

Electrostatic catalysis of a Diels-Alder reaction

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Summary

Traditional views have held that the ability to control reaction rates by means of an electrical potential gradient is unique to redox systems. However, recent theoretical studies suggest that oriented electric fields should affect the outcomes of a range of chemical reactions, regardless of whether a “redox” reaction is involved.¹⁻⁴ This possibility arises because many formally covalent species can be stabilized via minor charge-separated resonance contributors. When an electric field is aligned in such a way as to electrostatically stabilize these minor mesomeric forms, the degree of resonance increases, resulting in overall stabilization of the molecule or transition state. Thus, one should in principle be able to manipulate the kinetics and thermodynamics of non-redox processes using an external electric field. However, to harness external electric fields for catalysis of chemical reactions, the orientation of the approaching reactants with respect to the field stimulus needs to be controlled. Herein we address this problem and provide the first experimental evidence that carbon-carbon bond-forming is accelerated by an electric field. We have designed a surface model system to probe Diels-Alder chemical reactions and coupled this to a scanning tunnelling microscopy break-junction approach (STM-BJ).⁵⁻⁷ The STM-BJ is an electrical measurement performed at the single-molecule level, and is perfectly suited to deliver an electrical field-stimulus across approaching reactants. We show a 5-fold increase in the frequency of single-molecule junction formation due to the reaction when the electrical field is present and aligned in the direction to favour electron flow from the dienophile to the diene. The experimental results are qualitatively consistent with those predicted by quantum-chemical calculations on a theoretical model of this system and herald a new approach to chemical catalysis.

Main Text

All chemical reactions can be viewed as the movement of electrons and/or nuclei; as such one might expect that their kinetics and thermodynamics could be influenced by external electric fields. Even in non-redox reactions, theoretical studies predict that electrostatic effects should in principle influence the stabilities of chemical species by stabilizing or destabilizing charge-separated resonance contributors.¹⁻⁴ For example, in the 1990s, Shaik and co-workers argued that a covalent bond of the form X–Y can be thought of comprising multiple possible resonance contributors $[X-Y \leftrightarrow X^+-Y^- \leftrightarrow X^--Y^+]$.^{8,9} In the absence of an electric field, the extent to which either of the charge-separated structures contributes to the resonance stabilization of the bond will depend on the relative electronegativities of X and Y. Indeed they were able to use this concept to explain the trends in the Group 14 MH₃-Cl bond energies,¹⁰ among other examples. In this light, the presence of an appropriately oriented external electric field has the potential to further stabilize or destabilize these charge transfer contributors and thereby influence bond energy. Moreover, the participation of minor charge-separated resonance structures is not limited to covalent bond energies; it has been invoked to explain trends in kinetics and thermodynamics for a wide range of chemical reactions, including radical addition¹¹ and transfer¹² reactions. Thus, in principle, the scope of electrostatic catalysis – manipulating chemical reactions with electric fields – should be equally broad.

Electrostatic catalysis is the least developed form of catalysis in synthetic chemistry, even though it is widely harnessed by enzymes.¹³⁻¹⁶ This is because such electrostatic effects are strongly directional and effectively quenched in polar-media. Enzymes overcome these problems by creating a low polarity active site in which the substrate binds in a precisely oriented manner; one or more charged residues within this site can then create an oriented local electric field that can catalyse the reaction. In synthetic chemistry, one can mimic this to some extent using charged functional groups on the substrate or catalyst, however balancing the need for low solvent polarity with the limited solubility of charged residues in non-polar solvents leads to compromises that weaken the catalytic effect. For example, aminoxyl radicals (R₁R₂NO•) are stabilized via resonance with R₁R₂N⁺O⁻. Thus,

when a (remote) negatively charged functional group is placed on the left-hand side of the N–O• bond, the electrostatic stabilization of this minor contributor leads to further stabilization of the species.^{2,3} This stabilization, which has been verified experimentally, promotes dissociation of the R₁R₂NO–H and R₁R₂NO–R bonds by as much as 20 kJ mol⁻¹ in the gas phase²; however, the effect, while still of practical significance as a “pH switch” of radical stability, is effectively halved in energetic terms in low polarity solvents such as dichloromethane,¹⁷ and essentially quenched in polar solvents.¹⁸

If one could use external electric fields instead of charged chemical species as the “catalyst”, one could manipulate a much broader range of reactions, conveniently altering both reactivity and selectivity in a tuneable manner predictable by theory. However, to probe this concept experimentally one must develop a method of controlling the orientation of the external electric field (EEF) with respect to the reaction centre. Previously, EEFs have been used to guide the selectivity of isomerisation reactions in which polar intermediates or transition states are involved^{19,20}; but controlling the orientation of the EEF as two molecules collide in bimolecular reactions adds another dimension to the problem. Here we show that this can be achieved by combining surface chemistry procedures with state-of-the-art STM-based single-molecule techniques. STM-based single-molecule electrical measurements can reveal information on chemical coupling averaged over thousands of collisions. It gives us the ability to control the dynamics of the approaching reactants and deliver the field stimulus upon collision. Using this approach, we show that a simple textbook bimolecular carbon-carbon bond forming reaction, the Diels-Alder reaction, involving reagents of ostensibly negligible polarity, can be accelerated by an oriented EEF.

Diels-Alder reactions are a major family of chemical processes used in the preparation of fine chemicals.²¹ Our choice of this reaction was inspired by pioneering theoretical predictions by Shaik, who suggested that the barrier heights for certain Diels-Alder can be lowered significantly when an electric field is oriented appropriately.¹ In the present work we consider a surface tethered furan derivative as the diene and a norbornylogous bridge with a terminal double bond as a non-polar

dienophile ((±)-**NB**, tricyclo[4.2.1.0^{2,5}]non-7-ene-3,4-dimethanethiol; only the (1*R*,2*R*,3*R*,4*R*,5*S*,6*S*)-enantiomeric form is shown in Fig. 1a). Norbornylogous bridges are conformationally rigid molecules and have been extensively used as electrical conduits for probing how geometrical and structural factors influence chemical and electrochemical phenomena.^{22,23,24} The **NB** in Fig. 1a is a short rigid non-polar dienophile with two CH₂SH groups (feet) in *trans*-stereochemistry that allow unambiguous orientation of the distal double bond (dienophile) when assembled on flat gold surfaces.^{23,25} Its rigidity aids the positioning and alignment of the dienophile with respect to the EEF when the diene part of the system is brought in close proximity. The molecular length of the dienophile (**NB**) is kept to a minimum (5 sigma bonds) in order to maintain the Diels-Alder product within the conductance limit of our system.

To ascertain whether this Diels-Alder reaction would be sensitive to the presence of an oriented EEF, we used quantum chemistry to study the field effect on the reaction barrier. This reaction has four structurally distinct Diels-Alder products; results for the reaction with the lowest barrier (*exo-syn*) are shown in Fig. 2, full results are provided in the Supplementary Information. Each product has two diastereoisomers, with the substituents of the furan located either on the left or right of the molecule (see Fig. 2a). The positioning of these substituents leads to different interactions with the CH₂SH groups at the opposite end of the **NB**, resulting in slightly different energies when no EEF is present and very different responses to the applied field. Experimentally, the **NB** is known to sit at an angle to the gold surface,²⁶ tilted by 30° along the Y-axis and 25° along the Z-axis (Fig. 2c). For the *exo-syn* product, the 30° Y-axis tilt means the field lines are oriented roughly along the average vector of the forming bonds. However, the Z-axis tilt means the furan SH-group sits above the forming bonds for the blue diastereoisomer (as shown in Fig. 2c), whereas for the red diastereoisomer it is positioned to the side of the molecule. As a result, the blue structure is predicted to be quite insensitive to the EEF over the experimental range of field strengths, while the red structure shows strong field sensitivity (Section 3.3.2, SI). Specifically, for negative bias, the barrier of formation of the red isomer is predicted to decrease with increasing field strength, while for positive bias it is predicted to

increase (Fig. 2d). This trend is due to the ability of the negatively biased EEF to stabilize resonance contributor I (Fig. 1b), while a positively biased field destabilizes it. In principle, a positively biased field should also lower the barrier height by stabilizing resonance contributor III. However, configuration III has much less inherent stability than I, as the electronegative oxygen prefers to bear a negative rather than positive charge. As a result, this configuration only contributes at strong positive fields, outside of the experimental range (Fig. S3-8, SI). Within the experimental range, our calculations thus predict that the frequency of adduct formation should systematically increase with the field strength for a negative bias up to a factor of 1.5 at 0.75 V, while remaining relatively independent of EEF strength for positively biased fields.

To test these predictions experimentally, we attached the **NB** to the surface of a flat gold electrode and the furan to the STM gold tip. We then undertook a series of STM-BJ experiments known as “blinking”.^{7,27} The blinking technique detects the formation of molecular bridges between an STM tip and a substrate electrode while they are fixed at a specific electrode-electrode distance by imposing an initial setpoint tunnelling current (Fig. 3 and Fig. S2-1). After reaching the setpoint current, the feedback loop is turned off and the current is monitored. Current jumps (blinks) appear when a molecular bridge spans the gap between the electrodes (Fig. 3c). Blinks of conductance magnitude $1.5\text{--}2 \times 10^{-6} G_0$ were observed when the tip and the substrate were separated by a distance that allows the Diels-Alder reaction to occur (*ca.* 1 nm). The formation of these junctions was only seen when both reactants were present. When either reactant was removed from its respective electrode, or when their saturated analogues were used (2-methyl-3-tetrahydrofuranthiol on the tip or a hydrogenated version of **NB** on the surface, a system that is structurally identical but lacks the diene-dienophile character), no evidence of a molecular bridge formation was found (Fig. S2-2/S2-3 and S2-4/S2-5, respectively in the SI). Hence, the junctions are formed as a result of the Diels-Alder reaction. At positive voltage biases (surface positive), the frequency of the molecular bridge formation is constant (5 blinks/hr) over a wide applied bias range. In contrast, at negative biases the frequency is clearly affected by the strength of the field, and increases from 5 blinks/hr at -0.05 V bias to 25 blinks/hr

at -0.75 V bias (Fig. 4). These trends are in complete qualitative agreement with the theoretical predictions in Fig. 2d. Quantitatively, there are differences, which may relate to the difference in realms being studied experimentally and computationally (single molecule reaction rates versus bulk reaction rates), and/or the use of pre-complexes in calculating field effects on barrier heights (see the Supporting Information for further detail).

As further validation that the experiment is detecting C-C bond formation, we note that the average lifetime of the blinks was 0.4 s (Fig. 3d) with poor dependence on the electric field magnitude for positive biases up to 0.75 V (Fig. S2-1, SI). This lifetime is around the same as that observed for standard single-molecule wires thiolated from both ends.^{6,24} A bias value higher than $|0.75|V$ led to a drop in the lifetime of the junctions due to the instability of the gold-sulphur contacts. Hence, the upper limit of the bias was kept below $|0.75|V$ to allow the comparison of different biases while maintaining comparable junction stability. The formation of mechanically stable C-C bonds was also confirmed by collecting pulling curves during the blinking events (Fig. S2-6, SI), or by performing pushing/pulling cycles (Fig. S2-7, SI). Pulling curves collected over the “blinks” showed a plateau with an average pulling length of 0.2 nm, which corresponds to the stretching of the single-molecule bridge. When the pulling was exerted over the tunnelling background or on random noise (Fig. S2-6d), a clean exponential decay was observed, testifying that the above blinks are a consequence of a stable molecular junction rather than the migration of gold atoms or molecular conformational fluctuations.^{28,29}

The formation of a robust molecular junction was also confirmed using an STM-BJ approach^{5,30} referred to as tapping where the furan-modified tip was repeatedly driven in and out of contact with the **NB**-modified substrate (Fig. S2-7, SI). The reactants are mechanically brought together allowing junction formation and the tip is then pulled away, breaking the molecular junction. Plateaus in the current versus distance curves of the same conductance magnitude to that observed in the blinking experiments ($1.5-2 \times 10^{-6} G_0$) were detected during the pulling portion of the cycles (Fig. S2-7 and

Section 2.6, SI), further supporting the formation of stable molecular wires when the two reactants are brought together under an electrical field. Moreover, changes to the magnitude and the direction of the field applied across the reactants were found to affect the rate of the Diels-Alder in a similar manner to what was found via blinking. Tapping data (Fig. S2-7, SI) show that the product formation increases up to 4.4 fold from 4.2% (252 product molecules out of 6000 attempts) to 18.6 % (1116 product molecules out of 6000 attempts) when the surface is biased negatively with respect to the tip.

In conclusion, herein we present the first experimental evidence of a non-redox bond-forming process being accelerated by an oriented external electric field. The experimental results are qualitatively consistent with the theoretical calculations and result from the ability of the field to electrostatically stabilize a minor charge-separated resonance contributor of the transition state. This ability to manipulate chemical reactions with electric fields offers proof-of-principle for a step-change in our approach to heterogeneous catalysis.

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Author Contributions A.C.A., N.D., and I.D.-P. performed all the STM experiments and analysed the data. N.J.B. and N.L.H. performed the quantum-chemical modelling with input from M.L.C. S.C. carried out the synthetic work. All authors contributed to conceiving the work and designing and discussing the experiments. M.L.C and S.C. wrote the manuscript with significant contributions from the other authors.

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Figure Captions

Figure 1 | Electrostatic catalysis of a Diels-Alder reaction. **a**, The effects of an external electrical field on the reaction rate are studied using single-molecule STM-BJ conductance measurements, which provide the oriented electric field stimulus and count reaction events. A furan is attached to the STM tip via a thiol; the dienophile, a norbornylogous bridge, is attached in a known orientation²⁶ to a flat gold surface via two thiols. Four structurally distinct products may be formed, each having two diastereoisomers; the kinetic product is shown here. **b**, Possible resonance structures of the transition state. When a field is present, minor contributors *I* or *III* may be stabilized sufficiently to undergo resonance with *II*, lowering the reaction barrier. The arrows show the field direction most likely to stabilize *I* or *III*, with *I* expected to experience greater stabilisation at a given field magnitude.

Figure 2 | Computational modelling of the Diels-Alder reaction. **a**, The two diastereoisomers of the *exo-syn* product of this reaction. These were the kinetically favoured products; the six other products had much higher barriers over the experimental range of field strengths. **b**, The coordinate axes used to orient the field with respect to the molecule. The Z-axis lies along the double bond of the dienophile, while the X-axis is directed along the **NB** backbone. **c**, The scenario being modelled, showing the **NB** bridge sitting in the experimentally determined orientation with respect to the surface of the STM plate and the electric field lines passing through the reaction centre at an oblique angle to the **NB** double bond. **d**, The effect of field strength and direction on the barrier height (ΔE^\ddagger) for formation of the two *exo-syn* diastereoisomers in **a** (see Supplementary Information).

Figure 3 | Blinking experiments. **a**, Schematic of the STM tip and surface during a blinking experiment. The STM tip was modified by furan molecules and the surface was modified with the **NB** molecules using self-assembled monolayers procedures (see details in the SI). **b**, A cartoon detailing the stages encountered during a blinking event. **c**, The corresponding STM current response before (1), during (2) and after (3) the formation of a representative blink (junction). **d**, 2D maps overlaying hundreds of blinks. Counts have been normalized to a colour scale with 100 counts representing the maximum and 0 representing the minimum. The surface bias was -0.5 V in Figures **c** and **d**.

Figure 4 | Frequency of blinks (junctions) as a function of the applied bias. Positive and negative biases are plotted in red and blue, respectively. To keep the distance between the surface and tip constant across the bias range, the same set point current was used and the bias was changed while

the STM feedback was turned off. The blinking experiments were performed over time periods of 1 h. At the end of each 1 h period, the furan-modified STM tip and its lateral position with respect to the surface were changed to compensate for the loss of reactants. This procedure was repeated 8 times, giving each bias point (magnitude and direction) a total experimental time of 8 h. The chronology of the selected biases was changed randomly for each repeat. Error bars represent the standard deviation from the 8 (1 h) intervals.

Figure 1

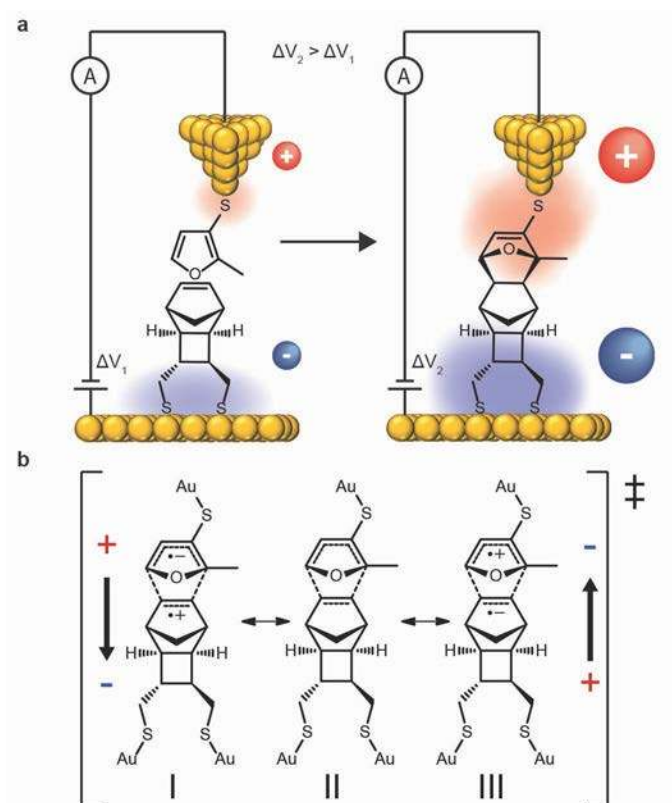


Figure 2

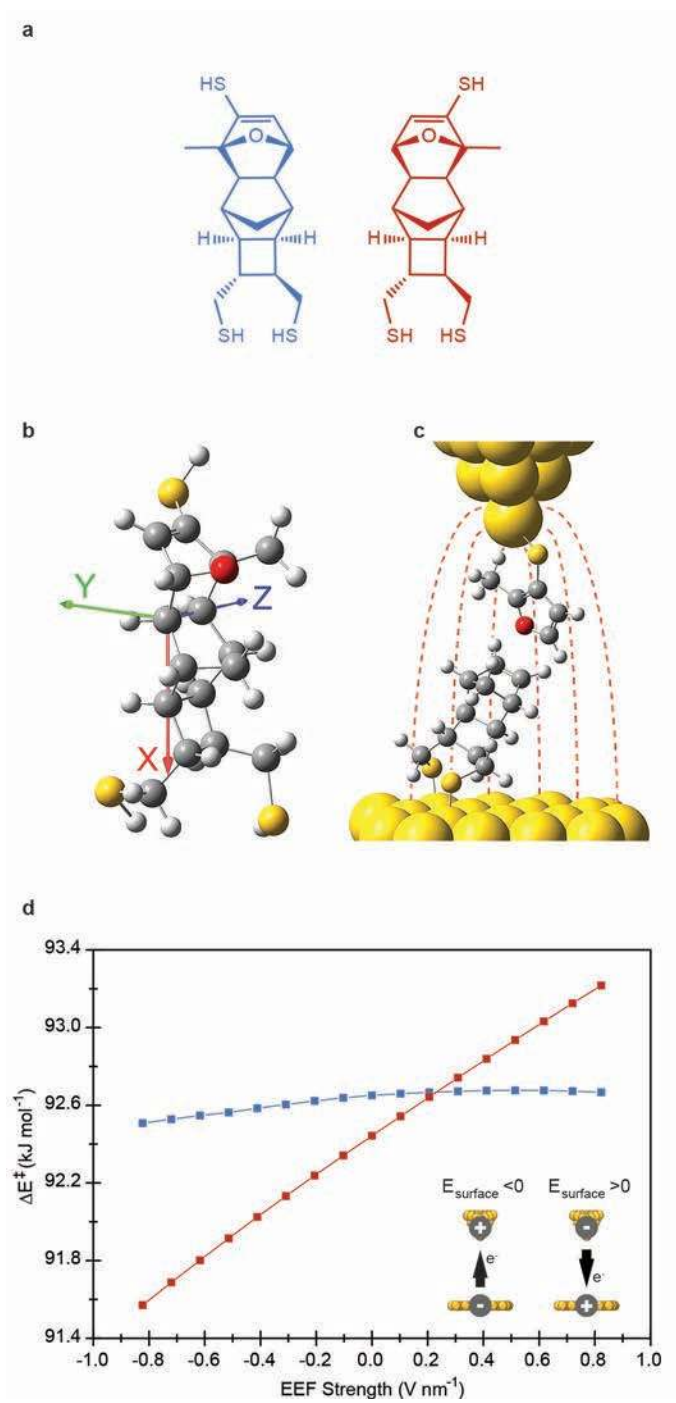


Figure 3

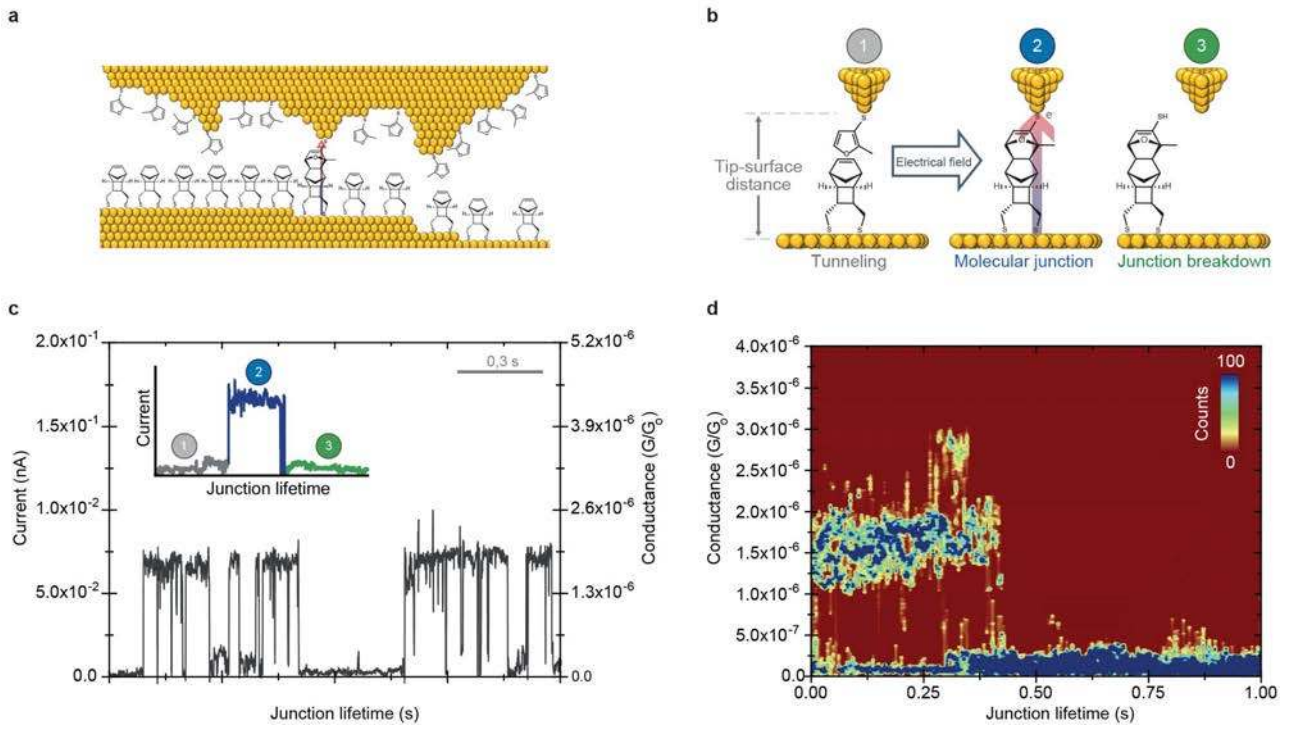
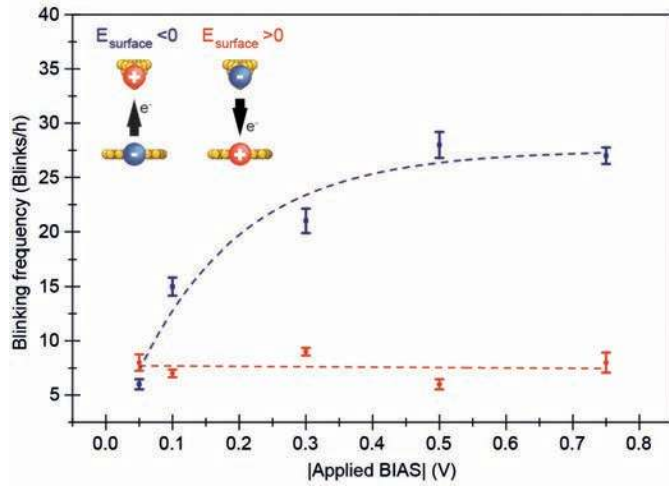


Figure 4



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