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Quantum Tunneling-Mediated Interfacial Synthesis of a Benzofuran Derivative

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Abstract: Reaction pathways involving quantum tunneling of protons are fundamental to chemistry and biology. They are responsible for essential aspects of interstellar synthesis, the degradation and isomerization of compounds, diffusion processes, enzymatic activity, and protein dynamics. On-surface conditions were demonstrated to open alternative routes for organic synthesis often with intricate pathways not accessible in solution. Here, we investigate a hydroalkoxylation reaction of a molecular species adsorbed on the Ag(111) surface with scanning tunneling microscopy complemented by X-ray electron spectroscopies and density functional theory. The furan ring-closure proceeds at low temperature (down to 150 K) and without detectable side-reactions. We theoretically unravel a protontunneling-mediated pathway and experimentally confirm its dominant contribution by the kinetic isotope effect with a deuterated derivative. Our findings provide unmatched insight into complex interfacial chemical transformations and open unexplored routes for on-surface synthesis rooted in quantum tunneling.

The tunneling of massive particles through potential barriers exceeding the particle energy is a fundamental concept of quantum mechanics and has significant impact on important processes in nature. It is essential for explaining the spectroscopic term schemes of molecules, e.g., in the case of ammonia reported by Hund in 1927.^[11] Already in 1933 Ronald P. Bell realized that tunneling can significantly contribute to the kinetic isotope effect (KIE) in hydrogen transfer reactions, rendering a quantum-mechanical treatment essential for the description of their kinetics.^[2] More recently, it was demonstrated

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Supporting information for this article is given via a link at the end of the document. that quantum tunneling can be responsible for the fast decay of compounds,^[3] direct reactions to products not accessible through classical pathways,^[4] while simultaneously enabling chemical conversions in extreme (e.g., interstellar) environments.^[5] Furthermore, the implications of tunneling-mediated reactions extend into biology, where quantum mechanical hydrogen transfer can cause mutations possibly leading to cancer and other diseases^[6] and influence enzyme activity^[7]. On atomically welldefined surfaces, proton tunneling has been hitherto reported to elementary processes like diffusion,[8] impact structural tautomerization,[10] dynamics.^[9] desorption,[11] and hydrogenation.^[12] However, in contrast to the plethora of complex, covalent reactions reported in the context of surface-assisted synthesis and heterogeneous catalysis, tunneling-mediated reaction pathways remained elusive.

Over the past few decades, intramolecular cyclization leading to the synthesis of biologically relevant heterocyclic compounds^[13] has gained much attention as one of the simplest and most efficient methods for constructing furan ring systems.^[14] Alkynylbenzene derivatives with a nucleophilic site at the oposition, such as o-alkynylphenols or o-alkynylphenyl ethers, are widely utilized as efficient precursors for constructing benzofurans. A number of methodologies using bases, transition or noble metal catalysts have been established on the basis of C–O cyclization.^[15]

Here, we investigate the chemical conversion of a 4"diethynyl-5,5"-dihydroxy-[1,1':4',1"-terphenyl]-3,3"-dicarbonitrile compound (Figure 1a, 1) on a noble metal surface by means of a multi-technique characterization. We identify a highly selective hydroalkoxylation reaction, intriguingly proceeding well below room temperature. A modeling analysis, based on density functional theory (DFT), identifies the underlying protontunneling-mediated pathway. In agreement, the KIE assessment confirms the quenching of the tunneling-mediated reaction for a deuterated isomer. Our work provides clear evidence for the tunneling-mediated pathway dominantly influencing the complex on-surface reactions.

We achieved the *de novo* synthesis of compound **1** (cf. SI and Figure S1) featuring three different functional groups ($-C\equiv N$, -OH and $-C\equiv CH$). The molecule was deposited onto the Ag(111) surface held at $T_{sub} \approx 100$ K. Subsequently, irregular aggregates of the precursor are observed in the scanning tunneling microscopy (STM) data (Figure S2) obtained at $T_{meas} \approx 4.5$ K, as for all images presented. The data indicates that limited diffusion prevents the formation of regular molecular assemblies, whereby species **1** retains pristine. Annealing the sample to an intermediate temperature ($T_{ann} = 250$ K) led to the formation of two distinct regular assemblies coexisting in segregated islands (Figure 1b) referred to as zig-zag (Z) and snake (S) phase. These two phases exhibit markedly different intramolecular contrast in

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Figure 1. Conversion of molecular assembly through on-surface hydroalkoxylation. (a) Lewis structure of **1** and **2** with scheme of the hydroalkoxylation reaction and typical STM appearances. (b-d) STM topographs after (b) deposition at $T_{sub} = 100$ K followed by annealing at $T_{ann} = 250$ K ($V_B = -1.0$ V, $I_T = 0.1$ nA), and (e) further annealing at $T_{ann} = 400$ K ($V_B = -1.0$ V, $I_T = 30$ pA). (c, d, f, g) Close-up STM images with superposed molecular models. (c) Intermolecular bonding scheme proposed for Z domains. (d) Close-up image of a Z domain. ($V_B = 300$ mV, $I_T = 100$ pA). (f) Intermolecular bonding scheme proposed for S domains. (g) Close-up of an S domain. ($V_B = 10$ mV, $I_T = 50$ pA, $T_{ann} = 400$ K).

STM data (highlighted in the lower panels of Figure 1a). Furthermore, they are clearly distinguishable by the unit cell parameters and their orientations with respect to the substrate high-symmetry directions (Figure S3). After further thermal treatment at $T_{ann} = 400$ K, exclusively the S-phase remains (Figure 1e). The evolution from phase Z into phase S is associated with a gradual chemical conversion from species 1 into 2, also depicted in Figure 1a. Recent reports on covalent transformations of precursors with similar functional groups^[16] suggest that the alkyne and hydroxy moieties undergo a hydroalkoxylation reaction as depicted in Figure 1a, whereby the functional groups fuse into a five-membered ring together with the involved part of the nearby phenyl ring, thus creating a furan moiety.

Modeling the STM data with scaled molecular units supports our hypothesis that the original precursor **1** (Figures 1c and 1d) is converted to product **2** (Figures 1f and g). The arrangement within Z domains can be rationalized through hydrogen bonding via O– H···N, C–H···O, and C–H···N interactions (denoted as α , β , γ in Figure 1d). The S assemblies optimize interactions between the potential proton acceptors O and N and nearby organic rings (red and blue outlines in Figure 1g).^[17] Notably, attempts to explain the S-phase with intact reactants 1 result in clearly prohibitive steric constraints (cf. Figure S3c,d). Force-field simulations of extended aggregates of species 1 and 2 on a substrate (Figure S4) corroborate the arrangement modes of both assemblies derived from the structural analysis.

To elucidate the chemical structure of the newly formed species as well as the reaction involved, we employed complementary spectroscopic techniques to assess the chemical shifts of the atomic constituents and the molecular orbital properties before and after the reaction, respectively. First, we performed X-ray photoelectron spectroscopy (XPS, cf. also SI) and analyzed the O 1s region of a series of samples exposed to the same amount of **1** and annealed to increasing temperature (Figure 2a). For $T_{ann} = 200$ K, we observed a broad O 1s peak containing two convoluted components. The binding energies E_B of these two peaks are 533.6 and 534.3 eV, respectively, which agree well with literature values for phenol and furan species adsorbed on Ag surfaces.^[18] Annealing freshly prepared samples at higher temperatures entails increased intensity of the furan

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Figure 2. Element-specific identification of the furan ring-closure by X-ray electron spectroscopies. (a) Comparison of the O 1s XPS signature for different annealing temperatures triggering the conversion of **1** to **2**. (b) NEXAFS C K-edge spectra, taken at an incidence angle (definition see inset) of $\theta = 90^{\circ}$, for a non-annealed (black) and an annealed (red) submonolayer-coverage sample. Experimental data (lower part) is compared to simulated spectra (upper part).

contribution, prevailing at $T_{ann} = 350$ K. The XPS data thus not only supports the proposed hydroalkoxylation scenario, but also excludes deprotonation of the hydroxy group as a dominant effect,^[19] since prominent features between 532 and 530 eV are absent.

While in the case of hydroalkoxylation all atoms of the reactant are still present in the products, alternative conversions involving substrate-mediated cracking would result in desorption of the abstracted subunits. Thus, temperature-programmed desorption (TPD) was employed to test for potential molecular fragmentation. In multiple heating ramps carried out after adsorption of various coverages of species **1** at 100 K, we detected neither small fragments (atomic mass < 50) nor any molecular or atomic H (Figure S5) that could be associated with dehydrogenation processes. Accordingly, the TPD investigation implies proton abstraction cannot explain the chemical conversion and supports the hydroalkoxylation scenario.

Near-edge X-ray absorption fine-structure (NEXAFS) data were collected toward further characterization of the reactants (precursors) and products. We compared the angle-dependent C K-edge spectra of a sample prepared via deposition of **1** at T_{sub} = 120 K with the spectra of the same sample after annealing to 400 K (Figure 2b and Figure S6a,b). We chose an incident angle θ = 90°, being sensitive to the in-plane π -systems of the CN and the CCH moieties. To distinguish contributions from different molecular orbitals, we performed DFT C K-edge spectra simulation for species **1** and **2**, respectively, as depicted in Figure 2b (cf. also Figure S6c,d). For the 120 K deposition, the

resonance at 285 eV originates from the phenyl moieties in the molecular backbone (cf. Figure S6a,b) and the pronounced dichroism reveals an overall near-to-flat adsorption geometry. The simulated NEXAFS spectrum of 1 (black curves in Figure 2b, cf. also Figure S6a,c) reproduces the double structure of feature A and the sharper peak B originating from the CCH and CN moieties, respectively. Thus, the data confirms the integrity of the precursor under such conditions. After 400 K annealing, the dichroism at 285 eV is preserved (Figure S6b), indicating that the flat adsorption geometry is maintained for the new species in agreement with the modeling of the STM data. Furthermore, the feature B is retained in the spectrum (lower red curve in Figure 2b), signaling that the CN group is not perturbed upon annealing as its in-plane π * orbital is preserved. By contrast, the spectral signature around 286 eV (CCH, labeled A), corresponding to the in-plane π * resonance of the terminal alkyne group is quenched, indicative of the conversion of the CC triple bond to a double bond. These three key features also nicely match the simulated spectra of the proposed species 2 (upper red curve in Figure 2b, also cf. Figure S6d). Therefore, the good agreement between simulated and experimental NEXAFS data in conjunction with the other observations is conclusive evidence for the proposed hydroalkoxylation scenario.

To analyze and rationalize the reaction mechanism, we carried out DFT-based harmonic transition state theory (HTST) calculations, using a simplified molecule with the central phenyl ring of 1 omitted. The most favorable free energy pathway calculated for T = 200 K is depicted in Figure 3, blue line. The twostep reaction proceeds through a hydrogen transfer from the hydroxyl to the alkyne group (IS to IntS) proceeding through the transition state TS1 followed by a ring-closing reaction via rotation of the involved C_2H_2 moiety (IntS to FS) forming the furan moiety. Importantly, the intermediate state IntS, where the original ethynyl group is effectively converted to an ethenylene, becomes favorable through the presence of the substrate, which enables bonding of the outermost carbon to surface atoms (see side view of **TS1**). In the HTST scenario, the classical reaction rate for T =200 K with a free energy of activation ΔG^{\ddagger} of 0.903 eV can be calculated by the Eyring equation as

$$\nu_{\rm C} = \frac{k_B T}{h} \cdot \exp\left(-\frac{\Delta G^{\ddagger}}{k_B T}\right) \approx 7 \times 10^{-11} \, {\rm s}^{-1}.$$

This minute value implies that in a classical picture the reaction should not proceed. Considering that its initial step is crucially influenced by a proton transfer, we investigated the role of quantum tunneling in this process. Examining the vicinity of TS1 with the de novo approach detailed in the Supporting Information (see M6), we indeed isolated two states suitable for proton tunneling, i.e., having the same energy and differing in structure only by the position of the H atom involved in the first reaction step. For transitioning between these states, the H atom has to move by only 0.60 Å, suggesting that they can serve as so-called turning points, i.e., positions where the mode of motion turns from classical behavior to quantum tunneling. The probability P of the related tunneling-mediated proton transfer process between the initial (TI) and final (TF) state (see Figure 3, red states) was calculated with the WKB approximation through the barrier obtained by a linear translation of the H atom from TI to TF, and integrating between the energy of the initial tunneling point ΔG_{TI} =

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Figure 3. Computational modeling of the reaction mechanism. (a) Scheme of the reaction pathway obtained from DFT-based HTST calculations, with the free energy profile of the classical (lowest energy) pathway shown in blue and the tunneling pathway in red, with top and side views of local minima referred to as initial, intermediate and final state (IS, IntS, FS) and transition states (TS1, TS2) as well as zoom-in of the quantum tunneling turning points (TI, TF). (b) Comparison of the reaction rates of the classical and tunneling-mediated pathways going from IS to IntS, with the axis for the rates being logarithmically scaled. (c) Electron density difference plots for TI and IntS, showing electron redistribution due to the molecule-surface interactions, where blue (red) indicates electron accumulation (depletion). Absolute value of contours is 0.01 e/Å³.

0.68 eV (for T = 200 K) and the maximum energy of the tunneling channel $\Delta G_{\rm T}^{\pm} = 0.97$ eV which is higher than the energy of the classical pathway **TS1** due to the constraints of the tunneling channel. We assumed that the tunneling barrier height is temperature independent. The rate of the thermally assisted tunneling process was calculated by integrating over the free energies between $\Delta G_{\rm TI}$ and $\Delta G_{\rm T}^{\pm}$

$$\nu_{\rm T} = \frac{k_B T}{h} \int_{\Delta G_{\rm TI}}^{\Delta G_{\rm T}^{\pm}} \exp\left(-\frac{\Delta G}{k_B T}\right) \frac{P(\Delta G)}{k_B T} d\Delta G.$$

In Figure 3 (right panel), it is clear that the tunneling-mediated rate $v_{\rm T}$ significantly exceeds the classical rate $v_{\rm C}$ throughout the relevant temperature range. Consequently, this relation implies a crucial role of proton tunneling in the reaction pathway. For example, at T = 200 K the quantum tunneling corrected rate is increased by a factor of ~100. Although the resulting reaction rate $\nu_{\rm T}$ is still relatively small (7 imes 10⁻⁹ s⁻¹ at 200 K), it represents just a lower limit for several reasons: As the rate depends exponentially on the energy at the turning point ΔG_{TI} , more appropriate turning points could enhance the rate of the tunneling pathway further. Furthermore, we are considering just one tunneling channel, instead of integrating over the entire phase space of the reaction, which is well beyond our computational reach. However, the decisive insight is the existence of a tunneling channel, which opens a significantly more efficient route for the proton transfer than the classical pathway.

Importantly, the calculations also unveil the crucial role of the Ag(111) surface: At the turning points (**TI**, **TF**) the terminating C atom of the original ethynyl group chemically interacts with the surface, stabilizing both these states as well as the identified intermediate state **IntS**, allowing two turning points coming close enough in configurational space and being at the same time sufficiently low in energy. The chemical role of the surface is exemplified for **TI** and **IntS** in Figure 3c, by the electron density differences ($\Delta \rho = \rho_{mol@Ag(111)} - \rho_{Ag(111)} - \rho_{mol}$) caused by molecule-surface interactions. For **TI**, there is a strong electron accumulation between the terminating C atom and a surface atom. **TF** has similar characteristics (see Figure S11). Furthermore, for **TI** there is an electron accumulation between the tunneling proton and the terminal alkyne, indicating that the surface-induced

charge redistribution promotes the tunneling process. For **IntS**, there is an accumulation surrounding the carbonyl oxygen signaling its chemical interaction with the substrate.

In view of the modeling insights, we experimentally crosschecked the proton-tunneling-mediated reaction via examining the KIE with a deuterated isomer (i.e., deuterated hydroxyl groups, cf. 1D in Figure 4). Figures 4a and b depict STM topographs of comparable coverages of 1 and 1D on Ag(111) annealed to 225 K (cf. Figure S7, S8): the Z- and S-phases clearly coexist for 1, whereas for 1D we find exclusively the Z-assembly. The absence of the S-phase is ascribed to a massively reduced deuterium tunneling probability, whence the ring-closure process is inhibited. For a quantification of the KIE, we analyzed a large set of STM images and found 50% reacted molecules for 1, contrasting spurious features for 1D well below 5%. All other molecules were found to be intact, i. e. assembled in the Z phase. This result sets a conservative lower bound for the KIE of 10 at 225 K, clearly indicating proton tunneling in the hydroalkoxylation reaction of 1.[20] Further examination of the KIE effect was obtained from XPS data. An example is depicted in Figure 4c, where the furan-related component dominating after annealing 1 at 250 K is practically absent in the 1D sample. The minor component at lower E_B is attributed to impurities resulting from the preparation of the hygroscopic powder (cf. SI). Consistently, an evaluation of the temperature dependence of the KIE from combined STM and XPS data (Figure S9a) indicates its prominent role in the sub-300 K regime. During the investigation of the reaction rates we also noticed high sensitivity to preparation conditions, which are consistent with the tunneling process (for details see SI A3).

In conclusion, through investigating a hydroalkoxylation reaction under on-surface conditions we have demonstrated that proton-tunneling-mediated mechanisms enable highly selective complex reactions via pathways inaccessible through conventional approaches. Our findings shone light on tunneling reactions, especially under interfacial conditions. With proper prepositioning and precursor design, it should be feasible to develop protocols steering intermolecular tunneling-mediated coupling under extreme conditions helping to engineer atomically

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Figure 4. Isotope dependence of the furan formation. Comparison of STM images (V_B = -1.0 V, I_T = 0.1 nA) after annealing at 225 K for (a) the original, non-deuterated reactant 1 and (b) its deuterated derivative 1D. (c) Comparison of XPS O 1s data of 1 and 1D after annealing at 250 K with the binding energies of the furan- and phenol-related moieties marked by vertical lines.

precise bottom-up constructed nanomaterials. In general, the extraordinary sensitivity to the local environment surrounding the reactive site paves the way toward novel approaches to chemical reactions and quantum processes.

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Tunneling enables interfacial synthesis: The hydroalkoxylation reaction of a molecular species adsorbed on the Ag(111) surface proceeds at low temperatures down to 150 K. The proton-tunneling-mediated pathway is theoretically disentangled and experimentally confirmed via the kinetic isotope effect.



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