest chemistry. Together, these highly selective, strong yet dynamic interactions can be exploited as an alternative methodology for applications in the field of programmable and controllable engineering of supramolecular soft materials through the reversible binding between complementary components.



Many processes in living systems such as biotransformation, transportation of matter, and energy transduction begin with interfacial molecular recognition, which is greatly influenced by various external stimuli at biointerfaces. Detailed investigations about the molecular recognition at interfaces can result in a better understanding of life science, and further guide us in developing new biomaterials and medicines. In order to mimic complicated molecular-recognition systems observed in nature that adapt to changes in their environment, combining host–guest chemistry and surface science is critical for fabricating the next generation of multifunctional biointerfaces with efficient stimuli-responsiveness and good biocompatibility. In this Account, we will summarize some recent progress on multifunctional stimuli-responsive biointerfaces and biosurfaces fabricated by cyclodextrin- or cucurbituril-based host–guest chemistry and highlight their potential applications including drug delivery, bioelectrocatalysis, and reversible adsorption and resistance of peptides, proteins, and cells. In addition, these biointerfaces and biosurfaces demonstrate efficient response toward various external stimuli, such as UV light, pH, redox chemistry, and competitive guests. All of these external stimuli can aid in mimicking the biological stimuli evident in complex biological environments. We begin by reviewing the current state of stimuli-responsive supramolecular assemblies formed by host–guest interactions, discussing how to transfer host–guest chemistry from solution onto surfaces required for fabricating multifunctional biosurfaces and biointerfaces. Then, we present different stimuli-responsive biosurfaces and biointerfaces, which have been prepared through a combination of cyclodextrin- or cucurbituril-based host–guest chemistry and various surface technologies such as self-assembled monolayers or layer-by-layer assembly. Moreover, we discuss the applications of these biointerfaces and biosurfaces in the fields of drug release, reversible adsorption and release of some organic molecules, peptides, proteins, and cells, and photoswitchable bioelectrocatalysis. In addition, we summarize the merits and current limitations of these methods for fabricating multifunctional stimuli-responsive biointerfaces in a dynamic noncovalent manner. Finally, we present possible strategies for future designs of stimuli-responsive multifunctional biointerfaces and biosurfaces by combining host–guest chemistry with surface science, which will lead to further critical development of supramolecular chemistry at interfaces.

1. INTRODUCTION

Host–guest chemistry is aimed at studying the selective interactions between host and guest molecules. Usually, a host is a molecule that contains a large cavity volume such as cyclodextrins (CD), cucurbiturils (CB), or calixarenes. Guests typically have both a complementary shape and interaction with the host, thus allowing for selectivity between the host and the guest, which is termed molecular recognition. These can include various noncovalent interactions, such as hydrogen bonding, electrostatics, and van der Waals and hydrophobic interactions. In general, host–guest chemistry can offer new insights into the development of traditional subjects and

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heralds many promises that range from biomimetics to the creation of programmable and controllable engineering of supramolecular soft materials.[1]

In many biological systems, some processes such as biotransformation, transportation of matter, and energy transduction usually begin with interfacial molecular recognition. These dynamic behaviors in biological systems are greatly influenced by various external stimuli at interfaces.[2,3] Therefore, the introduction of a variety of host–guest chemistries into surface technology is an important step forward in order to fabricate multifunctional biointerfaces with efficient stimuli-responsiveness, which demonstrates good biocompatibility to imitate the complicated molecular-recognition systems in nature, highly adaptive to the changes of their environment.[4−6]

In general, host–guest chemistry can be used for constructing multifunctional biointerfaces, which can be used to mimic biological systems. There are two methods to realize the fabrication and functionalization of biointerfaces by host–guest chemistry. Self-assembled monolayers (SAMs) are the most widely used method to fabricate functional biointerfaces on account of their simplicity and versatility.[7] Host–guest systems can be readily modified onto the surfaces through chemisorption with a thiol or silanol group. Layer-by-layer (LbL) assembly is another powerful method to fabricate functional biointerfaces, which can be combined with host–guest chemistry.[8] Such host–guest systems can be introduced into LbL multilayer films through various intermolecular interactions including electrostatic, hydrogen bonding, van der Waals forces, and charge transfer interactions. It is important to note that whereas many molecular devices work well in solution, problems can arise when they are transferred onto solid surfaces.[9−11] Thus, it remains a great challenge to fabricate multifunctional host–guest containing biointerfaces, which can work just as well at an interface as in solution.

Fortunately, stimuli-responsive supramolecular assembly formed by host–guest interactions has been well established in solution.[12−17] Based on previous work in solution, a variety of multifunctional biointerfaces can be designed and constructed by introducing host–guest chemistry onto surfaces as depicted in Figure 1, which have potential applications in drug release, reversible adsorption and resistance of peptides, proteins, and cells, and photoswitchable bioelectrocatalysis, to name a few.

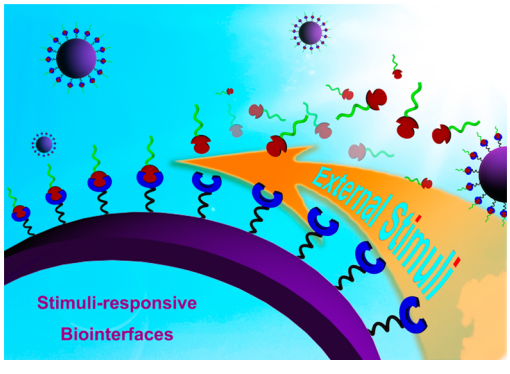

Figure 1. Schematic illustration of the activation of stimuli-responsive biointerfaces fabricated by host–guest chemistry through external stimuli.

2. STIMULI-RESPONSIVE BIOINTERFACES FABRICATED BY HOST–GUEST CHEMISTRY

2.1. Photocontrolled Biointerfaces

Light, as one of the most widely used stimuli, is well-known for its noninvasive nature and can be easily controlled simply by adjusting its wavelength and intensity.[18] Furthermore, photocontrolled host–guest complexes have significant interest in biocatalysis, controlled biosensors, energy conversion, and information storage. For example, photocontrolled molecular shuttles constructed by the host–guest interactions of azobenzene derivatives and α-CD have been mainly studied in solution on account of the well-documented photoisomerism of azobenzene.[19] In such a host–guest complex, α-CD can be described as a shuttle that can slide back and forth between the two states of *trans*- or *cis*-azobenzene in response to photostimuli in solution.[20]

It is important to note that the particular molecular shuttle described above works well in solution, however, it ceases to operate when transferred onto a solid surface. This issue arises from the fact that the system has more degrees of freedom in solution than on solid surfaces. We therefore proposed a strategy of mixed SAMs and fabricated a photocontrolled molecular shuttle by chemisorption of the host–guest complex on a rough gold surface.[21] When the host–guest complex was densely anchored onto the gold surface, the surface was superhydrophilic. However, the surface wettability did not change upon UV/vis irradiation because the density was so high that α-CD was not free to slide as shown in Figure 2a.[21,22]

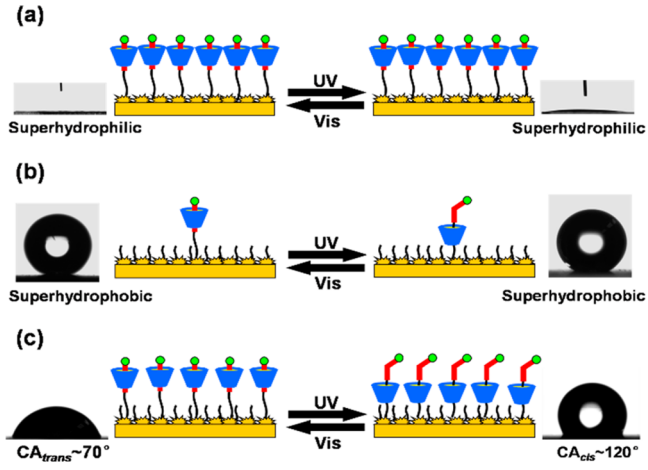

Figure 2. Surface wettability changes of photocontrolled switchable surface with different structure upon UV/vis irradiation. Adapted from ref 21 with permission from The Royal Society of Chemistry.

On the other hand, when a large amount of space was introduced with a loosely packed SAM, the surface was superhydrophobic (Figure 2b). Moreover, the surface wettability did not show significant change upon irradiation because the shuttle density was too low to induce remarkable change of surface energy as shown in Figure 2b. It was only at an intermediate molar ratio of free space to host–guest complex (5:1) that the surface wettability could be reversibly switched leading to the reversible conversion of contact angles between 70 ± 2° and 120 ± 2° upon UV/vis irradiation as shown in Figure 2c.

In order to fabricate more flexible and functional biointerfaces, smart surfaces may be fabricated by host–guest

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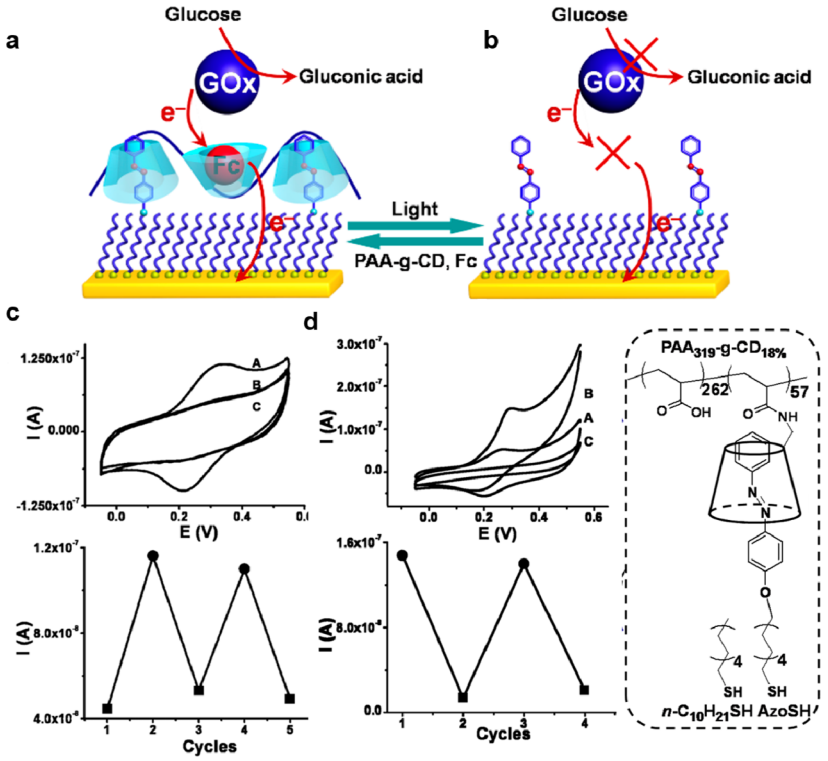

Figure 3. Photoswitchable reversible activation (a) and deactivation (b) of the biointerface for oxidation of glucose to gluconic acid; (c) cyclic voltammogram (CV) responses of redox-polymer-coated electrodes before and after light irradiation; (d) CV response and photocontrolled reversible switching of the electrocatalytic anodic current from bioelectrocatalyzed oxidation of glucose by GOx using host–guest biointerface before and after light irradiation. Adapted from ref 25 with pemission The Royal Society of Chemistry.

interactions of polymers, which could provide more flexibility and accessible functional groups than monolayer surfaces made up of small molecules. Willner and co-workers fabricated a photoisomerizable monolayer coupled with negatively charged particles by electrostatic interaction, which was applied for the photoelectrocatalysis and the catalytic generation of chemiluminescence.[23,24] In an attempt to move toward a more biocompatible photoresponsive interface, we fabricated photocontrolled bioelectrocatalyzed surfaces using ferrocene-labeled redox-polymers with the host–guest chemistry of α-CD and azobenzene derivatives (Figure 3). Ferrocene-labeled redox-polymers with α-CD (PAA-*g*-CD-Fc) were immobilized on gold surfaces by host–guest interactions between α-CD and azobenzene derivatives as shown in Figure 3a.[25] Moreover, when the photoresponsive bioelectrocatalyzed interfaces were immersed into the solution of glucose and glucose oxidase (GOx), these biointerfaces could control oxidation of glucose with the help of (GOx) using a ferrocene-labeled redox-polymer as mediate. However, after release of PAA-*g*-CD-Fc from the azobenzene-functionalized SAM surfaces, glucose could not be oxidized to gluconic acid due to the lack of ferrocene moieties (Figure 3b). Additionally, the reversible activation and deactivation of the host–guest biointerfaces could be repeated over many cycles triggered by light as shown in Figure 3c and d. These photoresponsive SAMs could therefore bioelectrocatalyze the oxidation of glucose to gluconic acid with the help of GOx by the photocontrolled reversible immobilization and release of the functionalized polymer PAA-*g*-CD-Fc. Considering that UV light can be harmful for living systems and has poor penetrability, it is anticipated that longer wavelength light, such as visible and near-infrared light, will be employed in future generations of stimuli-responsive biointerfaces leading to new applications in molecular motors, energy convertors and biological catalysis in natural systems.

2.2. Redox Chemistry Controlled Biointersurfaces

Compared with light, redox chemistry can be carried out either through electrochemistry or by addition of redox agents. Importantly, electrochemical stimuli are noninvasive and quantitative, both properties that are critical for understanding biological processes in living systems.[26−29] In addition, host–guest chemistry can greatly improve selectivity of biomolecule-ligand binding, resulting in a substantial decrease in the amount of "targeting" ligands for the desired biomolecules. The dynamic nature of host–guest interactions may provide a powerful tool for the separation of small molecules, peptides or cells through external stimuli, and avoid large amounts of eluent and/or competitive ligands in the future.

In order to develop a new route for supramolecular peptide separation, Scherman and co-workers have utilized the high selectivity of CB[8] and the well-studied electrochemistry of viologen derivatives, which could trap targeted peptides from a mixture by electrochemistry.[30] As shown in Figure 4a, the functionalized gold surfaces only complexed the N-tryptophan-containing peptide in the mixture as the 1:1 CB[8]-based binary host–guest complex immobilized on the surfaces could bind with N-tryptophan-group to form a stable ternary complex by host–guest interactions.[31] As shown in Figure 4b, only green fluorescent periodic dots were observed by fluorescence microscopy, indicating that N-tryptophan-containing peptides were successfully immobilized onto the surfaces as uniform peptide arrays. Interestingly, the N-tryptophan-containing peptides could also be released from the surfaces by electrochemical reduction of the viologen derivatives attached

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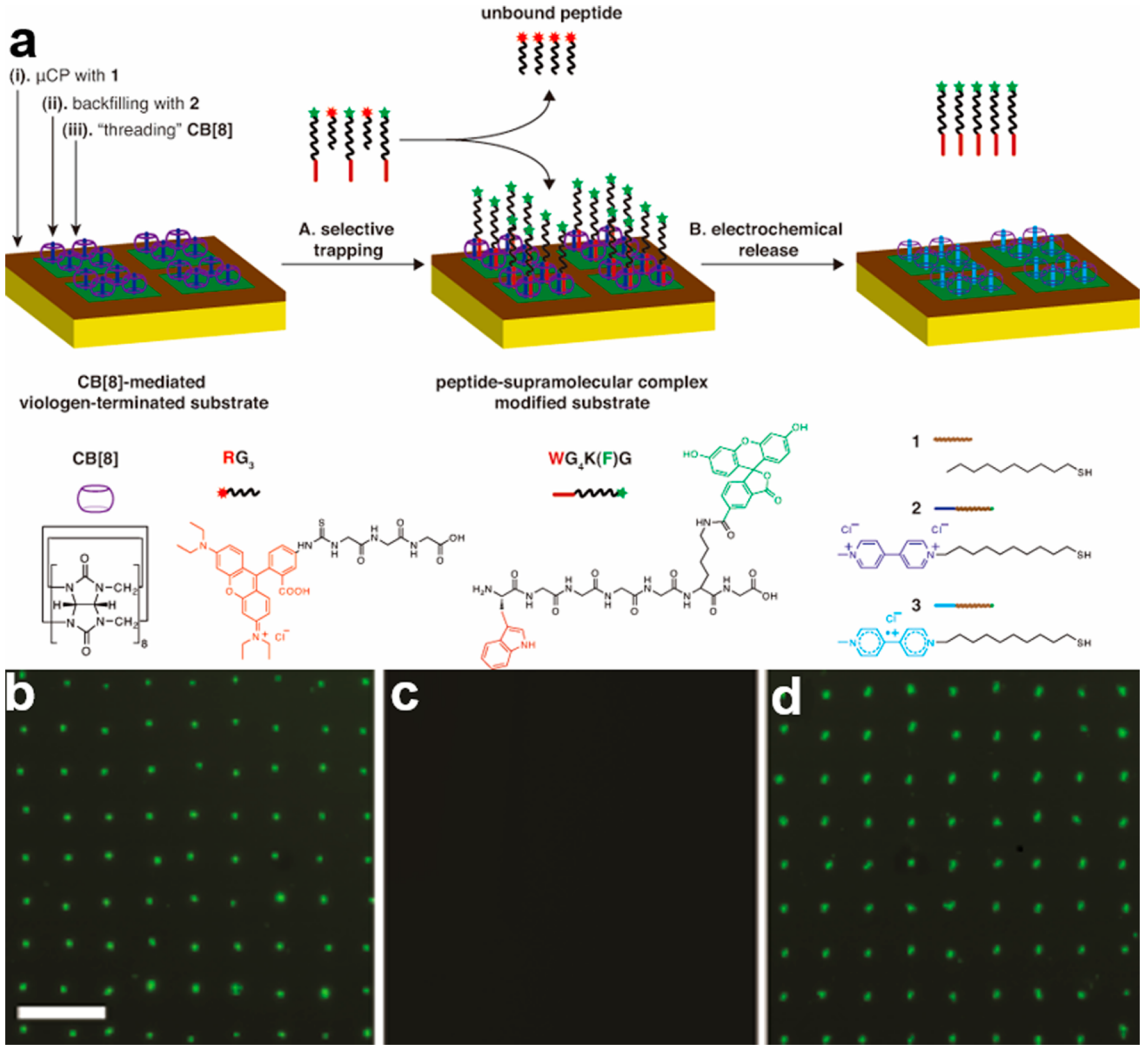

Figure 4. (a) CB[8]-based ternary complex for peptide trapping and electrochemical release. Fluorescence microscopy images of (b) the original peptide array, (c) no pattern after the reduction and washing of the substrate, and (d) the recovered peptide array. Reprinted with permission from ref 30. Copyright 2011 American Chemical Society.

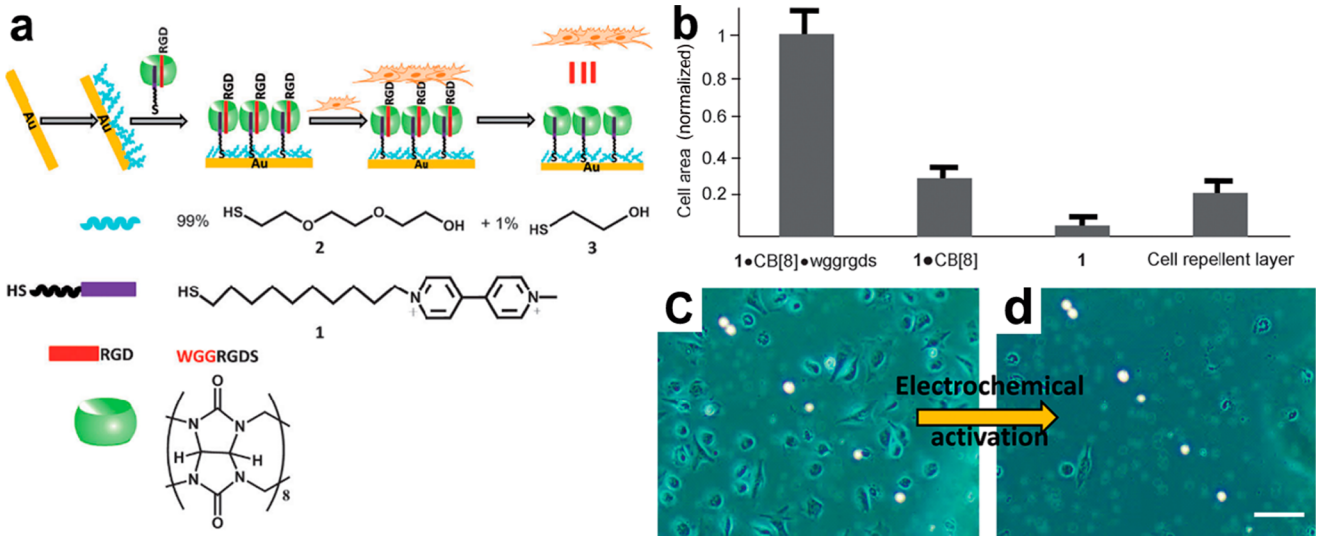

Figure 5. (a) Schematic illustration to assemble stable monolayers of the ternary complex and electrochemically controlled release of cells; (b) normalized projected cell area for different functionalized slides. Bright field images of cells before (c) and after (d) electrochemical activation. Reprinted with permission from ref 32. Copyright 2012 John Wiley and Sons.

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to the surface (Figure 4c). Importantly, the immobilization and subsequent release of the peptides was reproducible over many cycles, successfully providing a green and economic separation strategy for single peptides from peptide mixtures.

In addition to the purification of peptides, larger structures such as cells can also be adsorbed and released using surface bound host–guest chemistry. The groups of Jonkheijm and Huskens have reported a method to immobilize the tripeptide arginine-glycine-aspartic acid (RGD) ligands onto gold substrates fabricating an electrochemically controlled cell adhesive biosurface (Figure 5a).[32] Electrochemical activation led to the dissociation of the host–guest complex, resulting in the release of RGD ligands from the surface. Any cells that were bound to the RGD were thus also detached from the surface. In order to demonstrate controlled cellular adhesion and release by electrochemical activation, the biosurfaces were seeded with mouse myoblast cells for 1 h in cell culture medium. It was observed that cell adhesion was limited in the absence of the RGD peptides (Figure 5c). After cell culture, an electrical potential of −0.5 V was applied to the biosurfaces, which led to the removal of over 90% of the original adherent cells by simple washing with saline buffer as shown in Figure 5d.

In addition to the surface bound host–guest chemistry described above, the combination of host–guest chemistry and LbL assemblies has been another powerful and convenient method to fabricate versatile molecular-imprinted biointerfaces.[33−37] However, there are several shortcomings when combining molecular-imprinting techniques with LbL assembly. For example, during removal or rebinding of the template molecules, the shape and size of the imprinted sites on the LbL surfaces may change on account of the flexibility inherent in the polymer matrix. To overcome this issue, we combined LbL assembly and host–guest chemistry to prepare redox-responsive biointerfaces, which could reversibly adsorb and release fluorescent probes upon external redox stimuli as illustrated in Figure 6.[38] When these biointerfaces were immersed into a solution containing different anthracene derivatives (An-Py and 9An-Py), the multilayer biointerfaces only adsorbed An-Py on account of sterics and selective binding with the 1:1 binary host–guest complex of viologen-CB[8] available on the surface leading to a stable heteroternary host–guest complex. Moreover, when these biointerfaces were immersed into a reducing solution containing $NaBH_4$, the An-Py guest was washed out from the surface as the viologen units were reduced to their radical cation form inducing the disassociation of the heteroternary host–guest complex. This system demonstrated a straightforward and convenient route to fabricate a redox-controlled reversible biointerface by combining host–guest chemistry, redox chemistry with LbL methods. Such a strategy and combination of established techniques may very well be of great importance in mimicking the complicated molecular-recognition systems found in organisms, as well as find new applications in drug delivery, biosensing, and other exciting new developments in bionanotechnology.

This line of research, however, is far from completion. Most research to date has focused on the adsorption and release of small organic molecules. Extending such studies into the controlled adsorption and release of biomacromolecules and cells is both encouraged and critical. Moreover, several promising host–guest systems used in the fabrication of stimuli-responsive biointerfaces include biologically hazardous guest molecules such as viologen derivatives. We anticipate that the separation of complex peptide and protein mixtures as well as a wide variety of cells will attract extensive attention in the near future, and therefore the development of truly biocompatible and nontoxic host–guest systems will be important for the next generation of stimuli-responsive biointerfaces.

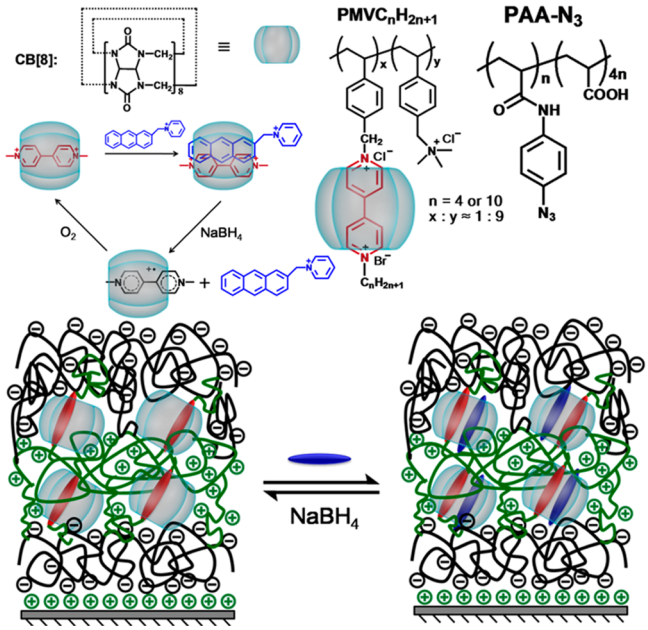

Figure 6. Proposed mechanism of the redox-controlled reversible encapsulation of 1-(anthracen-2-ylmethyl)pyridinium bromide (AnPy) in CB[8], and schematic representation of LbL assembly of the PMVC$_n$H$_{2n+1}$-CB[8] complex, and PAA-N$_3$. Adapted with permission from ref 38. Copyright 2012 John Wiley and Sons.

2.3. Guest Competition Controlled Biointerfaces

The use of competitive guests as an external stimulus for the adsorption and release of proteins on interfaces is significant in living systems, as many compounds in nature can be exploited in this manner. Therefore, many systems reported in the literature have taken inspiration from nature using competitive guests in targeting therapy or mimicking biocatalysis of enzymes in organisms. Kim and co-workers developed a method for isolating plasma membrane proteins by using highly selective host–guest interactions between CB[7] and a ferrocene derivative (AFc) as illustrated in Figure 7.[39] The host–guest chemistry described by Kim et al. captured model proteins from protein mixtures efficiently and selectively. Furthermore, the captured proteins were readily removed from the biointerfaces via the addition of a second ferrocene derivative (BAFc), which had a higher binding affinity for CB[7] than AFc. Thus, plasma membrane proteins could be separated using host–guest functionalized biointerfaces. This has advantages over the traditional method of streptavidin–biotin binding by avoiding interference of endogenous biotin and contamination from naturally biotinylated cytoplasmic proteins.[40]

In addition to the separation of proteins, combining guest competition with biointerfaces has also been used as a trigger in therapeutic systems. Rotello, Isaacs, and co-workers fabricated a therapeutic system, which exploited both host–guest chemistry and surface technology.[41] CB[7] was threaded onto a diaminohexane derivative, which was anchored to the surface of gold nanoparticles. Then, this host–guest complex on the nanoparticle surface was disassembled within cells by addition

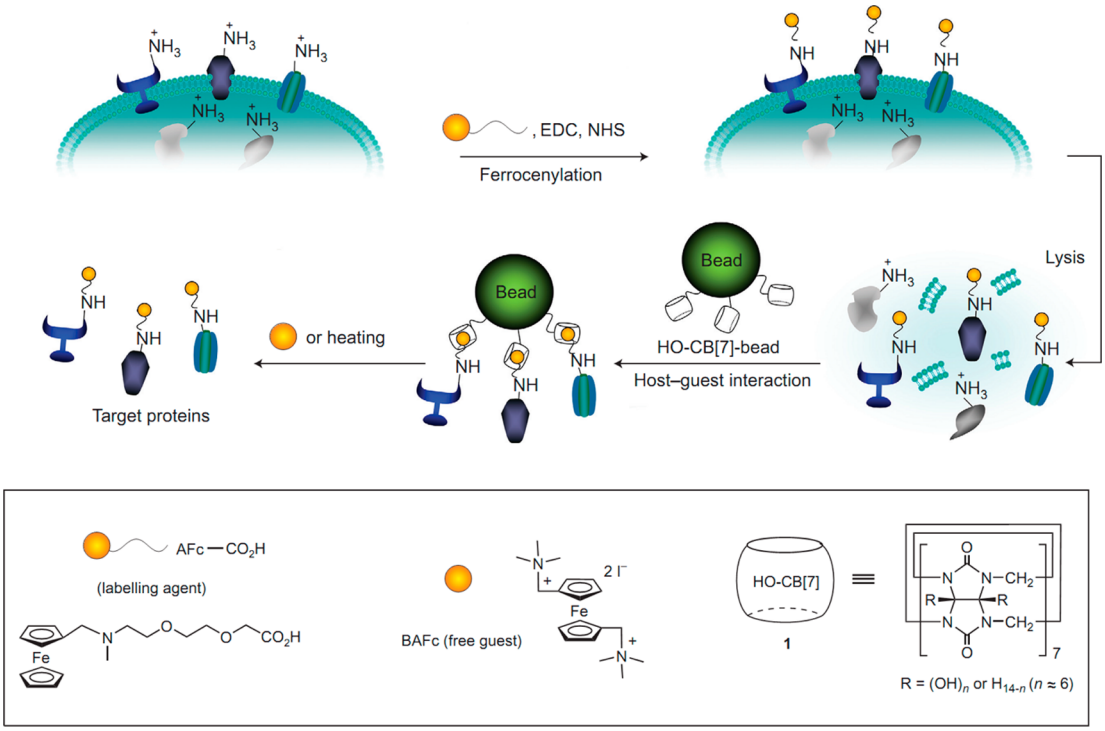

Figure 7. Strategy for isolation of plasma membrane proteins using an ultrastable synthetic binding pair system. Reprinted with permission from ref 39. Copyright 2011 Nature Publishing Group.

of another guest molecule, 1-adamantylamine (ADA), as ADA has a higher affinity for CB[7] than the diaminohexane derivative.[42] Intracellular dethreading of CB[7] from diaminohexane on the nanoparticle surface led to endosomal escape of the toxic gold nanoparticles. They thus employed guest competition as a trigger to adjust the toxicity of host–guest surfaces, which have potential applications in dosage control and dual-targeting therapies.

While competitive guests have been used for the separation of peptides and proteins and in drug release, the competitive guests typically used to date have been synthetic molecules, which are absent in biological and natural systems. It is therefore greatly anticipated that natural guests such as amino acids and peptides will be employed as competitive guests for controlling stimuli-responsive biointerfaces in the future.

2.4. pH Controlled Biointerfaces

A change in pH is often used in biological systems as different tissues and cellular compartments exhibit different pH values. Combining pH stimuli with host–guest chemistry represents an important strategy to control the release of drug molecules, biological macromolecules, and peptides and proteins.

Kim and co-workers fabricated pH-controlled biointerfaces through the surface-graft modification of pH-responsive biocompatible polypseudorotaxanes onto mesoporous silica particles[43] in order to fabricate host–guest biointerfaces for drug release. First, pH-responsive polypseudorotaxanes were formed through host–guest interaction between biocompatible low-molecular-weight linear polyethylenimine (PEI) and α- and γ-CDs. Next, these functionalized particles were shown to control the release of calcein guest molecules trapped in the pores of the mesoporous silica particles by reversible dethreading of CDs when the pH was decreased from 11 to 5.5.

In addition to control release of small molecules, we have employed pH controlled host–guest surfaces for selective adsorption and release of biomacromolecules such as cytochrome *c* (Cyt c). Cyt c is trapped in the mitochondrial membrane, which can be used as an electron carrier for biological reduction in the respiratory chain. In order to understand such reduction in biological systems, we fabricated pH-responsive surfaces through the host–guest interaction between pH-responsive block copolymers and an azobenzene-containing SAM.[44] The block copolymer contained two segments, one was a pH-responsive poly(acrylic acid) (PAA) block that was grafted with β-CD, and the other block was nontoxic poly(ethylene glycol) (PEG) that has been used extensively to prevent the adsorption of nonspecific proteins and cells.[45,46] Based on host–guest interactions between the azobenzene groups on the SAM and β-CD molecules pendent from the block copolymer, the pH-responsive copolymers were immobilized on the azobenzene-containing SAM surface, which was subsequently shown to inhibit peptide binding in a reversible manner. This was on account of the pH-responsive PAA reversibly switching between an electronegative state to trap Cyt c and an electroneutral state to resist Cyt c adsorption simply by adjusting pH (Figure 8a). It was observed that 100% release of the immobilized Cyt c could be obained on account of the cooperation between protein-resistant PEG and electroneutral PAA, compared to the 80% release of Cyt c without the introduction of the PEG segment in our previous work.[12] A rapid decrease in the current response and a simultaneous increase in ΔEp (peak-to-peak separation) were observed with increasing pH from 3.5 to 10.2, which illustrated the pH-sensitivity of the host–guest biointerface (Figure 8b). In addition, these biointerfaces could be switched over many cycles, indicating good stability.

It should be pointed out that the range of pH values that are used to control the host–guest biointerfaces is substantially wider than what exists in different tissues and cellular

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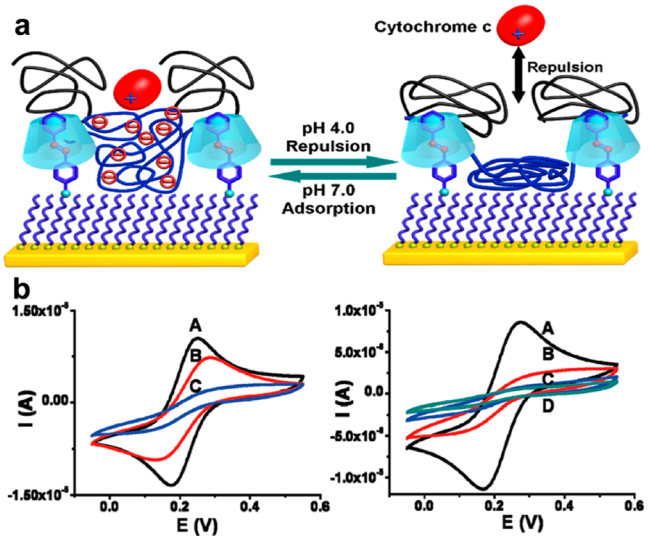

Figure 8. (a) pH-responsive host–guest biointerface with complete and reversible resistance of Cyt c; (b) cyclic voltammograms of the different modified gold electrodes. Adapted with permission from ref 44. Copyright 2010 American Chemical Society.

compartments in natural systems. Therefore, in the future, it will be critical to develop robust host–guest chemistry that can be readily controlled by a much smaller pH range to better fit that observed in biological and natural systems.

2.5. Orthogonal Stimuli-Responsive Biointerfaces

In contrast with systems that operate from a single stimulus, those which can be controlled with multiple stimuli that do not interfere with one another are said to be orthogonal. Orthogonal responsive biointerfaces can likely better adapt to biological environments and mimic biological processes because there are various complex changes in the microenvironment in living bodies, such as ionic concentration, pH, redox potential, and so forth. Furthermore, the evolution of orthogonal responsive systems can greatly enhance the versatility of materials in a variety of applications.

Effective immobilization of proteins on biointerfaces without denaturation and change in conformation is important for the development of biosensors, bioengineering, and bioseparation. Based on our work described above, we further developed the system to demonstrate a dual-stimuli responsive biointerface by the host–guest interaction between pH-responsive polymers grafted with β-CD (PAA-*g*-CD) and photoresponsive azobenzene-containing SAMs. In addition, these biointerfaces were used for reversible immobilization of Cyt c triggered by either light or pH as shown in Figure 9.[47] First, the photocontrolled switchable biointerfaces were tested for light-driven reversible adsorption and release of Cyt c as a result of the reversible attachment and detachment of PAA-*g*-CD. These biointerfaces were then demonstrated to be pH-responsive exhibiting reversible immobilization and release of Cyt c as a result of the conversion between an electronegative state and an electroneutral state of pH-responsive polymers. The integration of both light and pH activated biointerfaces for reversible adsorption and release of electroactive Cyt c mimicked the biological processes of biocatalysis and energy transfer.

Aiming to overcome the incompatibility between two different kinds of noncovalent interactions and to increase the complexity of the surfaces, Scherman and co-workers successfully fabricated orthogonal stimuli-responsive biointerfaces based on CB[8]-mediated ternary host–guest complexes with azobenzene tethered to gold surfaces and viologen derivatives bearing a fluorescent dye molecule as shown in Figure 10a.[48] After UV irradiation, the green fluorescent array indicating heteroternary complexation vanished (Figure 10b). Meanwhile, the increase in the water contact angle of these surfaces indicated that they were hydrophobic (Figure 10c). Moreover, the fluorescent pattern could be rewritten onto the surfaces by increasing the surface hydrophilicity after visible light irradiation. It is important to point out that this reversible light-induced on/off switch of fluorescence with the concomitant oscillation in surface wettability was repeated for at least three cycles. Moreover, the green fluorescent pattern completely disappeared when a −0.7 V versus SCE potential was applied as shown in Figure 10b and the hydrophobicity of

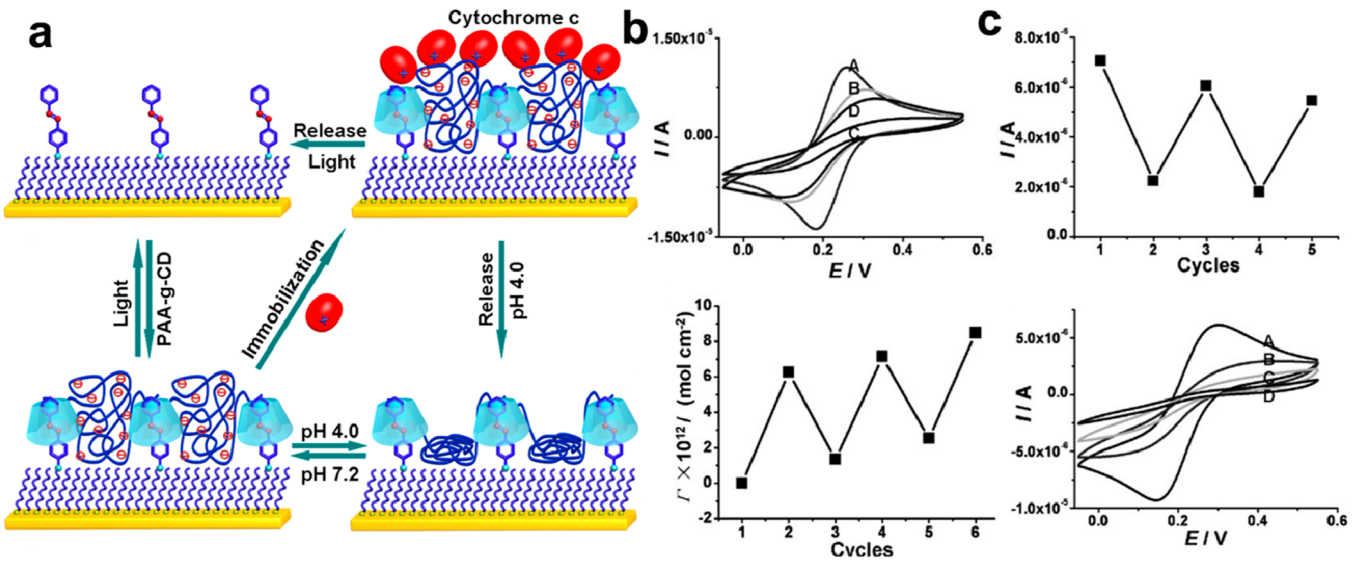

Figure 9. (a) pH and photocontrolled reactivated biointerfaces and reversible absorption and release of protein; (b and c) cyclic voltammograms of the different modified gold electrodes. Adapted with permission from ref 47. Copyright 2009 John Wiley and Sons.

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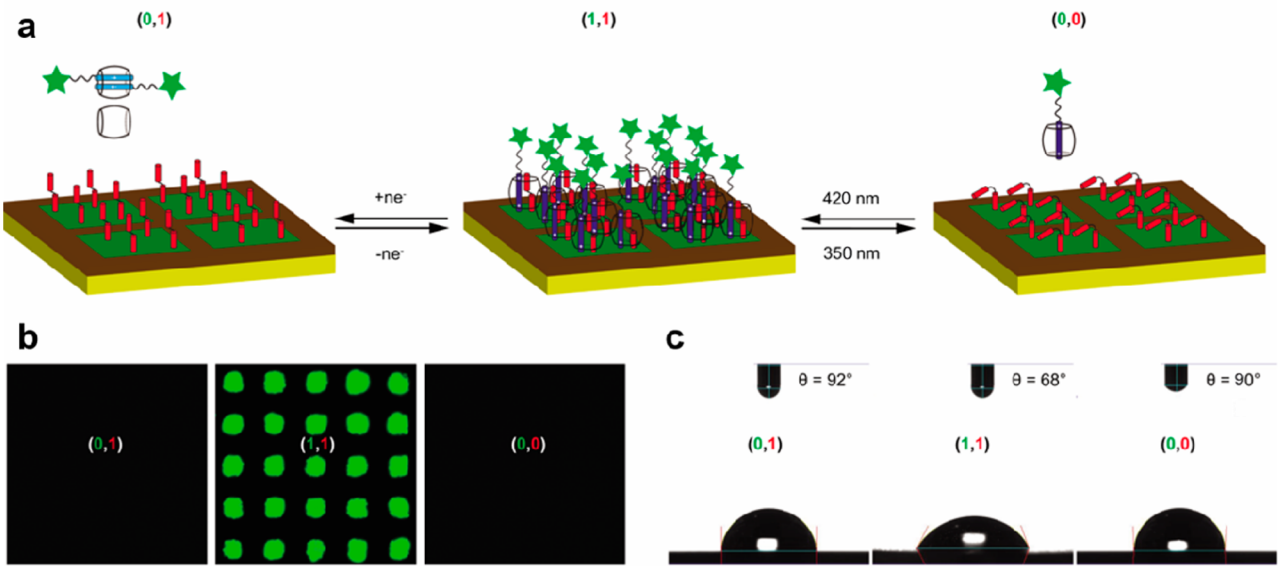

Figure 10. (a) Orthogonal stimuli-responsive biointerfaces on the base of CB[8]-mediated ternary host–guest complex; (b) fluorescence microscopy images and (c) water contact angle measurement of the corresponding states. Reprinted with permission from ref 48. Copyright 2012 Nature Publishing Group.

the original gold surface was recovered with an increase in the water contact angle. When a −0.3 V versus SCE potential was applied to the same solution, both the green fluorescent pattern and the hydrophilicity of the gold surfaces were recovered. This work demonstrated a straightforward host–guest process to fabricate orthogonal photochemical and electrochemical reversible control of the surfaces. In addition, amplification of dual external stimuli was easily observed on a macroscopic level, which gives rise to potential applications such as fabricating complicated molecular devices. Moreover, the "on" and "off" photoswitching could represent a writing-erasing mechanism required for data storage in a memory device. Although the orthogonal responsive surface system described here has the advantage of compatibility between two different noncovalent interactions, in order to adapt to biological systems, new orthogonal systems are highly desirable.

3. CONCLUDING REMARKS

By transferring host–guest chemistry from bulk solution onto surfaces, a number of stimuli-responsive multifunctional biointerfaces and biosurfaces with desirable and tunable properties were successfully achieved. These examples extend the horizon of host–guest chemistry considerably within the area of interfacial science. In addition, we have demonstrated that the combination of host–guest chemistry with LbL methods or SAMs provides a variety of excellent and straightforward routes for fabricating stimuli-responsive multifunctional biointerfaces. Furthermore, the emergence and development of orthogonal responsive surfaces is extremely promising as they can better adapt to biological environments and mimic biological processes. There is still, however, a long way to go in order to fully understand molecular recognition at interfaces in biological systems and utilize the multifunctional biointerfaces in complicated molecular devices. It is anticipated that the biological compatibility inherent from use of visible and near-infrared light, the development of a narrower pH range, and the discovery of natural and safer competitive guests will all represent important advances in the future generations of stimuli-responsive biointerfaces. Moreover, multifunctional biointerfaces with dual and even multiple stimuli-responsiveness may be fabricated by displaying high selectivity and sensitivity. In the future, these biointerfaces will be used to gain a detailed understanding of biological processes such as biocatalysis of enzymes, biosensing, and energy transfer, to name a few.

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Notes

The authors declare no competing financial interest.

Biographies

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Oren A. Scherman is the Director of the Melville Laboratory for Polymer Synthesis in the Department of Chemistry and the University of Cambridge. His research group is interested in dynamic supramolecular self-assembly at interfaces. Oren's current research projects include the application of macrocyclic host−guest chemistry using cucurbit[*n*]urils in the development of novel supramolecular hydrogels, drug-delivery systems based on dynamic hydrogels, the conservation and restoration of important historical artifacts through the exploitation of supramolecular polymer chemistry and sensing, and catalysis using self-assembled nanophotonic systems. Oren is also a cofounder of the recent spin-out company "aqdot" from Cambridge University working in the area of encapsulation. He is currently on sabbatical as the Xuetang Visiting Professor of Chemistry at Tsinghua University in Beijing, China.

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