Hybrid POSS-Containing Brush on Gold Surfaces for Protein Resistance[a]

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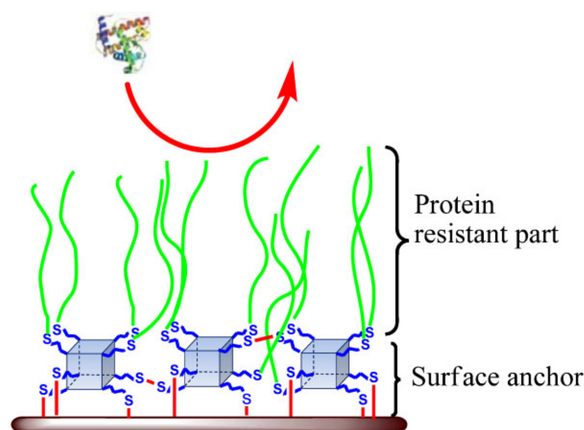
A hybrid polymer brush containing poly(ethylene glycol) (PEG) chains and polyhedral oligosilsesquioxane (POSS) on a gold surface is presented that exhibits an excellent protein resistance and long-term stability. A series of hybrid polymer brushes with different length and numbers of PEG chains are fabricated through chemisorption of PEG-POSS-SH on the gold surface. Protein adsorption of these hybrid brushes is investigated. The amount of protein adsorption decreases with increasing lengths and numbers of PEG chains. After immersion in BSA solution for two months, the PPS4 brushes retain their protein resistance, while a PEG-SH layer loses its non-fouling performance. These POSS-containing hybrid polymer brushes might offer an alternative for modification of gold surface with an excellent protein resistance for long-term applications.



1. Introduction

Gold is an attractive substrate for a number of micro- and nanofabrication processes and in biodiagnostic and bioanalytic devices due to its high conductivity, easy surface modification, and excellent resistance to oxidation.[1] When exposed to a biological environment containing proteins, however, the adsorption of proteins to the gold surface would reduce the sensitivity of the biomedical devices and may also result in harmful side effects.[2] Therefore, the protein resistance of gold surface is critical for its performance in biomedical devices and has attracted much attention.[1d,2b,3] Coating of gold surfaces with thiolate-containing poly(ethylene glycol) (PEG-SH) is one of the most common and prominent approaches to reduce protein adsorption.[4] Pioneering works by Whitesides et al. have demonstrated that self-assembled monolayers (SAMs) of oligo(ethylene glycol) (OEG) end groups on gold surfaces exhibit excellent non-specific resistance against proteins.[5] The highly hydrophilic layers provide an efficient enthalpic and entropic barrier for non-specific protein adsorption. This effect is supposed to be the main explanation for protein resistance.[2b,6] Because gold surfaces can easily be modified by chemisorption of thiol-containing species, SAM technology is a very powerful, convenient and efficient approach to reduce the adsorption of

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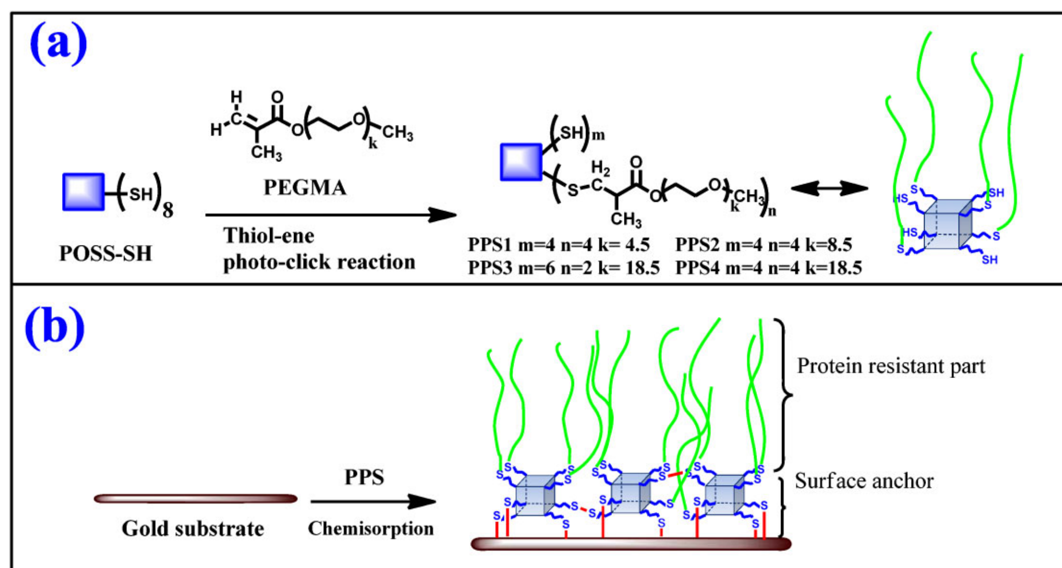
proteins.[1e,2b,2c,3,7] Due to the SAM layer's degradation under ambient environmental conditions, however, the main problematic feature is the limited stability of the Au-thiolate bond. This limits its utility for long-term applications.[1b,1c,8] The thiolate groups can be oxidized to sulfonate, and their affinity to Au becomes very weak. This results in the desorption of the SAM layer from Au surfaces when placed in a solubilizing solvent or exchanged by thiol-containing molecules such as proteins.[1e,8c,8d,9] Besides, if the grafted hydrophilic macromolecules grow large enough and the polymer/Au surface interaction becomes sufficiently unfavorable, the thiolate-Au bond can be broken up. This can be driven by enthalpy and entropy gained from more favorable interactions and conformational freedom with the solvent.[10] To enhance the stability and shelf life of thiolate-Au based SAM layers, several strategies have been explored, including the increasing of the hydrophobic part and the number of anchor groups (–SH). The hydrocarbon chain linked to the thiol head can stabilize the structure and prevent the removal of the oxidized species from the surface due to the van der Waals interaction between neighboring molecules.[1e,9c,11] For example, a hydrophobic peptide containing SAM could maintain its protein resistance for several months.[7a,12] Another approach to enhance the stability of the resulting SAM layer is to increase the number of anchoring sites. Hubbell et al. have reported that with the help of quite a few available chemisorption sites per polymer chain, the tri-block copolymer (PEG-PPS-PEG) exhibited a high stability as an assembled monolayer on gold.[3] Our group recently also described that poly(ether amine) containing multi-thiol groups can form SAM layers on gold surfaces, exhibiting an excellent resistance against protein with long-term stability.[1d] As a continuation of our work on polymer brushes for protein resistance of gold surfaces, we here demonstrate a hybrid brush which is fabricated through SAM technology. The general design of the hybrid polymer (POSS-PEG-SH) is illustrated in Scheme 1 (POSS = polyhedral oligosilsesquioxane). The PEG chains provide the resistance against protein adsorption. Multi-thiol groups linking to the strong hydrophobic POSS use a combination of the advantages of the multi-anchors and the strong van der Waals interaction between the adjacent molecules. This was expected to lead to a high stability of the resulting hybrid brush. To prove the efficiency of our design of the hybrid brush, we prepared a series of hybrid brushes with different numbers and length of PEG chains, and investigated their performance in the resistance against protein through atomic force microscopy (AFM), X-ray photoelectron spectroscopy (XPS) and surface plasmon resonance (SPR). Particular attention was paid to the long-term stability of the obtained hybrid brush.

2. Experimental Section

2.1. Fabrication of the PEG-POSS-SH Hybrid Brushes on a Gold Substrate

The gold substrate was prepared according to a previous report.[1] The hybrid brush was immobilized on the gold substrate through chemisorption according to Scheme 1. The PPS(1-4)/chloroform solution (20 wt%) was spin-coated on a cleaned gold substrate. After being deposited for 24 h, the substrates coated with PPS(1-4) were washed by ultrasonication in chloroform to remove the physically adsorbed PEG-POSS-SH, leaving only the covalently immobilized PPS brush. Subsequently, these substrates were dried



Scheme 1. (a) Synthesis and structure of PEG-POSS-SH (PPS1-4); (b) Strategy for preparation of hybrid brushes (PPS1-4) on a gold surface.

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under nitrogen. The thickness of the dry PPS brush was measured by ellipsometry. The successful immobilization of PPS brush on the gold surface was further confirmed by measurement of the water contact angle (WCA) and XPS spectra.

2.2. Protein Adsorption Experiments

The gold substrates modified with PPS(1-4) brush were dipped in a solution of fluorescein-labeled bovine serum albumin (BSA-FITC; $2\ mg \cdot mL^{-1}$) in phosphate-buffered saline (PBS, pH = 7.4) for 2 h and then washed extensively with pure water. The surface morphology and elements contents of the PPS films after protein adsorption were measured by AFM and XPS.

SPR measurements were carried out to measure the mass of protein adsorbed on the hybrid polymer brush: PPS brushes were immobilized on SPR chips by the same method as used for the gold substrate. On a different chip, a layer of PEG-SH was taken as reference. They were easily dropped-in and docked into the instrument. After priming with PBS buffer (pH = 7.4) for 10 min, a BSA solution ($1\ mg \cdot mL^{-1}$) in PBS was injected over the chip at a flow rate of $50\ \mu L \cdot min^{-1}$ for 30 min at 25 °C. Finally, the chip was washed with PBS at the same flow rate for 10 min to remove the loosely adsorbed protein.

2.3. Stability of the Hybrid Polymer Brush

The stability of the PPS4 brush in biological environment was measured, and the PEG-SH coated surface was taken as a reference. The gold substrates coated with PPS4 brush and PEG-SH brush, respectively, were exposed to an ambient environment for 24 h. Then they were immersed in BSA/PBS ($2\ mg\ mL^{-1}$, pH = 7.4) solution for 2 months, and thereafter washed thoroughly with pure water running for 30 min to remove loosely bound protein, and finally they were dried under nitrogen prior to analysis.

2.4. Instruments and Measurements

WCA measurements were measured by a contact angle meter (model CAM Micro) at room temperature. The precision of the angle measurement was ± 0.1°. Contact angles were averaged from at least three different spots for each sample.

AFM images were taken by SII Nanonavi E-sweep under ambient conditions. The AFM was operated in contact mode by using silicon nitride cantilevers with a force constant of $0.12\ N \cdot m^{-1}$. XPS experiments were carried out on a PHI-5000C ESCA system (Perkin–Elmer) with Al K_{α} radiation ($h\nu = 1486.6$ eV). In general, the X-ray anode was running at 250 W, and the high voltage was kept at 14.0 kV with a detection angle of 54°. The pass energy was fixed at 46.95 eV to ensure sufficient sensitivity. The base pressure of the analyzer chamber was ca. 5×10^{-8} Pa. The sample was directly pressed to a self-supported disk (10 mm × 10 mm) and mounted on a sample holder and then transferred to the analyzer chamber. The whole spectra (0–1200 eV) of all elements were recorded with high resolution. The data analysis was carried out by using the RBD AugerScan 3.21 software provided by RBD Enterprises or XPS Peak 4.1 provided by Raymund W. M. Kwok.

Protein adsorption was measured by Multi-Parametric SPR on a SPR Navi 200MW instrument (BioNavis, Finland). Blank SPR chips were prepared in a similar way as previously described.[6g] In brief, glass coverslips were coated with 500 Å of Au. After coating, they were cut into small pieces (12 mm × 20 mm).

3. Results and Discussion

The functions and structures of the different components of the hybrid brushes are illustrated in Scheme 1. Due to the excellent resistance against protein adsorption, PEG chains of varying length and different numbers can be easily introduced into the backbone of POSS-SH via the photo-click thiol-ene reaction.[13] A series of PEG-POSS-SH (PPS1-4) were synthesized accordingly and their characterization is provided in the Supporting Information. Through the efficient and convenient SAM technology, PEG-POSS-SH can chemisorb on the gold surface to form hybrid brushes because of the strong coordination interaction between –SH and Au. The thickness of the obtained PPS brushes was determined by ellipsometry, and the process for formation of PPS brushes was traced by WCA and XPS. The results are summarized in detail in Table 1. The thickness increases with increasing length and number of the grafted PEG chains of PEG-POSS-SH. Due to the hydrophilicity of PEG chains, the water wetting of gold surface was enhanced very obviously after chemisorption of PPS brush. Compared with the naked gold surface (88°), the WCA value of PPS4 brush layers decreased to 38°. From PPS1 to PPS4, WCA decreased from 53 to 38°, which might be ascribed to the increase of the length and number of PEG chains.

XPS measurements were performed to evaluate the chemical composition of the PPS brushes on the gold substrate. The expected elements especially for Si and S can be found in XPS spectra (Table 1), suggesting the successful immobilization of PPS brushes on the gold surface. Because the thickness of PPS brush is thinner than XPS probe depth (about 10 nm), the signals at 89 and 350 eV assigned to Au_{4f} and Au_{4d} can also be observed in XPS spectra (Table 1).[4a] The morphology of the obtained hybrid brush layers is revealed by AFM. A smooth and homogeneous surface of the typical SAM brush can be observed for four hybrid brushes (Figure 1), suggesting the high quality of brush layers on gold surface.

Generally, the structure of polymer brushes is important for the protein resistance. To check the protein resistance of the obtained hybrid brushes, the adsorption of protein (BSA) on the surface of the hybrid brushes was measured by AFM, XPS and SPR. The gold surface modified with PPS brushes was soaked in BSA solution at room temperature for 2 h, followed by thoroughly washing with Milli-Q water. Compared with the smooth and homogeneous morphology of PPS brushes, after adsorption the obvious aggregation of

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Table 1. Thickness, WCA and XPS surface elemental composition of the PPS brushes.

No	Composition	Thickness [nm]	Density ratio [mol · m^{-2}]	WCA [°]	BSA adsorption [ng · cm^{-2}]	Composition [at%]				
						C	O	Si	S	Au
PPS1	$(PEG300)_4$-POSS-SH_4	2.2	1.26×10^{-6}	53	50	22.41	36.30	14.84	2.92	25.52
PPS2	$(PEG475)_4$-POSS-SH_4	2.9	1.18×10^{-6}	48	30	23.16	36.95	18.87	2.52	18.50
PPS3	$(PEG900)_2$-POSS-SH_6	2.4	1.02×10^{-6}	44	20	35.21	35.89	18.23	1.59	9.09
PPS4	$(PEG900)_4$-POSS-SH_4	3.8	0.92×10^{-6}	38	3	30.77	33.38	27.20	1.14	7.31

BSA can be observed for PPS(1-3) brushes in AFM images (Figure 1a–c), while the morphology of PPS4 brushes did not change before and after adsorption of BSA (Figure 1d). These AFM results revealed that PPS4 brush possesses an excellent protein resistance. PPS4 brush with the long length and high grafting number of PEG chains leads to the most hydrophilic surface among these four PPS brushes, resulting in the best protein repellency. This was further confirmed by XPS spectra (Figure 2). The obvious signal at 400 eV assigned to N_{1s}, which should be from BSA protein, can be found in XPS spectra of PPS1 and PPS3. In the XPS spectra of the PPS1 and PPS3 brush, the atom concentration of N reached 2.87% and 3.81%, respectively, while for PPS4 brush it is almost 0. These XPS results demonstrate that the amounts of adsorbed protein varied with the length and grafting ratio of PEG chain. As for the shorter length and lower grafting ratio of PEG chain, the significant increase of the nitrogen signal in XPS spectra indicates that more protein is adsorbed. Protein adsorption over the PPS coated surface decreases with the increase of PEG coverage over the POSS unit, which is in good agreement with AFM results.

We also used SPR spectra to measure the adsorption of BSA protein to the PPS brushes quantitatively, as well as to the untreated gold surface and PEG-SH SAM as references. In the SPR experiment, which began with priming with PBS buffer for about 10 min, BSA in PBS buffer (1 mg · mL^{-1}) was injected into the sample cell and flow over the SPR sensor for about 30 min, subsequently the surface was rinsed with PBS for 10 min. The mass of protein adsorption was determined by the bulk change in refractive index of the sensor in PBS buffer before and after protein adsorption.[14] As shown in Figure 3, it can be seen that the amount of adsorbed protein on the sensor decreased obviously after modification by PPS brushes. The unmodified gold surface can adsorb BSA of 310 ng · cm^{-2}. As expected, BSA adsorption to the PPS brushes decreased very obviously with the increasing chain length and grafting ratio of PEG. The PPS4 brush exhibits a most excellent protein resistance: BSA adsorption is around only 3 ng · cm^{-2}, which is lower than the reference PEG-SH SAM. This value is comparable with the current standard for the antifouling surface.[15] Notably, the data presented by SPR is consistent with the results of AFM and XPS: the PPS brushes with more hydrophilic contents over the

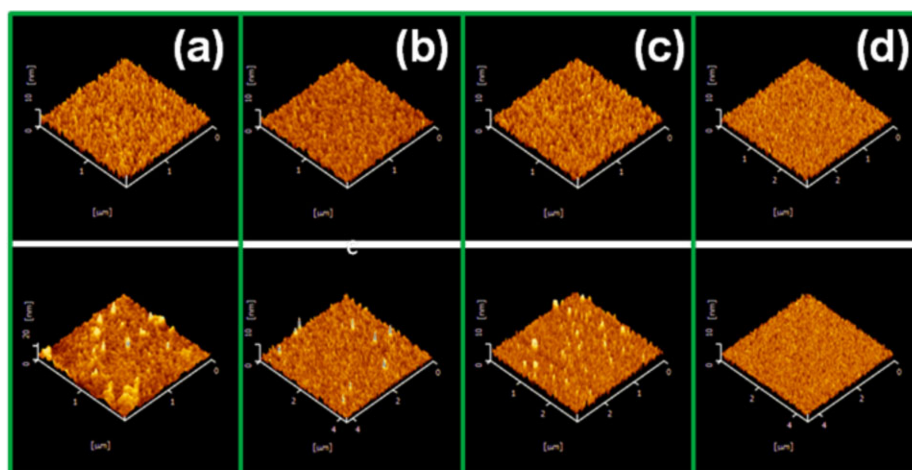

Figure 1. AFM surface topography of gold surfaces coated with PPS brushes: (a) PPS1; (b) PPS2; (c) PPS3; (d) PPS4) before (top) and after (down) adsorption of BSA. The gold substrate was immersed in BSA/PBS solution (1 mg · mL–1) for 2 h, followed by rinsing with Milli-Q water extensively and drying.

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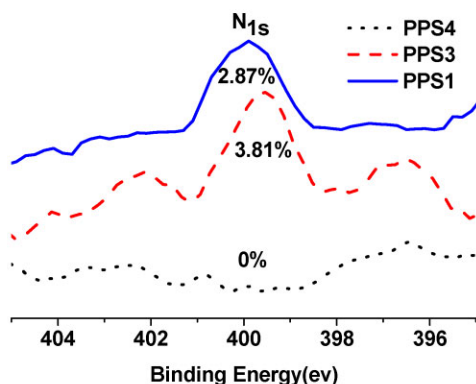

Figure 2. XPS narrow scans of N_{1s} region of the PPS1, PPS3 and PPS4 brushes modified Au surface after adsorption of BSA. The gold substrate was immersed in BSA/PBS solution (1 mg · mL^{-1}) for 2 h, followed by rinsing with Milli-Q water extensively and drying.

hydrophobic POSS unit exhibit the better protein resistance. The PPS4 brush containing four PEG950 chains is the threshold for achieving an ultralow fouling surface. Usually, the essential property to determine the protein resistance of the PEG coating is that the PEG layer should provide an interfacial barrier to prevent the protein from interacting with the underlying layer, which can adsorb protein nonspecifically.[16] With the strong hydrophobic inorganic POSS as the basic unit, the protein resistance of the PPS brushes was based on the hydrophilic dense PEG layer, which can facilitate the entry of water into the brush to form a barrier layer between the protein and the basic units.[17] Overall, the defects of the hydration layer were reduced by the increasing PEG chains and numbers, resulting in the decreasing mass of adsorbed protein. Thus, selection of an appropriate chain length and grafting ratio that allows PEG chains to be fully packed over the basic POSS layer is essential. Here we demonstrated the PPS4 brush containing four PEG chains with about 18.5 EG units as one possible option.

An important aspect of the PPS brush as a hybrid layer on gold is the expected long-term stability of protein resistance in comparison with alkanethiolate SAMs. To evaluate the long-term stability of the PPS brush, the gold substrates coated with the PPS4 brush and PEG-SH SAM as reference were incubated in BSA/PBS buffer at room temperature for two months. After rinsing with pure water and dried, the surfaces of PPS4 brush and PEG-SH SAM were checked by WCA and XPS. As shown in Figure 4, the WCA of the PPS4 brush coated surface keeps unchanged, whereas the WCA of the surface coated with PEG-SH SAM increased dramatically from 32 to 76°, indicating that the hydrophilic surface had turned hydrophobic. The obvious increase of WCA might be ascribed to the detachment of PEG-SH chain from gold surface. This can be caused by oxidation of thiolate into sulfonates, resulting in a weak affinity to Au atom and desorption of PEG-SH chains.[11] However, the WCA value of

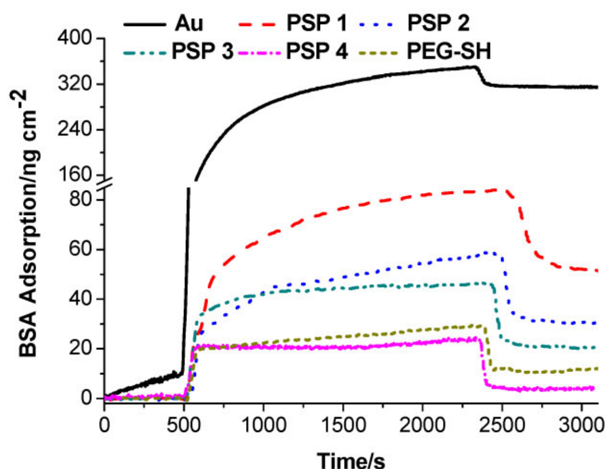

Figure 3. SPR sensograms of BSA adsorption to bare chip, PPS(1-4) brushes modified surfaces and PEG-SH SAMs coated surface. The sensograms illustrate the mass of protein adsorbed onto different PPS SAMs. The bare chip and PEG-SH SAM are taken as reference.

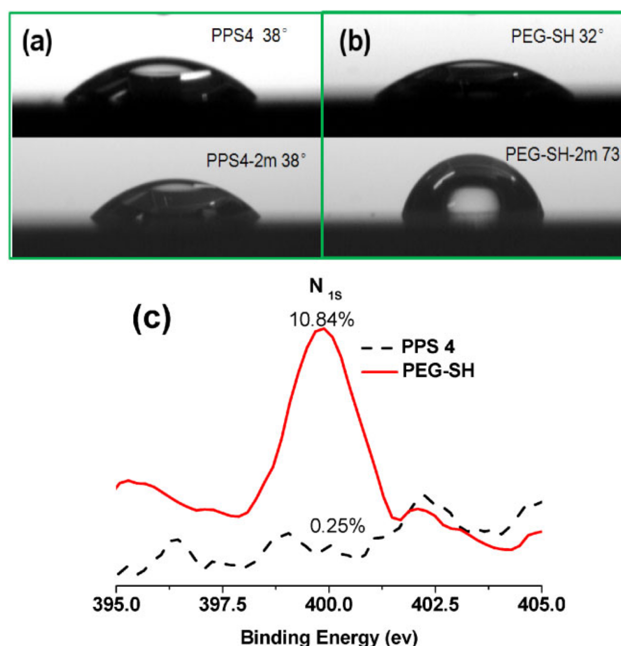

Figure 4. WCA of the fabricated PPS4 SAMs modified Au surface before and after two months of soaking in BSA/PBS solution (a), and of the PEG-SH SAMs on Au substrate before and after two months storage in BSA/PBS solution (b). XPS narrow scans of N_{1s} region of the PPS4 and PEG-SH SAMs modified Au surface after two months treatment with BSA/PBS solution (c), illustrating the long-term protein resistance of the PPS4 SAM.

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PPS4 brush remained unchanged after incubation of two months.

Further evidence for the long-term stability of the PPS4 brush comes from the XPS spectra (Figure 4C). After immersion into the protein solution for two months, N atomic concentration on the surface of PPS4 brush is still very low. In contrast, the atom concentration of N on the surface of the reference PEG-SH SAM reached 10.84%, demonstrating that a large amount of the BSA was adsorbed to the surface. Both WCA and XPS results suggest that the reference PEG-SH SAM lost its nonfouling property after two months of immersion, while the PPS4 brush kept long-term robustness in protein resistance. The excellent stability to protein resistance of PPS4 brush could be ascribed to the synergistic effect of multi-anchors and strong hydrophobic interaction between POSS units and gold surface. Furthermore, the unbound thiol groups of PPS4 brush could be further oxidized into disulfides, leading to a cross-linked layer of PPS4 brush, consequently enhancing the stability.

4. Conclusion

In this work, we demonstrate an example of a hybrid brush containing PEG chains and POSS units on a gold surface, which exhibits an excellent protein resistance with long-term stability. The effect of the length and grafting numbers of PEG chain of the hybrid brushes were investigated. The amount of protein adsorption decreased obviously with increasing length and numbers of PEG chains. The mass of BSA adsorption to the PPS4 brush surface is about $3\ \text{ng} \cdot \text{cm}^{-2}$, which is comparable with the current standard of a non-fouling surface. Due to the synergistic effect of multi-anchor and hydrophobic interaction between POSS and gold surface, PPS4 brush exhibited a much better protein resistance of long-term stability, in comparison with the reference PEG-SH. These POSS-containing hybrid polymer brushes are expected to be of potential use in the surface modification of gold for biodiagnostic and bio-analytic devices.

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