

Design and Screening of Zwitterionic Polymer Scaffold for Rapid Underwater Adhesion and Long-term Antifouling Stability

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Abstract

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Abstract

As key components of antifouling material surfaces, the design and screening of polymer molecules grafted on the substrate are critical. However, current experimental and computational models still retain an empirical flavor due to the complex structure of polymers. Here, we report a simple and general strategy that enables multi-scale design and screening of easily synthesized functional polymer molecules to address this challenge. Specifically, the required functions of the antifouling material are decomposed and assigned to different modules of the polymer molecules. By designing different modules, a novel bio-inspired polymer with three zwitterionic poly (sulfobetaine methacrylate) (PSBMA) chains, three catechol (DOPA) anchors (tri-DOPA-PSBMA), and a tris(2-aminoethyl) amine (TREN) scaffold were screened out. Moreover, it was successfully

synthesized via an atom transfer radical polymerization (ATRP). The excellent performance of tri-DOPA-PSBMA with a versatile and convenient grafting strategy makes it a promising material for marine devices, biomedical devices, and industrial applications.

Keywords: rational design, zwitterionic polymer, antifouling material surfaces, rapid adhesive, long-term stability

Introduction

Antifouling surfaces resisting nonspecific protein adsorption and biofilm adhesion improve function, efficiency, and safety in products such as water purification membranes, marine vehicle coatings, medical implants, and other industrial applications^{1, 2}. The strong hydrophilicity of zwitterionic polymer gives them good biocompatibility and anti-protein adhesion properties. Zwitterionic polymer grafted surfaces have been investigated to offer high resistance toward nonspecific protein adsorption and cell adhesion under physiological conditions. Due to their highly hydrophilic nature and flexibility, zwitterionic polymer grafted surface have met with varying success in vitro and in vivo antifouling tests³. Commonly, zwitterionic polymers were immobilized to the surfaces by two strategies, i.e., adsorption of polymer from solution (so-called “graft-to” approach) and surface-initiated polymerization (SIP) of monomers from surface-bound initiators (“graft-from” approach)^{4, 5}. In contrast to the “graft-from” approach, the “graft-to” method is simpler and more convenient, especially suitable for practical applications on a large scale. However, for the “graft-to” approach, especially for binding in the presence of water, specific surface functional groups with high binding energies and versatile feasibility to various substrate surfaces are required. Inspired by the adhesion mechanism of mussels, 3,4-dihydroxyphenylalanine (DOPA) is believed to be a versatile residue for wet adhesion. Various zwitterionic polymers with catechol adhesive groups have been designed to achieve surface adhesion in aqueous solutions⁶⁻⁸. Although these zwitterionic polymers, such as one zwitterionic chain with one catechol anchor, two zwitterionic chains with two catechol anchors, and zwitterionic copolymers with multiple anchors, have been proven to be effective for one-step anchoring and enhanced antifouling properties. Little attention has been paid to the adsorption kinetics and thermodynamics of rapid adhesion and long-term stability of polymer grafts, especially from the sophisticated design of different polymer structures with the construction scaffolds. Recently, Waite et al. reported that a siderophore with a robust tris(2-aminoethyl) amine (TREN) scaffold and three amino acid 3,4-dihydroxy-L-phenylalanine (DOPA) residues exhibited strong adsorption and adhesion behavior and retained adhesive integrity over a wide range of pH^{9, 10}. However, the effects of multiple conjugations, different hydrophilic groups, and different scaffolds on the properties of the materials were still unrevealing. Therefore, there is an ongoing need for rapid and precise polymer design strategies capable of robustly anchoring zwitterionic polymers onto various material surfaces and having excellent antifouling functions.

Due to the uncertainty of polymer properties and complicated experimental procedures, it is relatively difficult and time-consuming to screen polymers with excellent antifouling properties by synthesizing a number of polymers with different structures and determining their surface properties. Related reports on machine learning have enabled rapid polymer molecular design and high-throughput screening of optimal materials by drawing on concepts and ideas from combinatorial chemistry and materials informatics^{11, 12}, namely by combining “building blocks” of different structures or components in parallel, systematically, and repeatedly^{13, 14}. High-throughput screening gives us the idea of screening out advantageous “building blocks” according to the required functions. Moreover, due to the competition between the polymer chains dissolved in water and adsorbed on the solid surface, the hydrophilic-hydrophobic balance of the polymer and extensively optimized polymer grafting conformations should be considered and adjusted comprehensively to achieve effective underwater adhesion and good antifouling property. Especially, the complex system with multiple components and multiple interactions will result in differences in the underwater adhesion mechanism, solvation free energy (G_{solv}), and electrostatic potential of polymer molecules which need to be considered from the molecular microstructure and the adsorption configuration information^{15, 16}. Molecular simulation and density functional theory (DFT) calculation can be used to explain the adsorption kinetics and thermodynamics of polymer molecules from the molecular information of “block” properties¹⁷. Hence, it is necessary

to propose a strategy that combines multi-scale molecular design and molecular simulation based on the actual function of the polymer rather than the blind screening of large throughput, to design and screen the specific polymer molecules which are easy to synthesize.

Herein, we propose a design and screen strategy for a novel bio-inspired zwitterionic polymer for rapid underwater adhesion and long-term antifouling stability. The target molecule is divided into three parts according to the desired function: tail chain, head group, and scaffold. In molecular design, different colors represent different functions performed in polymer molecules (**Figure 1a**). Head groups conjugate to tail chains to fabricate the adhesive antifouling polymers which will be grafted to various substrates using catechol-mediated adhesion to resist protein adsorption. Twelve polymer molecules were designed by a preliminary screening of different head groups, tail chains, and scaffolds. The surface properties, G_{solv} , and adsorption energy (E_{ads}) with hydroxylated silicon surface of design molecules were calculated by DFT and molecular mechanics (MM) calculation, and the most stable adsorption configuration of molecules on the silica surface was analyzed by molecular dynamics (MD) annealing simulation. (**Figure 1b**). By comparing these results, we selected a zwitterionic polymer with a TREN scaffold and three DOPA residues for surface anchoring, and three PSBMA polymer chains for antifouling to synthesize and investigate its adhesion behavior and antifouling property. From the calculation and the experimental results, we demonstrated that this material has a fast surface adhesion and antifouling surfaces with long-term stability in an aqueous solution. On this basis, it is interesting to note that tri-DOPA-PSBMA tethered on hydroxylated silicon wafers in 10 minutes and remained stable for more than 30 days without compromising performance, which is of great significance to industrial application. (**Figure 1c**)

2. Experimental and Calculation Methods

2.1 Experimental materials and method

Materials. Tert-butyl chlorodimethylsilane (TBDMSCl, 99%), α -bromoisobutyric acid (BiBA, 98%), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 98%), α -bromoisobutyryl bromide (BiBB, 98%), tris(2-aminoethyl) amine (TREN, 98%), tetrabutylammonium fluoride (TBAF, 1 M solution in THF containing ca. 5% H₂O), 2,2'-bipyridine (Bpy, 99%), copper (I) bromide (purified before use), copper (II) bromide (99%), diisopropylethylamine (DIPEA, 99%), acetonitrile (MeCN, 99.9%, superdry, water [?] 30ppm), N,N-dimethylformamide (DMF, HPLC grade) and tetrahydrofuran (THF, 99.9%, superdry, stabilized with 250ppm BHT) were provided by J&K Chemical Ltd. (Shanghai, China). Dopamine hydrochloride (DOPA·HCl, 98%), L- β -(3,4-dihydroxyphenyl)alanine (L-DOPA, 98%), N-hydroxysuccinimide (NHS, 98%), dicyclohexylcarbodiimide (DCC, 99%), phosphate buffer saline (PBS, pH 7.4, 150 mM, 138 mM NaCl, 2.7 mM KCl), and sulfo-betaine methacrylate (SBMA, >98%) were purchased from Sigma-Aldrich (Shanghai, China). Imidazole (98%), dichloromethane (DCM, 99%), trimethylamine (N(Et)₃, 99%), deuterated chloroform (CDCl₃, 99%), deuterated methanol (CD₃OD, 99%), deuterated water (D₂O, 99%), concentrated sulfuric acid (98%), and hydrogen peroxide (30%) were obtained from Sinopharm Chemical Reagent Co. Ltd. (Shanghai, China). Silicon wafer (10mm×10mm) was purchased from Shanghai Guang Wei Electronic Material Ltd. Peroxidase-Labeled Antibody to Human IgG (PLA-IgG) and fluorescein isothiocyanate conjugated bovine serum albumin (FITC-BSA) was obtained from MOLBASE. Phosphate buffered saline (PBS) solution (0.01 M, pH 7.4) was prepared from PBS powder purchased from Sigma-Aldrich. All water used in the experiment was obtained from ultrapure water equipment.

Synthesis of sin-DOPA-PSBMA. The preparation of sin-DOPA-PSBMA was the same as the previously reported by Jiang^{18, 19}. Fabrication of sin-DOPA-PSBMA was in classical methanol/H₂O system using the ATRP method²⁰⁻²³.

Synthesis of tri-DOPA-PSBMA. Different from the polymerization of sin-DOPA-PSBMA in the methanol/H₂O system, the synthesis of tri-DOPA-PSBMA was stirred in DMF/H₂O system as the tri-DOPA-Br initiator was undissolved in the methanol/H₂O system. Briefly, tri-DOPA-Br powder (43.14 mg, 0.0238 mmol), CuBr (11.3 mg, 0.0786 mmol)/ CuBr₂(2.8 mg, 0.0125 mmol) and Bpy (31.3 mg, 0.2 mmol) were added to a Schlenk flask and filled with N₂ after degassed three times. Then degassed DMF (4 mL)

was added to the system via a syringe and kept stirring for 10min at r.t. After that, a degassed solution of SBMA (1.397 g, 5 mmol) in H₂O/DMF (3 mL / 6.5 mL) was injected into the reaction system via a syringe and placed into a 20 °C incubators for fifteen hours. Then the flask was put into liquid N₂ to quench the reaction and thawed after a while. The collected polymer precipitate was dissolved in water and dialyzed in water for three days. The white powder was obtained after lyophilization. Then the obtained powder with the protection of TBDMSCl (0.1128 mmol) was reacted with TBFA (0.282 mmol) in THF for twenty hours under an N₂ atmosphere. Unprotected white powder tri-DOPA-PSBMA was collected after rinsing three times with THF and dried in vacuum at room temperature.

In this work, DOPA-PSBMA with three different degrees of polymerization were prepared respectively by tuning the feed ratios of the initiator and the monomer (**Table S4**).

Fabrication of PSBMA coated substrates via “grafting to” method. The silicon wafer was sonicated with water, ethanol, and water in turn at a power of 30 Hz, then dried with N₂. The dried silicon wafer was immersed in a boiling ‘piranha’ solution (concentrated sulfide acid/hydrogen peroxide = 7/3) for 1 h. (Caution: Piranha solution is extremely dangerous and easily exploded when came across with organic material, and it’s forbidden to contact with boiling solution beaker directly unless it’s cold). Then the substrates were rinsed and sonicated with water at least three times. The cleaned silicon wafers were dipped in the sin-DOPA-PSBMA or tri-DOPA-PSBMA solutions in tris-buffer (10 mM, pH 8.5) at a polymer concentration of 2 mg/mL and incubated in a thermostatic oscillator at 25 °C. The “grafting to” protocol used in the experiment was the optimal condition^{24, 25}. Then the substrates were rinsed with PBS buffer three times and then with water three times and dried with N₂.

Characterizations. ¹H NMR and ¹³C NMR spectra were collected using a Brüker AV-400 nuclear magnetic resonance spectrometer in CD₃OD, CDCl₃, or D₂O. The ESI mass spectra were measured on a Waters orthogonal acceleration time of flight mass spectrometer. Hydrodynamic diameters of DOPA-PSBMA polymers in an aqueous solution were carried out using dynamic light scattering (DLS) (Malvern Zetasizer NanoZS, UK). The water contact angle was recorded at least three different areas on the substrate surfaces with a contact angle goniometer (Zhong Chen POWEREACH, Shanghai). The X-ray photoelectron spectroscopy (XPS) of modified substrates was performed using a Perkin-Elmer PHI 5000C ESCA system with an Al K α micro-focusing X-ray source at a power of 250 W and detected a depth of about 10 nm.

Protein adsorption test with ELISA and FITC-BSA protein adhesion. Protein adsorption on the substrates was performed using an enzyme-linked immunosorbent assay (ELISA) on a microplate spectrophotometer (Bio TeK, USA) in a standard protocol^{18, 26, 27}. Briefly, the samples were placed into a 24-well tissue culture plate containing 1 mL of 1 μ g/mL PLA-IgG mixed with PBS buffer in individual wells and incubated for one h in the thermostatic oscillator. All samples were transferred into new wells after being rinsed five times with 1mL of PBS and once with 1 mL of water. Then to each well was added 1 mL of 1 mg/mL o-Phenylenediamine (OPD) dissolved in 0.1 M citrate-phosphate buffer (pH 5.5) containing 0.03% hydrogen peroxide. 1 mL of 1 M HCl was added to each well to stop the reaction after 15 min without light. 150 μ L of solution in each well was added to a 96-well plate, and the light absorbance at 492 nm was measured on a microplate spectrophotometer. The absorption value of the uncoated silicon wafer was viewed as a standard 100% to compare with the relative absorbance of the others. Each kind of acquired absorbance was performed on at least three silicon wafers.

The substrates were incubated in each well of a 24-well plate with 0.5 mL of 0.25 mg/mL FITC-BSA in PBS buffer for two h at 37 °C in darkness. After five times rinsed with 1 mL of PBS buffer and once with 1 mL of water, the substrates were dried with N₂. The adhesive FITC-BSA was detected using Laser Scanning Confocal Microscopy (LSCM) (NIKON, Japan) at $\lambda_{\text{excitation}} = 488 \text{ nm}/\lambda_{\text{emission}} = 520 \text{ nm}$.

Stability of Coated Substrates in PBS Buffer. The evaluation method based on the stability of modified silicon wafers was used, as previously reported by Minko²⁸. Briefly, the coated substrates were placed in a 24-well plate with 2 mL PBS buffer in each well at r.t. The substrates were taken out after being incubated at different times and immersed in 0.5 mL of 0.25 mg/mL FITC-BSA in PBS buffer for 2 h at 37 °C in dark

surroundings. The stability of coated substrates was estimated by using LSCM after being rinsed with PBS buffer and water and dried with N_2 .

2.2 DFT calculation

Surface analysis and G_{solv} of designed molecules were calculated by DFT calculation. All electronic structures in this work were conducted using the Gaussian 09 suite of the program²⁹. The designed molecules investigated were fully optimized in the gas and solution phase by the B3LYP /6-31G(d)^{30, 31}, including empirical dispersion corrections DFT-D3 method^{32, 33}, and were performed using the tight convergence criterion, which was always followed by the calculation of harmonic vibrational modes. To utilize the SMD model consistently, we have performed calculations of G_{solv} at the same levels of theory utilized in the parameterization of SMD. We used M05-2X exchange-correlation functionals³⁴ along with 6-31G(d) to calculate the single point energy in gas and water, which has proved to be reliable for calculating the E_{ads} and E_{sol} ³⁵. G_{solv} could calculate by the formula as follow:

where G_{solv} is solvation free energy, E_{sol} and E_{gas} are the single-point energy calculated by M05-2X/6-31G(d). Based on the optimized molecular structures, the HOMO/LUMO electrostatic potential (ESP) and molecular polarity index (MPI) were analyzed by the Multiwfn program³⁶ and visualized via the VMD package³⁷. All basis sets are obtained from the Basis Set Exchange library.

2.3 MD simulation

The most stable molecular configuration for E_{ads} is obtained by MD annealing simulation. Implicit-solvent atomistic MD annealing simulation are carried out at 1 K to 1800 K which can overcome the rotational barrier in flexible molecules to search for conformation in a wider range the number of annealing cycles is 4000, and the heating and cooling ramps per cycle are 10^{38} . The simulation system is a $11.404 \text{ nm} \times 11.404 \text{ nm} \times 8.000 \text{ nm}$ box. The COMPASSII force field³⁹ modeled the Van der Waals interaction and the bonding interaction. The MD simulations were performed using an NVT ensemble, and the thermostat is Nose-Hoover⁴⁰. All the simulation starts with the structure of energy minimization and are carried out for 50 ps in the NVT ensemble. Another 1000 ps MD annealing simulation was performed for data collection at a frequency of 1 fs.

The molecular mechanics (MM) method⁴¹ was utilized to calculate the E_{ads} between the designed molecule and the -OH decorated SiO_2 surface. The Van der Waals interaction and the bonding interaction are modeled by COMPASSII force field³⁹. The electrostatic interaction is calculated by the Ewald summation method where the charges of each atom are calculated by the charge equilibrium (QEq) method^{42, 43}. The E_{ads} is calculated by:

where $E_{\text{SiO}_2/\text{designed}}$, E_{SiO_2} and $E_{\text{designedmolecule}}$ are the energy of SiO_2 /designed molecule complex SiO_2 and designed molecule, respectively. The implicit solvent model ($\epsilon_r = 78.5$) is used to consider the solvation effect³⁸. The accuracy of Ewald summation is set as 10^{-5} kcal/mol, and the long-range tail of the Lennard Jones potential is truncated at 1.85 nm with an extra 0.1 nm (cubic spline method) to guarantee the smoothness of the potential function. The system is considered to be equilibrium when the energy change is lower than 2×10^{-5} kcal/mol, force lower than 0.01 kcal/mol/nm, and displacement lower than 10^{-6} nm.

Results and Discussion

3.1 Multi-scale molecular design and molecular simulation for rapid underwater adhesion and long-term antifouling

The tail chain, scaffold, and head group of target molecules have different roles in practical applications. The tail chain is exposed to the water environment and plays an antifouling effect. Related studies have reported hydrophilic linear monomethoxy-terminated poly(ethylene glycol) (mPEG)⁴⁴, poly(sulfobetaine methacrylate) (PSBMA)¹⁸ or poly(N,N-dimethylamino ethyl methacrylate) (PDMAEMA)⁴⁵ can play a good anti-protein role in the aqueous environment. These three polymer segments are designed in Molecules 1,

2, and 3 to compare hydration degrees. The branching degree of the designed molecule will not only affect polymer aggregation morphology in solution, but also determine the surface electrostatic potential of the polymer molecule and the adsorption site with the substrate⁴⁶. Therefore, four designed Molecules 1, 4, 5, and 6 were designed to be a single head-single tail, a double head-double tail, a triple head-triple tail, and a quadruple head-quadruple tail, corresponding to the branching degrees of one, two, three, four. The conjugated scaffold connects the head group and the tail chain and its rigidity plays a decisive role in polymer adhesion configuration on the substrate surface. For this reason, soft and rigid scaffolds with similar chemical groups were selected and designed as Molecules 5, 7, 8, and 9 to consider their functions in the polymer. The head group binds to various substrates in water to play an adhesion role. The DOPA has been a powerful anchor for surface modification and can adhere to virtually almost any material surface⁴⁷⁻⁴⁹. So the DOPA will be selected to be the main component of the head group, and its function will also be confirmed through analyzing the designed Molecule 5, 10, 11, and 12. To summarize, the optimal structure of the target polymer was screened by adjusting the branching numbers of polymer molecules, changing the type of head groups, tail chain, and scaffold. (**Figure 1a**) In the process of theoretical calculation, molecules without dominant properties have been screened out and will not be compared in the next step.

After completing the molecule design, the calculated E_{ads} of all designed molecules on hydroxylated silicon dioxide surface and G_{solv} of designed molecules with different branching degrees are adopted to screen the most suitable molecule for rapid underwater adhesion and long-term antifouling. The E_{ads} is calculated by the most stable adsorption structure from MD annealing simulation (**Figure S1-12**), and the G_{solv} is acquired from DFT calculation. The calculated E_{ads} of 12 molecules on the hydroxylated silica is listed in **Table S1**. The E_{ads} of DOPA-PSBMA (Molecule 1), DOPA-mPEG (Molecule 2) and DOPA-PDMAEMA (Molecule 3) are -26.35, -6.47, -24.04 kcal/mol, respectively. We can find that E_{ads} (Molecule 1) $>$ E_{ads} (Molecule 2) $>$ E_{ads} (Molecule 3), indicating that Molecule 1 is expected to be selected as the dominant monomer for subsequent molecular design (**Figure 2a**). The adsorption energy in unit kcal/mol and J/g can express the adsorption capacity and adsorption efficiency of the molecules, respectively. The E_{ads} of Molecule 1, 4, 5 and 6 are -213.48, -86.10, -239.32, and -197.50 J/g, respectively. It is indicated that the adsorption efficiency of these molecules on hydroxylated silica surface is in the order of E_{ads} (Molecule 5) $>$ E_{ads} (Molecule 6) $>$ E_{ads} (Molecule 1) $>$ E_{ads} (Molecule 4) (**Figure 2b**), which beyond our expectation. From the optimal adsorption configurations of these molecules (**Figure S1**, **S4-6**), we found that the catechol groups of Molecule 1 and 5 are all attached to the substrate surface, however, those of Molecule 4 and Molecule 6 are only one in two and only three in four, respectively. It means that whether the molecule is suitable for the target molecule depends on the adsorption configuration rather than the degree of branching. The difference in molecular adsorption configuration is the discrepancy in G_{solv} . The calculated G_{solv} of Molecules 1, 4, 5, and 6 are -619.60, -435.99, -502.79, and -407.36 J/g, respectively (**Table S2**). The order of G_{solv} is G_{solv} (Molecule 1) $>$ G_{solv} (Molecule 5) $>$ G_{solv} (Molecule 4) $>$ G_{solv} (Molecule 6). As G_{solv} increases, the hydrophilic part of the molecule prefers to be in the stretched state in solution. Combining the two effects of E_{ads} and G_{solv} , we found that tri-DOPA-PSBMA (Molecule 5) with three branching degrees will be the most robust adhesive polymer molecule of the four molecules. According to the reports of Li et al.⁵⁰, the scaffolds connecting the head group and tail chain are crucial for the configuration of the modified surface. Molecules 5, 7, 8, and 9, all else being equal, have scaffolds of varying degrees of flexibility. Molecule 7 has a rigid connecting scaffold, whereas the scaffolds of Molecules 8 and 9 are soft with longer chain lengths. The E_{ads} of Molecules 7, 8, and 9 are 151.2, -163.72, and -212.99 J/g, respectively. Since Molecule 5 has the largest E_{ads} , it continued to be selected as the dominant target molecule. The possible reason is that the scaffold with too much flexibility is not conducive to the molecular support on the substrate, which results in a close distance between the hydrophilic group and the silica substrate (**Figure S8-9**). In contrast, the rigid scaffold will not ensure the simultaneous adsorption of multiple adsorption groups on the substrate, which will reduce the E_{ads} (**Figure S7**). TREN achieves a balance between the flexibility and rigidity of molecules, thus it is a suitable molecular scaffold for adhesion and antifouling. In addition to the scaffold connection, the molecule's headgroup also plays a significant role in the adhesion process. The E_{ads} of Molecules 10, 11, and 12 are -42.46, -14.80, and -165.77 J/g, respectively. From the E_{ads} values of Molecules 10, 11, 12 and 5, it can be inferred that the benzene ring does not contribute to the surface adsorption, but hinders it. Although

the E_{ads} of Molecule 12 with one phenolic hydroxyl group is much larger than that of Molecules 10 and 11, it is still much smaller than that of Molecule 5 which has two phenolic hydroxyls. Hence, we found that the hydroxyl groups bind firmly to the hydroxylated silica surface (**Figs. 2 a and b**). Based on these analyses of E_{ads} and G_{solv} on the surface of hydroxylated silica substrate, Molecule 5 stands out since it owns the significant advantages of adsorption and solvation properties and is chosen to be the most suitable molecule for rapid underwater adhesion and long-term antifouling.

The reason that four designed molecules (Molecules 1, 4, 5, and 6) showed different properties in their E_{ads} and G_{solv} on the silica surface lies in their diverse surface properties. The molecular polarity index (MPI)⁵¹ was employed to analyze the hydrophilicity of the designed molecules. The greater the polarity and the stronger hydrophilicity of the molecule is, the larger the MPI of the molecule is. The MPIs of the single head-single tail molecule (Molecule 1), double head-double tail molecule (Molecule 4), triple head-triple tail molecule (Molecule 5), and quadruple head-quadruple tail (Molecule 6) are 34.73, 23.91, 32.27 and 26.72 kcal/mol, respectively. Molecule 5 has the largest MPI, while molecule 4 has the smallest MPI, and the difference between them was 10.82 kcal/mol. Molecules 1 and 5 with MPI greater than 30 kcal/mol contain 1 and 3 sulfonate groups exposed to water, respectively. The number of odd sulfonate groups may result in a more stretched morphology of the molecule in water, which causes a larger polar surface area of the molecule. While the MPI of molecules 4 and 6 is less than 30 kcal/mol, the possible reason is the even number of sulfonate groups cause the molecules to curl up, resulting in a reduction in the polar surface area of the molecules (**Figure 2** and **Table S3**). The surfaces modified with hydrophilic molecules will lead to the good antifouling ability. Therefore, Molecule 5 is expected to be a favorite candidate for antifouling surface modifier due to its proper E_{ads} and G_{solv} and the suitable hydrophilicity.

To further elucidate the superiority of Molecule 5 in modifying the surface antifouling properties, the HOMO-LUMO and electrostatic potential distribution (ESP) of molecules 1, 4, 5, and 6 were analyzed (**Figure 2 d-e**). The calculated HOMO-LUMO gaps of Molecules 1, 4, 5, and 6 were 5.677 eV, 5.646 eV, 5.344 eV, and 5.443 eV, respectively. It is worth noting that Molecule 5 owns the smallest HOMO-LUMO gap. The HOMO energy is -5.450 eV and the LUMO energy is -0.106 eV, indicating that the electron excitation energy of Molecule 5 is quite small, which will enlarge the polarizability of Molecule 5⁵². Due to the high polarizability of Molecule 5, the electron in the molecule is delocalized, which facilitates the modification of the hydrophilicity of the silica surface. The ESP results reinforce our speculation. The head group and scaffold are positively charged, whereas the hydrophilic group sulfonate is negatively charged. Furthermore, as the electron withdrawing ability of groups bound to the sulfur element increased, the relative electrostatic potential absolute value decreased. The isoelectric point of silica is at a pH of 2.5, so silica surfaces immersed in water are known to exhibit a negative charge density⁵³. The adsorption of target molecules on the silica surface is mainly dominated by positively charged benzene ring moieties adsorbed on the substrate, while negatively charged sulfonate tail chains are far away from the substrate, which is consistent with the structure we speculated. The negatively-charged sulfonate group surrounded with highly hydrated layer will repel the protein contaminants in the solution and play an antifouling effect. The surface modified by Molecule 5 has a lot of negative electricity, which makes its antifouling performance greatly improved (**Figure 2e** and **Table S3**). MD simulation was performed on the surface of silica substrate modified by the target molecule with a polymerization degree of 10. The designed molecules quickly adhered to the substrate surface as shown from the snapshots and animation (**Figure 3a** and **Video 1**). There was no structural damage to the silica surface and modified molecules during MD simulation. Physical adsorption occurred between DOPA with catechol groups and hydroxylated silicon wafers, close to the silica surface, while PSBMA stretched away from the silica surface, which could play an antifouling role. The thermodynamic and kinetic stability of the silica surface modified by Molecule 5 during MD simulation indicates that the modification method is feasible. It is consistent with all the above analysis results, demonstrating that the designed molecules can be used for rapid underwater adhesion and long-term antifouling resistance.

3.2 Synthesis and characterization of tri-Dopa-PSBMA

Screening through theoretical calculation, the optimal block copolymer structure of tri-Dopa-PSBMA was

determined. To visually compare block copolymers' underwater adhesion and antifouling properties, the sin-Dopa-PSBMA and tri-Dopa-PSBMA polymers with different degrees of polymerization were synthesized (Scheme S1). The two polymers corresponded to the structures of Molecules 1 and 5 in the previous section. The characteristic peaks in the ^1H NMR spectrum of each compound correspond to their chemical structures, revealing that the target polymers have been successfully synthesized (**Figure S13-19**, **S22-23**). It was worth noting that the characteristic peaks of catechol were not observed in the ^1H NMR spectrum of sin-Dopa-PSBMA and tri-Dopa-PSBMA (Figure S11-12), which may be attributed to the low proportion and solubility of the catechol segment in the polymer.

As above mentioned, PSBMA shows the upper critical solution temperature (UCST) phase transition behavior in an aqueous solution⁵⁴. **Figure S24** shows the aggregation behaviors of sin-DOPA-PSBMA and tri-DOPA-PSBMA zwitterionic polymers in aqueous solutions measured by dynamic light scattering. Both polymers show the UCST phase transition in the temperature range of 15-65 °C, while the UCST of tri-DOPA-PSBMA is higher than that of sin-DOPA-PSBMA indicating a lower water solubility of the tri-DOPA-PSBMA. Insolubility of sulfobetaine (co) polymers at low temperatures is based on an interlocking of zwitterionic side groups of different polymer chains and incorporating rigid hydrophobic functionality into sulfobetaine copolymers will decrease their water solubility⁵⁵. Although there was a one-to-one correspondence between the PSBMA chain and rigid DOPA residue for both copolymers, the influence of the DOPA residue on the water solubility and the UCST of the two polymers was remarkably different. The presence of a single DOPA residue can be assumed to sterically interrupt this interlocking to a greater extent than the presence of a TREN scaffold with three DOPA residues groups, thereby a higher gain in entropy during the dissolution of a sin-DOPA-PSBMA compared to a tri-DOPA-PSBMA copolymer will induce a more soluble sin-DOPA-PSBMA⁵⁶. Additionally, the UCST decreased, and the water solubility of the tri-DOPA-PSBMA increased with the increase of the hydrophilic PSBMA chain length^{55, 57}. Since there is a balance between enthalpic polymer-substrate interaction favoring surface adsorption and mixing entropy favoring polymer dissolution, the hydrophilic-hydrophobic balance of the copolymer plays a vital role in the surface adsorption from the aqueous solution.

With a "grafting to" method, the DOPA-functionalized PSBMA was used to modify silicon wafers by a solution dip-coating method. XPS measurements indicate a change in chemical composition on the PSBMA-treated substrates (**Figure S25**). The new peak at the binding energy of 231.5 eV, assigned to S2s in PSBMA, appears. The reduction in silicon content and the appearance of sulfur element on the substrate surface confirm the successful grafting of PSBMA polymers. **Figure 3b-c** show the surface silicon element content as a function of treatment time measured by XPS. It can be seen that the silicon content in untreated silicon wafer substrate is about 45.0%, while the content is significantly reduced after dipping in the DOPA-PSBMA solution. It reaches the lowest value at the treatment time only after 10 min dipping in tri-DOPA-PSBMA solution and then the values do not vary much with the treatment time prolonging from 10 min to 6 hours (**Figure 3c**). Correspondingly, it is found that the surface silicon content decreases sharply after 1-hour dipping in sin-DOPA-PSBMA solution, and a gradual reduction comes until it reaches the lowest value after 11 hours of treatment (**Figure 3b**). These results demonstrate the successful attachment of both sin-DOPA-PSBMA and tri-DOPA-PSBMA chains on the silicon substrates and a shorter equilibrium time of adsorption from tri-DOPA-PSBMA solution than that from sin-DOPA-PSBMA solution⁵⁸. The significant enhancement of the surface adsorption of the PSBMA polymer on three dopamine anchors is consistent with the higher hydrophobic property from DLS results and the higher E_{ads} from the calculation. Interestingly, polymer surface modification in 10 minutes by using the solution dip-coating method is of great significance to industrial applications.

It is generally accepted that the best non-fouling properties can only be achieved when surface hydration and steric repulsion work together, where surface hydration is the primary factor^{59, 60}. Contact angle (CA) results show that the pristine silicon wafer's initial contact angle was approximately 34°. The lower contact angle (~11°) of the cleaned substrate indicates more hydroxylated groups and stronger surface hydration, which will enhance protein resistance. All DOPA-PSBMA polymer-modified substrates show similarly low contact angles as that modified before (i.e., hydroxylated silicon wafer), which may be contributed to resistance to

protein adsorption (**Figure 3d**). To evaluate the protein resistant property of DOPA-PSBMA modified silicon wafers, the relative fouling of IgG on various surfaces was measured at 4 °C and 37 °C by using ELISA with a reference of untreated silicon wafer protein adsorption and laser scanning confocal microscopy (LSCM) was used for monitoring the adsorption of FITC-BSA on substrates. **Figure 4a** shows that the relative adsorption amounts of DOPA-PSBMA modified surfaces are approximately 2-7 % at both 4 °C and 37 °C, demonstrating a much lower protein adsorption level than that of hydroxylated surfaces (39 ± 3 and $17 \pm 3\%$, respectively) with the similar surface hydrophilicity. The protein adsorption is reduced to an ultra-low fouling degree as compared with uncoated surfaces, comparable to the PSBMA surfaces modified by the “grafting-from” method⁶¹. However, protein adsorption on the sin-DOPA-PSBMA modified surface is still a little higher than that on the surface grafted with tri-DOPA-PSBMA. These results indicate that DOPA-PSBMA polymer can effectively adhere to the hydroxylated substrate by using a “grafting-to” method to provide a highly protein-resistant surface. Although all surfaces suffered slightly more fouling at low-temperature conditions of 4 °C than at physiological temperature of 37 °C, the adsorption level is such low to be super-low fouling even at low temperatures. On the other hand, the best non-fouling ability of DOPA-PSBMA modified surfaces achieved here has to be considered as the result of the combination of surface hydration from surface hydrophilicity and steric repulsion resulting from chain flexibility of the attached PSBMA polymer. The highly efficient protein resistance of DOPA-PSBMA coated silicon wafers was further proved by the LSCM image of FITC-BSA-adhered substrates.

The development of antifouling surfaces, especially for medical devices, requires strong anchoring of the polymer to the surface in order to withstand long-term in vivo exposure to physiological conditions^{62, 63}. To explore the long-term stability of the DOPA-PSBMA modified substrates, the substrates were incubated in PBS buffer at different time intervals till 30 days before being verified by LSCM images of the attachment tests of FITC-BSA (**Figure 3e**). As for the freshly modified substrates, the attachment of FITC-BSA was hardly observed, meanwhile FITC-BSA adsorption can be observed on the blank substrate (pristine silicon wafer in **Figure S13**). However, the adsorption for the sin-DOPA-PSBMA substrate incubated in PBS buffer for 18 days increased sharply, which is the same as that of the hydroxylated sample. In effect, the adsorption for the 30 days incubated tri-DOPA-PSBMA modified samples was still hardly observed, implying that the tri-DOPA-PSBMA was stable and has long-term antifouling properties. The relatively fouling area of the FITC-BSA adsorption substrate shows the same trend by quantitative fluorescence values (**Figure S14**). The high adsorption energy and solvation free energy of Molecule 5 provide theoretical support for the long-term adsorption stability and fouling resistance of polymer tri-DOPA-PSBMA.

3.3 Application of antifouling performance of tri-Dopa-PSBMA

To verify the effectiveness of this polymer on the commonly used hydrophobic surface, we compared the wettability of the bare PVDF and DOPA-PSBMA modified PVDF membranes (**Figure 4b**). The in-air water contact angle (WCA) of the bare PVDF membrane was 120°, while that of the PVDF-OH membrane decreased to 85°. The wettability of the DOPA-PSBMA modified PVDF membrane is indicated by a relatively low WCA ($\sim 20^\circ$), suggesting a successful attachment of DOPA-PSBMA on the PVDF surfaces. However, there is no significant difference between the in-air soybean oil contact angle (OCA) of the PVDF-OH and those of DOPA-PSBMA modified PVDF membranes with OCA of $25 \pm 5^\circ$. Although no superwettability has been reached on the DOPA-PSBMA modified PVDF membranes in the air⁶⁴, the unique underwater superoleophobicity can be obtained due to the presence of the highly polar PSBMA chains, which endows the surface with the underwater self-cleaning property⁶⁵. The soybean oil-stained bare PVDF-OH and DOPA-PSBMA-modified PVDF membranes were dipped into the water. Although partly dewetted, soybean oil droplets with high viscosity remained on the bare PVDF-OH and sin-DOPA-PSBMA modified PVDF membranes after 4 s of immersion. On the contrary, oil can be automatically detached from the tri-DOPA-PSBMA modified PVDF surface in 4 s (**Figure 4c** and **Video 2**). The excellent performance of tri-DOPA-PSBMA with different degrees of polymerization in water also shows its wide applicability. Consequently, the convenient modification technology with excellent self-cleaning properties will have great potential in industrial practice⁶⁶.

4. Conclusions

A designing and screening strategy for novel bio-inspired zwitterionic polymer for rapid underwater adhesion and long-term antifouling stability was proposed. The polymer molecules are divided into three parts to fulfill the different functions of the antifouling material and connect the different modules. In the process of the design of zwitterionic polymer, different head groups, tail chains, scaffolds, and degrees of branching are considered and compared. The adsorption capacity, fouling resistance, adsorption configuration, and surface properties of molecules on the hydroxylation silicon wafer are compared through multi-scale molecular simulation. By continuously screening different molecules of each module, Dopa, TREN, and PSBMA are the optimal molecules for the head group, scaffold, and tail chain in this system, respectively. All the calculation results are consistent and prove that tri-Dopa-PSBMA may become a target molecule with excellent properties.

In addition, tri-Dopa-PSBMA and sin-Dopa-PSBMA were successfully synthesized by an ATRP method to be used to compare the surface adsorption properties. From XPS characterization, surface adsorption kinetics of Dopa-PSBMA was monitored to show that tri-DOPA-PSBMA adheres to the substrate much faster than sin-Dopa-PSBMA in aqueous solutions. The facile dip-coating method under an ambient environment has important practical significance. At the same time, the LSCM image of FITC-BSA adhered substrates indicated that tri-Dopa-PSBMA has excellent anti-protein adsorption ability and long-term stability on the silica surface at 4 °C and 37 °C. More importantly, the adhesion time of the tri-Dopa-PSBMA to the target substrate underwater by the solution dip-coating method is less than ten minutes, and there are no relevant reports of surface modification of the polymer within ten minutes. Finally, tri-Dopa-PSBMA is applied to modify the commonly used hydrophobic PVDF membrane. The tri-Dopa-PSBMA can be efficiently grafted on the PVDF membrane surface to fabricate surfaces with good surface antifouling and self-cleaning ability.

In summary, all calculations and experimental characterizations corroborate each other, indicating a successful combination of theory and experiment for the rational design of antifouling material. The mode of theoretical design and screen, experimental synthesis, and practical application greatly enhance new functional materials' design efficiency. Our general molecular engineering strategy offers a rapid way to design and synthesize functional polymers for specific environments.

Conflict of interest

The authors declare no competing financial interest.

Author contributions

K.Z., X.H. and C.L. conceived the idea, performed theoretical computational simulation, analyzed data and wrote original draft. W.G. prepared the experiments samples. K.H. and H.J. interpreted the data and edited the paper. Q.X. and L.H. supervised this research. All authors discussed the results and commented on the manuscript.

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Data and materials availability

All data needed to evaluate the conclusions in the paper are present in the paper and/or the Supporting Information.

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