

Electric Field-Induced Sequential Prototropic Tautomerism in Enzyme-like Nanopocket Created by Single Molecular Break Junction

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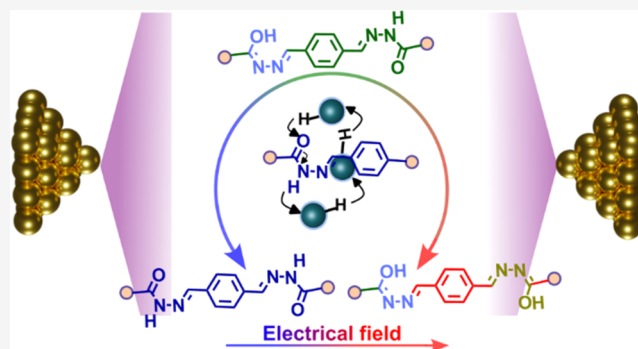


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ABSTRACT: Mastering the control of external stimuli-induced chemical transformations with detailed insights into the mechanistic pathway is the key for developing efficient synthetic strategies and designing functional molecular systems. Enzymes, the most potent biological catalysts, efficiently utilize their built-in electric field to catalyze and control complex chemical reactions within the active site. Herein, we have demonstrated the interfacial electric field-induced prototropic tautomerization reaction in acylhydrazone entities by creating an enzymatic-like nanopocket within the atomically sharp gold electrodes using a mechanically controlled break junction (MCBJ) technique. In addition to that, the molecular system used here contains two coupled acylhydrazone reaction centers, hence demonstrating a cooperative stepwise electric field-induced reaction realized at the single molecular level. Furthermore, the mechanistic studies revealed a proton relay-assisted tautomerization showing the importance of external factors such as solvent in such electric field-driven reactions. Finally, single-molecule charge transport and energetics calculations of different molecular species at various applied electric fields using a polarizable continuum solvent model confirm and support our experimental findings. Thus, this study demonstrates that mimicking an enzymatic pocket using a single molecular junction's interfacial electric field as a trigger for chemical reactions can open new avenues to the field of synthetic chemistry.



INTRODUCTION

Prototropic tautomers differ in the position of protons in an organic framework, with associated electronic redistribution. The energy difference of these tautomers is usually subtle, and their interconversion is decided by the ability of molecular structure to facilitate the proton transfer.^{1,2} However, one can selectively stabilize one tautomer over another by precisely modulating the surrounding interaction energies. Proton transfer reactions garnered extreme importance in biology by playing a key role in the proton-coupled electron transfer processes,³ functioning of the ion channels,^{4,5} and they are seminal in the energy-harnessing process as well.^{6,7} Additionally, minor tautomeric forms of biomolecules stabilized for a small period of time can lead to entirely different biochemistry. Studies have shown that the different ribozymes recognize their substrates by identifying minor tautomeric forms, thereby controlling the host–guest chemistry.⁸ Most importantly, excited state single and double proton transfer reactions underpin the photoisomeric reactions in genetic materials.⁹

Unveiling the complete machinery of this ultrafast tautomerism process is cumbersome and direct identification of the fundamental proton transfer process within the

constraints of the biological environment demands sophisticated experimental methods.^{10,11} Hence, the fundamentals of proton transfer reactions are consolidated from studies of simple model organic systems. Previous reports have demonstrated both ground and excited state proton transfer mechanisms and their underlying principles considerably overlap.^{12,13} Reaction initiates from a precursor where the proton donor and acceptor ends are connected by a hydrogen-bonded array followed by either proton tunneling or activated overbarrier proton motion.^{10,14,15} The proton relay allows the hopping of the proton from the upstream to the downstream end described by the Grothuss mechanism.^{16–18} Preorganized rigid framework of enzymes additionally enforces this coupling within the active site. Additionally, external factors including

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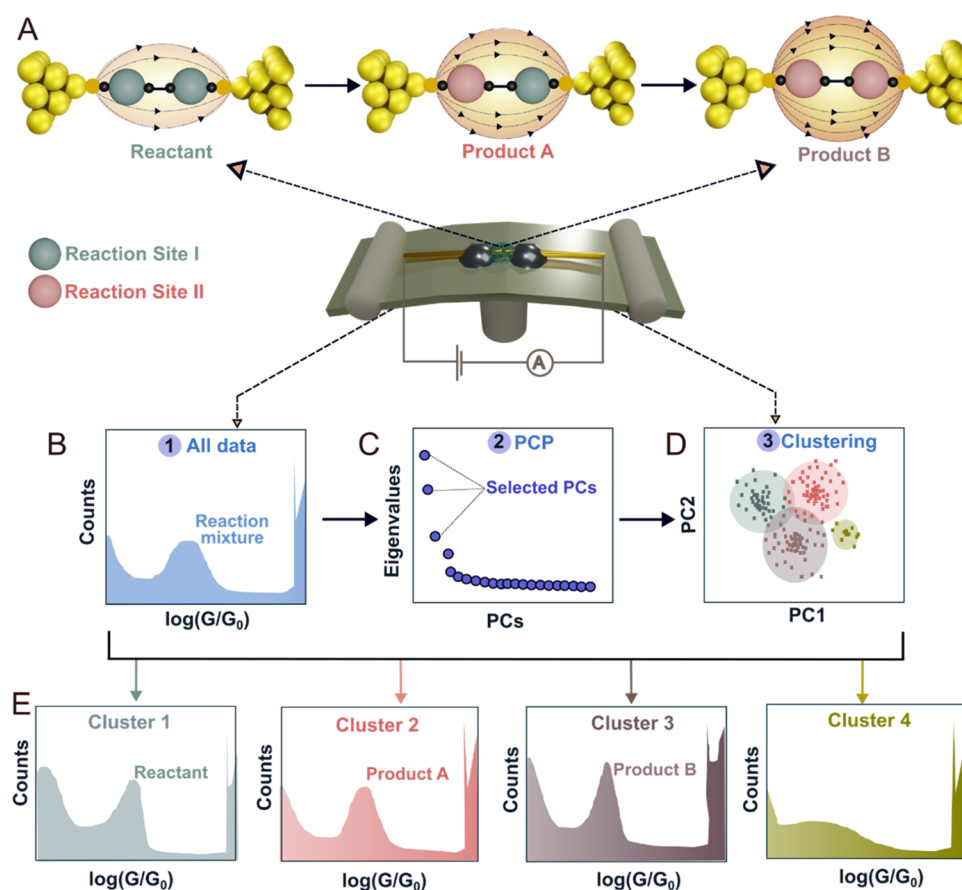


Figure 1. (A) Schematic representation of probing a coupled two-center chemical reaction induced by the electric field at the atomically sharp electrodes in the mechanically controlled break junction setup. (B) Schematic representation of 1D conductance histogram for the complete data collected during the reaction. (C) Representation of scree plot showing the selection of the first three principal components (PCs) in principal component projection (PCP) analysis. (D) Representation of different clusters formed after performing *k*-means++ clustering. (E) Pictorial representation of 1D conductance histograms corresponding to different clusters.

solvent polarity, temperature, hydrogen ion concentration, and surrounding electric field, profoundly influence the energetics and feasibility of the reaction. In biology, the orientation and magnitude of the external electric field own a prime position in dictating the tautomerization events due to their inevitable presence within enzymatic pockets.^{19,20}

Recently, ketosteroid isomerase involved in the steroid hormone isomerism where the proton transfer is a critical step, was found to be catalyzed by an in-built electric field of 144 MV/cm, making it the enzyme with one of the highest unimolecular rate constants.^{21–23} Hence, understanding the fundamental principle and mechanism of proton transfer reactions in the presence of an electric field is extremely important. Directly probing the effect of the electric field on prototropic tautomerism within the protein environment remains elusive. Studies so far reported on the effect of the electric field on proton transfer on model systems using ultrafast spectroscopic techniques have been shown to follow an excited state pathway.²⁴ However, a detailed solid mechanism of proton transfer in the presence of an electric field in the ground state has not yet been completely revealed at a single molecular level. As mentioned previously, the tautomeric forms of the organic substrate play a vital role in our biological systems, and understanding the influence of the external electric field on ground-state tautomerism appears to be a great necessity.

The present study demonstrates the effect of an external electric field on a synergistic double proton transfer reaction at a single molecular level. The reaction is probed by measuring the single molecular conductance of the organic substrate using the mechanically controlled break junction (MCBJ) technique by creating a small active site-like pocket in between two atomically sharp gold electrodes (Figure 1).^{25–29} The experiment revealed an electric field-induced tautomerization occurring at acylhydrazone centers assisted by a solvent-mediated proton relay. Further, all of our experimental observations are supported by theoretical calculations. Previously, different theoretical and experimental studies have revealed the dramatic effect of electric field in controlling chemical reactivity.^{30–33} Also, reports have shown the reliability of break junction experiments in studying field-induced reactions.^{26,34,35} However, a solvent-cage-mediated cooperative proton rearrangement is not discussed or realized at a single molecular level. Herein, we demonstrate, for the first time, a single molecular non-redox-active proton relay-based two-center proton transfer in acylhydrazone entities triggered by an external electric field.

RESULTS AND DISCUSSION

Herein, an acylhydrazone group containing molecular system (NPN-2H) has been synthesized following the procedure given in Supporting Information, section 1. NPN-2H contains

two acylhydrazone centers coupled via a phenyl group, allowing the study of the cooperative tautomerization effect at the single-molecule level (Figure 2A, inset). Thioether groups at both ends serve as the stable anchoring points for attaching molecules to the gold electrodes during the break junction experiment.³⁶ First, we performed the single molecular charge transport measurement of NPN-2H under a comparatively higher applied bias (1.50 V) using a home-built MCBJ setup. In all experiments, we used a 10 μ M concentration of NPN-2H dissolved in dimethyl sulfoxide (DMSO): 1,2,4 trichlorobenzene (TCB) (1:200 v/v) solvent mixture. In the break junction experiment, two atomically sharp electrodes are created to trap a single molecule from the surrounding molecular solution by mechanically pulling the electrodes apart from an initial metal–metal contact point. A constant bias applied across these electrodes serves as the source of the electric field and the nanometer-scale space created between them mimics the enzymatic pocket. The current response as a function of electrode–electrode distance is continuously probed over the junction-making-breaking cycle. The current signal collected during the breaking process is selected for further analysis³⁷ (more details are given in SI section 2). Figure 2A and SI Figure S9A show the 1D conductance and the corresponding 2D conductance–distance histogram built from a minimum of a thousand such current–distance traces collected from NPN-2H conductance measurement using MCBJ. It is evident from the 1D histogram that the conductance evolves from metal–metal contact $1 G_0$ ($G_0 = 77.5 \mu S$) region to molecular conductance feature in the range $10^{-5.0}$ to $10^{-6.0} G_0$ and subsequently leading to the instrument noise level at $10^{-7.5} G_0$. We further analyzed the data presented in Figure 2A by performing a principal component projection analysis followed by clustering using a reference-free clustering method (details are given in Figure 1 and SI section 2).^{38,39} Interestingly, we observed three different peaks ($10^{-5.0}$, $10^{-5.5}$, and $10^{-6.0} G_0$) corresponding to three different clusters (Figures 2B and S9). Analysis of data with both thousand traces and five thousand traces shows a similar observation (Figures S9 and S10), indicating that the observed results are independent of the sample size of the data.

Intrigued by the result, we probed the conductance of NPN-2H at lower biases ranging from 1.00 to 1.45 V. At 1.00 V, we observed that there is only a single conductance peak present at $10^{-6.0} G_0$ even after clustering the data. At 1.10 V, the new peak at $10^{-5.5} G_0$ begins to appear and the peak at $10^{-5.0} G_0$ starts to appear after increasing the bias to 1.45 V (see SI Figures S9–S17 for details). Further, we analyzed the relative amount of the three different species formed at different bias ranges. The results are summarized in Figure 2C. The trend clearly shows that the percentage of traces with a $10^{-6.0} G_0$ plateau decreases with an increase in voltage (1.00–1.50 V), while traces with $10^{-5.5} G_0$ plateau increase and then decrease. Finally, the fraction of traces with a plateau at $10^{-5.0} G_0$ gradually increases from an applied bias of 1.45 V.

We have also performed measurements with negative bias voltages and observed similar results (Figures 2C and S18–S23). To benchmark the native conductance of NPN-2H, we have performed the conductance measurement at 0.10 V. These measurements resulted in a single conductance peak at $10^{-6.0} G_0$ as seen at the applied bias of 1.00 V (Figure 2D). This implies that the conductance states at $10^{-5.5}$ and $10^{-5.0} G_0$ are a result of higher applied bias. These conductance states indicate the formation of new species at the electrode gap due

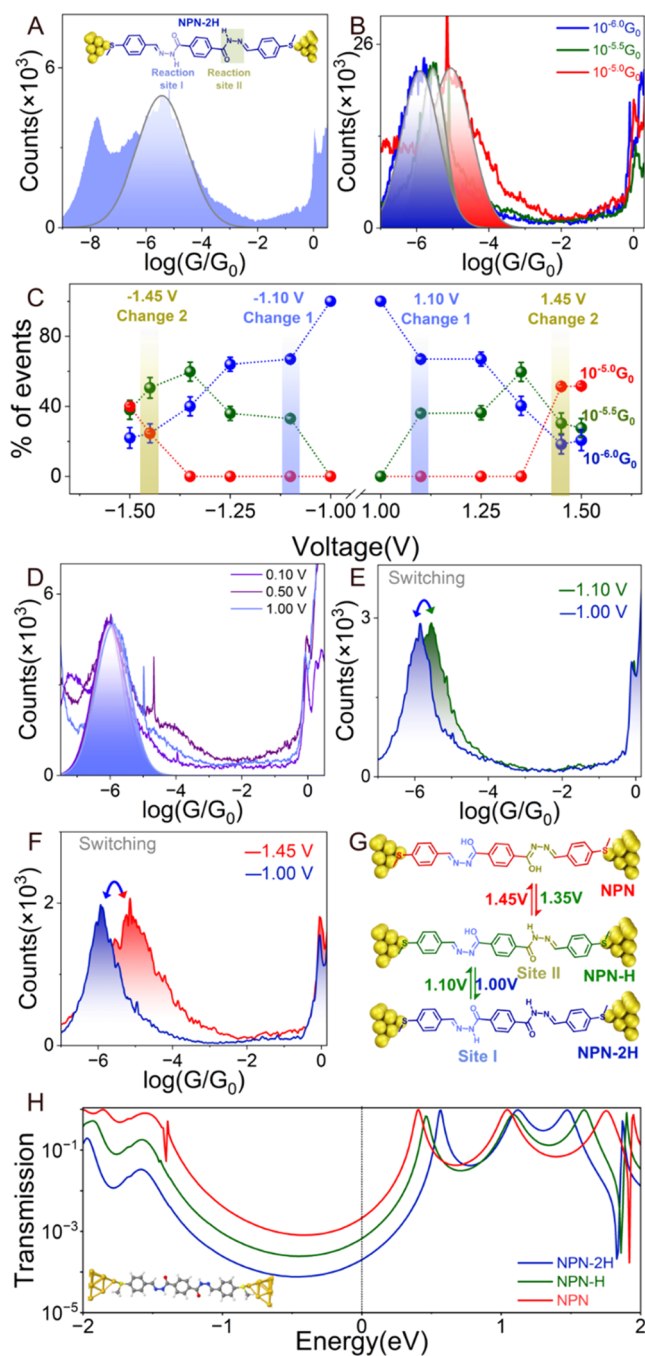


Figure 2. (A) 1D conductance histogram for the NPN-2H conductance measurement at 1.5 V. Schematic representation of molecular junction formed by NPN-2H is represented in the inset. (B) 1D conductance histograms of three different peaks formed at 1.50 V. (C) Trend in the percentage of three different species formed at different bias ranges. (D) 1D histograms for the measurements at 0.10, 0.50, and 1.00 V. (E) 1D conductance histogram showing the reversible formation of $10^{-6.0} G_0$ from $10^{-5.5} G_0$ species when the bias changed from 1.10 to 1.00 V. (F) 1D conductance histogram showing the reversible formation of $10^{-6.0} G_0$ from $10^{-5.0} G_0$ species when the bias changed from 1.45 to 1.00 V. (G) Proposed reason for the change in the conductance is the stepwise acylhydrazone tautomerization. (H) Zero bias transmission spectra for the proposed NPN-2H, NPN-H, and NPN system.

to the applied electric field. These two new species can be generated by two possible pathways: 1. By sequential redox

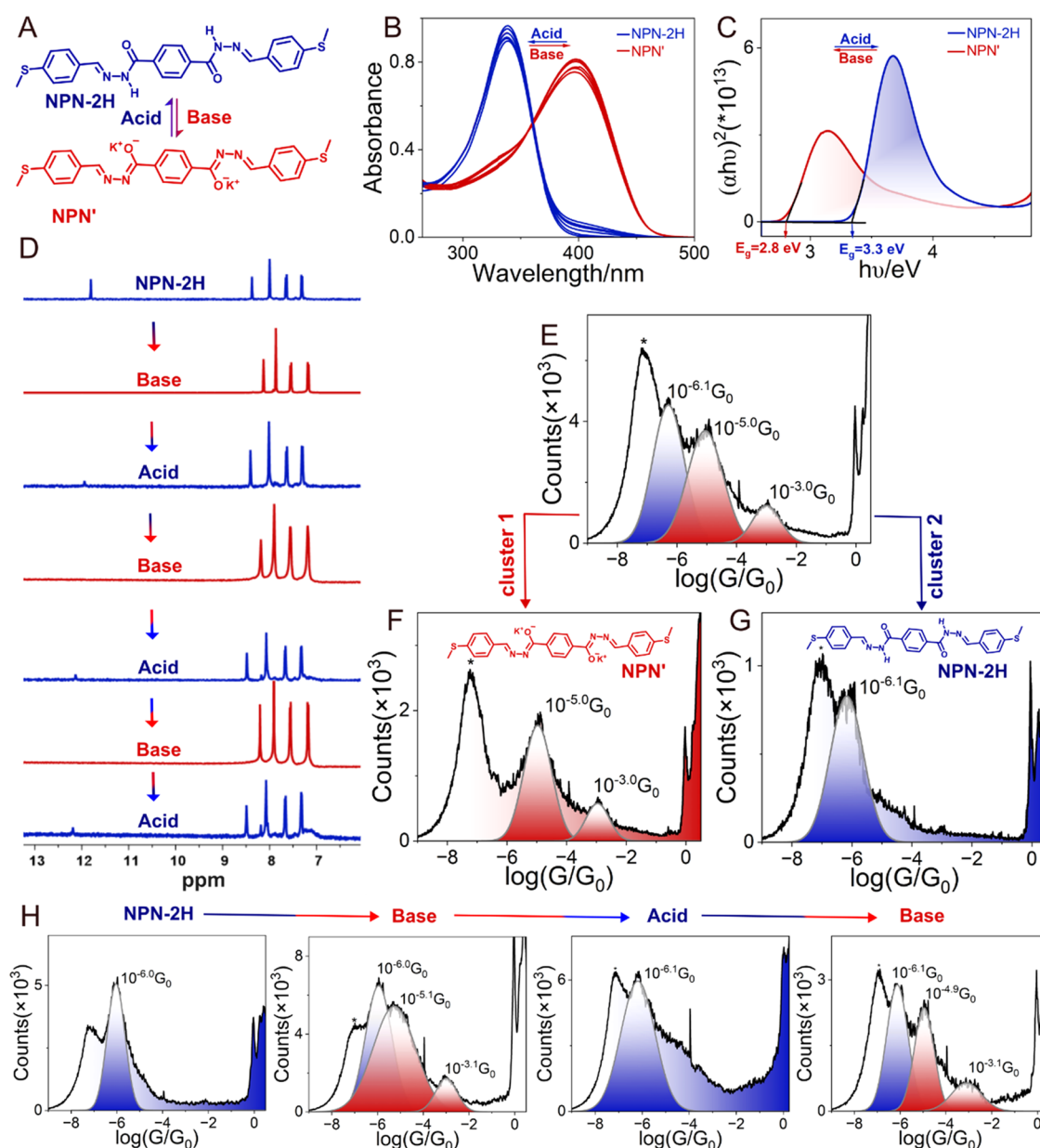


Figure 3. (A) Schematic representation of the reversible formation of NPN-2H and NPN' in acidic and basic media, respectively. (B) UV-vis spectra for Acid-Base reversible switching. (C) Tauc plot for the NPN-2H and NPN'. (D) NMR spectra for the reversible deprotonation reaction. (E) 1D conductance histogram for the deprotonated system at 0.1 V. (F, G) 1D histograms demonstrating the cluster of separated high conductance peaks and low conductance peaks, respectively, from the measurements of the deprotonated system. (H) 1D conductance histogram demonstrating the reversible acid-base-induced conductance switching.

reactions. 2. By nonredox sequential tautomerization leading to an increase in delocalization. The possibility of sequential redox reactions can be eliminated based on the large HOMO-LUMO gap of the molecule (3.3 eV), which means it needs large potentials to oxidize/reduce in a nonpolar solvent environment.⁴⁰ Second, we have observed the formation of $10^{-5.5} G_0$ and $10^{-5.0} G_0$ conductance states independent of bias direction (Figure 2C). This is highly unlikely that both dioxidized and direduced species of the molecule have the same conductance values. Hence, the redox pathway can be eliminated.

Figure 2E,F shows that the species with higher conductance values are only existing when the required amount of electric field is applied across the electrodes (for details, see SI Figures S24–S31). Apart from the redox pathway, the only possibility

for the appearance of new high conductance peaks at higher applied bias is an increase in conjugation within the molecular system, which hints toward a possible tautomerization reaction. Further, the appearance of two high conductance peaks can be explained by the consecutive tautomerization of two acylhydrazone centers, one after the other (Figure 2G). The theoretical transmission spectra calculated in TranSiesta⁴¹ shown in Figure 2H confirm the same observed trend in the zero bias conductance $G = G_0(T(E_F))$, i.e., $\text{NPN} > \text{NPN-H} > \text{NPN-2H}$. Additionally, the computational dI/dV curves, calculated from the transmission spectra at different applied voltages, support the observation of this trend in conductance at higher bias, and a nearly constant conductance for biases between 0 and 1 V (SI section 7).

To further confirm our hypothesis of the formation of tautomeric species under a higher electric field, a completely conjugated species (NPN') is generated *in situ* by deprotonating NPN-2H with a strong base potassium tertiary butoxide (Figure 3A). The deprotonation reaction is completely reversible as the native state can be regenerated by the addition of trifluoroacetic acid (TFA) and the reproducibility is confirmed by performing switching experiments using UV-vis absorption spectroscopy (Figure 3B). An immediate appearance of a yellow color after the addition of base to the molecular solution indicates the fast deprotonation reaction, forming a species with a lower HOMO-LUMO gap. This decrease in the band gap is expected, as the removal of hydrogen from the acylhydrazone group will increase the electron delocalization. UV-vis spectroscopy study shows that the molecule in its native state (NPN-2H form) has an absorption maximum of 338 nm and after the addition of base (NPN' form), the absorbance maximum shifted to 402 nm, indicating a clear decrease in the band gap (Figure 3B). Further, the optical band gap for both forms was calculated from the Tauc plot constructed using the absorption spectroscopy data, and a 0.5 eV decrease in HOMO-LUMO was found after the deprotonation (Figure 3C). The reversible deprotonation reaction is also probed with NMR spectroscopy, and the peak at 11.95 ppm corresponding to NH completely vanished and reappeared after the addition of base and acid, respectively (Figure 3D).

For the electrical characterization of the deprotonated species, we used a molecular solution of 10 μ M NPN-2H in DMSO:TCB, 1:200 (v/v) solvent mixture, together with excess potassium tertiary butoxide. Figure 3E shows the 1D conductance histogram for the deprotonated system, which shows three distinct molecular conductance features. A conductance peak at $10^{-6.1} G_0$, which is similar to that of the protonated form of the molecule and two new conductance peaks originated at $10^{-5.0}$ and $10^{-3.0} G_0$. Further analyses with clustering of the data and correlation spectrum analysis confirm the positive correlation between the two higher conductance peaks and their negative correlation with the lowest conductance peak (Figures 3F,G and S32).

Hence, we can conclude that the conductance peak at $10^{-6.1} G_0$ corresponds to the unconverted form of the molecule and the other two higher conductance peaks ($10^{-5.0}$ and $10^{-3.0} G_0$) are signatures of the deprotonated form (NPN'). Moreover, with an increase in the equivalence of base, the amount of converted form increased (SI Figures S33–S35 and Table S1). The conductance feature at $10^{-5.0} G_0$ is attributed to the end-to-end connected NPN' form since an increase in conductance from $10^{-6.0} G_0$ is expected as we are narrowing the HOMO-LUMO gap upon deprotonation. The highest conductance peak corresponds to the molecular junction with thiomethyl attached to one end and the lateral interaction of the molecular backbone at the other end of the junction. This interaction cannot be neglected as deprotonation will increase the electron density on the backbone and hence the affinity toward the gold electrode also increases. Additionally, flicker noise measurement for this highest conductance peak ($10^{-3.0} G_0$) and the calculated transmission spectra confirm one side through space coupling to the electrode (Figures S36 and S37).^{25,42} The characteristic conductance feature at $10^{-5.0} G_0$ for the deprotonated species (NPN') matches completely with the proposed tautomerized form of the molecule under higher bias (NPN). This observation further solidifies the formation of a

completely conjugated species under a higher electric field via prototropic tautomerization. The base-induced changes are further proven by the reversible conductance switching experiment performed in four steps (Figure 3H and complete data is given in Figure S38).

Further, to validate the voltage-driven tautomerization in other substrates, we designed a similar molecular system (PNP-2H) and measured the conductance properties under high electric fields following the same experimental procedure. Owing to its structural similarities with NPN-2H, the PNP-2H also showed three different conductance peaks at 1.50 V confirming the proposed electric field-induced prototropic tautomerism reaction (Figure 4A,B). The theoretical calcu-

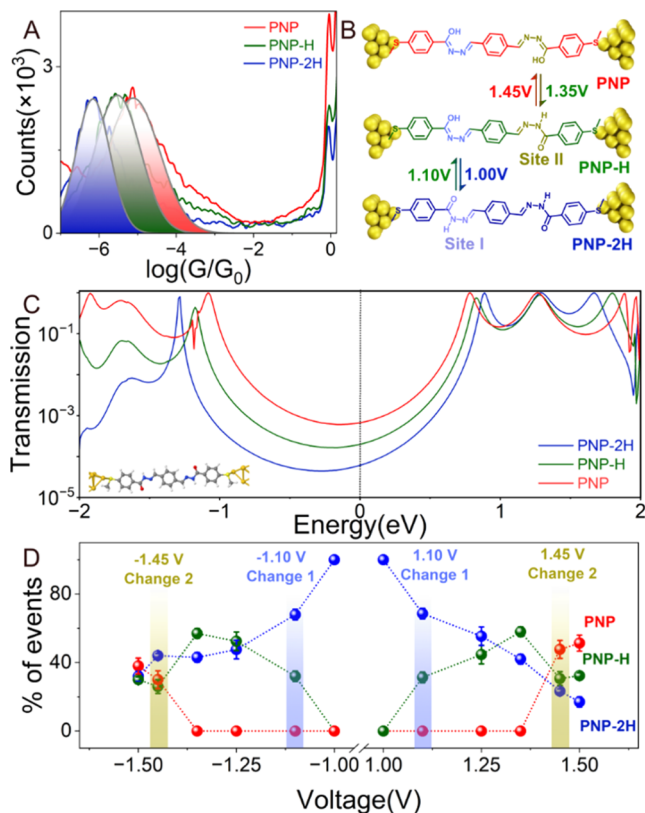


Figure 4. (A) 1D conductance histogram of three different peaks formed at 1.50 V for PNP-2H measurement. (B) Schematic representation of stepwise tautomerization reaction occurring as a function of bias in PNP-2H system. (C) Zero bias transmission spectra for the PNP-2H, PNP-H, and PNP. (D) Plot of experimental data showing a trend in the percentage of formation of three different species at different bias ranges of 1.00–1.50 V.

lations confirm the observed trend in conductance, PNP > PNP-H > PNP-2H, and increasing band gap from PNP to PNP-2H (Figure 4C). Further, we experimentally found a similar trend in the appearance of three different peaks at both positive and negative biases, proving the voltage-driven tautomerization (Figures 4D and S39–S52) and eliminating the redox pathway. The deprotonation of PNP-2H with potassium tertiary butoxide also produces PNP' with a conductance value of $10^{-5.0} G_0$ similar to the end species produced at higher electric field (details are given in Figure S53).

The observed electric field-induced tautomerization is a proton shuttling from nitrogen to oxygen within the

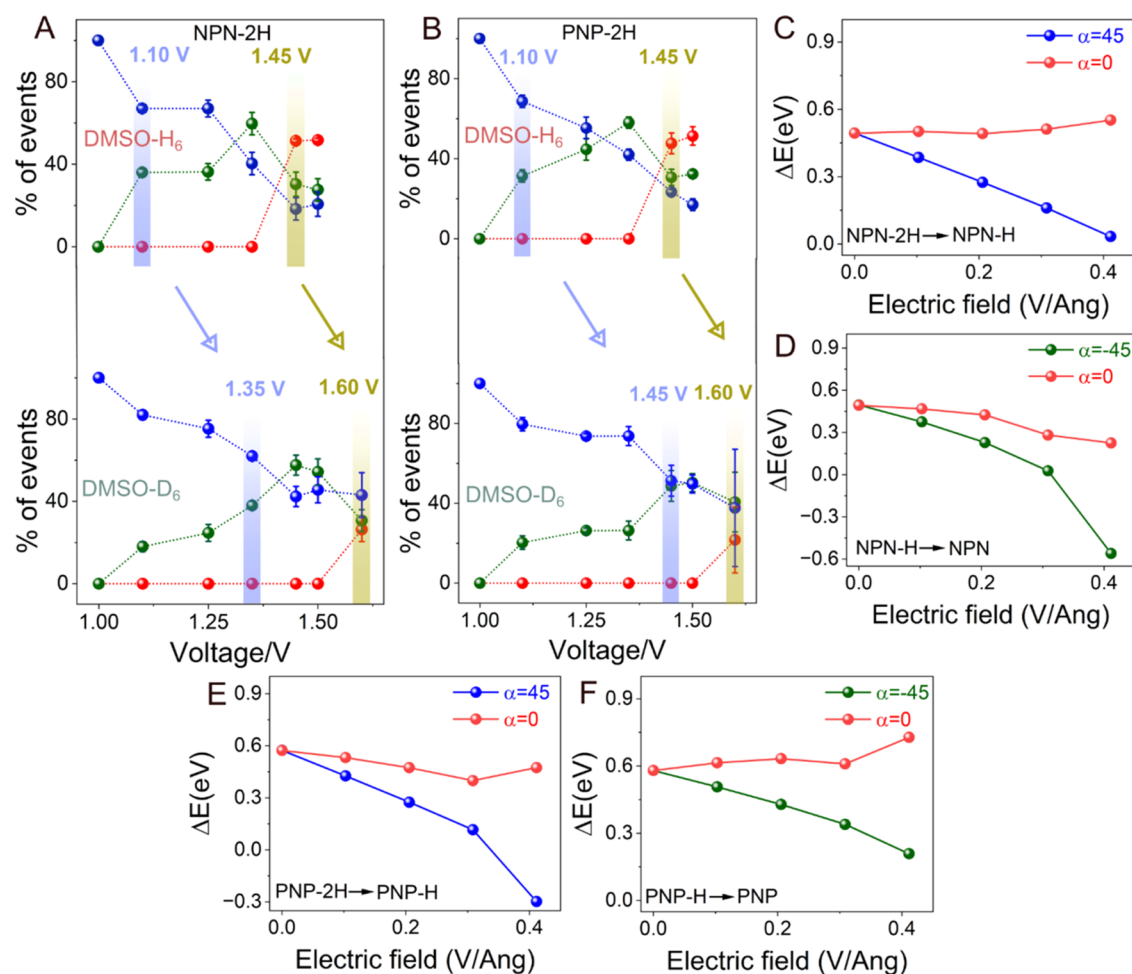


Figure 5. (A) Comparison plot of high bias measurement in DMSO and DMSO- D_6 for NPN-2H and (B) for the PNP-2H molecule. The difference in theoretically calculated total energy ΔE of the reactant and product (C) for the first reaction step (NPN-2H $\rightarrow$ NPN-H) and (D) for the second reaction set (NPN-H $\rightarrow$ NPN) as a function of the applied electric field E at different angles, α . Difference in theoretically calculated total energy ΔE of the reactant and product (E) for the first reaction step (PNP-2H $\rightarrow$ PNP-H) and (F) for the second reaction set (PNP-H $\rightarrow$ PNP) as a function of the applied electric field E at different angles, α . In all of the plots, α value of 0 or $\pm 45^\circ$ indicates the angle of alignment of molecules to the direction of the electric field.

acylhydrazone group.¹ Similar to ketones and all other carbonyl derivatives, the most stable form of the acylhydrazone group is one where the carbonyl group is intact, as in the NPN-2H form under normal conditions. Our study demonstrates that the energy profile and the stability of different species including tautomers can be altered by applying an external electric field.

As reported previously, one-step proton transfer is possible if the donor and acceptor ends are directly connected otherwise it is accompanied by multiple protons hopping steps.³ To completely elucidate the pathway of electric field-driven proton shuttling, conductance measurement was carried out in deuterated dimethyl sulfoxide (DMSO- d_6) anticipating a change in the energetics of the reaction. As evident from Figure 5A,B, in the deuterated solvent, 40% monotaomerization happened at a bias of 1.35 V or more. While in normal solvent conditions, 40% of monotaomerization is accomplished at a voltage of 1.25 V itself. Moreover, the voltage required to produce completely tautomerized species (NPN form) shifted from 1.45 to 1.60 V (more details are given in Figures S54–S67). This shift in the applied bias for inducing the changes verifies that both observed electric field-driven tautomerization is facilitated by a proton wire created by the

solvent molecules. An increase in energy for triggering tautomerization is expected if the proton transfer is solvent-assisted due to the increased X–D bond energy compared to X–H. These measurements with deuterated solvents indeed prove that the proton transfer is initiated by a hydrogen bond-assisted pathway stabilized under higher bias ranges. The acylhydrazone groups are known for *cis*–*trans* isomerization when illuminated with a light of a suitable wavelength.^{43,44} However, revealing the solvent-assisted transformation helps to completely exclude the possibility of *cis*–*trans* isomerization of acylhydrazone in the presence of an external electric field.

The appearance of new conductance peaks is indicative of the presence of the NPN-H and NPN species in the experimental results for both molecular systems when the electric field between the electrodes is high. We have calculated the total energies of each species at a finite electric field using Gaussian⁴⁵ (details in SI section 7), where the presence of the polar DMSO solvent in the junction is simulated using the supplemental polarizable continuum model (PCM).^{46,47}

The differences in total energy ΔE of the reactant and product for NPN-2H $\rightarrow$ NPN-H (and for PNP-2H $\rightarrow$ PNP-H) and NPN-H $\rightarrow$ NPN (and for PNP-H $\rightarrow$ PNP) over the electric field E are plotted in Figure 5C,D (Figure 5E,F). Also,

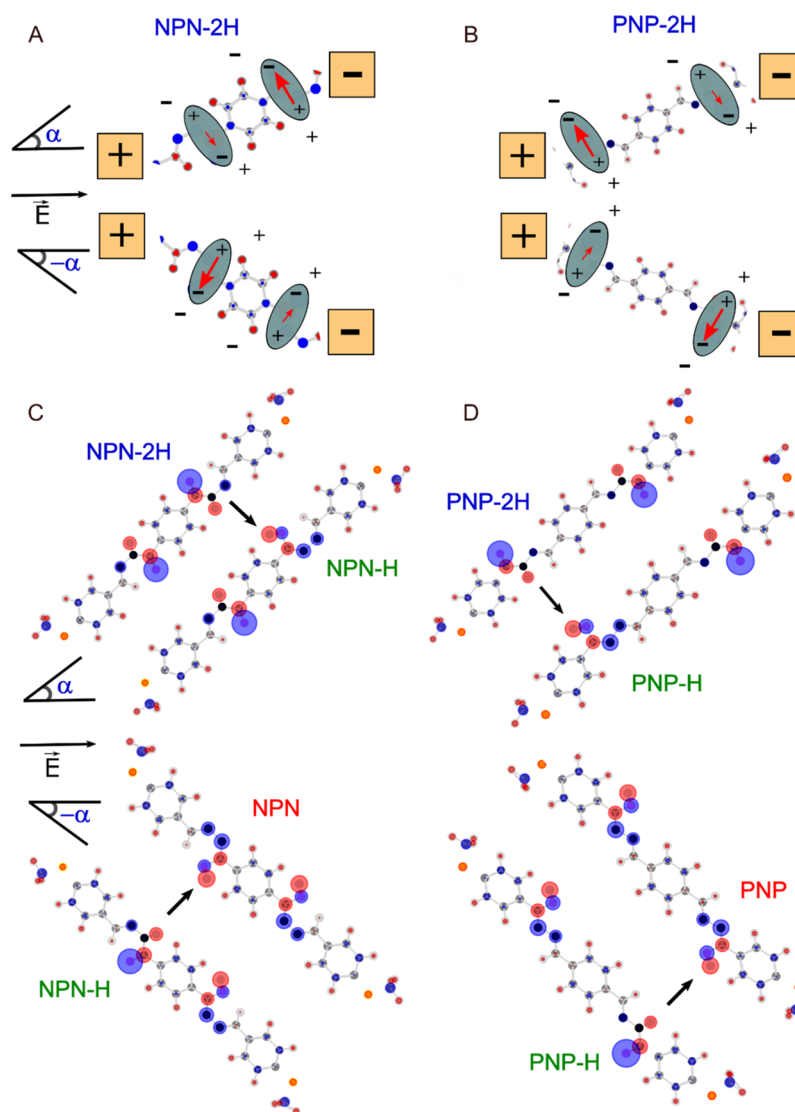


Figure 6. (A) Illustration of the response of the local dipoles on the acylhydrazone groups to the applied electric field when NPN-2H is aligned with an angle of α and $-\alpha$ to the field lines. (B) Same for PNP-2H. (C) Representation of sequential tautomerism (NPN-2H $\rightarrow$ NPN-H and NPN-H $\rightarrow$ NPN) with Mulliken charges calculated at $E = 0$ on the atomic geometries. (D) Representation of sequential tautomerism (PNP-2H $\rightarrow$ PNP-H and PNP-H $\rightarrow$ PNP) with Mulliken charges calculated at $E = 0$ on the atomic geometries. In these visualizations, red circles denote regions of positive charge, while blue circles signify areas of negative charge; the size of each circle reflects the magnitude of the atomic charge.

the energies relative to the total energy of NPN-2H (PNP-2H) at $E = 0$ V/Å over the electric field E are given in SI Figure S71A–C (Figure S71D–F). The homogeneous electric field is applied parallel to the molecular axis and at an angle $\alpha = \pm 45^\circ$ to the junction. We note that due to the limitations of the model, the applied fields exhibit significantly greater strength than anticipated in the experimental setup. At low electric fields, the total energies of all species are separated by about 0.5 (or 0.6) eV, which suggests that only NPN-2H and PNP-2H are present at low bias (Figures 5C–F and S71). When the molecule is aligned parallel to the electric field, we find a minimal impact on the ΔE of the two reactions (Figure 5C–F). However, when the molecule is not aligned parallel to the electric field, electric field strengths exceeding 0.3 V/Å result in energy levels that converge closely enough to suggest the presence of different species available within the junctions at those biases (SI Figure S71). We can infer that the field not only converges the energies of the reactions but also lowers the

energy barriers for their interconversion through a tunneling mechanism involving the proton.^{34,48}

The behavior of the total energies in response to increasing electric fields can be attributed to the charge redistribution within the molecules. As shown in Figure 6A,B, in the NPN-2H and PNP-2H species, local electric dipoles are observed at the two acylhydrazone centers, with a positive charge in the region of the H atom and negative charge at the O atom. Due to the antiparallel orientation of these dipoles, either one of them will be stabilized in the given direction of the electric field (Figure 6A,B). To further illustrate this phenomenon, we present the Mulliken charges at $E = 0$ V/ang on the atomic geometries of different species in Figure 6C,D. In these visualizations, red circles denote regions of positive charge, while blue circles signify areas of negative charge; the size of each circle reflects the magnitude of the atomic charge. Given that the local electric dipoles observed at two acylhydrazone centers are oriented antiparallel, we propose that proton tautomerization processes occur in opposite directions within

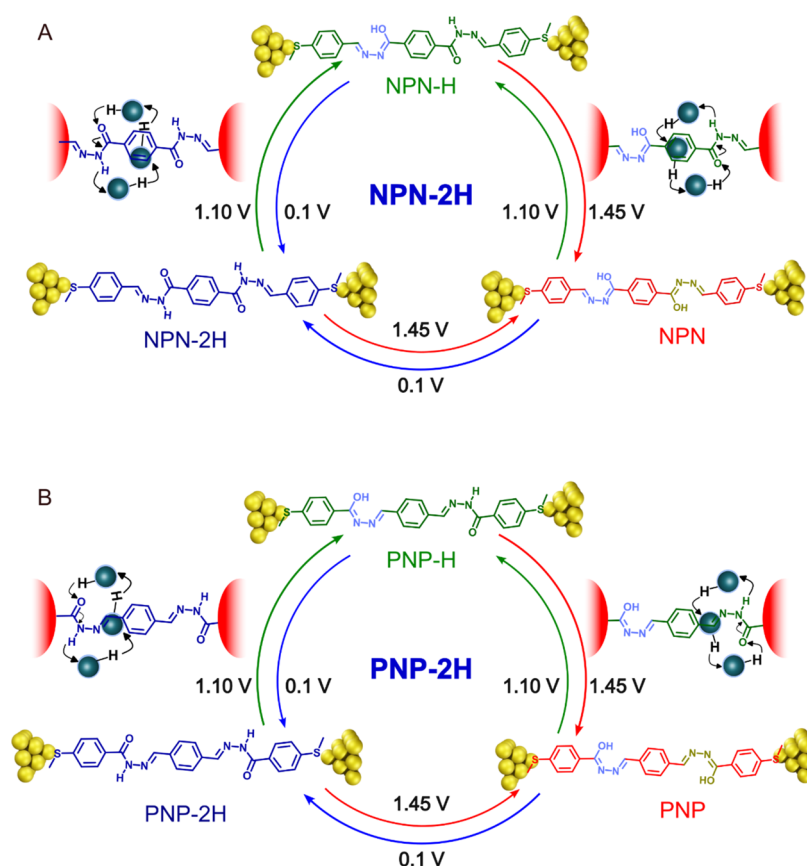


Figure 7. (A) Schematic representation of the mechanism of solvent-mediated sequential tautomerism occurring at different bias ranges for NPN-2H and (B) PNP-2H.

the molecules. When the electric field is aligned parallel to the long axis of the molecule, its influence on the charges of these dipoles is diminished. However, when the field is applied at an angle of α , one of the local dipoles is enhanced, facilitating proton transfer (Figure 6C,D). Based on the total energies, this interconverts the stability of conformers NPN-2H (and PNP-2H) and NPN-H (and PNP-H). Conversely, when the molecule is rotated to an angle $-\alpha$, the transfer of the second proton is induced at the other acylhydrazone group (NPN-H to NPN or PNP-H to PNP) (Figure 6C,D). Consequently, we observe a convergence of the total energy for the first reaction at angle α and for the second reaction at angle $-\alpha$. At room temperature, it is likely that the orientation of the molecules is not parallel to the electric field, at least some of the time due to thermal fluctuations affecting the molecules and electrodes. In this scenario, the total histogram of thousands of break junctions will likely have a statistical sampling of all three species, as is observed experimentally for break junctions performed at biases above 1.50 V.

Here in NPN-2H and PNP-2H, one must anticipate a selective catalysis of the tautomerization reaction in one of the acylhydrazone centers between the two, owing to the inversion symmetry of the molecules. However, due to the stochastic nature of measurements in a mechanically controlled break junction setup, we cannot distinguish or control the alignment of the molecules (any symmetric system for that matter) during the junction formation, which makes the alignment of at least one acylhydrazone center with the direction of the field that can facilitate the tautomerization. This tautomerization of one acylhydrazone center breaks the symmetry of the

molecule, and the tautomerization of the second center is catalyzed by the electric field only when aligned properly (when aligned in the reverse direction). This is further proven by the stepwise tautomerization of two acylhydrazone groups rather than a concerted one. Also, the tautomerization of one center alters the energetics of the molecule and hence necessitates a higher electric field for the second tautomerization to occur as both reaction centers are coupled together. From the measurements in the deuterated solvent, we can also conclude that each step is facilitated by a proton wire created around the reaction centers.^{14,15} Figure 7 shows the summary of this proposed sequential proton transfer facilitated by the surrounding solvent molecules in both NPN-2H and PNP-2H. A failure of proper orientation of the molecule to the electric field direction, the absence of the aid of surrounding solvent molecules, or the absence of the required strength of the electric field can lead to partial or no reaction as observed in our experiment. Hence, from the experimental and theoretical studies, we can conclude that for both PNP-2H and NPN-2H, a coupled tautomerization reaction is induced by the electric field with the assistance of surrounding solvent molecules.

CONCLUSIONS

This study demonstrates an electric field-induced reversible tautomerization reaction in two acylhydrazone centers connected by a phenyl ring. The process follows a cooperative proton transfer pathway, and the mechanistic studies unveil a hydrogen-bonded relay mechanism aided by the surrounding protic solvent. Here, the two atomistically sharp electrodes mimic the role of a protein scaffold in an enzymatic pocket.

More than realizing voltage-driven tautomerism occurred at an enzymatic-like break junction pocket, this finding sheds light on the importance of understanding the effect of an in-built electric field present at the enzyme active sites in defining the configurations/conformations of different organic substrates which will eventually take part in chemical transformations. These findings can also be extended to the scope of electric field-induced general chemical reactions. From the comparison of the effect of a chemical stimuli and external electric field on the same organic substrate, we could clearly observe that the electric field possesses the capability of fine-tuning and controlling a given multistep reaction. Making use of this superior power of electric fields can reveal different atypical chemical transformation routes. Moreover, the reversible change shown by our molecular system makes it a perfect example of a single molecular switch working under the principle of electric field-induced prototropic tautomerization. This gives the idea of designing molecular systems with similarly connected centers that can be used as a multistate molecular switch controlled by an external electric field.

■ ASSOCIATED CONTENT

SI Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/jacs.4c12423>.

Synthesis procedure and characterization; conductance measurement data; and theoretical calculations (PDF)

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