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Communication

# Nanomechanics of Anion−π Interaction in Aqueous Solution

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**ABSTRACT:** Noncovalent interactions play a constitutive role in numerous biological processes, including biomolecular adhesion, recognition, and transport. Unlike π−π and cation−π interactions, anion−π interaction was only recently and computationally recognized to participate in biomolecular science. Here, we present the first experimental identification and direct quantification of the nanomechanics of anion−π interaction in aqueous solution by using a surface forces apparatus with complementary computational simulations. Anionic phosphate ester and π-conjugated catecholic moieties that abound in marine bioadhesives were used as the model system. Robust adhesion was observed and attributed to anion−π interaction, which was found to be enabled by the cooperative cation−π interaction due to the coexistence of a cation. The anion−π interaction strength follows the trend phosphate ester > $HPO_4^{2-}$ > $SO_4^{2-}$ > $NO_3^-$, affected by charge density, polarity, and hydration effect.

Charged species and π-conjugated moieties ubiquitously exist in biological systems, and their involvement in noncovalent interactions is significant in molecular adhesion and recognition, protein folding, and many other important biological processes.[1−3] A comprehensive understanding of noncovalent interactions, e.g., π−π stacking, and cation−π interactions, holds great promise for biomedical techniques, supramolecular chemistry, and engineering applications.[4−8] Yet, anion−π interactions, as a relatively new type of noncovalent interaction, were only recognized recently and computationally to participate in biological processes (e.g., enzymatic activity of urate oxidase and DNA sequence recognition by phosphodiesterase).[2,9,10] However, experimental studies of anion−π interaction remain limited, and the nanomechanics nature remains unsurveyed.

In the field of wet adhesion, marine organisms can form robust bioadhesives on solid surfaces under an aqueous saline environment, which is a great challenge in technology to date. The π-conjugated catechol group in 3,4-dihydroxyphenylalanine (dopa, Figure 1a) has been identified as the pivotal adhesive promotor in bioadhesive proteins, which undergoes spontaneous oxidation and forms poly(catechol) under weak alkaline seawater conditions.[11−13] Recently, cation−π interactions between the abundant π-conjugated catecholic/poly(catechol) residues and cationic residues (e.g., Lys and Arg) have been recognized as a key mechanism in promoting the cohesion of bioadhesives.[1,14,15] While salt cations (e.g., $K^+$) have been found to tremendously undermine the cohesion between cationic residues and π-conjugated moieties due to competitive interactions, the extensive presence of cations in seawater has not frustrated the wet adhesion of marine organisms, suggesting an additional interaction mechanism was involved.[14,15]

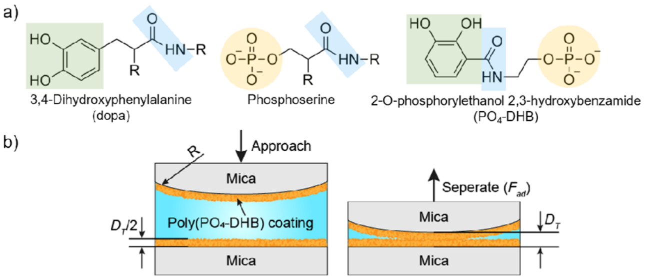

**Figure 1.** (a) Structures of dopa and phosphoserine residues, and $PO_4$-DHB. (b) Schematic of SFA measurement. Two opposing curved mica surfaces (radius *R*) coated with poly($PO_4$-DHB) films first approached each other and then were compressed and separated to measure the adhesion force ($F_{ad}$) and thickness of confined films ($D_T$).

In bioadhesives, anionic phosphoserine (with a phosphate ester group, Figure 1a) commonly abounds together with dopa.[16] For example, sandcastle worm glue proteins overall contain ∼30 mol % phosphoserine and 2−3 mol % dopa.[17,18] Mfp-5, a primary protein in surface adhesion of mussel, contains 10 mol % phosphoserine and 25 mol % dopa.[18,19] However, the noncovalent interactions between phosphate ester, intrinsically as an anion, and the π-conjugated catecholic moieties and the consequent contribution to under seawater adhesion are seldom considered. In this work, anion−π interaction is unraveled to exist between anionic phosphate ester and π-conjugated poly(catechol) moieties and indispensably contribute to wet adhesion, presenting the *first* experimental study on the nanomechanics of anion−π interaction.

2-*O*-Phosphorylethanol 2,3-hydroxybenzamide ($PO_4$-DHB, Figure 1a) was synthesized as a model compound to mimic the natural bioadhesives (synthesis and characterization shown in

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Supporting Information). A surface forces apparatus (SFA) was used to directly quantify the nanomechanics of the anion effect of a phosphate ester on the wet adhesion of π-conjugated catecholic adhesives in saline solution (pH 8.4, 50 mM bicine buffer). A typical SFA experimental setup is illustrated in Figure 1b.[20] Typically, a $PO_4$-DHB saline buffer solution was injected in the gap between two opposing atomically smooth mica surfaces (radius $R$); then $PO_4$-DHB polymerized and poly($PO_4$-DHB) coatings formed on both mica surfaces. Force−distance curves ($F/R$ vs $D$) between poly($PO_4$-DHB) coatings were obtained during their approach and separation, with the thickness of each coating determined as $D_T/2$. The deposition of a poly($PO_4$-DHB) coating on the mica substrate was also verified by atomic force microscopy (AFM) topographic imaging and time-of-flight secondary ion mass spectrometry (ToF-SIMS) analysis (Figures S1, S2).

In 150 mM $KNO_3$ buffer solution, both the adhesive forces and thickness of poly($PO_4$-DHB) films increased with deposition time $t$ (Figure 2). With $t$ = 1 h, the negatively charged poly($PO_4$-DHB) coatings present a robust adhesion ($F_{ad}/R$ ~7 mN/m) comparable to the dopa-$Fe^{3+}$ chelation system[21,22] and cation−π interaction systems such as poly(catecholamine).[15] The adhesion was repetitive and reversible (Figure S3), which should be attributed to noncovalent interactions.

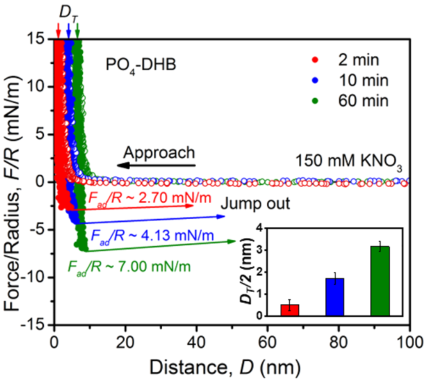

**Figure 2.** Force−distance profiles as a function of deposition time $t$ of poly($PO_4$-DHB) films in 150 mM $KNO_3$ buffer solution (50 mM bicine, pH 8.4) with initial concentration of $PO_4$-DHB as 2 mg/mL. The inset shows the thickness ($D_T/2$) of each poly($PO_4$-DHB) film.

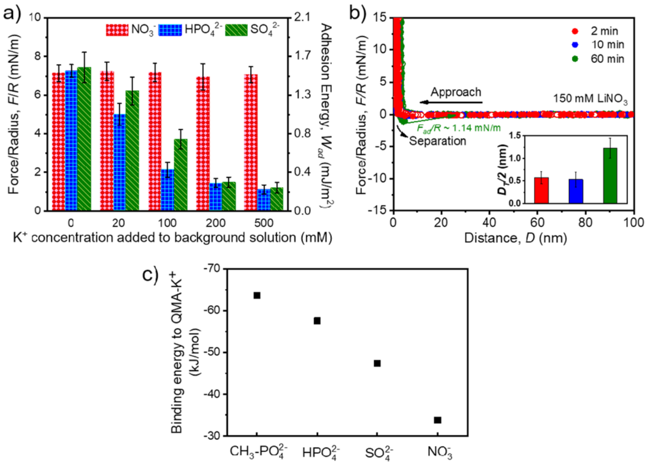

**Figure 3.** (a) Adhesion changes between poly($PO_4$-DHB) films (1 h deposition) in 150 mM $KNO_3$ background buffer solution after further addition of $NO_3^-$, $HPO_4^{2-}$, or $SO_4^{2-}$. (b) Force−distance profiles and thickness of poly($PO_4$-DHB) coatings as a function of $t$ in 150 mM $LiNO_3$ buffer solution. (c) Binding energies of different anions to methyl amide of the π-conjugated quinone (QMA)−$K^+$ pair in water obtained from DFT simulation.

The important role of the phosphate ester in the robust adhesion was further demonstrated through parallel SFA measurements by varying the species and concentrations of competition anions. The adhesion between two as-formed poly($PO_4$-DHB) coatings (1 h deposition) was measured in 150 mM $KNO_3$ background buffer solution (Figure 3a) as ~7.27 mN/m. To compare the competition effect of different anions, the further added $K^+$ concentrations were controlled to be ~20, 100, 200, and 500 mM, and the corresponding additional counterions were ~20, 100, 200, and 500 mM $NO_3^-$ and ~10, 50, 100, and 250 mM $HPO_4^{2-}$/$SO_4^{2-}$. By increasing concentrations of $NO_3^-$, the adhesion varied negligibly, suggesting negligible competition capability with phosphate ester groups. For $HPO_4^{2-}$ and $SO_4^{2-}$, the adhesion with addition of $HPO_4^{2-}$ decreased more dramatically than $SO_4^{2-}$. The successful competition by $HPO_4^{2-}$ and $SO_4^{2-}$ and decreased adhesion suggest the crucial role of the phosphate ester in enhancing adhesion, possibly through forming noncovalent bonding with π-conjugated poly(catechol) moieties. The binding strength of $HPO_4^{2-}$ to the π-conjugated moieties is stronger than $SO_4^{2-}$. When the additional concentration of $HPO_4^{2-}$/$SO_4^{2-}$ ≥ 100 mM, the adhesion almost leveled off and was similar (~1.47 mN/m), which should be due to the much higher concentration of $HPO_4^{2-}$/$SO_4^{2-}$ compared with phosphate ester groups; thus almost all phosphate ester groups in the binding complex were substituted by $HPO_4^{2-}$/$SO_4^{2-}$. When the added $HPO_4^{2-}$/$SO_4^{2-}$ concentration increased to 250 mM, the further decrease of adhesion was insignificant (~1.17 mN/m).

Because the initial concentration of $PO_4$-DHB was ~7 mM, and only a fraction would form poly($PO_4$-DHB) coatings during deposition, with 10 mM $HPO_4^{2-}$ in the solution, the amount of $HPO_4^{2-}$ would be much higher than that of the phosphate ester groups on the coating surface. Yet, the measured adhesion between poly($PO_4$-DHB) coatings decreased by only ~31.3%. Therefore, although $HPO_4^{2-}$ could compete with phosphate ester, its binding affinity to the π-conjugated moieties should still be lower than that of the phosphate ester. Thus, the affinity trend of anions to the π-conjugated moieties in poly($PO_4$-DHB) coatings should be phosphate ester > $HPO_4^{2-}$ > $SO_4^{2-}$ > $NO_3^-$.

Under the experimental condition (pH 8.4), catechol moieties in $PO_4$-DHB would undergo spontaneous oxidation to *o*-semiquinone radicals and quinones; then polymerization would be initiated.[23,24] The resulting poly(catechol) is a complex mixture containing cross-linked catechol, quinone, and intermediate *o*-semiquinone radical moieties, as electron-rich π systems.[15,25] The presence of these moieties in poly($PO_4$-DHB) was further substantiated by using an X-ray photoelectron spectrometer (XPS), electron paramagnetic spectroscopy (EPR), and UV−vis spectroscopy (Figures S12−S14) . The oxidation route and possible chemical structure of poly($PO_4$-DHB) are illustrated in Figure S15. The binary anion−π interaction between the electron-rich π system and anion was reported to be weakly attractive or repulsive.[2,26] However, with a cation (e.g., $K^+$, $Na^+$) on the other side of the π system to form cation−π bonding, the formation of anion−$\pi$ bonding was suggested to be enabled in previous pioneering computational investigations,[26,27] and the interaction in such an anion⋯$\pi$⋯cation orientation was found to be cooperative.[2,28] To test if the binding strength of anionic phosphate esters to $\pi$-conjugated moieties is relevant to cation−$\pi$ interactions, $Li^+$ was used as the cation instead of $K^+$ during film deposition (Figure 3b), due to the much weaker cation−$\pi$ interaction performed by $Li^+$ than $K^+$.[14] When $t$ reached 1 h, the adhesion in 150 mM $LiNO_3$ buffer solution increased to 1.14 mN/m, significantly lower than that with 150 mM $KNO_3$. As such, cation−$\pi$ was proved to facilitate anionic phosphate ester binding to $\pi$-conjugated moieties. Due to abundant $Na^+$ in seawater, the adhesion of poly($PO_4$-DHB) coatings was further investigated during film deposition in 150 mM $NaNO_3$ buffer solution. Strong adhesion was measured (Figure S16a, ∼6.00 mN/m with $t = 1$ h), slightly lower than that with $K^+$, possibly due to relatively higher desolvation penalty of $Na^+$ when forming a cation−$\pi$ complex.[14] The adhesion between poly($PO_4$-DHB) coatings (1 h deposition with $Na^+$) was also greatly undermined with further addition of 250 mM $HPO_4^{2-}$ in 150 mM $NaNO_3$ background buffer solution (Figure S16b, ∼1.14 mN/m), suggesting cooperative interactions were involved similar to that with $K^+$.

Density functional theory (DFT) simulation was performed to better understand the anion−$\pi$ interaction mechanisms with cooperative cation−$\pi$ interaction in promoting the adhesion of poly($PO_4$-DHB) coatings. Methyl amides of catechol (CMA), quinone (QMA), and *o*-semiquinone radical (QRMA) (Figure S4a) were used as the electron-rich $\pi$-conjugated moieties, and methyl phosphate ($MePO_4^{2-}$) was used as phosphate ester for simplicity.[25,29] The optimized geometries of $MePO_4^{2-}$-CMA/QMA/QRMA-$K^+$ complexes (Figure S4b) are consistent with exemplary anion−$\pi$−cation geometries in a previous study.[2] $MePO_4^{2-}$ formed stable complexes in all three cases, and the binding strength of $MePO_4^{2-}$ to QMA-$K^+$ pairs was the strongest (Table S1), possibly due to the more positive electrostatic potential (ESP) on the $\pi$-conjugated ring of the QMA-$K^+$ pair (Figure S4c). Hydrogen-bonding interaction also contributed to the binding of $MePO_4^{2-}$, indicated by linear N−H⋯O and O−H⋯O configurations.[30] Furthermore, the binding energies of $NO_3^-$, $HPO_4^{2-}$, and $SO_4^{2-}$ to the QMA-$K^+$ pair were calculated (optimized geometries shown in Figure S5). The affinity of anions to the QMA-$K^+$ pair followed $MePO_4^{2-} > HPO_4^{2-} > SO_4^{2-} > NO_3^-$ (Figure 3c), essentially consistent with SFA experiments. This affinity trend was relevant to charge density, polarity, and hydration effect.[31,32] Compared to monovalent $NO_3^-$, the electrostatic interaction between divalent anions and the $\pi$-$K^+$ pair should be much stronger, resulting in higher binding affinity. This finding agreed with the previous study that suggested electrostatic forces as the main contributor to anion−$\pi$ interaction cooperated with cation−$\pi$ interaction.[14,26] Phosphate ester/$MePO_4^{2-}$ is more hydrophobic than $HPO_4^{2-}$ and $SO_4^{2-}$ with strong hydration shells; thus their binding affinity to the hydrophobic $\pi$-conjugated moieties are stronger.[33] As shown in Figure S4b, the hydrophobic methyl group in $MePO_4^{2-}$ was close to the $\pi$-conjugated moieties. $HPO_4^{2-}$ possessed higher polarity than $SO_4^{2-}$, resulting in more negative ESP on the phosphate group (Figure S6), hence stronger binding affinity to the positively charged $\pi$-$K^+$ pair.

The $K^+$ concentration effect on the adhesion of poly($PO_4$-DHB) coatings (1 h deposition) was further investigated, with poly(pyrocatechol) coatings as contrast. In both systems cation−$\pi$ interaction was involved, whereas a huge difference was observed (Figure 4a). With 150 mM $KNO_3$ background buffer solution, the adhesion between poly($PO_4$-DHB) coatings was barely affected by further addition of $K^+$, while the adhesion of poly(pyrocatechol) coatings was significantly undermined, possibly due to the formation of higher amount of $\pi$-$K^+$ pairs, leading to the abolishment of a bridging effect of $K^+$ between two $\pi$-conjugated moieties (Figure 4b). As for poly($PO_4$-DHB) coatings (Figure 4c), the phosphate ester groups could bridge the $\pi$-conjugated moieties with $K^+$ on the other side, insusceptible to high concentrations of $K^+$. The bridging effect of anion−$\pi$ interaction showed great promise in resolving the undermined adhesion of binary cationic residues/dopa adhesives due to salt cation competition.

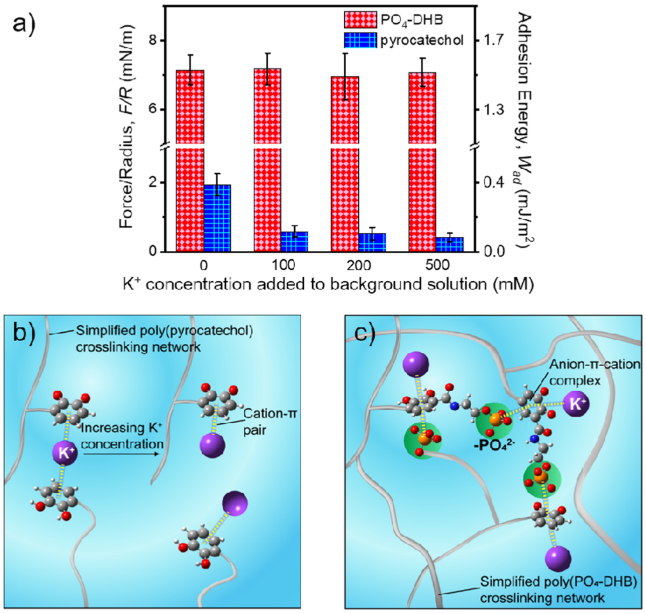

**Figure 4.** (a) Adhesion changes obtained from SFA experiments between two poly($PO_4$-DHB) or two poly(pyrocatechol) films (1 h deposition) in 150 mM $KNO_3$ background buffer solution with increased additional $K^+$ concentration. Schematics for (b) the abolishment of bridging with increasing concentration of $K^+$ due to the formation of more cation−$\pi$ pairs in poly(pyrocatechol) coating and (c) the formation of anion−$\pi$-cation complex in poly($PO_4$-DHB) coating.

In summary, for the *first* time, anion−$\pi$ interaction in aqueous solution and its nanomechanics were directly verified and evaluated through surface force measurements. In the marine bioadhesives-inspired phosphorylated catecholic system, robust and reversible wet adhesion was detected, and anion−$\pi$ interaction between anionic phosphate ester and $\pi$-conjugated poly(catechol) moieties was found as the primary contributor. Furthermore, such anion−$\pi$ interaction was found to be enabled by the cooperative effect of cation−$\pi$ interaction with the coexistence of a cation. The affinity trend of anions to the $\pi$-conjugated systems in poly($PO_4$-DHB) coating was phosphate ester > $HPO_4^{2-}$ > $SO_4^{2-}$ > $NO_3^-$, as further substantiated by DFT simulations. The wet-adhesion strength of poly($PO_4$-DHB) coatings was not affected by an increased concentration of cation ($K^+$), contrasted with severely undermined adhesion of poly(pyrocatechol). This insusceptible, strong, and reversible bridging effect of a phosphate ester to the $\pi$−cation pairs provides new insights into fundamental adhesion science of marine bioadhesives and shows great implications in biochemical and materials engineering. More broadly, the unravelled nanomechanical insights into the anion−π interaction in aqueous media are significant in understanding biomolecular interactions and rationalizing biomolecule assembly in diverse biological processes such as selective anion binding and protein folding.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.9b11552.

Figures S1−S16 and Table S1, synthesis and characterization, SFA measurement and quantum simulation details (PDF)

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### Author Contributions

⊥J.Z. and L.X. contributed equally.

### Notes

The authors declare no competing financial interest.

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