

On-Surface Azide–Alkyne Cycloaddition on Cu(111): Does It “Click” in Ultrahigh Vacuum?

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S Supporting Information

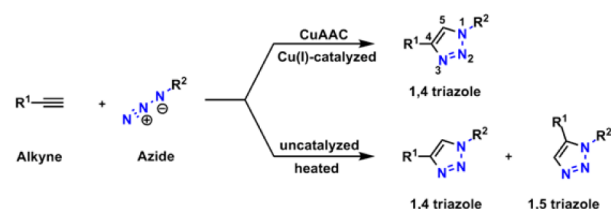
ABSTRACT: Using scanning tunneling microscopy, we demonstrate that the 1,3-dipolar cycloaddition between a terminal alkyne and an azide can be performed under solvent-free ultrahigh vacuum conditions with reactants adsorbed on a Cu(111) surface. XPS shows significant degradation of the azide upon adsorption, which is found to be the limiting factor for the reaction.

The field of on-surface synthesis aims at forming covalently interlinked molecular nanostructures adsorbed on solid surfaces^{1–3} to complement less robust counterparts formed by supramolecular (noncovalent) surface chemistry.^{4,5} This target has spurred much activity investigating to what extent a range of organic reactions can be performed under ultrahigh vacuum (UHV) conditions with reactants adsorbed on surfaces of metal single-crystals, e.g., imine condensation reactions,^{6,7} Ullmann coupling type reactions,^{8–10} boronic acid based chemistry,^{9,11} cyclodehydrogenation,¹² and formal cycloaddition reactions.¹³

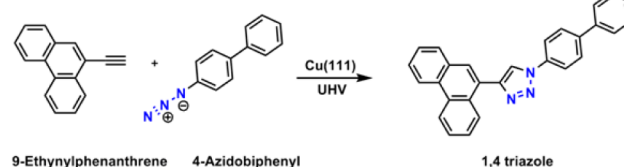
A highly interesting class of reactions with potential for surface chemistry are “click” reactions.¹⁴ Click transformations are general, give rise to their expected products in high yields, and have been used in numerous applications including bioconjugation,^{15,16} materials science,¹⁷ and drug discovery.¹⁸ The prototypical click reaction is the copper-catalyzed Huisgen 1,3-dipolar cycloaddition^{19,20} between a terminal alkyne and an azide to produce a 1,4-disubstituted 1,2,3-triazole (CuAAC reaction, Scheme 1). In contrast to the uncatalyzed Huisgen cycloaddition reaction, which often produces a mixture of 1,5- and 1,4-triazole regioisomers, the CuAAC reaction selectively produces the 1,4-triazole. The CuAAC reaction is especially interesting for on-surface synthesis, since it is byproduct free and proceeds with little thermal activation owing to the “spring-loaded” nature of the azide reactant. In particular, the calculated (gas-phase) activation energy barrier for the CuAAC reaction of ~0.65 eV²¹ is comparable to the binding energy in supramolecular surface assemblies stabilized by multiple hydrogen bonds,⁵ rendering the CuAAC reaction interesting for post self-assembly covalent capture.²² The CuAAC reaction has been used in solution for grafting/functionalizing self-assembled monolayers (SAMs) onto surfaces.^{23–25} However, it remains to be shown if the CuAAC reaction can be performed in an on-surface synthesis

Scheme 1. General Huisgen 1,3-Dipolar Cycloaddition of Azides and Alkynes^a

A. 1,3-dipolar cycloaddition of azides and alkynes



B. On-surface azide-alkyne cycloaddition



^a(A) The Cu catalyzed CuAAC reaction regioselectively produces the 1,4-triazole, while the uncatalyzed reaction often produces a mixture of 1,4- and 1,5-triazole regioisomers. (B) The on-surface reaction investigated here between 9-ethynylphenanthrene (alkyne) and 4-azidobiphenyl (azide) produces a 1,4-triazole.

scheme with the reacting groups adsorbed directly on a surface and in the absence of a solvent and the solvated Cu(I) ions normally catalyzing the reaction.

Here, we use a combination of STM and XPS to explore the feasibility of the CuAAC reaction under UHV conditions. We have designed the reactants 9-ethynylphenanthrene (alkyne) and 4-azidobiphenyl (azide) shown in Scheme 1. The aromatic residues on these reactant molecules have sizes that allow for thermal sublimation onto the surface and are sufficiently different to make them distinguishable by UHV-STM. Inspired by the use of Cu as catalyst for the solution-phase reaction, the experiments were performed on a Cu(111) surface. Our study demonstrates that it is indeed possible to react these two species on the Cu(111) surface to form the 1,4-triazole product. Implications of this finding regarding a catalyzed/uncatalyzed on-surface reaction path are discussed. Importantly, we furthermore find

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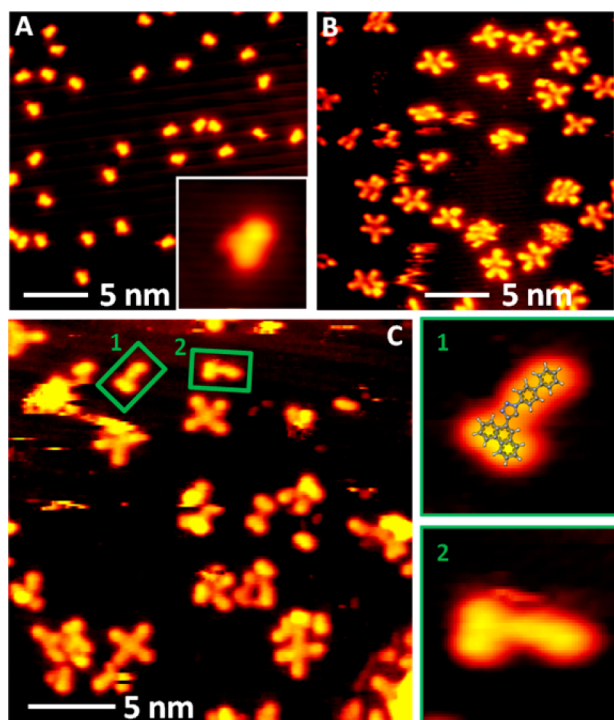


Figure 1. STM images showing reactants and products of the in situ Huisgen azide-alkyne cycloaddition on Cu(111). (A) 9-Ethynylphenanthrene (alkyne) adsorbed individually. (B) Clusters formed after deposition of 4-azidobiphenyl (azide). (C) Surface after codeposition of alkyne and azide. Two triazole reaction products are marked in green and shown to the right at high magnification and with a superimposed molecular model. All images acquired at 100–125 K with $I_t \approx 300$ pA, $V_t = -1.4$ V. Full color range (black to yellow) corresponds to ~ 1.5 Å.

that interaction with the surface causes the azide group to decompose in the majority of deposited azide reactants. This decomposition constitutes the limiting factor for the on-surface azide-alkyne cycloaddition reaction.

Figure 1A shows an STM image acquired at ~ 120 K after depositing the alkyne alone on a Cu(111) surface held at room temperature (rt, 300 K). The molecules adsorb as isolated entities, and the characteristic bent shape of the phenanthrenyl group is clearly resolved. The two outermost lobes of the phenanthrenyl group are imaged with different STM contrast, suggesting they have different interaction to the substrate. This asymmetry allows one to distinguish the two anticipated surface enantiomers for the prochiral alkyne molecule.²⁶ Statistical analysis of the rotation angles for the phenanthrenyl units in combination with overlay of molecular models (see Figure S1) shows a preferential alignment of the ethynyl group along the close-packed [1–10] directions. Such an alignment is consistent with di- σ bonding of the ethynyl group to the Cu(111) substrate, as proposed for phenyl-acetylene.^{27,28} At higher coverage, some dimers of the alkynes are observed, but condensed islands do not form. Deposition of the azide molecules alone results in a range of small clusters (Figure 1B). The clusters comprise two to five identical elongated entities, attributed to the biphenyl units, and exhibit a number of characteristic motifs in which the biphenyl units all point toward a central interaction node. The larger clusters comprising four or five biphenyl units are most common, especially at higher coverage. To explore the possibility of an on-surface CuAAC click reaction, the alkynes and azides were codeposited from separate crucibles onto the Cu(111) surface

held at rt. This procedure resulted in a surface covered by a large variety of different structures which were carefully surveyed by STM (e.g., Figure 1C). By comparing these images to the data set obtained for the individual molecules, we can assign a large portion of the observed features to either the clusters formed after deposition of pure azides (e.g., the cross like structures), the alkyne molecules (individual or dimers), or a combination of azide clusters/alkynes in close proximity on the surface. Interestingly, however, the survey also revealed a distinct and new structure (marked in green in Figure 1C). This new structure is considerably larger than any one of the reactant molecules alone, yet it behaves as one entity, e.g., it is observed to rotate as a whole. Overlaying this STM feature with a scaled molecular structure of the expected 1,4-triazole reaction product shows an excellent structural correspondence regarding the bent molecular shape and the positions/appearance of the assumed diphenyl and phenanthrenyl groups. In total, 35 observations of this new feature were made in 8 independent experiments (sampling ~ 3200 deposited molecules), and both anticipated surface enantiomers of the triazole product were observed.

To substantiate that this new species is the expected reaction product, we prepared the 1,4-triazole by conventional ex situ synthesis and deposited it on the Cu(111) surface. Figure 2 shows a side-by-side comparison of the STM signature of individually adsorbed, ex situ prepared 1,4-triazole molecules and the in situ product (cf. Figure S2 for more ex situ product STM images). The general appearance of the two species matches very well. The length (long molecular axis) and apparent height of the ex situ (in situ) synthesized 1,4-triazole are 23.8 ± 1.6 (22.2 ± 1.8) and 1.6 ± 0.1 (1.4 ± 0.4) Å, respectively, in good quantitative agreement. The ex situ product shows a strong tendency toward dimerization (cf. Figure S2). Dimerization is less likely to occur for the in situ product due to the low coverage, but a few instances of dimers from triazoles formed in situ were observed, further corroborating that it is indeed the same species.

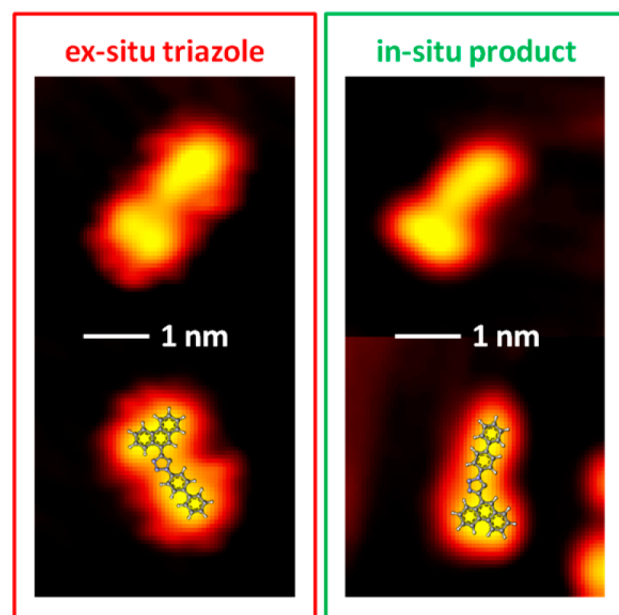


Figure 2. Side by side comparison of STM images of the ex situ prepared 1,4-triazole (left) and the in situ reaction product (right). Note that due to the pro-chirality of the alkyne, two different surface enantiomers are expected and observed for the triazole. Full color range corresponds to 1.6 Å.

We therefore conclude that the click reaction proceeds in the solvent-free UHV environment with reactants adsorbed on the Cu(111) surface at rt.

The observation of quite a number of unreacted molecules on the surface after codeposition indicates an incomplete reaction, which is somewhat surprising given the normally high yield of click reactions. Attempts to increase the number of successfully coupled molecules by varying the deposition order of the reactants, raising the substrate temperature during deposition to ~400 K, or post annealing at 400 K were not successful requiring us to investigate possible explanations.

One requirement for an on-surface reaction to occur is that the reactants can meet by surface diffusion. The observation of clusters formed from the azide (Figure 1B) and step edge decoration with alkynes after deposition at rt (cf. Figure S3) as well as occasional STM observations of lateral displacements of individual alkynes at 100–120 K, allows us to rule out kinetic limitations in mass transport as a limiting factor.

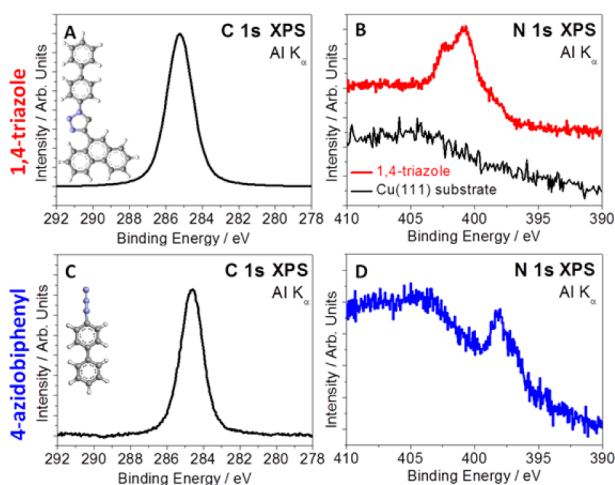


Figure 3. XPS of the C 1s and N 1s regions of ex situ prepared 1,4-triazole and 4-azidobiphenyl (azide) on Cu(111). To have appreciable intensity in the N 1s region, the spectra were acquired at higher coverage than shown in the STM images but still in the monolayer coverage regime.

To obtain further chemical information, we performed XPS measurements. Figure 3 shows XPS of the C 1s (left) and the N 1s regions (right) for the ex situ prepared 1,4-triazole (top) and the azide compound (bottom). For both species, the C 1s spectrum shows a single peak at a binding energy of 285.2 (triazole) and 284.6 eV (azide). A slight asymmetry resulting from the small proportion of carbon atoms in direct contact with nitrogen atoms is marginally visible. In the triazole N 1s spectrum, there are two main peaks at binding energies of 400.2 and 402.4 eV with an ~2:1 intensity ratio. These peaks correspond to N atoms at 1/3 and 2 positions of the triazole ring, respectively, and are in agreement with published spectra for the triazole moieties in alkane-thiol and Si–C grafted SAMs.^{29–31} (Further analysis of the spectrum is hampered by a highly nonlinear background from the clean Cu substrate, see Figure 3B). The azide group is expected to give rise to two N 1s XPS peaks, and XPS for azide moieties in SAMs has shown³⁰ these peaks to be separated by ~5 eV. The present N 1s spectrum for the azide on Cu(111), in contrast, shows only a single peak at 398.2 eV with a shoulder at the low-binding energy side (~396.7 eV). This XPS signature suggests that the azide group is not

intact on the surface. (Direct comparison of the binding energies on the surface and in the SAM is not possible due to the different bonding environments.) To further test for degradation of the azide group, we evaluated C/N ratios as shown in Table 1. The

Table 1. Quantitative Analysis of XPS in Figure 3

compound	C/N ratio ^a	integral area ^b	C/N by area ^c	expt C/N ^d
1,4-triazole	9.33	C 1s: 3.2 N 1s: 0.52	6.2	–
azide	4	C 1s: 1.3 N 1s: 0.07	18.6	28

^aFrom stoichiometry of intact molecules. ^bIn arbitrary units from the integrated areas under the curves after background subtraction. ^cCalculated from int. areas stated; note that this ratio may deviate from the stoichiometry due to different sensitivities for the two different elements under the given experimental conditions. ^dCalculated stoichiometry with the 1,4-triazole taken as the reference. The scaling factor translating the measured C/N peak area ratio for the triazole to the stoichiometric ratio was applied to obtain the experimental C/N ratio for the azide.

triazole was taken as reference compound since its XPS had the anticipated spectral features and the STM signature clearly corresponds to molecules adsorbed without decomposition. The analysis presented in Table 1 reveals an experimentally determined atomic C/N ratio of 28 for the deposited azides, much higher than the stoichiometric C/N ratio of 4 for the intact azide molecule. We therefore conclude from the XPS experiments that the predominant portion of the azides are not adsorbed intact on the surface but decompose and lose nitrogen (the upper limit for intact azides from the XPS data is 14% assuming the unrealistic scenario that all N atoms are in intact azides). A nitrene species formed via abstraction of dinitrogen from the azide group poses a potential intermediate degradation product on the Cu surface. The C/N ratio for biphenylnitrene is 12, so the experimental C/N ratio of 28 (cf. Table 1) strongly suggests degradation beyond this stage for some azides. The clusters in Figure 1B are thus ascribed to fragmented azides.

A number of possible causes for the azide degradation were tested. Storage prior to the experiments and heating under ambient conditions to 383 K (well above the UHV sublimation temperature) did not lead to degradation. In a control experiment, the azide was deposited onto a glass plate using our standard experimental parameters but for a prolonged dosing time (days). Subsequent analysis of the sublimate by FTIR and TLC both showed intact azides, demonstrating that the sublimation process is not the cause of degradation either. The degradation must therefore occur after adsorption on the Cu(111) surface. To test if the degradation is particular to interaction with Cu, we dosed the azide onto an inert Au(111) surface. Also here, XPS showed severe degradation, interestingly suggesting that the degradation is caused by adsorption on metal surfaces in general and not Cu(111) in particular. Possibly, charge transfer from the metal into the aromatic system of the adsorbed molecules plays a role in the observed degradation of the azide.

The apparent yield calculated from the number of reactant and product molecules observed on terraces of the Cu(111) surface is ~2%, conservatively assuming a 1:1 ratio of reactants and that all molecules are intact. The observed click reaction products must, however, stem from the small fraction of intact azide molecules present on the surface. The XPS data place an upper limit for this fraction at ~14%. Consequently, the reaction yield based solely

on intact azides is at least 15%, suggesting that the cycloaddition reaction may proceed quite readily on the surface.

The reaction mechanism for the liquid-phase CuAAC reaction involves a Cu(I) ion which forms a Cu-acetylide with the terminal alkyne group under replacement of the alkyne proton.²¹ The regioselectivity toward the 1,4-regioisomer results from preferential binding of the azide nitrogen closest to the residue to this Cu atom, aligning the alkyne and azide groups with their residues pointing in opposite directions. In a later reaction step, the Cu atom in the intermediate is replaced by a proton from the solvent. The activation energy barrier for this CuAAC reaction mechanism has been calculated to 0.65 eV.²¹ An equivalent on-surface scenario could be envisioned involving free Cu adatoms released thermally (or by interaction with alkynes) from Cu step-edges. Here, the Cu surface would have to replace the solvent as reservoir for released hydrogen, although it is noted that recombinant hydrogen desorption from Cu(111) occurs around rt,³² limiting the lifetime of H species on the surface. If, for some reason, the CuAAC catalyzed channel is blocked on the surface, a direct reaction should be considered. The energy barrier for the (gas-phase) direct reaction mechanism has been calculated to ~1.1 eV,²¹ i.e., within a few tenths of an eV from rendering it relevant at rt. The observed likely di- σ bonding of the alkyne to the Cu(111) substrate is somewhat analogous to the “concerted mechanism” involving formation of a Cu(I) π complex with the alkyne triple bond²¹ and could possibly help to lower the barrier for a direct (surface-catalyzed) reaction path. While the liquid-phase uncatalyzed reaction often produces a mixture of 1,5- and 1,4-regioisomers, we only find evidence for the 1,4-regioisomer in the STM data, apparently pointing toward the CuAAC mechanism. However, when we perform liquid-phase synthesis with the protocol of the uncatalyzed path, we also obtain only the 1,4-product. This regioselectivity is ascribed to steric hindrance making a prereaction arrangement with both bulky residues to the same side of the reacting azide and alkyne groups inaccessible. Steric hindrance will be even more important in a surface-confined situation. To fully establish the on-surface reaction path, further modeling will be required.

In conclusion, we have demonstrated that a cycloaddition can be performed between alkyne and azide reactants adsorbed on a Cu(111) surface under UHV conditions at rt to produce the 1,4-triazole click reaction product. The reaction has a low apparent yield, because a sizable fraction of the deposited azide molecules degrade on the surface. The reaction itself, however, proceeds readily provided that intact reactants are available on the surface. For the azide–alkyne cycloaddition reaction to be useful for on-surface synthesis of organized covalently bonded surface structures, conditions must be identified, e.g., molecular structure, substituent groups, substrates, adsorption temperatures, where the azide is stable upon adsorption, yet maintains sufficient reactivity.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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