High-performance mussel-inspired adhesives of reduced complexity

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Despite the recent progress in and demand for wet adhesives, practical underwater adhesion remains limited or non-existent for diverse applications. Translation of mussel-inspired wet adhesion typically entails catechol functionalization of polymers and/or polyelectrolytes, and solution processing of many complex components and steps that require optimization and stabilization. Here we reduced the complexity of a wet adhesive primer to synthetic low-molecular-weight catecholic zwitterionic surfactants that show very strong adhesion (~50 mJ m$^{-2}$) and retain the ability to coacervate. This catecholic zwitterion adheres to diverse surfaces and self-assembles into a molecularly smooth, thin (<4 nm) and strong glue layer. The catecholic zwitterion holds particular promise as an adhesive for nanofabrication. This study significantly simplifies bio-inspired themes for wet adhesion by combining catechol with hydrophobic and electrostatic functional groups in a small molecule.
Marine mussels attach to rocks by way of thread-like tethers on wind- and wave-swept seashores where wave velocities can reach 25 m s\(^{-1}\). Mussel attachment tenacity is enabled by adaptations at multiple length scales\(^2\), and the nanometre scale corresponds most closely to the chemistry of the interface\(^2\). Interfacial mussel foot proteins (mfps), especially mfp-3 and mfp-5, are rich in the catecholic amino acid, 3,4-dihydroxyphenylalanine (Dopa), which has been adopted for functionalizing diverse synthetic polymers\(^3,4\). Although the role of Dopa in wet adhesion is under increasing scrutiny, its introduction into polymers often endows them with strong underwater adhesion\(^2,4,5\) and self-healing\(^6-8\) capabilities. Other common amino acids, for example, lysine, phosphoserine and histidine, are also relevant to mfp adhesion\(^9,10\) and lend themselves to complex coacervation, which appears to be critical for the lossless fluidic delivery of mfps to target surfaces underwater\(^9,12\). Lysine and phosphoserine have been adopted to enhance adsorption\(^11\), but also to drive charge-dependent complexation\(^13\) needed for the dense fluid phase separation (coacervation) of adhesive polyelectrolytes from the equilibrium solution. Of particular interest here, mfp-5 and -3 function as adhesive primers\(^14\) at the plaque–substratum interface\(^15\). Despite recent progress in the science of wet adhesion, practical underwater adhesion remains limited or non-existent for a variety of potential applications. Biomimetic synthetic initiatives have aspired to remedy this by mimicking specific attributes of the bioadhesive model systems of mussels and sandcastle worms. These attributes include macromolecular adsorption to surfaces\(^2,3,16,17\), fluid–fluid phase separation (coacervation)\(^13,18\) and curing by oxidative catechol-based crosslinking\(^2,19,20\), and involve many complex components and steps requiring optimization and stabilization\(^21\).

In this study, both the strong wet adhesion\(^22\) of mfp-5 films and the coacervation\(^9\) of mfp-3 were translated into a smaller and simpler zwitterionic platform. We sought to simplify and combine several motifs borrowed from the interfacial adhesive mfps (including catechol, positive and negative charges, and nonpolar moieties) into a single, low-molecular-weight, one-component adhesive system. By taking a previously reported gemini zwitterionic surfactant\(^23\) with charged quaternary amine and phosphate groups and two alkyl tails, we replaced one of the tails with a catechol, and varied the other tail to create a family of mfp-mimetic zwitterionic adhesive homologues (mass \(< 500\) Da). These homologues exhibit very strong and spontaneous catechol-mediated binding to surfaces, stable phase separation as one-component coacervates or bilayer films, and periodate-mediated curing. The measured adhesion energy (\(W_{ad} \sim 50\) mJ m\(^{-2}\)) is the highest reported to date\(^22,24\) for a nm-thick film formed underwater, and 2–3 times greater than mfp-5 (ref. 22) or the recently engineered recombinant mfp–amyloid fusion protein\(^24\).

Zwitterion-mediated adhesion is likely to stimulate applications at multiple length scales including nanofabrications\(^25,26\) that require molecularly smooth and thin (\(\sim 4\) nm) adhesive layers, for example, in electronic\(^27\), lithographic\(^28\) and biomedical applications\(^2\).

**Results**

Zwitterionic adhesives design inspiration. The phosphate, amine, catechol and hydrophobic (alkyl or benzyl) functionalities in the zwitterions were adopted from the following mole percents of amino-acid residues in mfp-5, for example, anionic residues

![Figure 1](https://example.com/figure1.png)

**Figure 1** | The key features of natural and translated mussel adhesion. (a) A mussel anchored by byssal threads and plaques to a rock in the intertidal zone (Goleta Pier, California). (b) Schematic of the distribution of different mfps in a plaque. (c) Primary sequence of mfp-5; S (green) denotes phosphoserine. (d) Pie chart of key functionalities in mfp-5. (e) One example (Z-Cat-C10) of a zwitterionic surfactant inspired by mfp-5. (f) Light micrograph image of liquid-phase-separated Z-Cat-C10 at 100 mg ml\(^{-1}\) concentration. The scale bar on e corresponds to 200 \(\mu\)m.
Interfacial properties and redox stability. The aggregation tendency of each homologue in water was assessed by the critical aggregation concentration (CAC). The CAC is the concentration at which further addition of solute molecules to a solvent makes them go into finite-sized aggregates while the monomer concentration remains unchanged. The CAC was determined from the solution surface tension of varying homologue concentrations (Fig. 1e,f). Various homologues were designed by replacing one or both alkyl chains with mfp-mimetic functionalities (Fig. 2a) and their interfacial and adhesive properties were investigated.

Surface force measurements and interfacial interaction study. Thin films of the zwitterionic homologues were deposited on mica surfaces by adsorption from 5 mM solution (> CAC for all homologues; for concentrations below CAC see Supplementary Discussion), and investigated by the surface forces apparatus (SFA; Fig. 2c), atomic force microscopy (AFM; Supplementary Figs 4, 17 and 18) and quartz crystal microbalance with dissipation (QCM-D; Supplementary Figs 5 and 6). Surface force measurements between symmetric thin films on mica were investigated in the SFA. On approach of the two surfaces, Z-Ben-C8 films showed regular bilayer repulsion and jump-in instabilities typical for surfactant layers (Supplementary Fig. 8), whereas the catecholic homologues showed only slight or no repulsion (Fig. 2d). Z-Cat-C4 (19.2 ± 2.4 mJ m⁻²) exhibited the greatest cohesion (or adhesion) energies in deionized water, followed by Z-Cat-C10 (10.1 ± 2.3 mJ m⁻²), Z-Cat-C6 (9.6 ± 1.1 mJ m⁻²), and Z-Cat-C8 (7.7 ± 0.5 mJ m⁻²).
Z-Cat-C10 (8.1 ± 1.3 mJ m⁻²) and Z-Cat-C8 (2.5 ± 0.3 mJ m⁻²) (Fig. 2e). Notably, the interaction energies of Z-Cat-C10, -C8, -C6 and -C4 were closely correlated with the CAC (light blue parabola drawn in the plot in Fig. 2e as in Fig. 2b).

The hard-wall thickness (the limiting distance between the mica surfaces during the approach run in the SFA) of each homologue was measured and correlated with the CAC (Fig. 2f) corresponding to the catechol-containing zwitterions, which formed strongly cohesive \( W_{ad} = 2.2 - 21.6 \text{ mJ m}^{-2} \) bilayers (0.5–2.0 nm). In contrast, the non-catecholic Z-Ben-C8 formed multilayered films (~5 nm) without cohesive tendencies. In the catechol-containing homologues with alkyl tails (Fig. 2a), for example, Z-Cat-C10, -C8, -C6 and -C4, the hard-wall thickness and CAC were both correlated with alkyl tail length (light blue line in Fig. 2f).

Z-Cat-C10, which exhibited the lowest CAC among the homologues and readily phase separated into dense visible coacervates and equilibrium solution at high concentrations (100 mg ml⁻¹), was chosen for further scrutiny (Fig. 3a). Coalescence of the coacervate microdroplets in bulk solution was observed by microscopy (Fig. 3b and Supplementary Movie 1), and spreading of coacervates over a glass substrate was observed by microscopy (Fig. 3b and Supplementary Fig. 13) and copper (Supplementary Fig. 16).

Not limited to mica (Fig. 4d), 5 mM Z-Cat-C10 formed thin, molecularly smooth (~2 nm) films on silicon wafers (Supplementary Fig. 15) and copper (Supplementary Fig. 16). The wet and dry adhesion of these films (Supplementary Figs 17–20) on silicon wafers (SiO₂, root mean squared (r.m.s.) surface roughness <1 nm) and copper (CuO₂/Cu(OH)₂, r.m.s. surface roughness ~2 nm) surfaces was measured using silica (SiO₂) probes in the AFM (Fig. 4e). The surfaces were prepared by spreading 5 mM Z-Cat-C10 over the surfaces, followed by thorough rinsing and adhesive testing (Fig. 4f). The wet work of adhesion \( W_{ad} = F_{ad}/1.5\pi R \approx 7.7 \text{ mJ m}^{-2} \) for the SiO₂ and SiO₂ interface, resembled \( W_{ad} \approx 7.0 \text{ mJ m}^{-2} \) reported for catechol-functionalized polysiloxanes and SiO₂ interface31, and ~0.1 mJ m⁻² for adhesion between the CuO₂/Cu(OH)₂ and SiO₂ surfaces. After air drying the surfaces for ~5 min, the adhesion \( W_{ad} \) between CuO₂/Cu(OH)₂ and SiO₂ surfaces...
Figure 4 | Atomically smooth and thin nano-adhesives from mfp-mimetic zwitterion. (a,b) Representative force versus (vs) distance plots of symmetric (a) and asymmetric (b) periodate oxidized Z-Cat-C10 films on mica. Before periodate, the work of adhesion $W_{ad}$ did not change for contact times ($t_c$) from 2 min to 12 h (black). After oxidation with periodate (250 pmoles), $t_c < 10$ min (red points), $t_c = 60$ min (orange) and $t_c = 12$ h (green). Filled and open circles represent the forces measured during approach and separation of the surfaces, respectively. (c) Cartoon of the two self-assembled nano-glue layers (upper and lower, respectively) and the interface. (d) AFM image of atomically smooth adhesive layer formed from 5 mM Z-Cat-C10 on mica (the layer on SiO$_2$ and CuO$_2$/Cu(OH)$_2$ shown in Supplementary Figs 15 and 16, respectively). (e) Adhesion energy ($W_{ad}$ = $F_{ad}$/1.5R) of the nano-glue from Z-Cat-C10 measured on silicon wafer and copper plate, where adhesion force $F_{ad}$ (minimum of the potential well of the $F$ versus $D$ curves obtained from AFM measurements) and $R$ (radius of silicon dioxide probe). (f) Representative force versus distance plots of the nano-glue from 5 mM Z-Cat-C10 in AFM. (g) SEM image of underwater glued nano silica beads ($d = 100$ nm) on silicon wafer by the nano-glue from 5 mM Z-Cat-C10. The error bars indicate s.d.'s ($n = 5$, independent experiments). Scale bar, 500 μm; inset scale bar, 500 nm, DI, deionized.
increased significantly to \(~ 4 \text{mJ m}^{-2}\) and to \(~ 175 \text{mJ m}^{-2}\) between SiO\(_2\) and SiO\(_2\) surfaces, which, in the latter case, is 50-fold greater than the \(W_{\text{ad}}\) (\(~ 3.5 \text{mJ m}^{-2}\)) for catecholic polysiloxane adhesion to SiO\(_2\) as calculated from the \(F_{\text{ad}}\) (83 nN) measured using silica probes (\(\phi = 5 \mu\text{m}\)) in AFM\(^{31}\). Comparatively weaker adhesion to the copper plate is tentatively attributed to higher r.m.s. and hydroxides on its surface measured by AFM and X-ray photoelectron spectroscopy (XPS), respectively (Supplementary Figs 21–26). We also prepared a suspension of silica beads (\(\phi = 100 \text{ nm}\)) in deionized water, and spread it over a silicon wafer previously coated with 5 mM Z-Cat-C10. The silica beads remained glued to the film, even after rinsing with pulsed jets of running tap water (0.24 MPa; Fig. 4g).

Discussion

Catechol-functionalized zwitterionic surfactants are clearly more than detergents, and show the following favourable attributes as compared to detergents, and show the following favourable attributes as compared to detergents, and show the following favourable attributes as compared to detergents, and show the following favourable attributes as compared to detergents, and show the following favourable attributes as compared to detergents, and show the following favourable attributes as compared to detergents, and show the following favourable attributes as compared to detergents, and show the following favourable attributes as compared to detergents, and show the following favourable attributes as compared to detergents, and show the following favourable attributes as compared to detergents, and show the following favourable attributes as compared to detergents, and show the following favourable attributes as compared to detergents, and show the following favourable attributes as 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