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Remote regulation on the hydration sites of adenine molecules via derivatization

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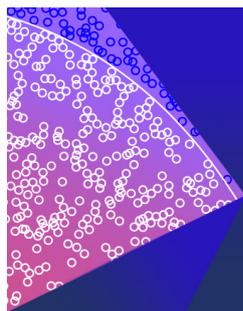
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ABSTRACT

Hydration, as a ubiquitous and vital phenomenon in nature, has attracted great attention in the field of surface science concerning the fundamental interactions between water and organic molecules. However, the role of functional group derivatization is still elusive in terms of its potential impact on hydration. By the combination of high-resolution scanning tunneling microscopy imaging and density functional theory calculations, the hydration of 9mA molecules was realized on Au(111) in real space, forming 9mA–H₂O–9mA structures. In comparison with the hydration of adenine molecules, methyl derivatization is experimentally found to remotely regulate the hydration sites from the imidazole ring to the pyrimidine ring and is further theoretically revealed to allow intramolecular electron redistribution and, therefore, steer the priority of the hydration sites. These results provide sub-molecular understandings of the relationship between derivatization and hydration, which would shed light on the regulation of hydration processes in chemically and biologically related systems.

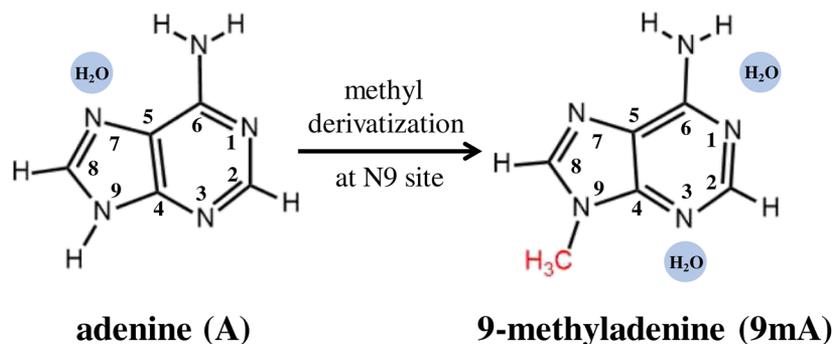
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INTRODUCTION

Hydration, a universal phenomenon in nature from single molecules to living organisms, is vital to many scientific fields such as bioscience, catalysis, and electrochemistry.^{1–6} Lots of organic molecules derive their structures, functions, and activities from their interactions with water.⁷ In recent years, the interactions between water and organic molecules have been extensively studied on surfaces by virtue of scanning probe microscopy (SPM) under ultra-high vacuum (UHV) conditions to gain single-molecule insights, where water molecules have been shown to play a crucial role in determining molecular conformations,^{8–10} regulating supramolecular assemblies,^{11–14} as well as inducing molecular tautomerization¹⁵ and chiral separation.¹⁶ These studies demonstrate the versatility of surface science methods in determining the detailed hydration structures and precise hydration sites,¹⁷ facilitating the mechanistic explorations of hydration at the atomic scale^{18–20} and inspiring the fundamental understandings in chemical and biological systems. However, functional group derivatization, which is ubiquitous in molecular systems, has not been fully understood in terms of its potential impact on hydration, to the best of our knowledge.

Therefore, it is intriguing to explore the hydration structures and action sites in the molecule–water interactions before and after derivatization at the single-molecule level, which would further elucidate the principle of molecular hydration and its regulation rule.

As an essential component of DNA molecules, the nucleobase adenine (A) and its dynamic hydration process have been well studied on Au(111), showing that adenine molecules interact with water molecules at the N7 site on the imidazole ring to form A–H₂O–A hydration structures (cf. Scheme 1).²¹ On this basis, a methyl group, an electron-donating group in general, is used to functionalize the adenine molecule, forming 9-methyladenine (shortened as 9mA; see Scheme 1, which is modified at the same derivatization site as that of the natural nucleoside). Accordingly, the 9mA molecule is selected as the candidate to investigate the interaction with water molecules on Au(111) and to further explore the influence of derivatization on hydration in comparison to the situation of the prototypical A molecule. From the interplay of high-resolution scanning tunneling microscopy (STM) imaging and density functional theory (DFT) calculations, we show the hydration of 9mA molecules on Au(111) in real space, forming 9mA–H₂O–9mA structures and, more impor-



SCHEME 1. The migration of the hydration sites from the imidazole ring (left side) to the pyrimidine ring (right one) on the adenine-based molecules after the methyl derivatization at the N9 site.

tantly, the hydration sites have been remotely regulated from the imidazole ring to the pyrimidine ring by the methyl derivatization. In addition, it is further determined that the hydration sites varied from the N7 site in the case of the A molecule to the N1 and N3 sites and the amino group in the 9mA molecule (cf. Scheme 1). Moreover, the electrostatic potential map and the Bader charge analysis reveal in detail the different charge distributions on the A and 9mA molecules, which theoretically elucidate the changes in the hydration sites due to the derivatization. These results provide sub-molecular understandings of the relationship between derivatization and hydration, which would shed light on the regulation of hydration processes in chemically and biologically related systems.

RESULTS AND DISCUSSION

After deposition of the 9mA molecules on Au(111) at room temperature (RT), well-ordered 9mA self-assembled structures are formed (Fig. 1).²² From the large-scale STM image [Fig. 1(a)], it can be recognized that the structure is constructed by parallel zigzag chains, as indicated by the dashed wavy lines. The close-up STM image [Fig. 1(b)] further provides the sub-molecularly resolved topography of each 9mA molecule involved, which is imaged as a triangle connected by a brighter dot. Based on the triangular topography of the A moiety as reported,^{21,23,24} the brighter dot is assigned to the tilted methyl group. Accordingly, DFT calculations are performed on the self-assembled structure, and the optimized structural models are superimposed on the STM image [Fig. 1(b)] with a good agreement. Each 9mA molecule binds to its neighbors via double $\text{NH}\cdots\text{N}$ hydrogen bonds (as depicted by the blue dashed lines), forming a zigzag chain, and the chains are further packed together, leading to the formation of the island structures.

To explore the influence of derivatization on hydration, water molecules are then introduced into the 9mA-precovered sample at a pressure of $\sim 1 \times 10^{-5}$ mbar for 10 min, following the conditions for the formation of A-H₂O structures.²¹ After exposure to water molecules at RT, interestingly, the well-ordered chain structures are disrupted and mixed with bright dots, as shown in Fig. 2(a). From the close-up STM image [Fig. 2(b)], several bowknot-like structures with the same morphology can be tentatively identified in the disordered phase, consisting of two elliptical molecular parts connected

by a bright round protrusion at the center, as depicted by the white contours. Based on the previous reports,^{8,14,21} the bright protrusions are attributed to the adsorbed water molecules interacting with organic molecules. Therefore, the involvement of water molecules in the mixture phase could be confirmed by the formation of possible 9mA-H₂O hydration structures on the surface.

Furthermore, annealing the 9mA-H₂O disordered phase at 320 K leads to the formation of a well-ordered network structure, as shown in Fig. 3(a), which is obviously distinct from the self-assembled 9mA chains [Fig. 1(a)]. A closer inspection [Fig. 3(b)] allows us to identify that the network is composed of bowknot-like structures as elementary units, represented by the same white contours as shown in Fig. 2(b). The high-resolution STM image [Fig. 3(c)] further reveals sub-molecular details of the 9mA hydration structure, where the water molecules (indicated by black circles) and the chirality of the 9mA molecules (represented by blue and green molecular contours and indicated by R and L notations, respectively) can be identified. Based on the typical STM topographies, it can be concluded that the 9mA hydration networks are constructed by the 9mA-H₂O-9mA structural units, similar to

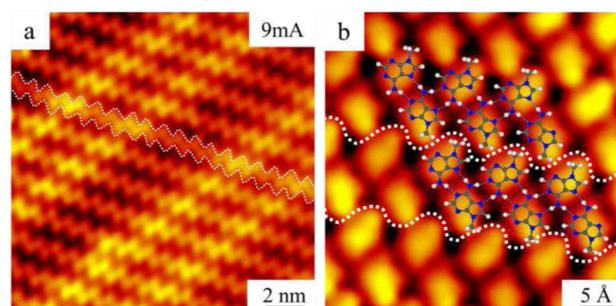


FIG. 1. STM images and DFT-optimized structural model showing the self-assembled structure of 9mA molecules on Au(111). (a) Large-scale STM image showing the zigzag chains within the self-assembled structure of 9mA molecules. (b) Close-up STM image superimposed with the DFT models optimized in gas phase showing more details of the molecular alignment in the zigzag chains, which are separated by the dashed wavy lines. Hydrogen bonds are depicted by the blue dashed lines. H: white; C: gray; N: blue.

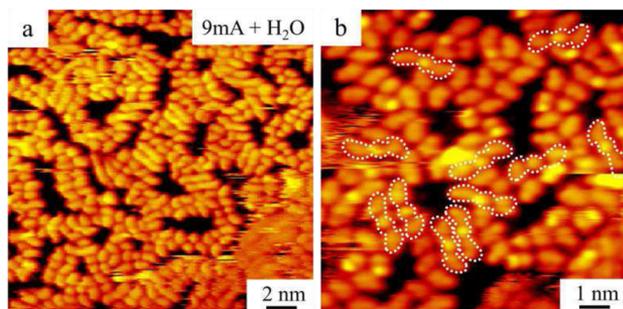


FIG. 2. STM images showing the appearance of bowknot-like structures (depicted by the white contours) after exposing the 9mA-precovered sample (held at RT) to the water environment at a pressure of $\sim 1 \times 10^{-5}$ mbar.

the A-H₂O-A motif in the hydration structures of prototypical A molecules.²¹ Thereafter, DFT calculations are performed to build up the atomic-scale models on the 9mA-H₂O-9mA hydration networks, and the DFT-optimized one is superimposed on the enlarged STM image [Fig. 3(d)], which accords well with the experimental one. In such a structure, water molecules interact with the neighboring 9mA molecules via the double OH \cdots N hydrogen

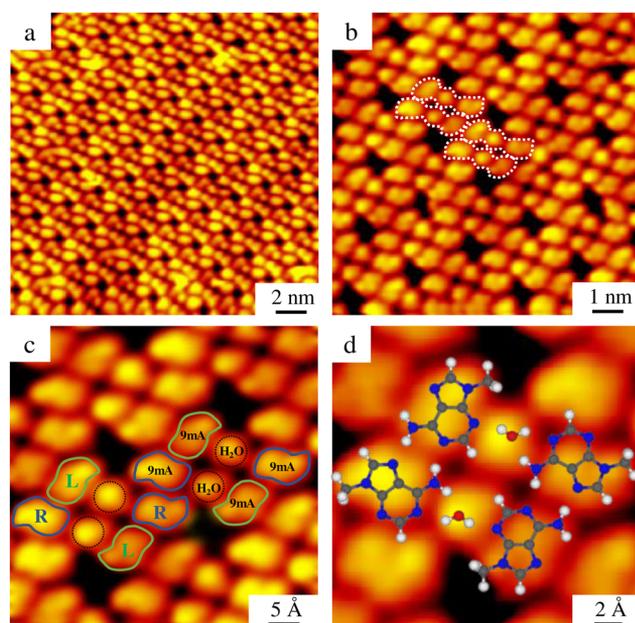


FIG. 3. Formation of well-ordered 9mA-H₂O-9mA hydration structures after annealing the mixture phase at 320 K on Au(111). (a) Large-scale STM image showing the formation of network hydration structure. (b) Close-up STM image clearly showing individual 9mA-H₂O-9mA bowknot-like structures (as depicted by the white contours) in the network. (c) High-resolution STM image allowing direct identification of the water molecules involved (depicted by black circles) and the chirality of 9mA molecules (as depicted by blue and green molecular contours and indicated by R and L notations, respectively). (d) Zoomed-in STM image of the 9mA-H₂O-9mA bowknot-like structures superimposed with the DFT models optimized in gas phase. H: white; C: gray; N: blue; O: red.

bonds (at N1 and N3 sites) and the NH \cdots O hydrogen bond (at the amino group), forming the 9mA-H₂O-9mA structural units. The 9mA-H₂O-9mA motif further connects to adjacent ones via the double NH \cdots N hydrogen bonds. More details of the whole network are shown in Fig. S1. Furthermore, annealing of the sample up to 340 and 380 K sequentially leads to the destruction and desorption of the hydration structure (Fig. S2).

To further explore the influence of derivatization on hydration, we perform a detailed comparison between the hydration structures of the prototypical A and derivative 9mA. Both of them possess similar A(9mA)-H₂O-A(9mA) motifs as the elementary unit, while the preferential hydration sites vary from the N7 site on the imidazole ring to the N1 and N3 sites and the amino group on the pyrimidine ring by the methyl derivatization. Interestingly, the N9 site is not the direct interaction site in the A-H₂O interaction,²¹ while it has been experimentally shown that the methyl derivatization at this site remotely regulates the hydration sites of the adenine moiety. Since water (H₂O) is a polar molecule, such a preferential binding between water and the different sites on molecules would be theoretically explained by the charge density analysis.¹⁶ The electrostatic potential and Bader charge analysis based on DFT calculations are performed, showing the different charge distributions on A and 9mA molecules (Fig. 4). As displayed in the top panel, the electrostatic potential maps qualitatively show the negatively charged nitrogen atoms and positively charged hydrogen atoms within the two molecules. In addition, the Bader charge analysis further quantifies the charges of each atom involved. Within the 9mA molecule, it can be seen that the pyrimidine ring is more negatively charged compared to the imidazole ring, indicating the preferential interaction between the water molecule and the pyrimidine ring (N1 and N3 sites) of 9mA molecules. In contrast, regarding the prototypical A molecule, the imidazole ring (N7 and N9 sites), rather than the pyrimidine ring (N1 and N3 sites), tends to preferentially bind with H₂O. It is noteworthy that the hydrogen bonding within the A dimer through the N3 and N9 sites is thermodynamically more favorable than that through the N7 sites, as extracted from A self-assembled structures (cf. Table S1).²³ Interestingly, the formation of the A-H₂O-A structure via the N7 sites is energetically more stable than that via the N3 sites, indicating the tendency of hydration with preferential perturbation of the N7 sites (detailed information on binding energy is listed in Table S1). This scenario is also in line with the experimental observations of the dynamic hydration process of A networks on Au(111).²¹ The comparison between A and 9mA shows that the N7 and N9 sites on the imidazole ring of the 9mA molecule are less negatively charged, while the pyrimidine ring (especially the N1 site and the amino group) becomes more electron-enriched within 9mA. This means intramolecular electrons are redistributed through the methyl derivatization at the N9 site, which transfers from the imidazole part to the pyrimidine one, resulting in the increased chemical activity of the pyrimidine ring. In this way, the priority of the hydration site to interact with the polar molecule H₂O is successfully regulated from the N7 site in the A molecule to the N1 and N3 sites and the amino group in the 9mA molecule. Therefore, based on the above-mentioned analysis, we can draw the conclusion that the derivatization with an electron-donating group changes the charge distribution on the whole adenine molecules, which regulates the specific hydration sites on the molecules remotely.

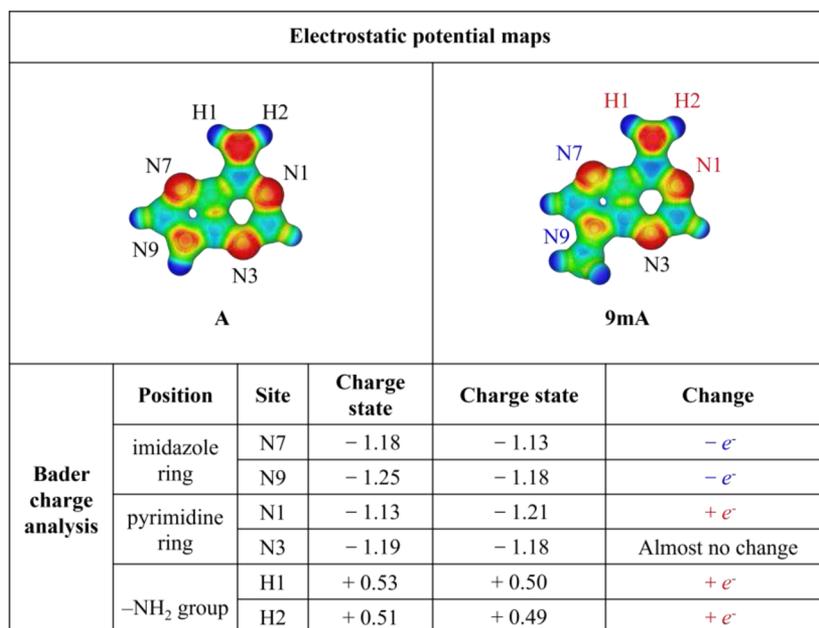


FIG. 4. Top panel: Electrostatic potential maps of A and 9mA molecules, where red and blue colors represent negative and positive potential regions, respectively. Bottom panel: Bader charge analysis for isolated molecules A and 9mA quantitatively showing the changes in the charged states of each atom before and after the methyl derivatization at the N9 site.

CONCLUSIONS

In conclusion, by the combination of STM imaging and DFT calculations, we report the hydration of the 9-methyl-functionalized adenine molecule on Au(111) and reveal the different hydration sites in direct comparison with those in the prototypical A-H₂O-A structure. The methyl derivatization is experimentally found to remotely regulate the hydration sites of the adenine molecules and is further theoretically revealed to allow intramolecular electron redistribution and thus steer the priority of the hydration sites. Our findings would shed light on the fundamental understandings of the interactions between water and organic molecules at the sub-molecular level. Moreover, explorations of molecular hydration should be further systematically extended to a series of derivatives, which may provide insights into hydration processes in chemical and biological fields.

SUPPLEMENTARY MATERIALS

The supplementary material associated with this article can be found in the online version.

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AUTHOR DECLARATIONS

Conflict of Interest

The authors have no conflicts to disclose.

Author Contributions

Yuanqi Ding: Data curation (equal); Formal analysis (equal); Funding acquisition (equal); Investigation (lead); Visualization (lead); Writing – original draft (lead); Writing – review & editing (equal). **Chi Zhang:** Funding acquisition (equal); Validation (equal); Writing – review & editing (lead). **Lei Xie:** Investigation (supporting). **Wei Xu:** Funding acquisition (equal); Methodology (equal); Resources (lead); Supervision (lead).

DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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