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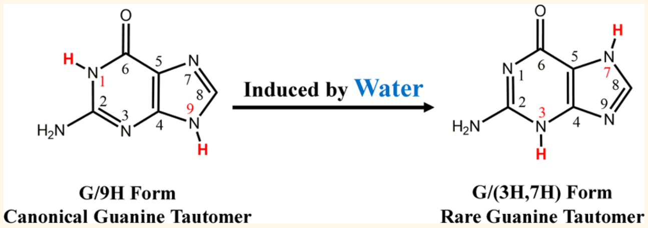
Real-Space Evidence of Rare Guanine Tautomer Induced by Water

Chi Zhang,[†] Lei Xie,[†] Yuanqi Ding, Qiang Sun, and Wei Xu*

Tongji-Aarhus Joint Research Center for Nanostructures and Functional Nanomaterials, College of Materials Science and Engineering, Tongji University, Caoan Road 4800, Shanghai 201804, People's Republic of China

Ⓢ *Supporting Information*



ABSTRACT: **Water is vital for life as a solvent. Specifically, it has been well established that DNA molecules are hydrated in vivo, and water has been found to be responsible for the presence of some noncanonical DNA base tautomers. Theoretical investigations have shown that the existence of water could significantly influence the relative stability of different DNA base tautomers, reduce the energy barrier of tautomeric conversions, and thus promote the formation of some rare base tautomers. In this work, we report the real-space experimental evidence of rare base tautomers. From the high-resolution scanning tunneling microscopy imaging, we surprisingly find the formation of the rare guanine tautomer, *i.e.*, G/(3H,7H) form, on the Au(111) surface by delicately introducing water into the system. The key to the formation of this rare tautomer is proposed to be the "water bridge" that largely reduces the energy barriers of intramolecular proton-transfer processes as revealed by extensive density functional theory calculations. The real-space experimental evidence and the proposed mechanism make a step forward toward the fundamental understanding of water-assisted base tautomerization processes.**

KEYWORDS: *scanning tunneling microscopy, density functional theory, tautomerization, guanine, surface chemistry*

Water is vital for life as a solvent and also an essential metabolic participant. It has been well established that DNA molecules are hydrated *in vivo* and derive their structures, functions, and activities from their interactions with water molecules.[1] Moreover, water has also been found to be an important factor that may be responsible for the presence of some noncanonical tautomeric forms of DNA bases.[2−4] Because of the significance of nucleobase tautomerization, many experimental and theoretical efforts have been devoted to investigating the possible tautomeric forms and their stabilities under various environments over several decades.[2−12] Theoretical studies have proposed model systems of DNA bases in the gas phase, microhydrated environment, and also aqueous solution,[2−4,9−12] respectively, and proved that water molecules (1) significantly influence the relative stability of different DNA base tautomers, (2) reduce the energy barriers of tautomeric conversions, and (3) thus affect the tautomeric equilibria and promote the formation of some rare base tautomers. Recently, on-surface tautomerization of guanine molecule from the canonical G/9H form to the noncanonical G/7H one has been experimentally achieved by thermal treatment,[13] and furthermore tautomeric recognition, separation, and interconversion of these two tautomers have also been achieved[14] by our group. However, to the best of our knowledge, real-space experimental evidence of the rare base tautomers has not been reported so far. It is therefore of utmost interest and also challenging to explore DNA base tautomerization processes under a well-controlled clean water atmosphere that may allow us to unravel the fundamental interactions between bases and water molecules and, more importantly, provide us the real-space atomic-scale evidence on the formation of possible rare base tautomers.

As is known,[8,13] the guanine (G) molecule has various tautomeric forms in different environments, and generally, the canonical G/9H form and the noncanonical G/7H form are the two most stable ones. Nevertheless, it is theoretically predicted that in the aqueous solution environment there are some rare G tautomers that are energetically more favorable; among others, the most stable one is the noncanonical G/(3H,7H) form[3] as shown in Scheme 1. It thus may provide us a model system to explore fundamental issues of water-induced tautomerization processes of G molecules under UHV conditions on the surface. Herein, from the interplay of high-resolution scanning tunneling microscopy (STM) imaging and density functional theory (DFT) calculations, we show that (1) deposition of G molecules in a delicately controlled water atmosphere could indeed result in the formation of the rare G tautomer, *i.e.*, the G/(3H,7H) form, on the Au(111) surface; (2) the key to the formation of this rare tautomer is proposed to be the "water bridge" that largely reduces the energy barriers of intra-

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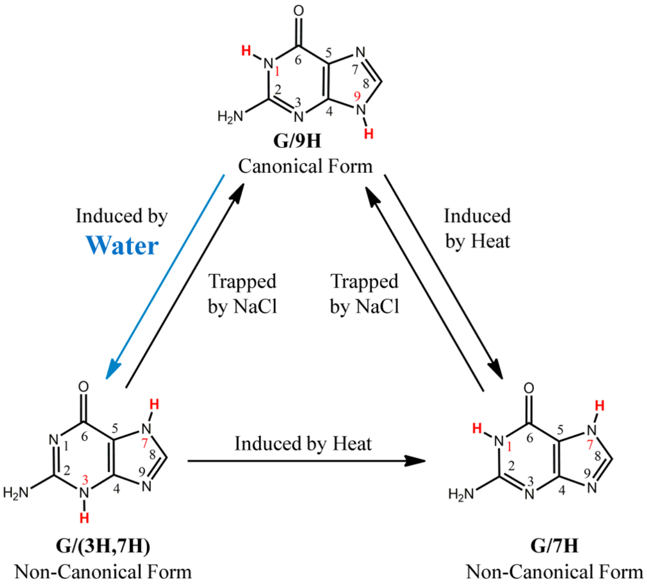
Scheme 1. Schematic Illustration of the Water-Assisted Formation of the Rare G Tautomer (*i.e.* G/(3H,7H) Form) from the Canonical G/9H Form and the Conversions among the G/(3H,7H), G/9H, and Another Noncanonical G/7H Forms, Respectively



molecular proton-transfer processes of G tautomers; and (3) furthermore, we also achieve the tautomeric conversions from the G/(3H,7H) form to the canonical G/9H form and another noncanonical G/7H form, respectively. These findings demonstrate the first real-space experimental evidence on the formation of the rare base tautomer, which makes a step forward toward the fundamental understanding of water-assisted base-tautomerization processes.

RESULTS AND DISCUSSION

After deposition of G molecules on Au(111) at rt, a disordered phase is formed which has been identified as the mixture of G/9H and G/7H forms as reported[14] previously and also shown in Figure 1a. Subsequent exposure of the G-precovered Au(111) surface (held at rt) to the water atmosphere at a pressure of ∼10^{-5} mbar, surprisingly, results in the conversion from the disordered phase to an unprecedented chain structure coexisting with some six-membered ring structures as shown in Figure 1b. The chains are discretely distributed on the surface and mainly connect with each other through six-membered rings. As this newly formed nanostructure has never been observed before in other conditions, we suppose that water molecules should play a certain role in such a process. Further control experiments are performed by direct deposition of G molecules (at different coverage) in the same water atmosphere as shown in Figure 1c,d. At very low G coverage (<0.1 monolayer), chain structures are predominantly found (Figure 1c), while at much higher G coverage (∼0.8 monolayer), some patches of six-membered ring structures coexisting with the chains are formed (Figure 1d). Note that at increased G coverage more six-membered ring structures tend to form. Furthermore, a series of other control experiments are performed at different water pressures (*i.e.*, 10^{-9}, 10^{-8}, 10^{-7}, and 10^{-6} mbar, respectively) to verify the role of water molecules, and only a relatively large number of water molecules (*i.e.*, 10^{-5} mbar in this case) could induce the formation of chains and six-membered ring structures. From the above findings, we conclude that the formation of chains and six-membered ring structures must result from the existence of bulk water molecules.

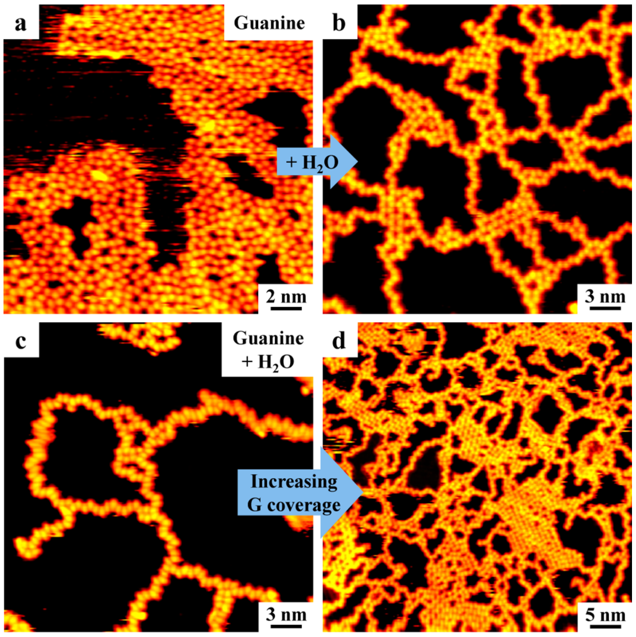


Figure 1. STM images showing the formation of chain structures coexisting with some patches of six-membered ring structures on Au(111) in the water atmosphere. (a) STM image showing the formation of disordered structures after deposition of G molecules on Au(111) at rt. (b) STM image showing the formation of chain structures coexisting with some six-membered ring structures after exposing the G-precovered surface (held at rt) to the water atmosphere at a pressure of ∼10^{-5} mbar. (c) STM image showing the formation of chain structures with similar characteristics to the one shown in (b) after direct deposition of G molecules in the same water atmosphere at rt. (d) STM image showing the coexistence of patches of six-membered ring structures and chains by increasing the coverage of G molecules in the same water atmosphere. Scanning conditions: I_t = 0.8 nA, V_t = 1.2 V.

Interestingly, gentle annealing of the surface to 310 K after deposition of G molecules in the above-mentioned water atmosphere results in the formation of large islands composed of six-membered ring network structures, and a typical one is shown in Figure 2a. From the submolecularly resolved STM image (Figure 2d), we can distinguish that the molecular ribbons (separated by the wavy lines) are made up of homochiral molecules and the whole network structure is enantiomerically pure, which is dramatically different from the racemic network structure of G/7H reported previously[13,14] (for clear comparison the G/7H network structure is shown in Figure 2e). Moreover, the network structure shown in Figure 2d is composed of parallel six-membered rings while the G/7H network is composed of orthogonal six-membered rings as highlighted by blue rounded rectangles in parts d and e, respectively, of Figure 2. On the basis of the above analysis and our previous findings,[13−15] neither G/9H nor G/7H form (the two most stable tautomeric forms of G molecule in the gas phase) can agree with this newly formed network structure with rational intermolecular hydrogen bonds.

Note that this parallel six-membered ring network is only obtained after exposure to the water atmosphere, and on the other hand, it is difficult for water molecules to adsorb on the

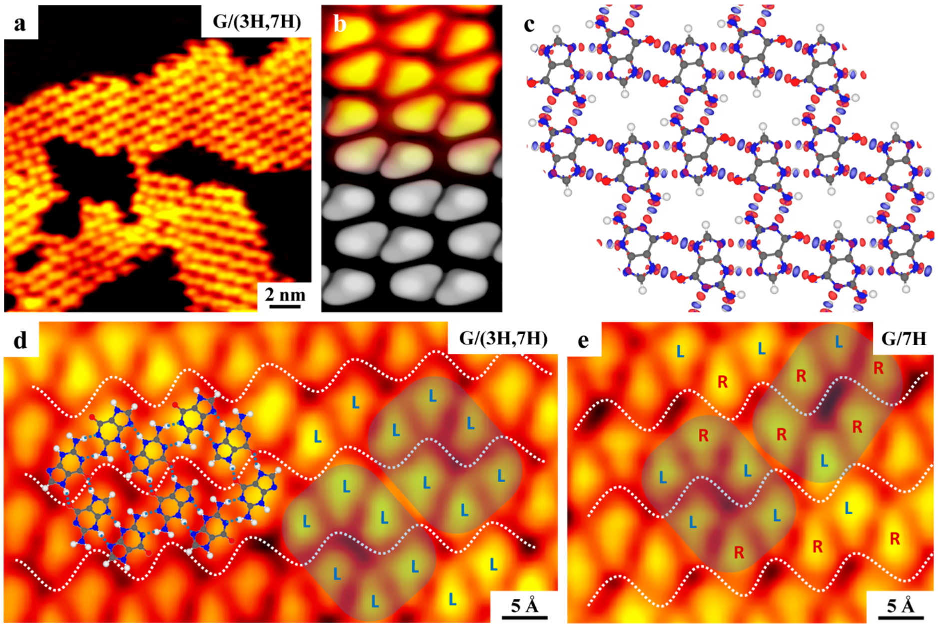


Figure 2. STM images and DFT-optimized structural models of the six-membered ring network structure. (a) Large-scale STM image showing the formation of islands of the six-membered ring network structure after gentle annealing the surface to 310 K for 10 min. (b) High-resolution close-up STM image of (a) partially superimposed with the STM simulation (the gray part) at a bias voltage of 1.4 V. (c) Charge-density-difference map of the network structure showing the intermolecular hydrogen bonds at the isosurface value of 0.005 e Å^{-3}. The red and blue isosurfaces indicate charge accumulation and depletion, respectively. (d) and (e) Submolecularly resolved STM images allowing us to identify the molecular chiralities (as indicated by L and R notation) within this newly formed network structure and the previously reported G/7H network structure, respectively. The wavy lines and the blue rounded rectangles are depicted for clear comparison between these two networks. The corresponding DFT-optimized structural model is superimposed on the STM image in (d), where the intermolecular hydrogen bonds are depicted by blue dashed lines. H: white; C: gray; N: blue; O: red. Scanning conditions: I_t = 0.6 nA, V_t = 1.4 V.

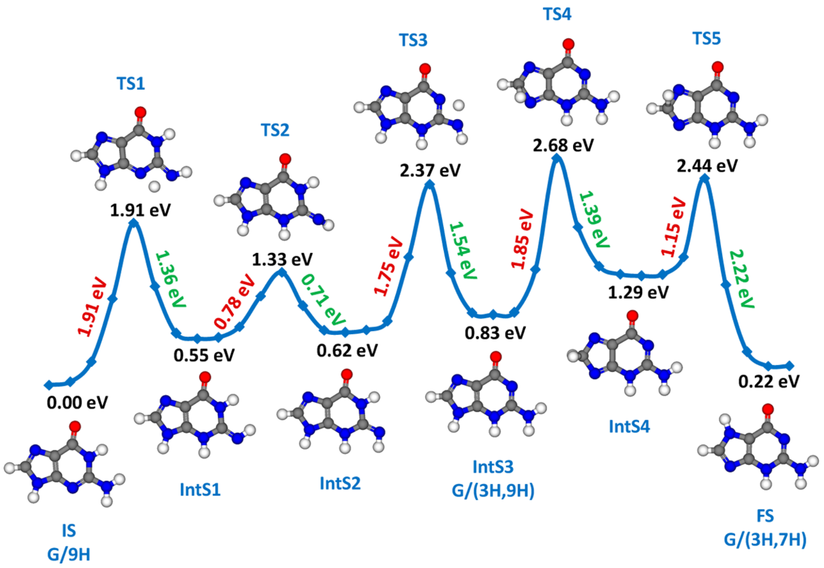


Figure 3. DFT-calculated reaction pathway for the tautomerization from G/9H to G/(3H,7H) in the gas phase. The pathway involves a proton-transfer process from N1 to N3 forming the G/(3H,9H) intermediate as the first step and a subsequent proton-transfer process from N9 to N7 forming the final state G/(3H,7H). Relative energies of the local minima (IS, IntS1, IntS2, IntS3, IntS4, and FS) and the transition states (TS1, TS2, TS3, TS4, and TS5) along the reaction path are given with respect to the initial state IS.

Au(111) surface at rt[16,17] and then be directly involved in the molecular network structure shown above. However, as revealed by the theoretical study,[3] bulk water strongly favors some rare G tautomers, and the most stable one (G/(3H,7H), as shown in Scheme 1) is even energetically more favorable than the canonical G/9H form in the water phase. Hence, we tentatively speculate that G molecules have undergone the conversion to its rare tautomeric G/(3H,7H) form under our experimental conditions. We then build up several models according to the STM morphology based on the G/(3H,7H) form and relax by DFT methods. The energetically most favorable one is superimposed on the STM image (Figure 2d) where a good agreement is achieved. The corresponding charge-density-difference map (Figure 2c) clearly displays the

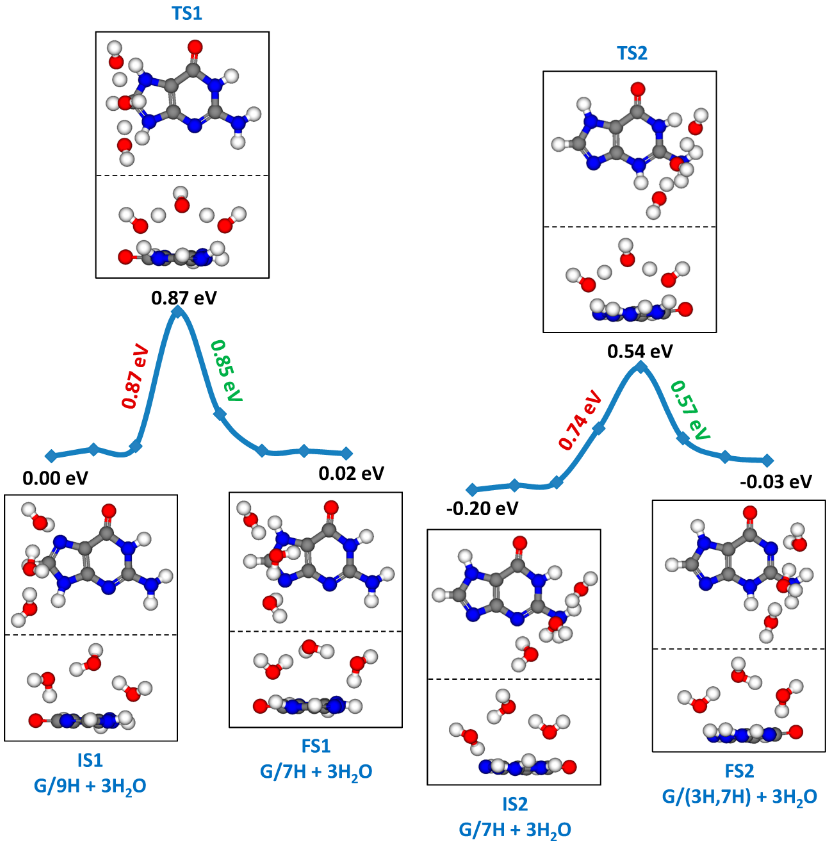


Figure 4. DFT-calculated reaction pathway for the tautomerization from G/9H to G/(3H,7H) with the assistance of water molecules in the gas phase. The pathway involves a proton-transfer process from N9 to N7 forming the G/7H intermediate with the assistance of three water molecules on the side of the imidazole ring as the first step and a subsequent proton-transfer process from N1 to N3 forming the final state G/(3H,7H) with three water molecules on the side of the pyrimidine ring. Relative energies of the local minima (IS1, FS1, IS2, and FS2) and the transition states (TS1 and TS2) along the reaction path are given with respect to the initial state IS1.

intermolecular NH···N and NH···O hydrogen bonds that stabilize the network structure. Furthermore, STM simulation (the gray part that is partially superimposed on the STM image) is performed at the same bias voltage as the experimental one as depicted in Figure 2b. Comparison of the experimental STM image with the simulated one demonstrates that both the structural motif and the single-molecule topography correspond quite well. Based on this structural model, we can also identify that in most cases the chain structures (Figure 1b−d) are the components of the G/(3H,7H) network structure as shown in Figure S1. In addition, we have also analyzed other tautomeric forms (Figure S2) as considered in the theoretical study.[3] Based on the STM images of the typical water-induced network structure (Figure S3) and some different nodes (Figure S4) coexisting with the parallel six-membered rings, these other tautomeric forms are ruled out as none of them can account for the observed structures with reasonable intermolecular hydrogen bonds. From the above analyses, we then draw the conclusion that both the chains and parallel six-membered ring networks are formed by the rare G/(3H,7H) form; that is, water-induced tautomerization from G/9H to G/(3H,7H) is experimentally evidenced.

To further verify this unprecedented water-induced tautomerization process and unravel the underlying mechanism, extensive state-of-the-art DFT calculations are performed where a systematic DFT-based transition-state search is carried out to discover the possible reaction pathways. As is known,[14] the initial G disordered phase is composed of predominant G/9H tautomers and very minor G/7H ones. We then take the G/9H form as the initial state (IS) for the following calculations. First, we calculate the possible reaction pathways of tautomerization from G/9H to G/(3H,7H) in the gas phase without water where a double-proton-transfer process from N9 to N7 and from N1 to N3 is involved. Taking all the possible pathways into account (as detailed in Figures S5−S8), we find that the most favorable one in this scenario involves the steps from G/9H through G/(3H,9H) to G/(3H,7H) as illustrated in Figure 3. Accordingly, the reaction energy barrier for the whole pathway is determined to be 1.91 eV (more detailed information is provided in the Supporting Information), which is obviously too high for this double-proton-transfer process to occur in the gas phase without external stimuli. In addition, the final product G/(3H,7H) form is less stable than the initial G/9H form by 0.22 eV for the individual molecule, and thus, such a tautomeric process is thermodynamically unfavorable. Therefore, it is arduous to generate and "see" this rare G/(3H,7H) tautomer under normal experimental conditions.[13,14,18,19]

As predicted by theoretical studies,[2−4,10−12,20,21] the tautomeric situation is different with the participation of water as water molecules can influence the relative stabilities of tautomers and thus affect the tautomeric equilibria. Taking it a step further, we calculate the possible reaction pathways of tautomerization from G/9H to G/(3H,7H) in the gas phase with the assistance of water. As pointed out in the theoretical study,[3] a bulk water phase rather than a microhydrated environment (one and two water molecules) would strongly

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favor some rare G tautomers. As also shown in another theoretical work,[21] a single-proton transfer across an imidazole ring is energetically favorable by the assistance of three water molecules. We thus considered involving three water molecules in our calculations for each proton-transfer process on both the imidazole ring and pyrimidine ring sides. However, simultaneous involvement of six water molecules in the system results in rather time-consuming and expensive calculations, and then we simplified the system by only involving three water molecules in one proton-transfer round.

Two pathways involving tautomerization processes from G/9H through G/(3H,9H) to G/(3H,7H) and from G/9H through G/7H to G/(3H,7H) with the assistance of water molecules are calculated, respectively. We find the latter one is energetically more favorable as shown in Figure 4, and another pathway is displayed in Figure S9. It is noteworthy that in these proposed proton-transfer processes three water molecules are located on the top of G molecular plane forming a suspended "water bridge" (see side views of the corresponding configurations in Figure 4 and also Figure S9). In such configurations, three water molecules form OH···O hydrogen bonds with each other and also NH···O and OH···N hydrogen bonds with either imidazole or pyrimidine moiety of the G molecules as the first step, and then one water molecule grabs a H atom from one side of the G molecule and transfers the additional H atom one-by-one (just like the domino effect) through the "water bridge" to the other side of the G molecule to finish this loop. Consequently, the reaction energy barriers for such water-induced tautomerization processes from G/9H through G/7H to G/(3H,7H) are calculated to be 0.87 and 0.74 eV, respectively, as illustrated in Figure 4. Surprisingly, the reaction energy barrier for the whole pathway (0.87 eV) is largely reduced in this scenario in comparison with that of the direct tautomerization process (1.91 eV), which may also account for the experimental findings that such a rare tautomerization process can take place at rt.

Note that, experimentally, water molecules are found to be able to induce this rare tautomerization process not only by deposition of G molecules in the water atmosphere but also by exposure of the G-precovered surface to the water atmosphere. It is known that water molecules can hardly adsorb on the Au(111) surface at rt,[16,17] meaning the water-induced proton-transfer process is not confined in the molecular plane of G, which also nicely agrees with the proposed "water bridge" model. It should also be noted that the proposed model system could well account for the water-assisted double-proton-transfer processes by unraveling the significant role of water molecules in largely reducing the energy barriers, while it may not present an actual scenario to quantify the absolute stabilities of different tautomeric forms as the exact number of water molecules involved in such a process is hardly determined. From the reaction pathway (Figure 4), we would also see that in such a three-water model system G/(3H,7H) has the possibility to convert back to G/7H and even G/9H. Only on the basis of the relative energies of one G molecule with three water molecules does the G/(3H,7H) form seem energetically unfavorable, which actually agrees with the theoretical findings in the situation of microhydrated environment.[3] However, it is proposed that in the bulk water atmosphere these G tautomers inevitably interact with more water molecules simultaneously (where the situation might be much more complicated than the proposed model system here), resulting in the reversed stability of the G/(3H,7H) form as predicted in the theoretical study.[3]

Since it is known that G/9H and G/7H can be interconverted,[13,14] as a step further, it is of utmost interest to explore the feasibility of tautomeric interconversions among G/9H, G/7H, and G/(3H,7H) to obtain an overview of these three tautomers. As demonstrated in our previous work,[14] conversion from G/7H to G/9H is feasible with the assistance of NaCl. Inspired from that, we employ the same trick by deposition of NaCl on the G/(3H,7H)-precovered surface as shown in Figure 5a. After further annealing the sample to ~330 K, interestingly enough, we find the formation of a G-quartet-Na network structure on the surface as shown in Figure 5b, which indicates G/(3H,7H) tautomers are converted back to G/9H ones. Hence, the conversion between G/9H and G/(3H,7H) forms is reversible. Moreover, direct annealing of the G/(3H,7H) structures to ~420 K results in the formation of a thermodynamically more stable G/7H network structure composed of orthogonal six-membered rings (*cf.* Figure 2e for details) as shown in Figure 5c,d, indicating conversion from G/(3H,7H) to G/7H is also feasible.

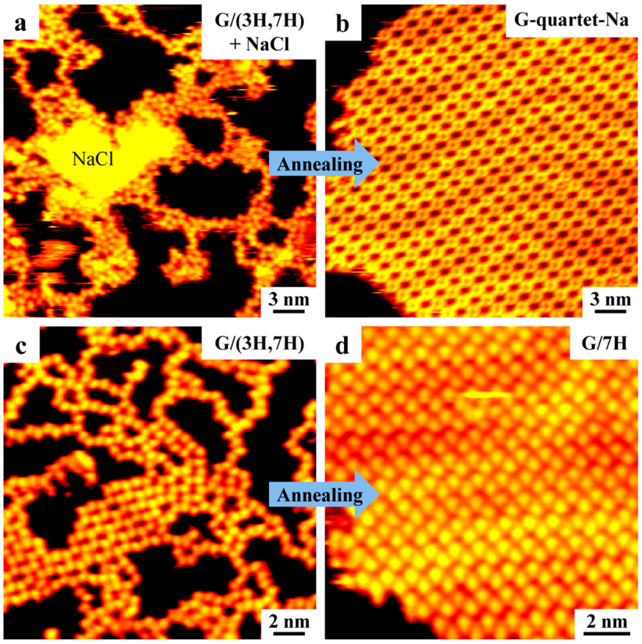

Figure 5. STM images showing the tautomeric conversions from G/(3H,7H) to G/9H and G/7H, respectively. (a) STM image showing coexistence of the G/(3H,7H) structures and the NaCl islands at rt. (b) STM image showing the formation of G-quartet-Na network structure after annealing the sample to ~330 K. (c) STM image showing the G/(3H,7H) structures at rt. (d) STM image showing the formation of G/7H network structure after annealing the sample to ~420 K. Scanning conditions: I_t = 1.0 nA, V_t = −1.2 V.

CONCLUSIONS

In conclusion, from the interplay of high-resolution STM imaging and detailed DFT calculations, we have provided first real-space experimental evidence on the rare guanine tautomer (*i.e.*, G/(3H,7H) one) where water molecules are revealed to be able to largely reduce the tautomeric reaction energy barrier and thus facilitate the formation of this rare tautomer. Moreover, interconversions among G/9H, G/7H, and G/(3H,7H) have been achieved. These findings provide important insight into the role of water in the DNA base tautomerization process, and the experimental strategy may be extended to other more general cases for gaining atomic-scale real-space fundamental understandings of water-induced physicochemical phenomena.

METHODS

All STM experiments were performed in a UHV chamber (base pressure 1 × 10^{-10} mbar) equipped with a variable-temperature, fast-scanning "Aarhus-type" STM using electrochemically etched W tips purchased from SPECS,[22,23] a molecular evaporator and an e-beam evaporator, and other standard instrumentation for sample preparation. The Au(111) substrate was prepared by several cycles of 1.5 keV Ar^+ sputtering followed by annealing to 800 K for 15 min, resulting in clean and flat terraces separated by monatomic steps. The guanine molecule was purchased from Alfa-Aesar (purity >98%). The pure distilled water was loaded in a dosing tube positioned in the preparation chamber and further purified under vacuum by several freeze−thaw cycles to remove remaining impurities.[24] Water molecules were then continuously dosed *in situ* onto the Au(111) surface through a leak valve at a pressure of $\sim 10^{-5}$ mbar. After a thorough degassing, the G molecules were deposited onto the Au(111) surface by thermal sublimation at 390 K. The sample was thereafter transferred within the UHV chamber to the STM, where measurements were carried out at ∼150 K. All of the STM images were further smoothed to eliminate noises.

The calculations were performed in the framework of DFT by using the Vienna *ab initio* simulation package (VASP).[25,26] The projector-augmented wave method was used to describe the interaction between ions and electrons;[27,28] the Perdew−Burke−Ernzerhof GGA exchange-correlation functional was employed;[29] and van der Waals interactions were included using the dispersion-corrected DFT-D2 method of Grimme.[30] The atomic structures were relaxed using the conjugate gradient algorithm scheme as implemented in the VASP code until the forces on all unconstrained atoms were ≤0.03 eV/Å. The simulated STM images were obtained by the Hive program based on the Tersoff−Hamann method.[31,32] The climbing-image nudged elastic band was applied to locate the transition state,[33] and the transition path was optimized until the forces acting to the path were typically ≤0.03 eV/Å.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsnano.6b00393.

> STM images, the eight stable G tautomers considered in the theoretical study, and DFT-calculated pathways (PDF)

AUTHOR INFORMATION

Corresponding Author

* xuwei@tongji.edu.cn.

Author Contributions

† C.Z. and L.X. contributed equally to this work.

Notes

The authors declare no competing financial interests.

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