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Bio-inspired Chemistry

Poly(norepinephrine): Ultrasmooth Material-Independent Surface Chemistry and Nanodepot for Nitric Oxide**

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Norepinephrine (NE) is a small-molecule catecholamine which has a variety of functions in the body. The most important function of NE is its role as a neurohormone and neurotransmitter for controlling responsiveness to stress and fear (Figure 1, bottom).[1] In addition to its use in the brain, NE is also released into the bloodstream to maintain heart rate and blood pressure.[2] Catecholamines are also found in underwater living creatures, such as mussels. The adhesive foot proteins in mussels are catecholamine-rich proteins in which the catechol is derived from a side chain of 3,4-dihydroxy-L-phenylalanine (DOPA; Figure 1, top), and the amine is a side chain of the basic amino acid lysine. Thus, the robust adhesion of mussels shares an interesting chemical similarity with a variety of other biological functions in neurons.

The aforementioned adhesive properties of catecholamine have inspired researchers to develop new surface chemistries.[3] A well-known example of utilizing surface chemistry is a poly(dopamine) (pDA) coating. The most distinguished property of a pDA coating is its material-independent performance which is defined as the ability of functionalizing virtually any material surface, including hydrophobic, synthetic polymers[4] [poly(ethylene), silicone rubber, poly(dimethylsiloxane), poly(tetrafluoroethylene) (PTFE or Teflon), and others], noble metals and metal oxides (Au, Ag, Pt, Cu, TiO_2, ZnO, SiO_2, MnO_2, etc.),[3,5–9] ceramics,[9,10] carbon materials [graphene, carbon nanotubes (CNTs), and peptide nanowires],[7,11,12] and living cells.[13] The applications for catecholamines have also become widespread for biomaterials (neural interfaces,[14] biocompatible surface modifications,[4,5] antibacterial surface preparation,[15] biomineralization,[16] and single-cell encapsulation,[13]), sensors/catalysts,[12,17] microfluidics,[18] mass spectrometry,[9] ultrafiltration membrane preparation,[19] corrosion resistance,[8] and energy storage devices including lithium ion batteries[20] and capacitors.[21]

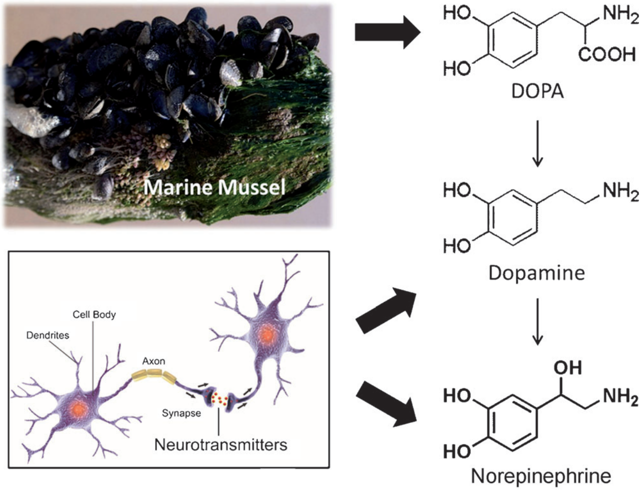

Figure 1. Bio-inspired flow from DOPA to dopamine to norepinephrine.

Despite the extensive use of pDA as a coating, the resulting uncontrollable surface morphology after functionalization is still a significant problem associated with pDA surface chemistry. The oxidation of dopamine yields an important intermediate called 5,6-dihydroxyindole (DHI), which acts as a monomer for subsequent polymerization.[22,23] During polymerization, unavoidable nano-/microparticulate aggregates of pDA or oligoDA can be found. The molecular driving forces for pDA aggregation are π–π bonding and van der Waals forces.[23,24] The large aggregates form in solution and attach to functionalized surfaces, thus resulting in significant increases in surface roughness. Simultaneously, another route might be that aggregates are grown from surfaces by polymerization. Therefore, the current understanding of the emergence of uncontrollable roughness during the pDA coating process is that pDA particles in solution simultaneously attach and grow directly from surfaces. This is a significant drawback when compared to other existing

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surface modification chemistries such as self-assembled monolayers (SAM) and layer-by-layer assembly (LbL),[25] which exhibit well-defined molecular architectures. Thus, smooth molecular architecture remains an important issue. Despite the advantage of its material-independent functionalization ability, the uncontrollable surface roughness after pDA coating has been an obstacle for potential applications. For example, the functionalization of nanomaterial surfaces, such as particles, rods, plates, and wires, have been critical problems.

Herein, we report a material-independent catecholamine surface chemistry with a well-defined molecular architecture which is comparable to SAM and LbL assemblies. The surface chemistry studied herein utilizes oxidative polymerization of norepinephrine to yield a poly(norepinephrine) (pNE) coating. Nearly perfect smoothness at the nanometer scale allows a variety of experiments which have not been feasible using pDA surface chemistry. Studies at the Molecular level revealed that a new intermediate, 3,4-dihydroxybenzaldehyde (DHBA), resulted in a remarkable difference in surface morphology. In fact, the role of DHBA in decreasing the surface roughness can be generalized for catecholamine surface chemistry. The roughness of pDA-coated surfaces was also decreased. Finally, a novel property was found in which pNE layers can be a universal depot for storing and releasing small therapeutics such as nitric oxide (NO). This property can be useful for various types of biomedical devices which require an NO-releasing functionality.

The aforementioned disadvantage of significant surface roughness resulted from catecholamine surface chemistry, specifically for pDA coatings, and was experimentally demonstrated. (Figure 2A) We used the same concentration of dopamine (2 mg mL^{-1}) and a pH value of 8.5 as reported in the original study.[3] Large pDA particles with a diameter of less than 1 µm were attached to the surface of poly(styrene) (PS) beads (Figure 2B). The areas of the surface without pDA particles were also functionalized using a thin adhesive nanolayer of pDA, which was imaged using transmission electron microscopy (TEM; Figure 2C). A pDA layer on silver microparticles with a thickness ranging from 50 to 100 nanometers (50.4, 102.1, 73.4, and 86.2 nm) was visualized (arrows). The pDA layer in the TEM image also showed a rough morphology at the molecular level. However, a well-controlled, ultrasmooth coating was observed after the pNE surface functionalization. The pNE coating was introduced using the same method used for the pDA functionalization (2 mg mL^{-1}, pH 8.5). No large aggregates were observed on the PS microbeads (Figure 2D). The TEM image showed that the thickness of the pNE coating layer was remarkably consistent, thus producing an excellent conformal coating on the nanometer scale (Figure 2E). The thickness values measured at the chosen points were 12.2, 12.3, 12.7, and 12.6 nm (arrows). Even under stronger oxidation conditions in the presence of sodium periodate ($NaIO_4$), the surface roughness was still smoother than that of the pDA coating (see Figure S1 in the Supporting Information). Thus, pNE surface chemistry exhibits unparalleled properties for forming well-defined thin molecular architectures on virtually any type of surface.[26] In some cases of LbL assembly, the surface morphology often showed significant wobbling or nanoscale aggregation, depending on the molecular weight and charge densities of the assembled polymers.[27] Another aspect observed during pDA coating is the formation of pDA microparticles which are precipitated in the coating solution. The precipitates are indirectly related to the rough surface formation of pDA layers. These aggregates were observed within three hours of the pDA coating. Quantitative analysis of the microparticle aggregations showed that approximately 6 mg of the aggregates were collected from the pDA coating solution after a 6 hour polymerization. The amount of pDA aggregates increased to 11 mg after 24 hours of pDA formation (gray bars, Figure 2F). However, a negligible amount of aggregates were collected for pNE (black bars). The color of the container was also significantly different for the pNE and pDA solutions (Figure 2G).

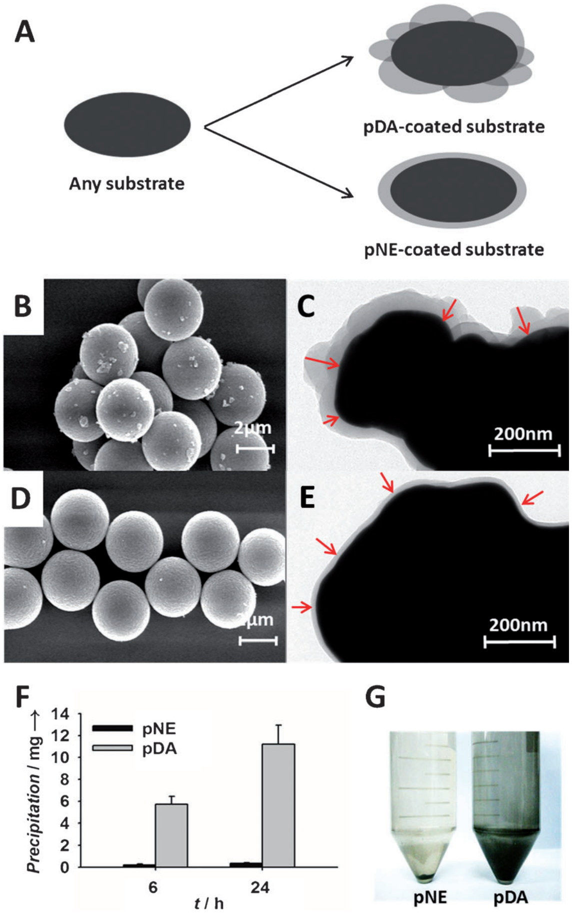

Figure 2. A) pNE/pDA coating processes. B) Scanning electron microscopy (SEM) and C) TEM snapshots of the rough surface morphology from the pDA coating on PS and silver particles. D) SEM and E) TEM snapshots of the ultrasmooth surface morphology from the pNE coating on PS and silver particles. F,G) Amount of precipitate formed during the pNE and pDE coating processes.

As shown in the chemical structure of NE (Figure 1), the hydroxy group that is linked to the aliphatic carbon atom beside the catechol enhances the hydrophilicity of the functionalized surfaces. High-resolution C1s X-ray photoelectron spectroscopy (XPS) analysis revealed that the pNE-coated surfaces showed a greater C−O bond content (at 285.5 eV) compared to those coated with pDA (see Figures S2A and S2B in the Supporting Information). The additional OH might result in a hydrophilic conversion of the substrates. Water contact angle measurements showed 8.6° for a Si wafer and 22.8° for gold (see Figure S2C in the Supporting Information). These values were lower than the contact angle results obtained after coating with pDA: 31.2° for Si and 34.0° for gold substrates.

Understanding the ultrasmooth surface coating which results from using a pNE coating without pDA chemistry at the molecular level is an important subject. We hypothesized that early intermediates formed during oxidative polymerization might contribute to the remarkable difference in surface morphologies. The early-stage intermediates were analyzed using high-performance liquid chromatography and mass spectrometry (HPLC-MS). After 1 minute of the oxidation reaction (detailed in the Supporting Information), the solution contained a major intermediate which was eluted at 14.2 minutes. The corresponding mass of the eluted molecule was 138.9 *m*/*z* (see Figure S3 in the Supporting Information). We collected this intermediate by preparative liquid chromatography (prep-LC) and analyzed its chemical structure using ^{1}H NMR spectroscopy (Figure 3 A). The intermediate with the mass of 138.9 *m*/*z* showed two peaks in the ^{1}H NMR spectrum corresponding to aldehyde protons around $\delta = 9.8$ ppm. Interpretation of the two kinds of aldehyde protons suggests that one might be the proton next to catechol, and the other might be adjacent to the catechol-quinone. The two structurally similar molecules might be formed as a dimer in solution phase. In fact, the nearly one to one ratio of the integral value between DHBA and DHBA-quinone (Figure 3 A, upper panel) supports the dimer formation. Furthermore, the physical trimer of (dopamine)$_2$/DHI was previously characterized to exist in solution phase.[22] In contrast, the detection of the mass value 138.9 *m*/*z* can be interpreted as the dissociation of the DHBA/DHBA-quinone dimer, existing in an aqueous phase, into two protonated DHBA units in the process of gas-phase ionization. The subsequent reaction may be a reversible Schiff-base formation reaction between DHBA and NE with subsequent reduction of the imine bond (Figure 3 E, box). Two tentative mechanisms of the C=N imine bond reduction are proposed in Figure S4 in the Supporting Information. An intramolecular reduction triggered by the catechol in DHBA (2nd pathway) rather than in NE (1st pathway) results in the final DHBA-NE product with a mass value of 292 *m*/*z* (Figure 3 B) as detected in the model reaction (Figure 3 C) as well as in the pNE coating solution (Figure 3 D). However, the yield of DHBA-NE was low compared to that of the model reaction possibly because of the surface immobilization of DHBA-NE. The DHBA-NE plays an important role in decreasing the roughness of functionalized surfaces. The simple addition of DHBA during the pDA coating process markedly decreased the surface roughness (see Figure S5 in the Supporting Information). In particular, adding a five molar equivalent of DHBA resulted in the disappearance of the large pDA aggregates (3rd atomic force microscopy (AFM) image in Figure S5).

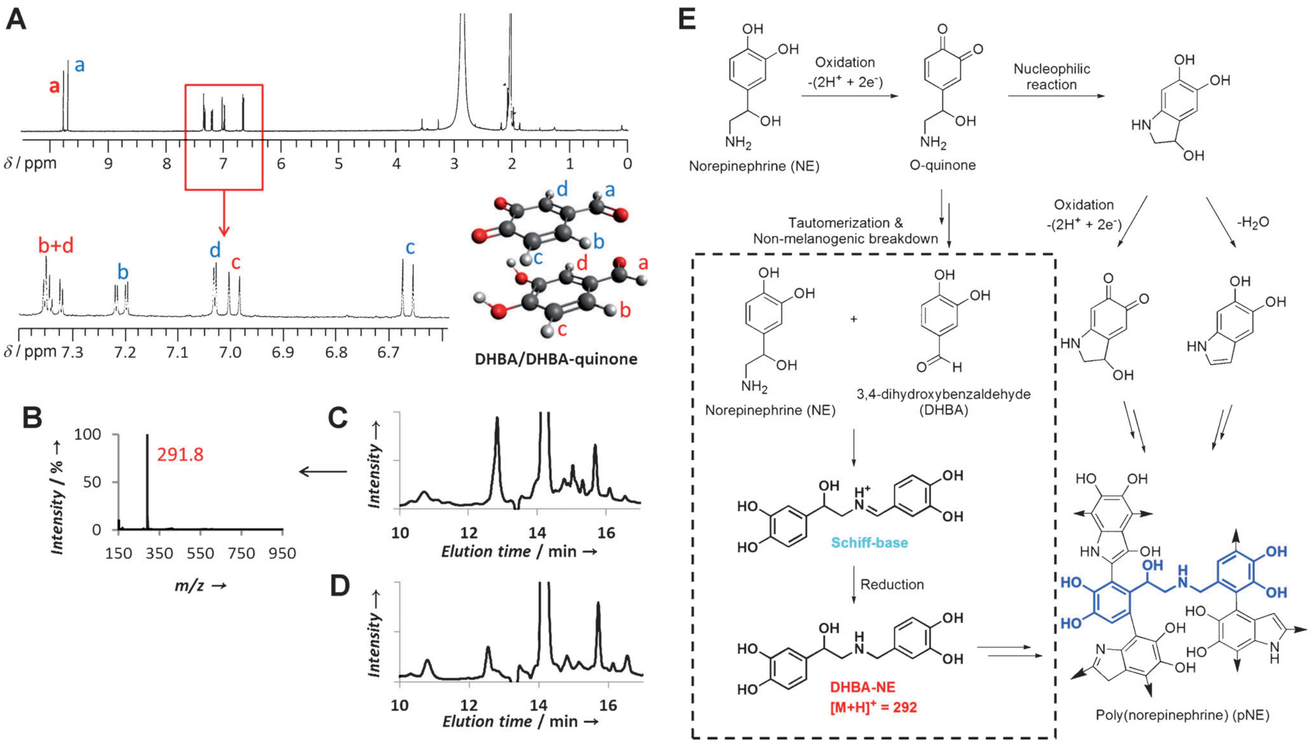

Figure 3. A) ^{1}H NMR spectroscopic analysis of a major intermediate, the dimer of DHBA, during NE polymerization. B,C) HPLC-MS analysis of the DHBA-NE Schiff-base formation by reduction and D) the actual existence of DHBA-NE in the pNE coating solution without reduction. E) Scheme of the oxidation pathways of pNE in which the new catecholamine intermediate called DHBA-NE was identified.

The aliphatic secondary amine of DHBA-NE, shown in Figure 3E, can be useful for biomedical applications. We hypothesized that the secondary amine can be an excellent NO-loading molecular platform. Previous approaches for the loading and release of NO utilize physical adsorption of NO-containing compounds[28] or matrices which encapsulate NO-releasing compounds.[29] However, the stability of the adsorbed materials in physiological conditions remains an unsolved problem. Another frequently employed strategy involves aminosilane-based sol-gel chemistry, which is generally difficult to prepare precursors for NO-immobilization and is limited to chemistry of material surfaces such as metal oxides. Furthermore, this silane coating provides a thick layer with thickness typically in the micro- to millimeter range.[30] NO release achieved by SAMs was also reported,[31] but the SAM method is limited to noble metals which are not commonly used in medical devices. If the NO loading onto the pNE layer was successful, material-independent NO immobilization and release would be achievable. Thus, we performed the following experiment to prepare NO-loaded surfaces. First, pNE-coated substrates were prepared. Second, the functionalized substrates immersed in basic solutions were exposed to high-pressure NO gas. These steps resulted in the surface-conjugated diazeniumdiolates groups reacting with the secondary amines on the respective pNE layers. The plausible chemical structures after the NO-loading procedures are shown in Figure S6 in the Supporting Information. Diazeniumdiolates generally react with secondary amino groups to store NO. The spontaneous dissociation of diazeniumdiolates releases two equivalents of NO gas molecules. We expected that the amount of surface-loaded NO utilizing the pNE-coated substrates could be significantly large for biomedical applications because of the existence of DHBA-NE on the coated surfaces. Additionally, the presence of the hydroxy group within the pNE layer presumably facilitates the surface installation of diazeniumdiolates and NO release by forming hydrogen bonds with diazeniumdiolates.[32]

The NO reaction was confirmed by Fourier transform infrared (FT-IR) spectroscopy. The FT-IR data showed the characteristic peaks for N-N (1068 cm^{-1}, 1480–1540 cm^{-1}),[33,34] N-O (1390–1410 cm^{-1}),[33] N=N stretches (1620–1630 cm^{-1}),[35] and NO vibrations (1735 cm^{-1})[36] (see Figure S7 A in the Supporting Information). The surface-immobilized diazeniumdiolate moieties on the pNE-coated surfaces (pNE-NO) or on the pDA-coated surfaces (pDA-NO) were characterized by XPS. The analysis of N1s and C1s spectra of pNE-NO and pDA-NO surfaces confirmed the diazeniumdiolate reaction by the presence of new peaks in N1s binding energy (401.3 eV for pNE-NO and 402.1 eV for pDA-NO) and upshifted C1s peaks (286.3 eV for pNE-NO and 286.1 eV for pDA-NO) (Figure S7B). These results show the successful storing of NO in pNE layers by formation of diazeniumdiolates without any damage to the underlying layers. Interestingly, the pNE-NO surface exhibited a higher increased N/C ratio compared to the surface-immobilized diazeniumdiolates moieties on the pDA-coated surface (pDA-NO): 0.7 for pNE-NO and 0.3 for pDA-NO (data not shown). This result indicates that pNE has a higher capacity for NO storage than pDA. The NO release from the NO-modified surfaces was measured in Dulbecco's phosphate-buffered saline (DPBS) solution under physiological conditions (37 °C, pH 7.0) using Sievers NOA 280i chemiluminescence NO analyzer (Figure 4, and Table S1 in the Supporting Information). As shown in Figure 4, the pNE-NO surfaces showed a noticeable amount of NO release with long duration despite the thin layer (ca. 60 nm). Even under similar reaction and releasing conditions, the pNE-NO (1789 nmol cm^{-2}) can store larger amounts of total NO on its surface than pDA-NO (69.5 nmol cm^{-2}), thus demonstrating the viability of our previous hypothesis regarding the secondary amine contribution in DHBA-NE on the immobilization of diazeniumdiolates might be reasonable one (Figure 4, Table S1). This NO loading capacity is higher than or comparable with aminosilane-based sol-gel method,[30] which is the representative NO-coating method, and the conventional NO-releasing materials.[28–29,32] It could be attributed to the high amine content and hydrogen bonding within its surface adherent layers.

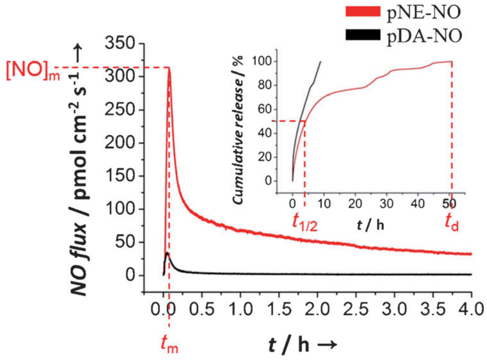

Figure 4. Comparison of NO flux and cumulative NO release from pNE-NO versus pDA-NO (inset).

In conclusion, the ultrasmooth, material-independent surface coating made from pNE is described. The pNE coating is inspired by catecholamine found in neurotransmitters and the adhesive proteins of mussels. A newly found early intermediate, DHBA-NE, plays an important role in the creation of such ultrasmooth coatings. Additionally, the secondary amine in DHBA-NE becomes a general platform for an unprecedented amount of NO storage, and is potentially useful for biomedical applications.

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