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Bio-inspired multifunctional catecholic assembly for photo-programmable biointerface

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ABSTRACT

This article reports a novel multifunctional mussel-inspired zwitterionic catecholic assembly to form a photoresponsive biointerface. The assembly is the combination of the antifouling sulfobetaine and photocleavable *o*-nitrophenyl moieties into a molecule, becoming sulfobetaine nitrodopamine (SB-nDA). We demonstrated the formation of a compact thin SB-nDA film on TiO_2 by using the pH transition approach. The film thickness, surface wettability and elemental composition were characterized using ellipsometry, contact angle goniometer, atomic force microscopy and X-ray photoelectron spectroscopy, respectively. The SB-nDA thin films can effectively resist adhesion of both Gram-positive *Staphylococcus epidermidis* and Gram-negative *Pseudomonas aeruginosa* by more than 95% relative to bare TiO_2. Quartz crystal microbalance with dissipation (QCM-D) sensor was employed for protein fouling tests, showing the comparable antifouling property of SB-nDA with thiol- or silane-based surface ligands. More importantly, the spatiotemporal control over the bioinertness by UV irradiation has been studied with bacterial and protein adsorption. Therefore, the catecholic chemistry can be used for programmable tailoring of interfacial properties, permitting potential application in light-guided targeting for nanomedicine.

1. Introduction

Appropriate biointerfaces between materials and living systems are customized for use in biomedical applications such as diagnostics, therapeutics, and supplementary. The materials are in contact with proteins, cells, and living tissues under various physiological conditions. In some cases, materials can be transported through various target compartments and experience more than one stimulus in vivo. Switching of the interfacial properties of materials for specific functions with spatiotemporal control is highly desirable, particularly for applications in nanomedicine. Numerous studies have attempted to tailor the surface chemistry of materials to make them responsive to environmental stimulus and perform specific actions [1,2]. These active responsive behaviors have been regulated by physiological mechanisms that, however, can vary significantly among individuals. A passive approach has also been established, in which the responsiveness of materials is actuated by external stimuli, such as electricity, magnetic fields, heat, and light [3]. This approach has attracted increasing attention because it facilitates the fine tuning of the interaction of materials with living systems. Light irradiation is a promising approach due to the advantages of triggering responsive actions on reasonable timescales at the physiological temperature, allowing accurate spatiotemporal control in vivo, and eliminating unwanted damage to normal tissue [4]. Therefore, considerable achievements have been accomplished in the development of light-responsive biointerfaces, and these have been observed to adapt to dynamic conditions [5–7]. However, a design of surface coating allowing excellent biocompatibility, photo-responsiveness and rapid manufacturing is yet to be fulfilled.

With the rapid advance in biocompatible coatings for implants and blood-contacting medical devices, various materials have been developed to resist nonspecific adsorption to avoid complications, such as thrombosis, inflammation, and infection [8]. Adsorption is associated with thermodynamic preference when the net entropy increases and the net enthalpy decreases at an interface in a defined system. Two classes of polymers have been well documented as antifouling materials – ethylene glycol-based polymers and polyzwitterions – for a broad range of applications under complex conditions [9,10]. Effectiveness of these polymers is due mainly to their properties of charge balance and hydrophilicity. Polyzwitterions are particularly attractive because of their high thermal and hydrolytic stability and relatively low susceptibility to

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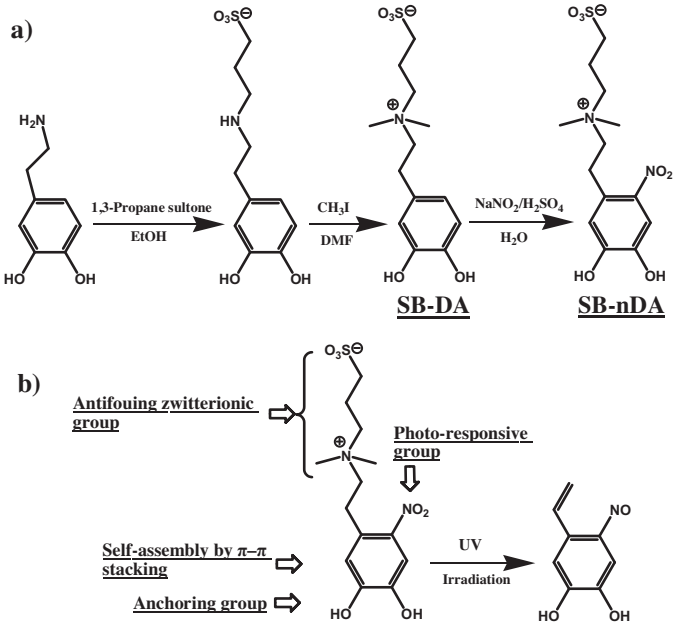

Scheme 1. (a) Synthetic route and chemical structures of SB-DA and SB-nDA. (b) Functions and photochemical mechanism of SB-nDA.

pH value and temperature changes [11,12]. Zwitterionic moieties of sulfobetaine (SB), carboxybetaine, and phosphorylcholine appear not only as pendant groups in polymers but also as head groups of self-assembled monolayers (SAMs) for the quick preparation of antifouling interfaces in multidimensional materials [13–16].

Numerous dopamine derivatives have recently been developed for the surface modification and functionalization to make the devices biocompatible, to introduce bactericidal properties, or to promote integration with living systems [17–24]. 3,4-dihydroxy-L-phenylalanine (DOPA) has been observed to be responsible for the adsorption of mussel onto almost all types of substrates, even chemically inert fluoropolymers [18]. A new zwitterionic bioderived building block has been developed based on dopamine for use in MRI contrast agents [20]. The molecule is synthesized by converting primary amine groups into SB moieties (denoted as SB-DA, Scheme 1a). The catechol of SB-DA acts as an anchoring group and forms covalent bonds with metallic oxides. Our group has found that the SB-DA can form highly compact thin film via a pH transition approach to covert hydrogen bonds to bidentate bonds [25]. The zwitterionic SB-DA film effectively resists protein and bacterial adsorption. Despite the improvement in its molecular packing and stability, SB-DA remains immune to environmental stimuli and is less versatile.

The aim of this study is to develop photocleavable zwitterionic dopamine that allows self-assembly on surfaces to give a programmable biointerface. The assembly is the combination of the SB and photoresponsive *o*-nitrophenyl moieties, becoming a novel catecholic molecule named sulfobetaine nitrodopamine (SB-nDA). The SB-nDA was readily synthesized through nitration of SB-DA, as depicted in Scheme 1a. The *o*-nitrophenyl moiety was shown to be photoactive, as illustrated by the photochemical mechanism in Scheme 1b. Therefore, the design of SB-nDA is such that a single molecule exhibits several functions, including surface anchoring, self-assembly, antifouling, and photocleavable properties. We applied SB-nDA onto a TiO_2 surface by using the pH transition approach, to form a compact thin film [25]. The antifouling property of SB-nDA was demonstrated by exposing it to solutions containing bovine serum albumin (BSA), Gram-negative, and Gram-positive bacteria under physiological conditions for comparison with unmodified TiO_2 and SB-DA modified substrates. The photocleavable property of SB-nDA was indicated by the results of contact angle and X-ray photoelectron spectroscopy (XPS) analysis. More remarkably, patterning of bacteria and triggering of protein adsorption under UV illumination showed the possibility of spatiotemporal control over the bioinertness.

2. Materials and methods

2.1. Chemicals

Chemicals including dopamine hydrochloride, absolute ethanol, 28% ammonium hydroxide, 1,3-propanesultone, iodomethane, anhydrous sodium carbonate, dimethylformamide (DMF), acetone, bovine serum albumin (BSA), and sodium nitrite were obtained from Sigma–Aldrich (MO, USA). Sulfuric acid was purchased from Katayama Chemical Industries (Osaka, JAPAN). The Live/Dead *Bac*Light Bacterial viability dye was purchased from Life Technologies (CA, USA). LB (Luria-Bertani) agar was obtained from BD (NJ, USA). All chemicals and solvents were used as purchased. Deionized water with minimum resistivity of 18.0 M Ω cm used in the experiment was obtained from a Millipore water purification system (Billerica, MA).

2.2. Synthesis of SB-DA and SB-nDA

The organic synthesis of SB-DA was performed according to previous work done by Bawendi's group [20]. Dopamine hydrochloride (1.137 g, 6 mmol) was dissolved in ethanol (70 mL) in a round bottom flask and dropped 1,3-propanesultone (799 mg, 6.5 mmol) in ethanol (5 mL). 28% ammonium hydroxide (416 μl, 3 mmol) was slowly added to the flask and stirred at room temperature for 10 min. The solution was heated to 65 °C and then stirred for 18 h. The white precipitate was collected by filtration and washed with ethanol three times. The residual white solid was dried under reduced pressure to remove residue solvent. The product was dopamine sulfonate and the yield was estimated as 80%.

Dopamine sulfonate (0.3286 g, 1 mmol) was dissolved in DMF (25 mL) in a round bottom flask. Sodium carbonate (0.2544 g, 2.4 mmol) was dissolved in DMF (50 mL) in protection of N_2. The dopamine sulfonate solution was dropped into sodium carbonate solution and stirred at 0 °C, followed by the addition of iodomethane (836 μl, 35 mmol) and stirring at 0 °C for 10 min. The solution was kept at 50 °C in the protection of N_2 for 20 h. The color of the solution turned to yellow. The DMF was removed by the rotary evaporator at 45 °C and an oily mixture was obtained. 50 mL ethyl acetate was added to precipitate out a pale-yellow product. 50 mL acetone was added to the crude product and the mixture was refluxed at 55 °C for 2 h. The solution mixture was filtered again and the precipitate was collected. The white solid product of SB-DA was dried under reduced pressure.

For the SB-nDA synthesis, SB-DA (500 mg) was first dissolved in deionized water (9 mL). In addition, sodium nitrite (630 mg) was dissolved also in deionized water (6 mL). Two solutions were mixed and stirred in an ice bath for 10 min, followed by adding dropwise 2.5% H_2SO_4 (2.5 mL) and violent stirring for 5 min. Afterwards, the solution was filtrated by a 4G filter and the solid product was washed twice with cold mixture of water and methanol (the volume ratio of 1:10). Then, the solid was washed with cold methanol of 5 mL and dried under vacuum. The solid was collected and analyzed. The 1H NMR spectra for DA, dopamine sulfonate, SB-DA and SB-nDA are present in Fig. S1 in Supplementary content.