

Local Chiral Inversion of Thymine Dimers by Manipulating Single Water Molecules

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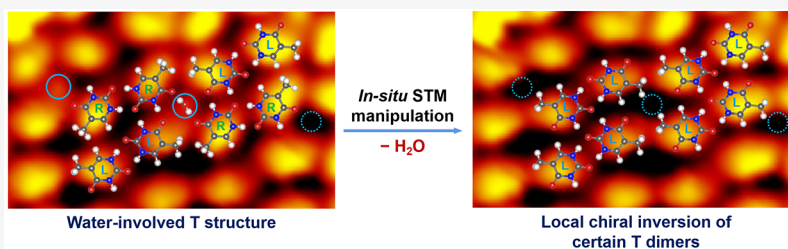
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ABSTRACT: Water, as one of the most important and indispensable small molecules *in vivo*, plays a crucial role in driving biological self-assembly processes. Real-space detection and identification of water-induced organic structures and further capture of dynamic dehydration processes are important yet challenging, which would help to reveal the cooperation and competition mechanisms among water-involved noncovalent interactions. Herein, introduction of water molecules onto the self-assembled thymine (T) structures under ultrahigh vacuum (UHV) conditions results in the hydration of hydrogen-bonded T dimers forming a well-ordered water-involved T structure. Reversibly, a local dehydration process is achieved by *in situ* scanning tunneling microscopy (STM) manipulation on single water molecules, where the adjacent T dimers connected with water molecules undergo a local chiral inversion process with the hydrogen-bonding configuration preserved. Such a strategy enables real-space identification and detection of the interactions between water and organic molecules, which may also shed light on the understanding of biologically relevant self-assembly processes driven by water.

INTRODUCTION

As the most abundant and indispensable compound *in vivo*, water plays a crucial role in driving biological self-assembly processes.^{1–3} Weak interactions extensively exist among biomolecules in an aqueous solvent, including hydrogen bonds and ionic, hydrophobic, and van der Waals interactions, which ensure both the structures and functions of biomolecules, such as proteins, nucleic acids, and membranes.^{4–7} Moreover, the properties of water^{8–17} and the interactions between water and organic molecules^{18–22} have also aroused great interest in the field of surface science. Water molecules were applied to identify specific functional groups and determine the molecular conformation^{18,19} and further influence the supramolecular network of azobenzene molecules.²⁰ Very recently, bulk water was introduced into UHV systems to explore the dynamic hydration of biologically relevant organic molecules on surfaces.^{23–26} Interestingly, these water molecules were demonstrated to be able to detect and identify various hydrogen-bonding configurations within a complicated cytosine (C) structure resulting in a distinct structural transformation²⁶ and in another case to transform disordered uracil (U) structures into an ordered one.²⁵ Owing to the relatively weak interactions between water and organic

molecules, the incorporated water molecules normally desorb from the hydrated structures by delicate annealing processes,^{23,25} which facilitates the exploration of dynamic hydration/dehydration processes in a global manner. However, no local information on the interactions between water and organic molecules could be obtained. Thus, it is generally intriguing to manipulate each single water molecule in a water-involved structure *in situ* to detect local intermolecular interactions.^{27–35}

In this study, we choose one of the DNA bases, thymine molecule, to study the hydration and dehydration processes. It was previously shown that upon deposition of T molecules onto a Au(111) surface under UHV conditions, T molecules self-assemble into molecular chains composed of hydrogen-bonded T dimers, and these chains are further linked laterally by van der Waals interactions forming islands on the surface

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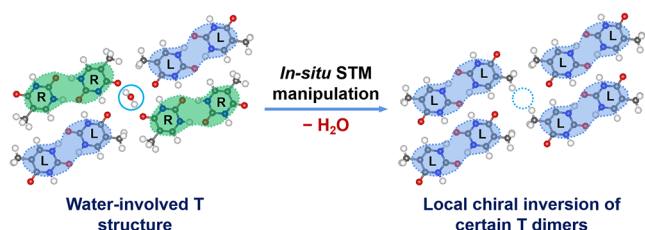
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(cf. Figure S1).³⁰ Herein, from the interplay of STM imaging/manipulation, bond-resolved non-contact atomic force microscopy (nc-AFM) imaging, and density functional theory (DFT) calculations, we demonstrate that the introduction of water molecules onto the self-assembled T structures leads to the hydration of T dimers forming a well-ordered water-involved T structure, and a local dehydration process is reversibly achieved by *in situ* STM manipulations on single water molecules. Upon water exposure onto the T islands and delicate thermal treatment, a water-involved T structure could be formed on the surface. As shown in Scheme 1, the structural motif is

Scheme 1. Schematic Illustration Showing the Local Chiral Inversion of Certain T Dimers from R to L as Depicted by Green and Blue Contours, Respectively, Which Is Induced by *In Situ* STM Manipulation on the Single Water Molecule^a



^aThe corresponding T dimers are defined as green and blue T dimers thereafter. H: white; C: gray; N: blue; and O: red.

composed of four most stable hydrogen-bonded T dimers and a water molecule, in which the two T dimers (depicted in green contours with R chirality) linked with a water molecule are in the opposite chirality with respect to the other two (depicted in blue contours with L chirality). Interestingly, the water molecule can be precisely removed by *in situ* STM manipulation, which surprisingly leads to a local structural transformation (chiral inversion in this case) of certain T dimers from R chirality (green) to the L one (blue) with the hydrogen-bonding configuration preserved (cf. Scheme 1). DFT calculations indicate that the local chiral inversion induced by *in situ* dehydration should be driven by the difference in thermodynamic stabilities of the corresponding structures. These findings reveal the influence of the dehydration process on the water-involved structures at the single-molecule level and thus provide the real-space evidence of interactions between water and organic molecules, which may also shed light on the understanding of biologically relevant self-assembly processes driven by water molecules *in vivo*.

RESULTS AND DISCUSSION

Deposition of T molecules onto Au(111) at room temperature (RT) under UHV conditions results in the formation of molecular chain structures composed of hydrogen-bonded T dimers, and the chains (separated by white dashed lines) further self-assemble laterally by van der Waals interactions forming T islands, as shown in Figure S1a,b.¹⁹ The corresponding nc-AFM image with tentative structural models overlaid is shown in Figure S1c. In the next step, we introduce water molecules at a pressure of $\sim 1 \times 10^{-5}$ mbar for 10 min to the T island structure at RT, and a disordered phase with randomly distributed T molecules and water molecules is observed (Figure S2). Surprisingly, further annealing the

sample at 330 K for 1 h leads to the formation of an ordered water-involved T structure, as shown in Figure 1a, where small

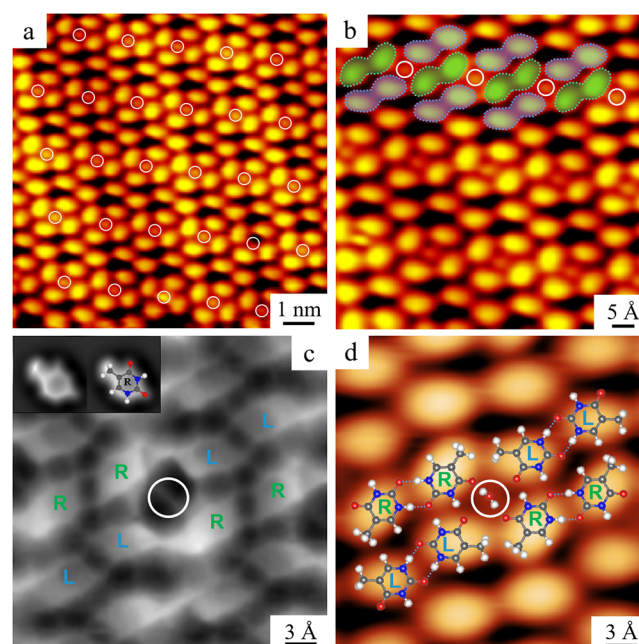


Figure 1. (a) STM image of the water-involved T structure where the incorporated water molecules are resolved as dot protrusions depicted by circles. (b) Close-up STM image of the water-involved T structure composed of both green and blue T dimers within the network. (c) Nc-AFM image of the water-involved T structure with molecular chiralities and intermolecular hydrogen bonds resolved. The chiralities of T molecules are denoted by R and L, respectively. Inset: Simulated nc-AFM image of the T molecule (left) and the assignment of R chirality (right) with a structural model overlaid. (d) Corresponding STM image of (c) superimposed with DFT-optimized structural model on the surface (the substrate is omitted for clarity) including two green and two blue T dimers together with a water molecule. Hydrogen bonds within dimers are depicted by dotted lines. Scanning parameters: (a,b) $I_t = 0.9$ nA, $V_t = -1.7$ V; (d) $I_t = 20$ pA, $V_t = -0.3$ V.

dots (highlighted by white circles) uniformly distributed within the structure are attributed to the absorbed water molecules. A closer inspection allows us to identify that each water molecule is always surrounded by two green and two blue T dimers, as depicted in Figure 1b. To further reveal the atomic-scale details of the structure, we obtain the nc-AFM image with bond resolution (Figure 1c), in which the molecular chiralities can be identified and labeled R and L based on the simulated nc-AFM image shown in the inset (also see Figure S3). Accordingly, the green and blue T dimers are attributed to R–R and L–L, respectively. It is interesting to note that the line feature^{36,37} indicated by the circle demonstrates the intermolecular interactions between water and the green T molecules. Based on the experimental observations, DFT calculations have been performed, and the optimized structural model including two green and two blue T dimers together with a water molecule is superimposed on the corresponding STM image (Figure 1d). The green and the blue T dimers shown in the model have the same hydrogen-bonding configuration, which is the most stable one among all possible T dimers. The water molecule forms two OH...O hydrogen bonds with the adjacent T molecules of green dimers, as the

distance between two R conformers around the water molecule is smaller than that between L ones. Moreover, the simulated STM and nc-AFM images are shown in Figure S4 with a good agreement with the experimental results.

Also note that such a water-involved T structure is different from other structures formed by DNA base molecules C^{26} or RNA base molecule U^{25} under a water atmosphere, where water molecules can desorb globally from the structures by annealing. Instead, the water-involved T structure can endure thermal treatment up to 350 K (followed by desorption) without breakage of water-involved hydrogen bonds, indicating relatively strong intermolecular interactions between water and T molecules. It thus may provide us a model system to manipulate single water molecules *in situ* to capture the influence of water molecules on the local intermolecular interactions in real space.

Subsequently, to explore the dehydration process, we perform a series of precise *in situ* STM manipulations on the water-involved T structure, as shown in Figure 2. The manipulations are typically performed by increasing the tunneling current to ~ 1.7 nA and meanwhile decreasing the bias voltage to ~ 10 mV. First, we remove one of the water molecules (indicated by the blue solid circle) from the structure leaving a vacancy (indicated by the blue dotted circle), and it is found that the two relevant green T dimers remain unchanged (Figure 2a,b). As a step further, once two water molecules on both sides of a green T dimer (indicated by a white arrow) are removed, surprisingly, this specific green dimer directly interacting with water molecules simultaneously undergoes a structural transformation, as shown in Figure 2c,d. According to the STM morphology, four possible circumstances of this dimer configuration transformation could be proposed, as shown in Figure S5. Based on the calculated stability of the corresponding dimer structure, we believe that a chiral inversion from the green dimer to the blue one is the most possible and reasonable one. Moreover, the identification on the green-to-blue dimer transformation is further confirmed by the following experimental evidence. A naturally existing circumstance with the same characteristics as that shown in (d) is found in the island (cf. Figure 2e), where no water molecules are bonded at either side of the dimer (indicated by the white arrow) and the vacancies are depicted by the white dotted circles. The corresponding nc-AFM image (Figure 2g) unambiguously verifies the attribution of the dimer (as indicated by the white arrow in Figure 2e,f) to a blue T dimer, which also implies the situation shown in Figure 2d.

To demonstrate the generality of such a chiral inversion process, we further perform STM manipulations in a more complicated case, in which the water molecules on both sides of three green T dimers are removed, and as expected, the three relevant green T dimers are all transformed to the blue ones, as shown in Figure 2h,i. The resulting homochiral patch of blue dimers resembles the original self-assembled T structure shown in Figure S6 and is confirmed by the corresponding nc-AFM image with the structural model overlaid. It thus further rationalizes the scenario that the green T dimers tend to transform to the blue ones once the water molecules are precisely removed.

Notably, manipulations with the same parameters directly applied on T molecules could not result in the chiral inversion of either green dimers (R–R) (i.e., interacting with water molecules) or blue dimers (L–L) (i.e., not interacting with

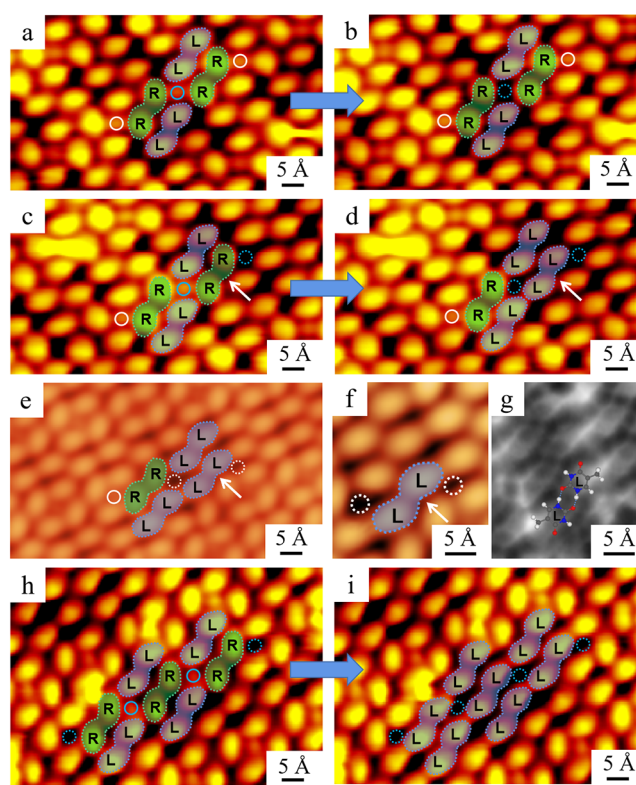


Figure 2. (a,b,c,d,h,i) Sequential STM images showing the precise removal of water molecules from water-involved T structures by STM manipulations, where the target water molecules and resulting vacancies are highlighted by blue solid and dotted circles, respectively, and the remaining water molecules are indicated by white solid circles. (a,b) One of the water molecules from one side of the green T dimer is removed, and the two green T dimers remain unchanged. (c,d) Two water molecules on both sides of the green T dimer are removed, and the green dimer simultaneously changes to the blue one. (e) STM image showing a naturally formed circumstance with the same characteristics as that shown in (d). The naturally existing water vacancies are depicted by the white dotted circles in (e,f). (f,g) Close-up STM image and the corresponding nc-AFM image (superimposed with the model) confirming that the dimer indicated by the white arrow in (e) is a blue T dimer. (h,i) Water molecules on both sides of three green T dimers are removed, and all of the three green T dimers change to the blue ones. Scanning parameters: (a,b,c,d,h,i) $I_t = 0.9$ nA, $V_t = -1.5$ V; (e, f) $I_t = 20$ pA, $V_t = -0.3$ V.

water molecules), indicating that the force exerted by the STM tip applied on T molecules cannot drive the flip of T dimers. Moreover, as shown in the case of Figure 2a,b, when only one water molecule is removed in such a structure, the green dimer is not observed to be converted to the blue one, indicating that the interaction between the T molecule and another water molecule on the other side is strong enough to hold the green dimer. Until two water molecules at both sides of the green dimer are precisely removed, simultaneously, only this specific green dimer is converted to the blue one, and the original blue dimers are unchanged. Therefore, the local chiral inversion of specific T dimers is facilitated by precisely removing the water molecules which form hydrogen bonds at both sides of these T dimers rather than the force exerted from the STM tip. In addition, we also track the further evolution of these converted blue dimers, and it turns out that they are stable during scanning and no reversed conversion is observed. Therefore, by *in situ* manipulation of single water molecules, we have

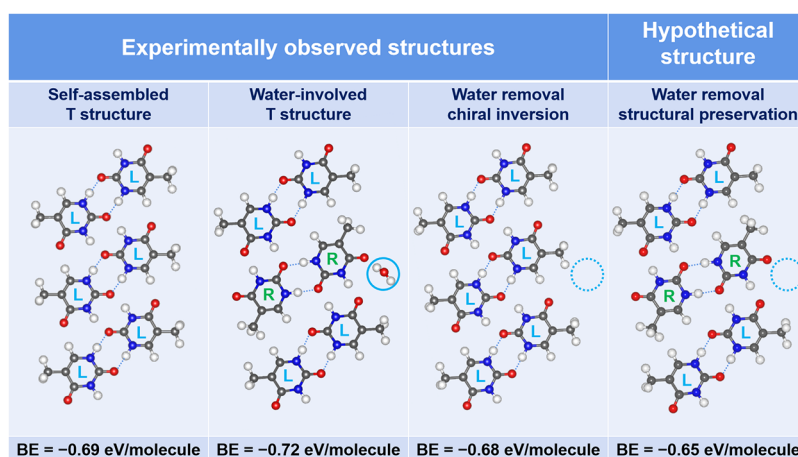


Figure 3. DFT-optimized structural models on Au(111) and the corresponding BE of different motifs (the substrate was omitted here for clarity). From left to right: the optimized self-assembled T structure, water-involved T structure, chiral inversion structure after water removal, and a hypothetical preserved structure after water removal. The corresponding BEs are shown below.

captured the influence of the local dehydration process on the intermolecular interactions, that is, chiral inversion of certain hydrogen-bonded T dimers in this case.

In order to understand the driving force of this local chiral inversion of T dimers after water removal, DFT calculations have been conducted involving the Au(111) substrate from energetics point of view.^{38,39} The left two panels of Figure 3 show the optimized models of experimentally observed typical self-assembled T structure and water-involved T structure with the binding energy (BE) of -0.69 and -0.72 eV/molecule, respectively. It indicates that the water-involved structure is energetically more stable than the self-assembled one, which rationalizes the structural transformation after dosing water molecules and thermal treatment. After the local removal of a single water molecule, we observe the chiral inversion of the adjacent hydrogen-bonded T dimer experimentally, and the calculated BE of the structure is reduced to -0.68 eV/molecule (the difference with respect to the self-assembled structure results from the different unit cells involved). In comparison with the chiral inversion structure, we also optimize a hypothetical structure with structural preservation after water removal, and such a structure has a BE of -0.65 eV/molecule. Thus, it is seen that water-involved T structure is calculated to be the most stable one, and the chiral inversion from the relevant green dimer (R chirality) to the blue one (L chirality) after water removal is also energetically more favorable compared to structural preservation.

CONCLUSIONS

In conclusion, by introducing water molecules onto self-assembled T structures under UHV conditions, we have successfully constructed a stable water-involved T structure with relatively strong intermolecular interactions between water and T molecules (i.e., hydration process). More interestingly, precise dehydration of single water molecules by *in situ* STM manipulation is also achieved resulting in the local chiral inversion of certain T dimers, and the hydrogen-bonding configuration of the dimers is preserved. The subtle manipulations provide an ideal workbench for direct detection of local noncovalent interactions between water molecules and biomolecules. Our findings reveal how a single water molecule influences the local structure of biomolecules, which is important for understanding the fundamental mechanisms in

biological self-assembly processes especially driven by water in vivo. As DNA is hydrated and surrounded by hydration shells, our precise determination of the local interactions between a single water molecule and bases is crucial to revealing hydration of bases at a single-molecule level. The strategy could also be extended to other self-assembled systems to detect and identify different types of noncovalent interactions, which will enrich the knowledge base of the cooperation, competition, and regulation mechanisms in molecular self-assembly processes.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/jacs.1c13344>.

Methods for STM/nc-AFM measurements and DFT calculations; STM and nc-AFM images (with tentative models) of the self-assembled T structure; water-involved disordered T structures; simulated nc-AFM images of T molecule with R and L chiralities; simulated STM and nc-AFM images of ordered water-involved T structure; four possible circumstances on the local transformation of green T dimer after water removal and the corresponding calculated BEs and original STM and nc-AFM images of Figures 1 and 2 without visual aids (PDF)

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Notes

The authors declare no competing financial interest.

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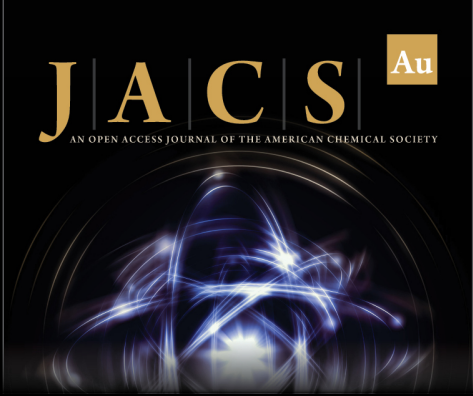
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