# Single-Electron Catalysis of Reversible Cycloadditions under Nanoconfinement

Xin Zhu,<sup> $\perp$ </sup> Hongliang Chen,<sup>\*, $\perp$ </sup> Jinying Wang,<sup> $\perp$ </sup> Agostino Migliore,<sup> $\perp$ </sup> Xingxing Li,<sup> $\perp$ </sup> Yanwei Li, Boyu Wang, Chen Yang, Yang Jiao, Jiawen Cao, Caiyao Yang, Chunyan Gao, Suhang He, Kendall N. Houk, Jinlong Yang,<sup>\*</sup> J. Fraser Stoddart,<sup>\*</sup> Chuancheng Jia,<sup>\*</sup> and Xuefeng Guo<sup>\*</sup>



forms. Experimental and theoretical results consistently demonstrate that combining single ET processes with nanoconfinement involving cucurbit[8]uril can lower the reaction energy barrier and promote reversible cycloaddition. Moreover, we show that the bias voltage can fine-tune ET processes and chemical equilibria in bond formation and cleavage. Our results provide a novel approach to elucidate, modulate, and design electron-involved reactions and functionalized devices.

# ■ INTRODUCTION

The electron, as an elementary particle, can act as an effective catalyst of redox reactions with radical intermediates of paramount importance in biology, biomedicine, and chemical synthesis.<sup>1</sup> Energy barriers can be lowered through the addition or removal of an electron in the reaction substrate. Electron catalysis has thus received widespread attention in synthetic chemistry.<sup>2-5</sup> Chemical reactions initiated<sup>6-9</sup> by redox agents, photocatalysts, and electrochemistry commonly involve electron catalysis, leading to the formation of radical intermediates.<sup>5,10,11</sup> A thorough understanding of the catalytic function of electrons is essential for the design and optimization of these reactions. Recent advances in time-resolved techniques such as transient absorption spectroscopy and laser flash photolysis have boosted their use to study reactions involving electrons but are limited to photoinduced reactions.<sup>12</sup> Single-molecule electrical detection techniques immobilize a single molecule between electrodes separated by nanogaps to form robust linkages, thus enabling the investigation of the dynamic behavior and reaction trajectories of single molecules with label-free, nondestructive, and high-resolution characteristics.<sup>13-17</sup> Moreover, molecular engineering and gate modulation can be utilized to regulate the quantity of electrons on a single-molecule bridge.<sup>18,19</sup>

cycloadditions through advanced single-molecule detection plat-

Technological advances in the confinement of supramolecular complexes between electrodes can enable a richer, controllable

chemistry. In fact, supramolecular systems have been the subject of continued interest in catalyzed reactions, as they can effectively position two coencapsulated guests within a confined cavity,<sup>20</sup> thus favoring specific reaction pathways that improve the reaction rate and efficiency. Despite the potential benefits of combining nanoconfinement catalysis and electron catalysis in catalyzed reactions (including many radical reactions), little research has been reported on their joint application.

Cycloadditions are one of the most fundamental reactions in organic and synthetic chemistry, and play a particularly significant role in the synthesis of carbocyclic compounds.<sup>21,22</sup> Both (2 + 2) and (4 + 4) cycloadditions can be triggered not only by UV-light irradiation<sup>23</sup> but also by electrons.<sup>24,25</sup> In recent years, cycloadditions involving electrons have attracted considerable interest from chemists due to their rapid reaction rates, low activation energy barriers, and remarkable stereoselectivity. Here, we present a new approach to quantitatively investigate and control cycloadditions involving electron

Received:December 17, 2024Revised:January 30, 2025Accepted:January 31, 2025Published:February 6, 2025





**Figure 1.** Structure and characterization of supermolecule-based single-molecule junctions (SMJs). (a) Schematic of a supermolecule-based SMJ. (b) SEM and AFM images of a representative indented graphene point contact array. (c) Fluorescence super-resolution imaging of the single-molecule connection. (d) I-V curves of open circuits with graphene point contacts (black) and single-molecule junctions after supramolecular connection (red). Insets show open circuit and molecular junction devices, respectively.

catalysis by means of electrical measurements and bias voltage regulation within a molecular junction setup. Our strategy combines chemistry, molecular-scale electronics, and other nanotechnology, using a nanoconfined positively charged supramolecular complex to regulate the single-electron catalysis of (2 + 2) and (4 + 4) cycloadditions (Figure 1a).

## RESULTS AND DISCUSSIONS

Nanoplatform for Controllable Single Electron-Catalyzed Cycloadditions. We fabricated stable supramolecular assembly-based single-molecule junctions (SMJs) that are the scene of the chemical reactions studied (Figure 1a). Cucurbit[8]uril (CB[8])-mediated ternary host-guest complexes are the reaction center for the intermolecular cycloadditions.<sup>26,27</sup> CB[8] works as the source of nanoconfinement for the charged guest molecules.<sup>28</sup> (*E*)-1-(3-Aminopropyl)-4-(2-(pyridin-4-yl)vinyl)pyridin-1-ium (PVP) and 1-(3-aminopropyl)-4-(anthracen-2-yl)pyridin-1-ium (AnPy) are the guest molecules for (2 + 2) and (4 + 4) cycloadditions, respectively. PVP and AnPy contain terminal amine groups for covalent linkage to carboxyl-terminated graphene electrodes.<sup>29</sup> At the heart of this design is the fact that the positively charged guest molecules excel at accepting electrons that can initiate electron catalysis. In addition, CB[8], which serves as the host molecule, can prevent radical intermediates generated during the catalytic process from being quenched by the environment. The quenching of intermediate states by the electrodes is prevented by the insertion of three methylene ( $-CH_2-$ ) groups as spacers between the central molecular core and the electrode-anchoring tails, which reduce the interfacial electronic couplings and strengthen the redox character of the electron localization at the molecular centers.<sup>30</sup>

Our label-free, nondestructive single-molecule electrical platform offers great opportunities to gain an understanding and control of the mechanism underlying electron-catalyzed cycloadditions. The approach is implemented by directly monitoring the time trajectories and reaction pathways of individual intermediates and transition states in catalytic processes occurring within the confined supramolecular region. In the molecular junction established by the supramolecular system bridging the graphene electrodes (Figure 1a), each distinct reaction species in the single electron-catalyzed



**Figure 2.** Electrical signals and electron-catalysis mechanism for the (2 + 2) cycloaddition. (a) Representative *I*–*t* traces and corresponding statistical histograms with a bias voltage of 500 mV at 300 K, showing four distinguishable conductance levels. (b) Enlarged *I*–*t* trajectories illustrating two types of oscillations between states 1/3 and states 2/4. (c) Number of transition events to each state within 30 s. (d) Time sequence of transitions between different reactants, intermediates, and products during a (2 + 2) cycloaddition, in which state 5 is observed. (e) Theoretical energy profiles of a single electron-catalyzed cycloaddition. TS: transition state; MS: metastable state. (f) Plausible mechanism for a reversible single electron-catalyzed cycloaddition and reversible transition rates between states 1, 2, 3, and 4. (g) Marcus parabolas depicting an ET process between states 1 and 3.  $\lambda = 0.28$  eV is obtained for this ET.

cycloadditions is identified through a unique conduction state (namely, it is the support of a well-distinguishable charge transport channel<sup>31</sup>), and each reaction step corresponds to a variation of the current through the molecular junction (Figure 2).

**Resulting Cycloaddition Reaction Pathways.** For (2 + 2) cycloadditions, we determine (vide infra) the following reaction trajectory (Figure 2f): (i) the injection of one electron from an electrode into the **PVP** substrate (which corresponds to conduction state 4) produces a **PVP** radical intermediate (state 2); then, (ii) a cyclized radical intermediate (state 1) is generated by passing through the formation of a metastable intermediate species in which the two pyridine-containing

subunits are linked by a single C–C bond (state 5); (iii) finally, a cyclized product (state 3) is obtained by releasing the electron back to the electrode, after which the process can be repeated. The conduction states, except for state 5, which is hardly populated, are characterized by different molecular structures and/or redox states (see analysis in Figures 2 and 3). The nanoconfined chemical systems show more conduction channels than standard redox junctions, corresponding to different redox states of the same molecular structure.<sup>31,32</sup>

A plausible mechanism for the electron-catalyzed (4 + 4) dimerization involves three steps (Figure 4a): (i) one electron is injected from a graphene electrode into the reactant (state 4'), resulting in the formation of a radical complex (state 2'); (ii) a



**Figure 3.** Bias-dependent kinetics for a (2 + 2) cycloaddition. (a) Recorded *I*-*t* traces and corresponding enlarged images (right inset) under different bias voltages, at a temperature of 300 K. (b) Corresponding proportion statistics of each molecular species. (c) Species lifetimes during ET under different bias voltages. (d) Linear relationships between lnk and V<sub>d</sub> for the reversible ET processes. (e) Linear relationship between lnk and V<sub>d</sub> for reversible transitions between states 1 and 2.

cycloaddition occurs within this complex to produce a cyclized radical species (state 1'); (iii) the electron is released back to the electrode, leading to the formation of the dimerization product (state 3').

Next, we describe the combined experimental and theoretical investigations that led to the formulation of the reaction mechanisms. Moreover, we propose a strategy to manipulate the reaction kinetics by regulating physical parameters, such as the bias voltage applied to the junction.

**Device Characterization.** The characterization of the SMJs is summarized in Figure 1b–d, while details on the molecular synthesis, characterization, and formation of the host–guest complexes are provided in the Supporting Information (Schemes S1–S7 and Figures S1–S6), and details of the device fabrication process are reported in the Supporting Information

(Methods and Figures S7–S9). Scanning electron microscopy (SEM, Figure 1b, top) and atomic force microscopy (AFM, Figure 1b, bottom) images demonstrate that a graphene sheet was cut, resulting in indented point contacts that create a nanogap. The statistically estimated size of the gap is 1 to 10 nm, which provides an ideal range of distances for supramolecular connection. Using stochastic optical reconstruction microscopy,<sup>33</sup> a single fluorescent spot was detected between the graphene nanoelectrodes (Figure 1c), thus providing direct evidence for the successful incorporation of a single fluorescent supramolecular complex between the electrodes and therefore the formation of an SMJ.<sup>34</sup> Indeed, the clear and consistent observation of fluorescent spots also gives support for the linkage of the supramolecular complex to the nanoelectrodes. The successful formation of SMJs was further confirmed by



**Figure 4.** Single electron-catalyzed (4 + 4) cycloaddition. (a) A plausible mechanism for a (4 + 4) cycloaddition. (b) Theoretical potential profiles for the (4 + 4) cycloaddition. TS: transition state; MS: metastable state. (c) Idealized *I*–*t* trace with four distinguishable conductance levels under a 500 mV bias voltage at 300 K. (d) Corresponding reversible transition rates between states 1', 2', 3', and 4'. (e) *I*–*t* traces and corresponding enlarged images (right inset) under different bias voltages.

electrical measurements (Figure 1d and Figure S10), which show nano-Siemens (nS)-level conductance. In fact, these conductance values indicate that the targeted supramolecular complexes were successfully connected to the nanoelectrodes. Furthermore, through inelastic electron tunneling spectroscopy (IETS) performed at 2 K, we identified specific molecular vibrations that are consistent with our theoretical infrared and Raman spectra (Figure S11). These combined experimental results as well as the accompanying theoretical analysis provide strong evidence for the successful creation of supramolecular SMJs.

Identification of (2 + 2) Cycloaddition Species and Reaction Path. The study of single-molecule conductance can

provide valuable information about the electrical and conformational properties of molecules, or molecular complexes, and their perturbation.<sup>35</sup> Here, real-time current—time (I-t) measurements (Figure 2a) with a temporal resolution of approximately 17  $\mu$ s using SMJs help us track the trajectory of the (2 + 2)cycloaddition. These measurements are performed in vacuum at a constant bias voltage of 500 mV and a temperature of 300 K. Statistical histogram analysis of the I-t curve shows (Figure 2a, right inset) four dominant sequential conduction states, labeled as state 1, state 2, state 3, and state 4, and a barely populated state 5 (vide infra). Next, we show that these states correspond to the molecular species in the energy profile of Figure 2e, kinetically

First, our extensive analysis of the I-t measurements (Figure 2b-d) shows that (i) there are no direct transitions between states 1/4, states 2/3, and states 3/4 (Figure 2c), (ii) there are rapid and very frequent oscillations between states 1/3 and states 2/4 (Figure 2b), and (iii) switching between states 1/2(Figure 2c) is relatively slow. Point (i) indicates that the absence of communication between the molecular species corresponding to states 3 and 4 has a structural basis, while (ii) suggests that states 1/3, as well as states 2/4, are connected by ET steps. Moreover, the higher conductance of states 1 and 2 compared to states 3 and 4 supports that the latter are characterized by a redox state with a higher positive charge, which increases the effect of orbital (electrostatic) gating,  $^{31,32,36}$  favoring a more localized transient distribution of the electronic charge transferring between the electrodes and hence an accordingly lower current. These considerations, together with point iii, concur to locate the structural change involved in the cycloaddition between states 1 and 2. In fact, through analysis of the I-t curve on a magnified time scale, we find a new conduction state (state 5) (Figure 2d) that may be identified as a structural intermediate, although it has a low probability of occurrence as a distinct nonvirtual state in the transitions between states 1 and 2.

In a control experiment (Figure S12), the C=C double bond linking the two pyridine-containing units in the PVP substrate is replaced with a C–C single bond, and real-time I-t measurements are conducted. The bias-dependent results display no current fluctuations under identical circumstances, therefore indicating that the oscillations between conduction states arise from the conversion of the double bonds to a cyclobutane ring. Furthermore, the (2 + 2) reaction was analyzed through singlemolecule conductance measurements using the scanning tunneling microscope-break junction technique (Figure S13), revealing that two distinct conductance states correspond to the PVP reactant and the cyclobutane product. This conclusion is supported by the direct detection of the cyclized product in the ESI-Mass spectrum, conducted 48 h after initiating the reaction (Figure S14). Therefore, mass spectrometry analysis confirms the formation of the cyclobutene product, providing critical experimental evidence to validate the proposed reaction mechanism.

At this point, we need to attribute molecular species to states 1-4. Since the corresponding currents are of the same order of magnitude, we can expect that states 1 and 3, as well as 2 and 4, differ by a single electron charge and are thus connected by oneelectron processes. To verify this hypothesis, which supports the set of molecular species in Figure 2f, we first examined cyclic voltammograms of **PVP** and the  $CB[8] \supset 2PVP$  complex taken on a macroscopic scale (Figure S15). The guest molecule PVP displays a single redox wave at  $\sim -0.87$  V versus Ag/AgCl, while the host–guest complex  $CB[8] \supset 2PVP$  shows two redox peaks at  $\sim -0.66$  and  $\sim -0.88$  V, respectively. These results suggest that the host-guest complex holds remarkable promise for implementing an ET process through one-electron injection with a low potential voltage. Then, theoretical simulations based on density functional theory (DFT) were used to investigate three potential reaction pathways; no-electron (Figure S16), one-electron (Figure 2e), and two-electron (Figure S17) reactions. Both no-electron and two-electron mechanisms are ruled out because of the predicted high kinetic energy barriers of  ${\sim}1.97$  and  ${\sim}1.93$  eV, respectively, for the cycloaddition.

The molecular species in Figure 2e,f are safely assigned to the different conduction states in Figure 2a-d by modeling the SMJs bridged by the different species (Figure S18) and calculating the corresponding electron transmission spectra (Figure S19), whose information is then consistently combined with kinetic modeling and charge-transfer analysis (Supporting Information Sections 4, 6, and 7). Despite the approximations underlying the theoretical calculations, such as the narrowing of the energy gap between the highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO), the transmission functions indicate that the charge transport involves the LUMOs of the cationic supramolecular bridge and that the conduction states 1-4 can be associated, in the order, with the following molecular species in the reaction path: cyclobutane radical intermediate (state 1), PVP dimer radical intermediate (state 2), dicationic cyclobutane product (state 3), and dicationic PVP dimer (state 4).

The precise correlation between *I*–*t* measurements and DFT calculations greatly enhances our understanding of the different reaction species and the reaction steps connecting them. In the one-electron pathway of Figure 2f, the presence of CB[8] decreases by nearly 1 order of magnitude the activation energies  $(E^{a})$  of the ET processes that deliver one electron to the electrodes (compare energy profiles in Figure 2e and Figure S20), thus making the transitions from state 2 to 4 and from state 1 to 3 feasible, although much slower than the converse ones (see theoretical analysis in Supporting Information Sections 4 and 6). The lifetime of each conduction state (hence, the corresponding rate of transition to the partner redox state) measured experimentally is consistent with the activation energy of each reaction step calculated using DFT with the framework of Marcus ET theory<sup>37</sup> (Figure 2g and Table S1). Analyzing the I-t curves, we find that the intermediate radical (state 2) is generated at a rate of  $\sim$ 5405 s<sup>-1</sup> by electron injection from the electrodes (Figure 2f, left red arrow), while the reverse process of electron release occurs, under the same bias voltage, at a slower rate of  $\sim$ 136 s<sup>-1</sup> (Figure 2f, left blue arrow). A similar ET kinetics occurs in the cycloreversion between the cyclobutane product (state 3) and its radical intermediate (state 1). These rates are in line with the fact that the activation energies of the electron-gaining steps ( $E_{4 \rightarrow 2}^{a} = \sim 0.099$  eV and  $E_{3 \rightarrow 1}^{a} = \sim 0.020$ eV) are lower than those of the electron-releasing steps  $(E_{2}^{a} \rightarrow 4 =$ ~0.529 eV and  $E_{1 \rightarrow 3}^{a} = \sim 0.150 \text{ eV}$  (Figure S21, Tables S1 and S2). In addition, the experimental activation energies for state 4 to 2 (or state 1 to 3) transition, presented in Table S3, are consistent with the calculated values, showing consistency between experimental observations and theoretical predictions.

CB[8] also influences the energy barriers for the creation of the metastable intermediate 5, dramatically reducing the barrier between states 2 and 5, while slightly increasing that between states 1 and 5 (Figure 2e and Figure S20). Nevertheless, the bond formation and cleavage are characterized by theoretical values of the activation energies of  $\sim 0.35$  and  $\sim 0.66$  eV, respectively, in the presence of CB[8]. These high values are in qualitative agreement with the low effective rates of bond formation and cleavage (~187 and ~149 s<sup>-1</sup>, respectively) derived from the experimental I-t traces and also consistent with the extremely short lifetime of conduction state 5 (metastable reaction intermediate state), where it does not behave as virtual state in the transitions between states 1 and 2 (the possibility that this occurs prevents a quantitative agreement between the relative values of the calculated effective rates and the corresponding activation energies).

Overall, both single electrons and CB[8] can function as catalysts by reducing the reaction energy barriers and promoting cycloaddition and retro-cycloaddition. This is particularly true for the reaction pathway in the direction of cycloaddition (from state 4 to 3; see Figure 2e,f), but both reaction directions can be influenced by the application of appropriate bias voltages.

**ET** in the Reaction Path and Its Tuning By Temperature and Voltage. Measurements and theoretical analysis of electron transitions between states 1/3 and those between states 2/4 provide further validation of the reaction mechanism while also providing a deeper understanding of the ET processes involved and highlighting opportunities for tuning of the reaction rate through changes in temperature and voltage.

Our *I*–*t* measurements at temperatures ranging from 180 to 300 K and different bias voltages show a strong dependence of states 2/4 and states 1/3 transitions on temperature (Figures S22–S27), as is expected for incoherent Marcus-type ET.<sup>32,38</sup> Additional analysis of the 1-to-3 transition shows, indeed, remarkable (340-fold at 50 mV and 129-fold at 500 mV) increases of the ET rate as the temperature is varied from 240 to 300 K (Figure S28). These large variations may result from temperature effects on factors such as the molecule-graphene coupling (see Supporting Information Section 7) and the related density of states for charge carriers in the electrodes near their Fermi level,<sup>39</sup> as well as room or near room temperature stereoelectronic effects (see discussion in Figure S26).

The transitions between different redox states through interfacial incoherent ET processes (Figure 2f) provide negligible contributions to the junction current, because these reaction steps involve well-localized charge distributions in the molecular system, thereby representing slow conduction channels.<sup>31</sup> In terms of electric current, the function of these redox steps is to switch between the various redox states, each supporting a different fast conduction channel with a distinct current (Figure 2a) (this is easily understood in a qualitative single-particle picture: the charge responsible for a given redox state is described by a localized molecular orbital, while another, more spread molecular orbital is transiently occupied by the quickly transferring electron charge<sup>31</sup>). The charge transport through the fast channels mainly occurs via incoherent or coherent tunneling depending on the temperature.

Through analysis of the current-voltage (I-V) characteristics (Figure 1d and Figures S29–S32) on individual supramolecular junctions, we observe a noticeable increase in current in the (2 + 2) (Figures S29 and S30) systems when the temperature is raised from 2 to 300 K. The same applies to (4 + 4) systems; see Figure S31). It is worth stressing that the continuous I-V curves result from a current measurement integration time in which many of the current oscillations visible along the I-t traces take place.

The monotonic increase of the current with temperature means a thermally activated conduction of the junction, as expected from the redox character of the supramolecular system, which is accentuated by the presence of a positive charge. <sup>31,32,37,40</sup> Furthermore, the current increase with temperature at all voltages (hence, also for bias voltages much larger than the thermal voltage  $k_{\rm B}T$ ) excludes that high-temperature coherent transport is at stake <sup>39,41</sup> (see Supporting Information Section 6). The free energy landscape in Figure 2g implies that the rate of the transition from state 3 to 1 is appreciable even at zero bias (Supporting Information Sections 6 and 7) and no threshold bias voltage is expected to enable at least the charge transport channel involving state 1,<sup>32,37</sup> in agreement with

Figure 1d and Figures S29–S32. Furthermore, the existence of conduction channels with relatively large inner-sphere reorganization energies and different free energy parameters, accessible at different voltages, can explain the continuous growth of current over the explored voltage ranges.<sup>31</sup>

Arrhenius analysis shows the typical transition from the temperature-dependent incoherent conduction mechanism to coherent tunneling at sufficiently low temperatures (this is the charge transport regime for all devices and biases applied as the temperature is less than 60 K). In addition, the I-V characteristics of the (2 + 2) SMJ in Figure S29c suggest a possible occurrence of an inverted Marcus regime for some of the conduction states, resulting in near activationless charge transport at sufficiently large bias voltages<sup>31,32,36,37</sup> (see details in Supporting Information Section 6).

To examine how the bias voltage impacts the thermodynamics and kinetics of single electron-catalyzed cycloaddition, I-t traces are monitored at varying bias voltages (Figure 3a). The statistics obtained from the histograms of the current distribution reveal how the bias voltage influences the reaction equilibrium (Figure 3b and Figure S33). As the voltage is increased from 0.05 to 0.5 V, we see a steady increase in the percentage of the PVP radical (state 2) from about 7 to 58%, and a decrease in the proportion of the cyclobutene radical (state 1) from approximately 80 to 40%. Therefore, the area ratio of the PVP radical (state 2) to the cyclobutene radical (state 1), ascertained through the statistical histograms, experiences a more than 17-fold increase (Figure S34, orange). The observation that increasing the voltage leads to the stabilization of state 2 can be explained by the radical's (state 2) greater degree of conjugation and electron delocalization. Moreover, the area ratio of the PVP reactant (state 4) to the cyclized product (state 3) has an 18-fold increase (Figure S34, green), indicating a shift in the reaction equilibrium toward cycloreversion. The proportion of state 5 is too small to allow for a meaningful statistical analysis of voltage effects on it.

Detailed kinetic data for the reversible electron-catalyzed cycloaddition are derived from a vast analysis of I-t traces (Figure S35). Figure 3c illustrates the bias-dependent transition lifetimes  $(\tau)$  for electron injection and removal. As the bias voltage changes from 0.05 to 0.5 V, the electron injection by the electrode leading from cyclobutene (state 3) to the cyclized radical (state 1) exhibits a significant reduction in the lifetime, decreasing from approximately 122 to 17  $\mu$ s. Conversely, the reversible electron removal process (which brings the molecular system from state 1 to state 3) shows an increase in the lifetime from about 4.28 to 7.16 ms. These trends were quantified by calculating the transition rate (k) for each step as  $k = 1/\tau$ . The result is a linear relationship between lnk and the voltage (Figure 3d), with a positive slope of approximately 4.1 for the electron injection (forward ET process) and a negative slope of about -0.9 for the electron removal (backward ET process). These findings demonstrate that the bias voltage significantly promotes electron injection while opposing electron removal. These opposite trends are in full agreement with the expectations based on Marcus' expressions for the interfacial ET rates with biasdependent reaction-free energies and their later developments (see also Supporting Information Sections 6 and 7).<sup>32,37,38,42</sup> In fact, the increasing bias voltage changes the reaction free energy for the interfacial ET processes so as to increasingly favor the electron injection into the molecular system and oppose the converse electron removal process. A similar trend is observed for the PVP reactant (state 4) and PVP radical (state 2) (Figure

3d). Compared to cyclobutane (state 3) and its radical (state 1), the linear relationships between lnk and the voltage for the **PVP** reactant (state 4) and its radical (state 2) show a reduced slope of ~1.7 for electron injection and an increased negative slope of ~-1.7 for electron removal. This is expected based on the zerobias values of the two transition rates for states 2/4 and their predicted saturation to the same values as those for states 1/3 at high enough voltages<sup>32,37</sup> (see also Figure S36 and its discussion).

In conclusion, the bias voltage has a significant impact on adjusting the reaction kinetics of the electron injection and removal steps in the cycloreversion reaction, promoting the formation of the cyclized radical (state 1) while also inhibiting the consumption of the **PVP** radical (state 2).

Regarding the kinetics of bond formation and cleavage, the transition lifetimes of states 1 and 2 increase gradually with increasing bias voltage (Figure S37), thus indicating that both the **PVP** radical (state 2) and cyclized radical (state 1) are stabilized by electric fields. The linear relationships between lnk and the voltage suggest that the reversible processes of chemical bond formation and cleavage are inhibited by the voltage (Figure 3e). However, the effective rates of interconversion of states 1 and 2 include the rates of the transitions involving state 5 (see the kinetic model in Supporting Information Section 7), which cannot be calculated with sufficient statistical accuracy from the available data, thus preventing a closer comparison between the kinetic analysis and the population analysis in Figure 3b and also the kinetic model in Supporting Information Section 7).

(4 + 4) Cycloaddition Species and Reaction Path. A (4 + 4) dimerization was also examined to confirm the general applicability of our SMJ technique to (positively charged) nanoconfined single electron-catalyzed cycloadditions. The DFT-calculated energy profile (Figure 4b) for the one-electron-catalyzed pathway in Figure 4a shows that the energy barriers for cycloaddition and cycloreversion (which are around 0.47 and 0.73 eV, respectively) are comparable to those for (2 + 2) cycloaddition, thus suggesting that the one-electron-catalyzed (4 + 4) cycloaddition pathway can also be reversible.

The reaction pathway is identified based on theoretical calculations and the time sequences of the four conduction states (Figure 4c), labeled as state 1', state 2', state 3', and state 4'. In line with the findings from the (2 + 2) cycloaddition experiments, we observe rapid and frequent oscillations between states 1'/3' or states 2'/4', which are linked to the electron injection/release processes. The transition rates for each step, as determined from real-time data, demonstrate that electron injection is faster than electron release (Figure 4d). The process of chemical bond formation between the radical complex (state 2') and the cyclized radical (state 1') includes a step in which a single bond forms (Figure 4b) between two anthracene units, resulting in a metastable state (MS 5'). The rate of the transition from state 2' to 1' in the (4 + 4) cycloaddition (~3039 s<sup>-1</sup>) is much higher than that for the transition from state 2 to 1 in the (2 + 2) cycloaddition (~187 s<sup>-1</sup>). This explains why we are unable to detect an electrical signal for MS 5'.

We explore the impact of voltage on electron-catalyzed (4 + 4) cycloaddition through bias-dependent *I*-*t* measurements (Figure 4e and Figure S38). When a bias voltage of 100 mV is applied to the SMJ, only one conduction state is noticeable, suggesting that a threshold voltage is required to initiate the (4 + 4) cycloaddition.<sup>32</sup> Although the energy profiles in Figures 2e and 4b will change with the voltage, their shapes at zero bias

voltage indicate that a more appreciable voltage is necessary to carry out the full reaction path in the (4 + 4) compared to the (2 + 2) system. On the other hand, the much greater extent of conjugation in the (4 + 4) complex than in the (2 + 2) complex favors the delocalization of electron charge across the supramolecular system, with more extended tails in the anchoring regions and therefore larger electronic couplings to the electrodes. It is thus not surprising that, at the bias voltage of 500 mV, the charge-transfer rates for the (4 + 4) system (Figure 4b) are larger than those observed in the (2 + 2) system (Figure 2f).

When the bias voltage is increased to 400 mV, four distinct conduction states of the (4 + 4) system appear with specific time sequences (inset in Figure 4e). As the voltage is increased, the lifetimes of all species participating in the reaction tend to decrease (Figure S39a). Similarly, the linear correlations between lnk and the voltage demonstrate that both the electron injection and release steps are speeded up with increasing voltage (Figure S39b). In summary, it is possible to expand the electron catalysis paradigm from (2 + 2) to (4 + 4) cycloadditions, which unleashes the vast potential of electrons in facilitating cycloadditions in SMJs.

#### CONCLUSIONS

In short, we demonstrate reversible single electron-catalyzed cycloadditions in positively charged nanoconfinements, where one electron effectively reduces the energy barriers for both (2 +2) and (4 + 4) cycloadditions. In fact, we show that the electron transitions enable the reaction mechanism while sequentially selecting different conduction channels of the molecular junction. The time-resolved electrical currents monitor and distinguish different steps of the single electron-catalyzed cycloadditions, while their analysis for different bias voltages indicates a strategy to control the kinetics of the cycloaddition reactions by tuning the voltage applied to the junction. Thanks to the properties of the ET processes investigated here, temperature can also be used as an effective physical parameter to tune the reaction mechanism. Considering the importance of electron-catalyzed biological and chemical reactions, the ability to detect and manipulate electrons as catalysts offers opportunities to create high-performance catalytic systems and optimize their reactions. From a technical point of view, establishing a platform for high-resolution real-time electrical measurements at the single-molecule level offers great potential for the exploration of reaction mechanisms and the development of high-performance devices.

#### ASSOCIATED CONTENT

#### **③** Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.4c18064.

Molecular synthesis, experimental methods, theoretical calculations, supporting results and figures including NMR spectra, I-V measurements, IETS spectra, and I-t measurements (PDF)

Atomic coordinates for key structures (ZIP)

#### AUTHOR INFORMATION

#### Corresponding Authors

Hongliang Chen – Stoddart Institute of Molecular Science, Department of Chemistry, Zhejiang University, Hangzhou 310021, P.R. China; ZJU-Hangzhou Global Scientific and

- Jinlong Yang Hefei National Laboratory for Physical Sciences at Microscale, University of Science and Technology of China, Hefei, Anhui 230026, P.R. China; orcid.org/0000-0002-5651-5340; Email: jlyang@ustc.edu.cn
- J. Fraser Stoddart Stoddart Institute of Molecular Science, Department of Chemistry, Zhejiang University, Hangzhou 310021, P.R. China; ZJU-Hangzhou Global Scientific and Technological Innovation Center, Zhejiang University, Hangzhou 311215, P.R. China; Department of Chemistry, Northwestern University, Evanston, Illinois 60208, United States; Department of Chemistry, The University of Hong Kong, Hong Kong SAR 999077, P.R. China; School of Chemistry, University of New South Wales, Sydney, NSW 2052, Australia; • orcid.org/0000-0003-3161-3697; Email: stoddart@northwestern.edu
- Chuancheng Jia Center of Single-Molecule Sciences, Institute of Modern Optics, Frontiers Science Center for New Organic Matter, Tianjin Key Laboratory of Micro-Scale Optical Information Science and Technology, College of Electronic Information and Optical Engineering, Nankai University, Tianjin 300350, P.R. China; Email: jiacc@nankai.edu.cn
- Xuefeng Guo Center of Single-Molecule Sciences, Institute of Modern Optics, Frontiers Science Center for New Organic Matter, Tianjin Key Laboratory of Micro-Scale Optical Information Science and Technology, College of Electronic Information and Optical Engineering, Nankai University, Tianjin 300350, P.R. China; Beijing National Laboratory for Molecular Sciences, National Biomedical Imaging Center, College of Chemistry and Molecular Engineering, Peking University, Beijing 100871, P.R. China; o orcid.org/0000-0001-5723-8528; Email: guoxf@pku.edu.cn

## Authors

- Xin Zhu Center of Single-Molecule Sciences, Institute of Modern Optics, Frontiers Science Center for New Organic Matter, Tianjin Key Laboratory of Micro-Scale Optical Information Science and Technology, College of Electronic Information and Optical Engineering, Nankai University, Tianjin 300350, P.R. China; Beijing National Laboratory for Molecular Sciences, National Biomedical Imaging Center, College of Chemistry and Molecular Engineering, Peking University, Beijing 100871, P.R. China
- Jinying Wang Center of Single-Molecule Sciences, Institute of Modern Optics, Frontiers Science Center for New Organic Matter, Tianjin Key Laboratory of Micro-Scale Optical Information Science and Technology, College of Electronic Information and Optical Engineering, Nankai University, Tianjin 300350, P.R. China
- Agostino Migliore Department of Chemical Sciences, University of Padova, Padova 35131, Italy; orcid.org/ 0000-0001-7780-2296
- Xingxing Li Hefei National Laboratory for Physical Sciences at Microscale, University of Science and Technology of China, Hefei, Anhui 230026, P.R. China; ◎ orcid.org/0000-0001-7820-0772
- Yanwei Li Environment Research Institute, Shandong University, Qingdao 266237, P.R. China; Shenzhen Research Institute, Shandong University, Shenzhen 518057, P.R. China; orcid.org/0000-0003-4089-9789

- Boyu Wang Center of Single-Molecule Sciences, Institute of Modern Optics, Frontiers Science Center for New Organic Matter, Tianjin Key Laboratory of Micro-Scale Optical Information Science and Technology, College of Electronic Information and Optical Engineering, Nankai University, Tianjin 300350, P.R. China
- Chen Yang Beijing National Laboratory for Molecular Sciences, National Biomedical Imaging Center, College of Chemistry and Molecular Engineering, Peking University, Beijing 100871, P.R. China
- Yang Jiao Department of Chemistry, Northwestern University, Evanston, Illinois 60208, United States; @ orcid.org/0000-0002-8437-0038
- Jiawen Cao Beijing National Laboratory for Molecular Sciences, National Biomedical Imaging Center, College of Chemistry and Molecular Engineering, Peking University, Beijing 100871, P.R. China
- **Caiyao Yang** Beijing National Laboratory for Molecular Sciences, National Biomedical Imaging Center, College of Chemistry and Molecular Engineering, Peking University, Beijing 100871, P.R. China
- Chunyan Gao Center of Single-Molecule Sciences, Institute of Modern Optics, Frontiers Science Center for New Organic Matter, Tianjin Key Laboratory of Micro-Scale Optical Information Science and Technology, College of Electronic Information and Optical Engineering, Nankai University, Tianjin 300350, P.R. China
- Suhang He Center of Single-Molecule Sciences, Institute of Modern Optics, Frontiers Science Center for New Organic Matter, Tianjin Key Laboratory of Micro-Scale Optical Information Science and Technology, College of Electronic Information and Optical Engineering, Nankai University, Tianjin 300350, P.R. China
- Kendall N. Houk Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90095, United States; orcid.org/0000-0002-8387-5261

Complete contact information is available at: https://pubs.acs.org/10.1021/jacs.4c18064

#### **Author Contributions**

 $^{\perp}$ X.Z., H.C., J.W., A.M., and X.L. contributed equally to this work.

## Notes

# ACKNOWLEDGMENTS

We acknowledge primary financial support from the National Key R&D Program of China (2024YFA1208100, 2021YFA1200102, 2021YFA1200101, 2022YFE0128700, and 2023YFF1205803), the National Natural Science Foundation of China (22150013, 22173050, 21933001, 21727806, and 22273085), Beijing National Laboratory for Molecular Sciences (BNLMS-CXXM-202407), the Youth Innovation Promotion Association CAS (2019441), and the Starry Night Science Fund of Zhejiang University Shanghai Institute for Advanced Study (no. SN-ZJU-SIAS-006). The authors also thank Northwestern University (NU) for its continued support of this research and acknowledge the Integrated Molecular Structure Education and Research Center (IMSERC) at NU for providing access to equipment for relevant experiments.

(1) Studer, A.; Curran, D. P. The electron is a catalyst. *Nat. Chem.* **2014**, *6*, 765–773.

(2) Jiao, Y.; Qiu, Y.; Zhang, L.; Liu, W. G.; Mao, H.; Chen, H.; Feng, Y.; Cai, K.; Shen, D.; Song, B.; Chen, X. Y.; Li, X.; Zhao, X.; Young, R. M.; Stern, C. L.; Wasielewski, M. R.; Astumian, R. D.; Goddard, W. A., 3rd; Stoddart, J. F. Electron-catalysed molecular recognition. *Nature* **2022**, *603*, 265–270.

(3) Francke, R.; Little, R. D. Electrons and holes as catalysts in organic electrosynthesis. *ChemElectroChem.* **2019**, *6*, 4373–4382.

(4) Luca, O. R.; Gustafson, J. L.; Maddox, S. M.; Fenwick, A. Q.; Smith, D. C. Catalysis by electrons and holes: Formal potential scales and preparative organic electrochemistry. *Org. Chem. Front.* **2015**, *2*, 823–848.

(5) Chen, H.; Jiang, F.; Hu, C.; Jiao, Y.; Chen, S.; Qiu, Y.; Zhou, P.; Zhang, L.; Cai, K.; Song, B.; Chen, X. Y.; Zhao, X.; Wasielewski, M. R.; Guo, H.; Hong, W.; Stoddart, J. F. Electron-catalyzed dehydrogenation in a single-molecule junction. *J. Am. Chem. Soc.* **2021**, *143*, 8476–8487.

(6) Giese, B.; Carl, B.; Carl, T.; Carell, T.; Behrens, C.; Hennecke, U.; Schiemann, O.; Feresin, E. Excess electron transport through DNA: A single electron repairs more than one UV-induced lesion. *Angew. Chem., Int. Ed.* **2004**, *43*, 1848–1851.

(7) Yan, M.; Kawamata, Y.; Baran, P. S. Synthetic organic electrochemical methods since 2000: On the verge of a renaissance. *Chem. Rev.* **2017**, *117*, 13230–13319.

(8) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. Visible light photoredox catalysis with transition metal complexes: Applications in organic synthesis. *Chem. Rev.* **2013**, *113*, 5322–5363.

(9) Shirakawa, E.; Itoh, K.-I.; Higashino, T.; Hayashi, T. *Tert*butoxide-mediated arylation of benzene with aryl halides in the presence of a catalytic 1,10-phenanthroline derivative. *J. Am. Chem. Soc.* **2010**, *132*, 15537–15539.

(10) Studer, A.; Curran, D. P. Organocatalysis and C-H activation meet radical- and electron-transfer reactions. *Angew. Chem., Int. Ed.* **2011**, *50*, 5018–5022.

(11) Huang, H.-M.; Procter, D. J. Dearomatizing radical cyclizations and cyclization cascades triggered by electron-transfer reduction of amide-type carbonyls. *J. Am. Chem. Soc.* **2017**, *139*, 1661–1667.

(12) Graml, A.; Neveselý, T.; Jan Kutta, R.; Cibulka, R.; König, B. Deazaflavin reductive photocatalysis involves excited semiquinone radicals. *Nat. Commun.* **2020**, *11*, 3174.

(13) Yang, C.; Zhang, L.; Li, H.; Guo, Y.; Jia, C.; Zhu, W.; Mo, F.; Guo, X. Single-molecule electrical spectroscopy of organocatalysis. *Matter* **2021**, *4*, 2874–2885.

(14) Li, Y.; Yang, C.; Guo, X. Single-molecule electrical detection: A promising route toward the fundamental limits of chemistry and life science. *Acc. Chem. Res.* **2020**, *53*, 159–169.

(15) Yang, C.; Zhang, L.; Lu, C.; Zhou, S.; Li, X.; Li, Y.; Yang, Y.; Li, Y.; Liu, Z.; Yang, J.; Houk, K. N.; Mo, F.; Guo, X. Unveiling the full reaction path of the Suzuki–Miyaura cross-coupling in a single-molecule junction. *Nat. Nanotechnol.* **2021**, *16*, 1214–1223.

(16) Stone, I.; Starr, R. L.; Zang, Y.; Nuckolls, C.; Steigerwald, M. L.; Lambert, T. H.; Roy, X.; Venkataraman, L. A single-molecule blueprint for synthesis. *Nat. Rev. Chem.* **2021**, *5*, 695–710.

(17) Chen, H.; Jia, C.; Zhu, X.; Yang, C.; Guo, X.; Stoddart, J. F. Reactions in single-molecule junctions. *Nat. Rev. Mater.* **2023**, *8*, 165–185.

(18) Kubatkin, S.; Danilov, A.; Hjort, M.; Cornil, J.; Brédas, J. L.; Stuhr-Hansen, N.; Hedegård, P.; Bjørnholm, T. Single-electron transistor of a single organic molecule with access to several redox states. *Nature* **2003**, *425*, 698–701.

(19) Perrin, M. L.; Burzurí, E.; van der Zant, H. S. J. Single-molecule transistors. *Chem. Soc. Rev.* **2015**, *44*, 902–919.

(20) Hong, C. M.; Bergman, R. G.; Raymond, K. N.; Toste, F. D. Selfassembled tetrahedral hosts as supramolecular catalysts. *Acc. Chem. Res.* **2018**, *51*, 2447–2455.

(21) Poplata, S.; Tröster, A.; Zou, Y.-Q.; Bach, T. Recent advances in the synthesis of cyclobutanes by olefin [2 + 2] photocycloaddition reactions. *Chem. Rev.* **2016**, *116*, 9748–9815.

(22) Ramamurthy, V.; Sivaguru, J. Supramolecular photochemistry as a potential synthetic tool: Photocycloaddition. *Chem. Rev.* **2016**, *116*, 9914–9993.

(23) Becker, H. D. Unimolecular photochemistry of anthracenes. *Chem. Rev.* **1993**, 93, 145–172.

(24) Yang, J.; Felton, G. A. N.; Bauld, N. L.; Krische, M. J. Chemically induced anion radical cycloadditions: Intramolecular cyclobutanation of bis(enones) via homogeneous electron transfer. *J. Am. Chem. Soc.* **2004**, *126*, 1634–1635.

(25) Janssen, R. G.; Motevalli, M. Electroreductive coupling of vinylpyridines and vinylquinolines: Radical anion-substrate cyclo-addition? *Chem. Commun.* **1998**, 539–540.

(26) Pazos, E.; Novo, P.; Peinador, C.; Kaifer, A. E.; García, M. D. Cucurbit[8]uril (CB[8])-based supramolecular switches. *Angew. Chem., Int. Ed.* **2019**, 58, 403–416.

(27) Yu, H.; Li, J.; Li, S.; Liu, Y.; Jackson, N. E.; Moore, J. S.; Schroeder, C. M. Efficient intermolecular charge transport in  $\pi$ -stacked pyridinium dimers using cucurbit[8]uril supramolecular complexes. *J. Am. Chem. Soc.* **2022**, *144*, 3162–3173.

(28) Vallavoju, N.; Sivaguru, J. Supramolecular photocatalysis: Combining confinement and non-covalent interactions to control light initiated reactions. *Chem. Soc. Rev.* **2014**, *43*, 4084–4101.

(29) Cao, Y.; Dong, S.; Liu, S.; He, L.; Gan, L.; Yu, X.; Steigerwald, M. L.; Wu, X.; Liu, Z.; Guo, X. Building high-throughput molecular junctions using indented graphene point contacts. *Angew. Chem., Int. Ed.* **2012**, *51*, 12228–12232.

(30) Jia, C.; Migliore, A.; Xin, N.; Huang, S.; Wang, J.; Yang, Q.; Wang, S.; Chen, H.; Wang, D.; Feng, B.; Liu, Z.; Zhang, G.; Qu, D.-H.; Tian, H.; Ratner, M. A.; Xu, H. Q.; Nitzan, A.; Guo, X. Covalently bonded single-molecule junctions with stable and reversible photoswitched conductivity. *Science* **2016**, *352*, 1443–1445.

(31) Migliore, A.; Nitzan, A. Irreversibility and hysteresis in redox molecular conduction junctions. *J. Am. Chem. Soc.* **2013**, *135*, 9420–9432.

(32) Migliore, A.; Nitzan, A. Nonlinear charge transport in redox molecular junctions: A Marcus perspective. *ACS Nano* **2011**, *5*, 6669–6685.

(33) Rust, M. J.; Bates, M.; Zhuang, X. Sub-diffraction-limit imaging by stochastic optical reconstruction microscopy (STORM). *Nat. Methods* **2006**, *3*, 793–796.

(34) Kang, Y.; Tang, X.; Yu, H.; Cai, Z.; Huang, Z.; Wang, D.; Xu, J.-F.; Zhang, X. Supramolecular catalyst functions in catalytic amount: Cucurbit[8]uril accelerates the photodimerization of brooker's merocyanine. *Chem. Sci.* **201**7, *8*, 8357–8361.

(35) Xin, N.; Guan, J.; Zhou, C.; Chen, X.; Gu, C.; Li, Y.; Ratner, M. A.; Nitzan, A.; Stoddart, J. F.; Guo, X. Concepts in the design and engineering of single-molecule electronic devices. *Nat. Rev. Phys.* **2019**, *1*, 211–230.

(36) Yuan, L.; Wang, L.; Garrigues, A. R.; Jiang, L.; Annadata, H. V.; Anguera Antonana, M.; Barco, E.; Nijhuis, C. A. Transition from direct to inverted charge transport Marcus regions in molecular junctions via molecular orbital gating. *Nat. Nanotechnol.* **2018**, *13*, 322–329.

(37) Migliore, A.; Schiff, P.; Nitzan, A. On the relationship between molecular state and single electron pictures in simple electrochemical junctions. *Phys. Chem. Chem. Phys.* **2012**, *14*, 13746–13753.

(38) Marcus, R. A. On the theory of electron-transfer reactions. Vi. Unified treatment for homogeneous and electrode reactions. *J. Chem. Phys.* **1965**, 43, 679–701.

(39) Gupta, N. K.; Karuppannan, S. K.; Pasula, R. R.; Vilan, A.; Martin, J.; Xu, W.; May, E. M.; Pike, A. R.; Astier, H. P. A. G.; Salim, T.; Lim, S.; Nijhuis, C. A. Temperature-dependent coherent tunneling across graphene–ferritin biomolecular junctions. *ACS Appl. Mater. Interfaces* **2022**, *14*, 44665–44675.

(40) Zhu, X.; Wang, B.; Xiong, W.; Zhou, S.; Qu, K.; Lü, J.-T.; Chen, H.; Jia, C.; Guo, X. Vibration-assisted charge transport through positively charged dimer junctions. *Angew. Chem., Int. Ed.* **2022**, *61*, No. e202210939.

(41) Bâldea, I. Protocol for disentangling the thermally activated contribution to the tunneling-assisted charge transport. Analytical

results and experimental relevance. Phys. Chem. Chem. Phys. 2017, 19, 11759-11770.

(42) Marcus, R. A. Chemical and electrochemical electron-transfer theory. *Annu. Rev. Phys. Chem.* **1964**, *15*, 155–196.