

Understanding Emergent Complexity from a Single-Molecule Perspective

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Cite This: *JACS Au* 2024, 4, 1278–1294

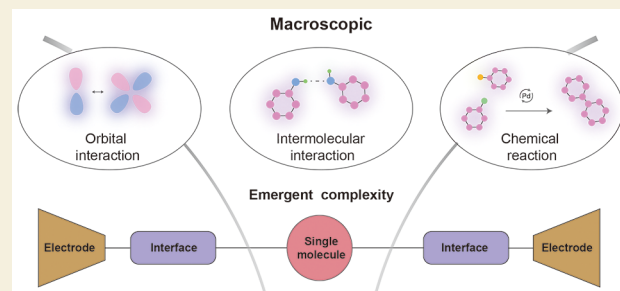
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ABSTRACT: Molecules, with structural, scaling, and interaction diversities, are crucial for the emergence of complex behaviors. Interactions are essential prerequisites for complex systems to exhibit emergent properties that surpass the sum of individual component characteristics. Tracing the origin of complex molecular behaviors from interactions is critical to understanding ensemble emergence, and requires insights at the single-molecule level. Electrical signals from single-molecule junctions enable the observation of individual molecular behaviors, as well as intramolecular and intermolecular interactions. This technique provides a foundation for bottom-up explorations of emergent complexity. This Perspective highlights investigations of various interactions via single-molecule junctions, including intramolecular orbital and weak intermolecular interactions and interactions in chemical reactions. It also provides



KEYWORDS: interaction diversity, emergent complexity, single-molecule junction, molecular electronics, charge transport, chemical reaction

1. INTRODUCTION

The macroscopic world is not just a collection of microscopic molecules, but a complex system formed by the intricate functions of individual molecules and their interactions. Single molecules, as the basic units of chemical reactions, form the foundation of the material world, and play a vital role in the regulation of biological processes. Therefore, it is essential to overcome ensemble averages and delve into inherent relations from a single-molecule perspective. However, collective behaviors depend on multiscale hierarchical structures within the ensemble, rather than a simple sum of individual properties.^{1,2} Complexity research is an emerging frontier of increasing importance in molecular science. In the context of reductionism, it is generally accepted that comprehending a single molecule paves the way for understanding behaviors in a collection. For a long time, scientists have focused on the properties of individual molecules and ignored interactions.³ With the rapid advancement of analytical technologies, the interactions in molecular systems are being investigated with regard to complexity science. Molecular systems exhibit behaviors that cannot be observed in individual molecules or events, but arise from interactions and interconversions among multiple components.^{4–6} Understanding the nature of these interactions and the associated emergent properties is a major task in complexity research. The characterization of complex systems with multiscale hierarchical structures mainly adopts

traditional macroscopic approaches based on thermodynamics and statistical mechanics to obtain ensemble-averaged properties, without focusing on the behavior of individual molecules.⁷

The internal structures of molecules, their intermolecular interactions, and their chemical reactions together provide the foundation for the complex world. Therefore, it is essential to uncover and elucidate the principles that govern the functions of complex systems from the single-molecule perspective.^{8,9} Studies of the behavior of very simple systems (such as single molecules) and explorations of how their properties aggregate into average properties of corresponding macroscopic ensembles will help us to further understand the complexity of molecular systems.⁷ The behavior of each molecule in the system is diverse and interactive. The emergence of ordered behavior from such a vast number of disordered components may require a hierarchical decomposition approach starting from the bottom. This would involve examining the behavior of a single molecule, understanding the interactions between molecules, and finally, analyzing the properties of a massive

Received: December 29, 2023

Revised: February 27, 2024

Accepted: February 27, 2024

Published: March 20, 2024



molecular collection. Therefore, the study of complex molecular systems necessitates detection techniques at the single-molecule level and the capability to analyze multi-component interactions.

Single-molecule detection (SMD) has flourished for decades by focusing on only one molecule without ensemble-averaging effects, using optical,^{10,11} mechanical,^{12,13} or electrical^{14,15} methods. However, more is different;¹ i.e., the behavior of individual molecules cannot be directly extrapolated to that of the ensemble. Hence, the gap between single molecules and an ensemble should be bridged. SMD can be regarded as the starting point for bottom-up research on the emergent complexity in molecular systems. An example would be the measurement of chain polymerization dynamics to elucidate the emergent behavior with the increasing number of incorporated monomers.¹³ However, it is not only the increased number of molecules that may create complexity. The study of resulting emergent behaviors, even for a simple molecule fraught with complex intramolecular interactions, remains a formidable challenge that requires SMD.

SMD techniques provide information by precisely capturing individual molecules and accurately detecting weak signals. In particular, single-molecule junctions enable electrical measurements of molecular conductance through the molecular structure, providing information about conformations and configurations. They provide sufficient resolution and have revealed a series of intrinsic characteristics determined by individual molecules, including physical properties such as Kondo effect,¹⁶ Coulomb blockade,¹⁷ and quantum interference,^{18,19} and chemical reactions such as hidden intermediates,²⁰ reaction trajectories,²¹ and autocorrelation behaviors¹⁰ at different time scales. The advantages of single-molecule junction techniques, such as high temporal resolution and in situ monitoring, have inspired a variety of approaches. These electrode-molecule-electrode heterojunctions integrate a single molecule within a pair of electrodes. This requires preparation of nanogapped electrodes and anchoring the single molecules. Through technological optimization, various single-molecule junctions have been developed, which can be categorized into two groups. One is the dynamic single-molecule junction, involving adjustable nanogapped electrodes, such as the mechanically controllable break junction (MCBJ)²² and the scanning tunneling microscopy break junction (STM-BJ).^{23,24} By repeatedly constructing nanogaps, individual molecules can be anchored between electrode pairs. The other technique is the static single-molecule junction, in which nanogaps are constructed directly between fixed electrodes to form stable junctions, including electromigration break junctions²⁵ and lithography-defined single-molecule junctions.^{26,27} On the basis of the close structure–property relationship between a single molecule and its conductance, these techniques provide a reliable platform for characterizing intramolecular orbital interactions, weak intermolecular interactions, and interactions in chemical reactions.

Reviews^{8,9,14,15,28–33} on single-molecule electronics are mostly written from the perspectives of molecule design, device fabrication, conductance measurement, and charge-transport characteristics. The complexity research in single-molecule junctions has received little attention. A timely review on this topic will facilitate the resolution of problems arising from the increased complexity due to the introduction of multiple interactions in single molecules. It is also beneficial to bridge the gap between single molecules and the ensemble. In

addition, compared with other major scientific disciplines, including engineering, economics, computer science, biology, mathematics, and physics, the complexity research was established relatively late in chemistry,³ let alone in single-molecule chemistry. In this Perspective, we concentrate on the interactions and the derived complex behaviors in single-molecule junctions, which is expected to enrich the research implications of single-molecule electronics and provide a single-molecule perspective for the complexity science.

Complexity is ubiquitous, and therefore, this Perspective will mainly focus on selected examples of pioneering experimental work on diverse interactions based on single-molecule junctions. In Section 2, we summarize intramolecular orbital interactions, involving stereoelectronic effects, quantum interference (QI), and superposition effects. In Section 3, we discuss weak intermolecular interactions, including π – π stacking, σ – σ stacking, hydrogen bonding, and host–guest interactions. In Section 4, we discuss interactions in chemical reactions, including substrate–substrate, substrate–catalyst, and catalyst–catalyst interactions. Finally, we conclude with an outlook on future single-molecule junction techniques for the study of complex interacting systems.

2. INTRAMOLECULAR ORBITAL INTERACTIONS

Intramolecular orbital interactions give rise to the intricate electronic structure within molecules, which introduce numerous nonlinear effects in multibody systems. When the orbitals of multiple atoms overlap to form molecular orbitals (MOs), various effects arise, such as stereoelectronic effects,³⁴ quantum interference effects (QIE),^{18,19} and superposition effects,³⁵ which potentially lead to complex system properties. The stereoelectronic effect refers to the influence of the spatial rearrangement of molecular conformations on the properties of the molecules. Such effect introduces complex electron distributions that characterize the molecular geometry. Minute changes in both the molecular geometry and electron distribution can lead to the significant property changes for the entire system that may exhibit unpredictable complexity in response to these variations. QI arises from the wave-like nature of electrons within molecules that may produce highly diverse interaction patterns. The combination and interference of these patterns can contribute to the emergence of complex structures. Interactions between conductive channels at multiple regions in the molecules generate a superposition effect, leading to changes in the internal electron distributions. Superposition effects can also result in the manifestation of different properties under varying conditions, contributing to the complexity of the system. Single-molecule techniques that exhibit precise control, high sensitivity, and high resolution, enable experimental conditions for direct observations of the above effects, which is crucial for unveiling the complexity within molecules. Furthermore, these concepts are closely related and provide an understanding of the electronic structure, shape, and volatility of molecules. Together they constitute a complex and interesting theoretical system.

2.1. Stereoelectronic Effect

The complexity of molecular structures can affect and determine properties and behaviors of the entire system. Different combinations of atoms, bond types, and stereochemical configurations can result in molecular diversity, and the combination and arrangement of these factors determine the complexity. According to the various spatial orientations of

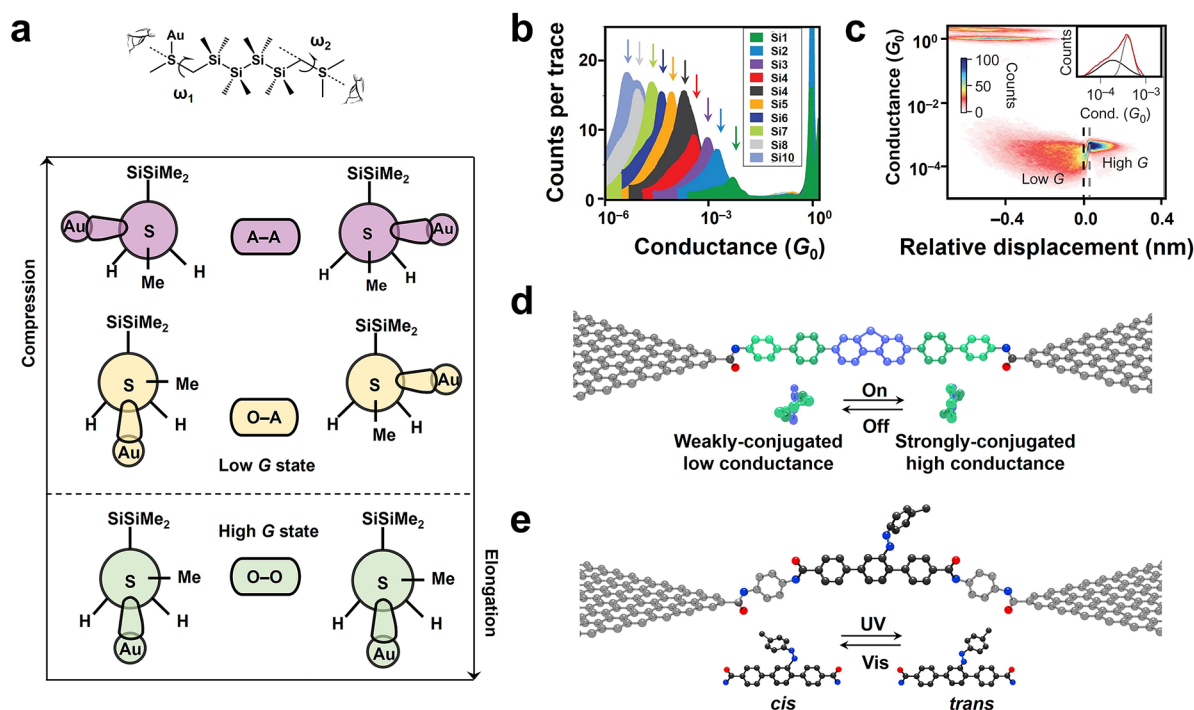


Figure 1. Stereoelectronic effects based on single-molecule junctions. (a) Newman projections for the A–A (purple), O–A (yellow), and O–O (green) dihedral configurations viewed from the perspective of the sulfur–methylene σ bond. (b) Logarithmic-binned one-dimensional histograms for Si1–Si10. (c) Two-dimensional conductance–displacement histogram for Si4 constructed from traces exhibiting switching behaviors. Reprinted with permission from ref 34. Copyright 2015 Springer Nature. (d) Schematic of hexaphenyl aromatic chain single-molecule junctions and its conformational transition of terphenyl units. Reprinted from ref 36. Copyright 2017 American Chemical Society. (e) Schematic of single-molecule junctions with the structure of the functional center that can isomerize reversibly between *cis* and *trans* forms. Reprinted with permission from ref 37. Copyright 2019 Springer Nature.

molecular orbitals, stereoelectronic effects determine the characteristics and reactivities of molecules that reflect complex emergent attributes. The stereoelectronic effects can also direct molecular conformations by controlling electronics at the single-molecule level, creating complex molecular structures and properties in turn.

Stereoelectronic effects in single-molecule junctions have been widely used in molecular switches. The subångström level ability in an STM-BJ to control dihedral angles in permethyloligosilanes with aurophilic methylthio methyl electrode contacts was reported by Su et al. (Figure 1a).³⁴ By elongating/decreasing the single-molecule (Si1–Si10) junctions, the conductance could be controlled. One-dimensional conductance histograms of Si1–Si10 are shown in Figure 1b, which exhibited an exponential decrease with the increasing molecular length. Because of the additional delocalization in the silanes, the different conductance values could be detected in rotational isomers of a single molecule. When the tip–substrate electrode gap was widened, an abrupt increase in conductance was observed in the single-molecule junction. The lower conductance was the before-switch state, while the higher conductance was the after-switch state, as shown in Figure 1c. The length of the conductance-plateau for the lower conductance state increased from Si1 to Si10. The stereoelectronic effects of the two terminal dihedral angles of ($\text{H}_3\text{C}-\text{S}-\text{CH}_2-\text{SiMe}_2-$) that terminated the oligosilanes were the primary reason for the switching. The dihedral angles were susceptible to being changed in the tip–substrate distance because of the torque exerted by gold atoms on the molecule. The dihedral angle of the two terminal $\text{Me}-\text{S}-\text{CH}_2-$

SiMe_2- in $\text{Au}-\text{Si}_4-\text{Au}$ geometries with the lowest energy changed from A–A (purple) to O–A (yellow) to O–O (green) (Figure 1a). O–A and A–A had a similar tunneling coupling, and thus there were two conductance states in the system. The structural changes of the sulfur–methylene bond resulted in a nonuniform electron distribution and movement, giving rise to the stereoelectronic effect. The diversity arising from the complexity of molecular structures, and from the presence of stereoelectronic effects, operates at the molecular level, and manifests as complexity at the system level via many-body interactions.

Biphenyl and its derivatives play diverse roles in organic electronics, organic synthesis, pharmaceutical and medical applications, and many other chemical and material fields. The stereoelectronic effect of the biphenyl group was investigated via a graphene-molecule-graphene single-molecule junction (GMG-SMJ) shown in Figure 1d.³⁶ A hexaphenyl aromatic chain molecule was designed for covalent encapsulation between nanogapped graphene point contacts to form a single-molecule junction. In general, phenyl twisting in the aromatic chain molecule generates the different conjugation degrees, potentially resulting in high/low conductance states. Both theoretical analyses and temperature-dependent experimental findings consistently reveal that phenyl twisting in the aromatic chain molecule generates distinct microstates characterized by varying degrees of conjugation. By investigating the electrical characteristics of the single-molecule junction featuring a hexaphenyl aromatic chain, we gain insights into the dynamic rotation of the benzene ring, which illustrates the complexity of benzene rotation dynamics.

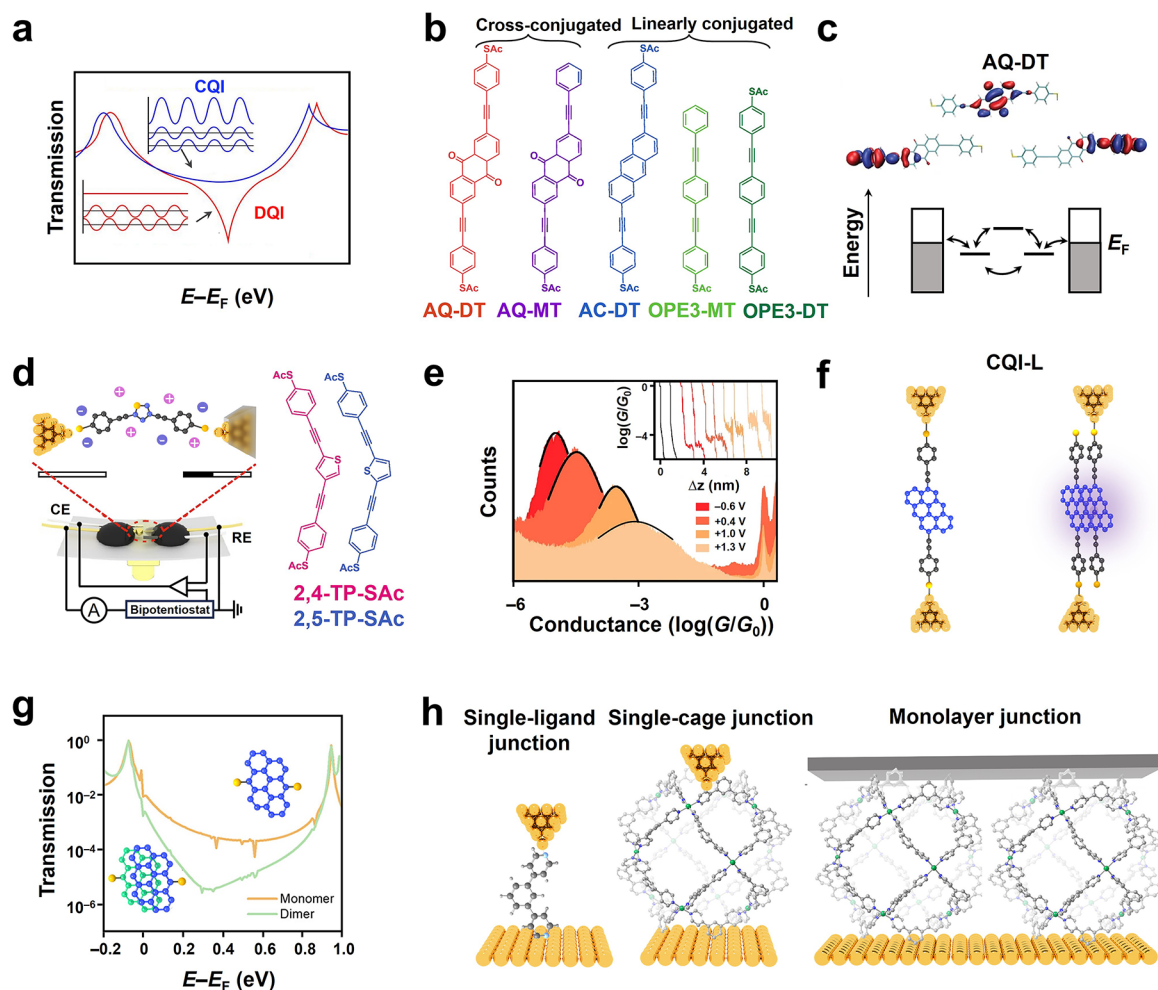


Figure 2. Quantum interference (QI) based on single-molecule junctions. (a) Principles of single-molecule QI. Reprinted from ref 43. Copyright 2019 American Chemical Society. (b) Molecular structures of AQ-DT, AQ-MT, AC-DT, OPE3-DT, and OPE3-MT (OPE3 = oligo-phenyleneethynylene). AQ-DT and AQ-MT are cross-conjugated, while AC-DT, OPE3-DT, and OPE3-MT are linearly conjugated. (c) The two charge transport paths of AQ-DT. Reprinted with permission from ref 49. Copyright 2012 Springer Nature. (d) Schematic of an electrochemically gated MCBJ technique and molecular structures of 2,4-TP-Sac and 2,5-TP-Sac. (e) Two-dimensional conductance-displacement histograms of 2,4-TP-Sac at 1.0 V. Reprinted with permission from ref 50. Copyright 2019 Springer Nature. (f) Schematic of monomer and dimer for CQI-L. (g) Theoretical transmission spectra of a monomer and a dimer for CQI-H. Reprinted from ref 51. Copyright 2022 American Chemical Society. (h) Schematic of single-ligand junctions, single-molecule cages, and monolayer junction. Reprinted with permission from ref 52. Copyright 2022 National Academy of Science.

Two distinct conductance states of a terphenyl molecule corresponded to the bistability of outer phenyl rings at each end. Introducing asymmetric substituents on the side of biphenyl induced more complex behaviors. Terphenyl with an azobenzene side group could be reversibly isomerized between *trans* and *cis* forms via electronic or optical stimuli. Azobenzene can transform between two distinct states under ultraviolet/visible light.³⁷ An azobenzene side group was introduced to the central ring of terphenyl to modulate charge transport via the stereoelectronic effect. Hence, under an electric field, the azobenzene unit was isomerized between *trans* and *cis* configurations (Figure 1e). The dynamics of the phenyl ring was significantly affected by the side chain structures; that is, the azobenzene could adjust the rotation barrier of the phenyl ring. Therefore, the side group was a means to adjust stereoelectronic effects in single-molecule junctions. Consequently, stochastic transitions between high- and low-conductance states were observed. 9,10-diphenyl-9,10-methanoanthracen-11-one had three stable intramolecular con-

formations attributed to the stereoelectronic effect.³⁸ The two terminal benzene rings had three electronic coupling modes: weak coupling, decoupling, and strong coupling, which had order-of-magnitude differences in theoretical simulations. The solvent effect and an external electric field could tune the populations of the three conformations. Thus, molecular switching could be adjusted precisely.

2.2. Quantum Interference

Multiple conductive channels generate complexity. QI, as a fundamental behavior of electrons, manifests its complexity in the intricacies of electron transport channels. Analogous to double-slit interference, the QIE is similar when electrons undergo transport between distinct orbitals within molecules. QIEs originating from the interference among the wave functions of electrons propagated through distinct molecular orbitals can tune charge transport in molecules via subtle adjustments in their structure or environment. QIEs are strongly dependent on the connectivity patterns. For example,

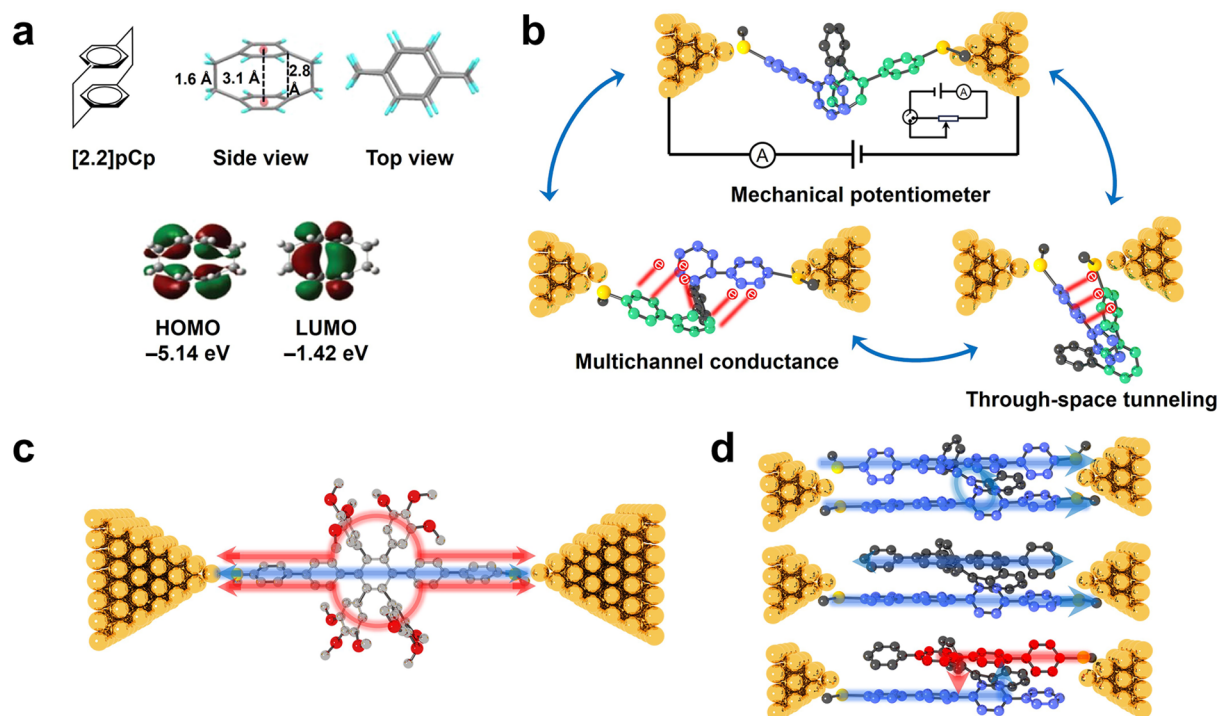


Figure 3. Superposition effect based on single-molecule junctions. (a) Chemical structure, crystal structure and HOMO and LUMO orbital distributions of [2.2]pCp. Reprinted with permission from ref 55. Copyright 2019 Chinese Chemical Society. (b) Schematic of a mechanical single-molecule potentiometer based on ortho-pentaphenylene-2SMe. The inset is the circuit diagram containing the potentiometer. Reprinted with permission from ref 62. Copyright 2021 Springer Nature. (c) Schematic of a circuit from hexaphenylbenzene anchored onto gold electrodes. Reprinted from ref 63. Copyright 2018 American Chemical Society. (d) Schematic of the electron-transport mechanism in *f*-4Ph-4SMe, *f*-4Ph-4SMe-A, and *f*-4Ph-4SMe-B. Reprinted with permission from ref 64. Copyright 2020 Wiley-VCH.

the theory³⁹ predicted that the benzene system with meta connectivity is less conductive than those with para and ortho connectivities by destructive quantum interference (DQI), which has been confirmed experimentally.⁴⁰ Yuta Tsuji et al. link QI features with the determinant of the molecule's Hückel matrix. It has been demonstrated that the presence of QI implies the existence of a biradical, and *vice versa*.⁴¹ Studies on QIEs offer new insights into the fundamental relationships between structure and electronics in molecular devices and materials (Figure 2a).^{14,28,42,43}

QIEs facilitate molecules in states of constructive quantum interference (CQI) or DQI, which increase or decrease the electron transmission probability, respectively.^{28,29,39,43} With substantial on/off ratios, this capability brings functional complexity to molecular devices. In addition, QIEs in conjugated molecules and saturated molecules are quite different.⁴⁴ In conjugated molecules, DQI rises from interference terms between paired occupied and virtual orbitals. Meanwhile, the charge transport in conjugated molecular structures is predominantly governed by σ -electrons.⁴⁵ On the other hand, in saturated molecules, DQI originates from the nonpaired orbital cancellation.⁴⁴

On the basis of two charge-transport paths, anthraquinone (AQ) is a typical cross-conjugated system predicted to exhibit lower conductance relative to linear-conjugated anthracene (AC) and broken-conjugated dihydroanthracene (AH).^{46,47} With an MCBJ technique, the conductance of AQ was approximately $10^{-7} G_0$, while those for AC and AH were approximately $10^{-4.5} G_0$ and $10^{-6.3} G_0$, respectively, which were consistent with the prediction.⁴⁸ Guédon et al. investigated

DQI in charge transport via two-terminal molecular junctions (Figure 2b).⁴⁹ The AQ-DT conductance was two orders-of-magnitude lower than that of AC-DT. Because of the nearly degenerate highest-occupied molecular orbital (HOMO) and HOMO-1 of AQ-DT and AQ-MT, charge transport via two paths within the gap between the HOMO and the lowest-unoccupied molecular orbital (LUMO) could produce a phase difference, causing partial waves to destructively interfere and reduce molecular conductance (Figure 2c).

By introducing external regulation, it is possible to control QI phenomena within molecular systems, leading to novel properties and behaviors. This holds profound significance for obtaining complexity in molecular devices and materials. Bai et al. reported a single-molecule electrochemical transistor in an ionic liquid that acted as an electrochemical gate; further gate control induced changes in transport conductivity.⁵⁰ At approximately -0.4 V in the nonfaradaic region, the antiresonance from DQI versus an Ag/AgCl quasi-reference electrode was observed, which was direct evidence that charge transport could be controlled by DQI. The single-molecule conductance was measured on an electrochemical tip-bead chip integrated with four electrodes (Figure 2d). The charge-transport properties of molecules with (2,4-TP-SAc) and without (2,4-TP-SAc) DQI were studied. As the electrode potentials increased, the position of the molecular plateau shifted right because of DQI (Figure 2e). This indicated that the Fermi level could be positioned between resonance and antiresonance by applying a gate to single-molecule thiophene junctions via DQI. There was an approximately 100-fold variation in conductance that occurred by adjusting the

electron potential from -0.4 to 1.3 V. This conductance variation was more than one order-of-magnitude greater than the case without DQI. Thus, electrochemical gating is an effective strategy for optimal electrical performance in QI devices, and further enriches the complexity of charge transport regulation in molecules.

Anthanthrene- and pyrene-containing conjugated central units could be used as models to study QIE complexity in going from a single-molecule system to a two-molecule system switched between CQI and DQI. Li et al. investigated QI-controlled conductance enhancement in stacked graphene-like dimers via an STM-BJ technique and density functional theory simulations.⁵¹ For the molecule CQI-L (Figure 2f), the conductance of the dimer increased by as much as 25 times relative to that of the monomer. Conversely, for CQI-H (Figure 2g), the conductance of the dimer was approximately 40 times lower than that of the monomer, which was confirmed by the calculations. Therefore, DQI observed in the motion of a single-molecule system at a specific binding site transformed into CQI in a two-molecule system at the same binding site. QIEs from the single-molecule to two-molecule systems reflect the diversity in charge transport, and simultaneously, the existence of multiple electron pathways further enriched the QI complexity.

QIEs offer great potential for single-molecule devices, and can be transferred to larger and more complex molecular systems. Xu et al. studied QIEs via single-ligand junctions, single-molecule cages, and monolayer junctions (Figure 2h).⁵² Power-density spectra generated from flicker noise analyses could determine the charge transport forms (through-space or through-bond). For the single 1,3-dipyridylbenzene ligand junctions, the DQI-induced through-space mechanism was confirmed by the spectra. QIEs still existed in the molecular cages, indicating that DQI could be transferred from the ligands to the cages. The results suggested that QIEs could be transferred from ligands to monolayer thin films. The transport remained phase-coherent at the single-ligand, the single-cage, and the assembled monolayer scales, and the QI could be scaled up within the phase-coherent distance.

The QIE complexity originates from the diversity of charge transport channels leading to complex electronic structures of a single molecule. Subtle alterations in the chemical structure would lead to amplified changes in the electronic structure by fine-tuning interference patterns. In-depth research would provide significant implications for materials science and quantum physics, and gain a fundamental understanding of complex molecular systems.

2.3. Superposition Effect

Complex charge-transport channel interactions in multiple regions of molecules generate superposition effects. There are two classical mechanisms that are called parallel paths and space-conjugated multichannel conductance. The latter is the main mechanism for conductive channels at multiple regions in molecules. The space conjugation facilitates spatial electron communication with closely stacked π systems, which diverges from the reliance on covalent bonds. This enables multi-dimensional energy and charge transport. In 1949, space-conjugation research began with [2.2]paracyclophane ([2.2]pCp) because its π system could be delocalized between two phenyl rings stacked approximately 3.1 Å apart, which was typical for a through-space conjugated conformation (Figure 3a).^{53–55} From theoretical analysis, the energy bandgap

between the HOMO and the LUMO of [2.2]pCp was ~ 3.72 eV. This was less than that of benzene (~ 5.15 eV), which indicated that [2.2]pCp had a more effective and expansive π system because of strong through-space conjugation.⁵⁶

Benefiting from the complexity of conductance channels, the mechanisms and applications of superposition can be further explored to deepen its understanding. Large fluctuations in molecular conformations, coupled with changes in the charge-transport mechanism, are sought to significantly modify the conductance and establish a controllable conductance-displacement relationship. This is instrumental for realizing molecular potentiometers with substantial switching factors.⁵⁷ The simultaneous presence of offset π - π stacking interactions parallel to the helix axis and through-bond conjugation can confer ortho-phenylenes with multichannel charge transport in multidimensions.⁵⁸ Ortho-pentaphenylene derivatives, equipped with anchoring groups, have exhibited diverse folded conformations as well as conformational changes in solution.^{59–61} Solvent-sensitive multiple conductance arising from various conformers was observed via STM-BJ (Figure 3b).⁶² These pseudoelastic folded molecules could be mechanically stretched or compressed, resulting in two orders-of-magnitude variations in conductance. This yielded an exceptionally high switching factor (approximately 1–25) that surpassed other reported values. Multichannel conductance governed by through-space and through-bond conducting pathways was identified as the charge transport mechanism for folded ortho-pentaphenylene derivatives. The relationship between superposition complexity and multiple conductance channels suggests the diversity and complexity of charge transport at the molecular scale.

The superposition effect can also be realized via multichannel conductance within single-molecule junctions. Zhen et al. investigated the multichannel conductance of single-molecule wires via through-space conjugated hexaphenylbenzene (Figure 3c).⁶³ This was measured via STM-BJ, and the conductance increased with improved through-space conjugation. The final conductance reached 12.28 nS, which was much larger than that of the through-bond conductance (2.45 nS). The toroidal through-space conjugation established between the circularly aligned, face-to-face, phenyl rings made a substantial contribution and compensated for the conductance loss associated with weakened through-bond conjugation. Integrating through-space and through-bond conjugations into a multichannel conducting model would be a strategic approach for designing robust single-molecule wires with high levels of conductance and stability. Single-molecule parallel circuits with multiple conductive channels were an effective yet infrequently reported strategy to enhance conductance. Shen et al. introduced a through-space conjugated single-molecule parallel circuit (denoted as *f*-4Ph-4SMe) that consisted of two closely aligned *p*-quaterphenyl chains tethered by a vinyl bridge and terminated with four SMe anchoring groups (Figure 3d).⁶⁴ From STM-BJ data and transmission calculations, *f*-4Ph-4SMe exhibited multiple conductance states attributed to distinct contact configurations. When all four SMe groups made simultaneous contact with the electrodes, through-bond and through-space conductive channels synergistically contributed, resulting in a significantly higher conductance relative to analogous molecules with two SMe groups or the sum of two individual *p*-quaterphenyl chains. This system served as an ideal model for elucidating charge transport via stacked parallel molecular

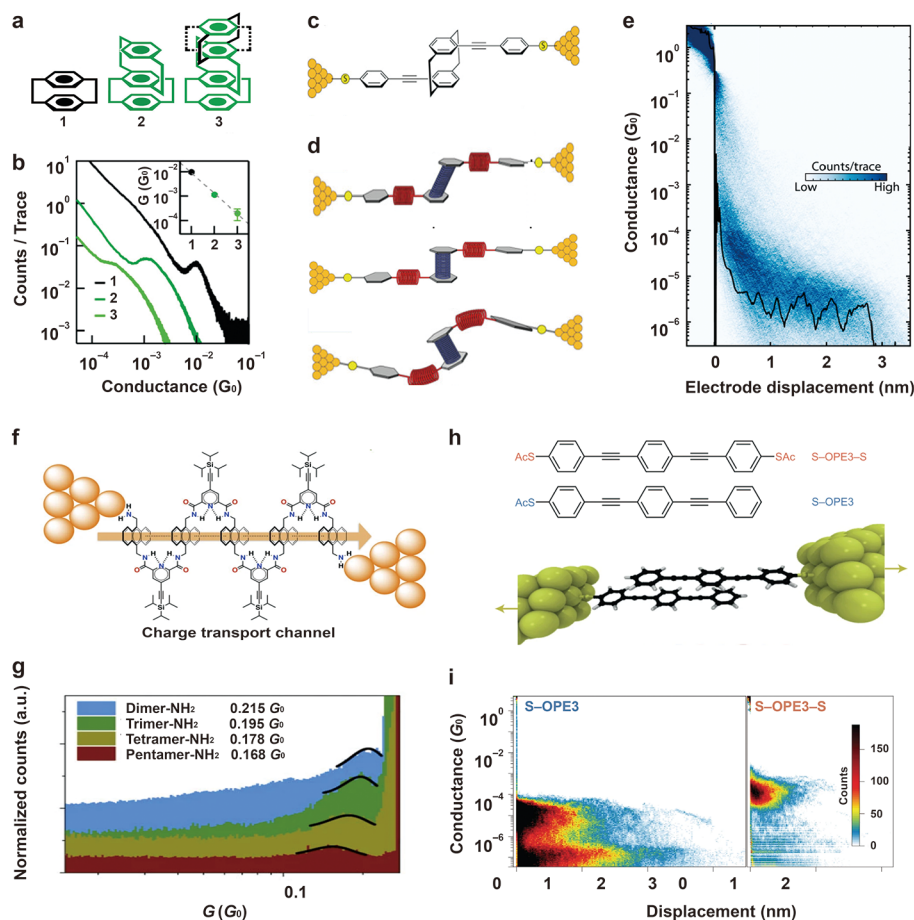


Figure 4. π - π stacking based on single-molecule junctions. (a) Molecular wires containing multiple, π - π stacked aromatic rings. (b) Conductance histograms of compounds 1–3. Inset: Conductance histogram peak versus the number of paracyclophane units. Reprinted from ref 72. Copyright 2011 American Chemical Society. (c) Schematic of the integration of oligo-phenyleneethynylene rod with terminal binding groups into gold electrodes. (d) Three possible behaviors when exerting a mechanical shear force on the molecular bridge. (e) Two-dimensional histogram of the molecule shown in (c). Reprinted from ref 73. Copyright 2018 American Chemical Society. (f) Schematic of intramolecular π -folded molecular junctions. (g) Conductance histograms of the different foldamers. Reprinted with permission from ref 75. Copyright 2017 Springer Nature. (h) Top panel: Chemical structures of the two molecules: an oligo-phenylene-ethynylene (OPE3) with either one (S-OPE3) or two (S-OPE3-S) thiol anchoring groups. Bottom panel: Schematic of the π -stacked dimer in the break junction. (i) Two-dimensional histograms of molecular conductance versus STM tip-sample displacement for S-OPE3 and S-OPE3-S. Reprinted with permission from ref 81. Copyright 2016 Springer Nature.

systems and illustrated the complexity of multichannel charge transport and the superposition effect.

3. INTERMOLECULAR INTERACTIONS

Intermolecular interactions are very important in complex molecular systems, and in the context of dynamic combinatorial chemistry, analytical tools have been used to probe these systems, rather than ignore them.⁶⁵ Characterization and analysis of these interactions enable a better understanding and the ability to regulate emergent properties. Complex molecules, especially supermolecules, exhibit both covalent and nonbonding interactions that can lead to molecular recognition and self-assembly processes that may ultimately generate more complex structural and functional diversity. Therefore, a comprehensive understanding of molecular interactions is crucial for developing new functional molecular systems. Single-molecule junction techniques have enabled characterization and manipulation of weak intermolecular interactions. The structure-property relationship between a single molecule and its conductance has been extensively

studied.^{9,43,66} Single-molecule junctions extend beyond charge transport and have been used to detect weak intermolecular interactions between molecular components, including π - π stacking, σ - σ stacking, hydrogen bonding, and host-guest interactions. These interactions can affect conductance in electronic devices, resulting in molecules with emergent properties not present in their individual components.^{15,67–69} A comprehensive investigation of intermolecular interactions that serve as building blocks of complex molecular systems, and the underlying factors in developing the properties, will help to regulate these interactions at the single-molecule level and provide insights into molecular recognition and self-assembly.

3.1. π - π Stacking

The significance of π - π stacking has long been recognized in thin-film organic electronics and molecular mechanics, especially in biomolecular and supramolecular chemistry.⁷⁰ Such interactions are prevalent in biological macromolecular systems, where they perform vital functions in maintaining the stability of nucleobase stacking in DNA and RNA, preserving

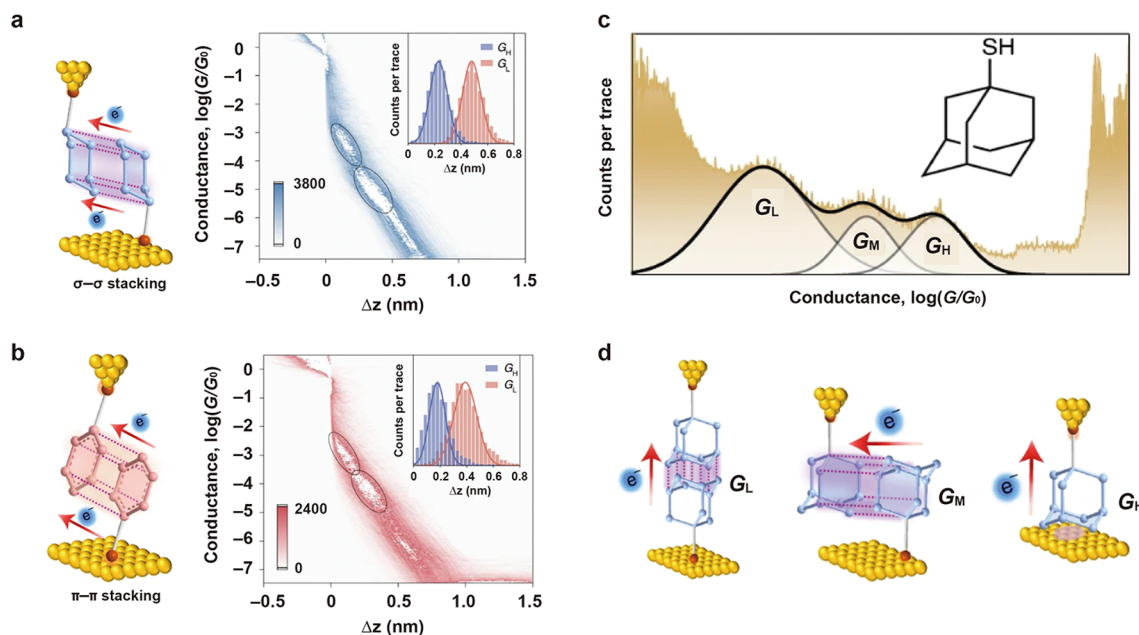


Figure 5. σ - σ stacking based on single-molecule junctions. (a) Schematic of σ - σ stacked molecular junctions of cyclohexanethiol dimer (left panel) and corresponding two-dimensional conductance-distance histograms (right panel). (b) Schematic of σ - σ stacked molecular junctions of benzenethiol dimer (left panel) and corresponding two-dimensional conductance-distance histograms (right panel). (c) Conductance histogram of 1-adamantanethiol. (d) Schematic of three configurations of 1-adamantanethiol junctions formed between gold electrode pairs with G_L , G_M , and G_H states. Reprinted with permission from ref 90. Copyright 2022 Springer Nature.

protein structures, and facilitating protein-ligand recognitions. Therefore, an in-depth investigation of π - π stacking benefits the understanding of the emergence and evolution of the complexity in living systems. Charge-transport mechanisms via aromatic molecules can be divided into two main categories. One is the conjugation of electrons delocalized in the molecular plane (through-bond conjugation); the other is the conjugation of π electrons delocalized in the region between adjacent π -stacked aromatic units (through-space conjugation).⁵⁵ The latter has exhibited effective charge-transport like normal through-bond conjugation. Intramolecular and intermolecular π - π stacking are two strategies for the fabrication of π - π stacking systems with through-space conjugation.

Intramolecular π - π stacking occurs when a single molecule has π -electrons stacked on two or more adjacent aromatic rings, resulting in through-space conjugation.⁷¹⁻⁷⁴ [2.2]pCp is a typical model for detecting intramolecular π - π stacking. Schneebeli et al. used STM-BJ to determine the single-molecule conductance of a molecular wire containing multiple tightly π - π stacked aromatic rings (Figure 4a).⁷² There was an exponential decay in conductance with an increasing number of stacked benzene rings, indicating a nonresonant tunneling mechanism (Figure 4b). STM tip-substrate displacement data and simulations indicated that charge transport was through the π system, rather than through σ -type molecular orbitals of the ethylene linking groups.

π - π stacking interactions are strongly dependent on the relative geometric arrangement of aromatic units. Stefani et al. modulated these interactions and the resulting conductance by applying tensile or compressive strains to cyclophane-centered molecular bridges.⁷³ Specifically, they integrated an oligophenylene ethynylene (OPE) rod with terminal binding groups into gold electrode gaps (Figure 4c). MCBJ was used to exert shear forces on the molecular bridge, which could cause

elongation, relaxation, or shortening of the molecule length (Figure 4d). When the electrodes were pulled away from one another, pronounced oscillations in the conductance were observed with amplitudes up to an order of magnitude for different samples (Figure 4e). Density functional theory revealed that the oscillations could be explained by the QI of frontier orbitals, coupled with the molecule acting like a spring when subjected to mechanical deformations.

Intramolecular π - π stacking also occurs in foldamers that can be mechanically folded in situ. The folding changes their conformations to provide a through-space charge transport channel for π -electrons.^{62,64,75-77} Carini et al. reported a family of foldamers with an increasing number of anthracene units that adopted a folded sigmoidal conformation via combined intramolecular hydrogen bonds and aromatic interactions.⁷⁵ Folding opened up a through-space charge-transport channel between the interacting anthracene moieties (Figure 4f). Single-molecule STM-BJ conductance values in this series of foldamers were exceptionally high, but decreased exponentially with an increasing number of anthracenes in the backbone. Single-molecule STM-BJ conductance values in this series of foldamers were exceptionally high, but decreased exponentially with an increasing number of anthracenes in the backbone (Figure 4g). Other foldamers, such as f-TPE-PPy,⁷⁷ f-4Ph-4SMe,⁶⁴ and ortho-phenylenes,⁶² have both through-bond and through-space conjugation conduction channels. These stable π - π stacking interactions were perfect models for investigating complex folding systems, thus laying the foundation for understanding derived emergent properties.

A π -stacked dimer is the standard model for intermolecular π - π stacking, where two identical molecules, each with only one linker bonded to the electrode, are bonded via π - π interactions.^{51,70,78-83} The strength of the π - π stacking interactions is highly dependent on environmental conditions such as steric hindrance,⁸³ solvent effect,⁸⁴ stacking con-

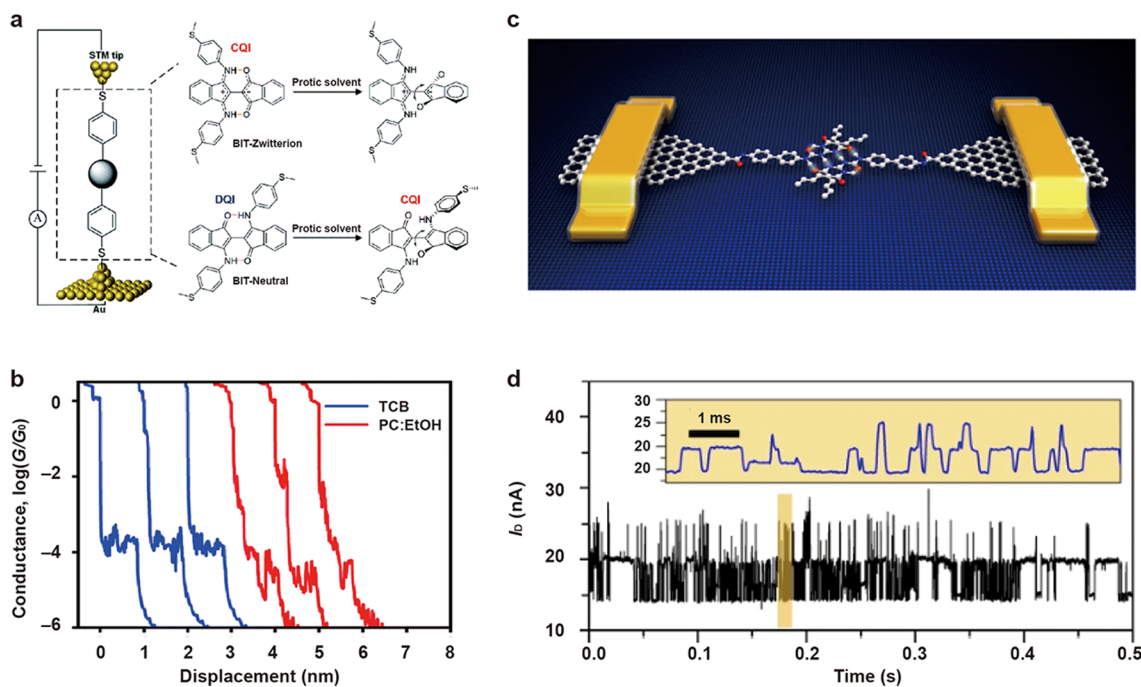


Figure 6. Hydrogen bonding based on single-molecule junctions. (a) Schematic of a STM-BJ setup and two BIT isomers (BIT-Zwitterion and BIT-Neutral). (b) Conductance–displacement traces of BIT-Zwitterion in TCB and PC:EtOH solutions. Reprinted with permission from ref 92. Copyright 2022 Royal Society of Chemistry. (c) Schematic of a hydrogen bond-bridged junction. (d) $I-t$ curves of the GMG-SMJ in diphenyl ether solution. Reprinted with permission from ref 91. Copyright 2018 Springer Nature.

formation,⁸⁵ and concentration.⁸² All of these factors can affect charge transport, leading to tunable electronic properties.¹⁵ π -stacked dimers have crucial impacts on supramolecular assembly and molecular recognition. Frisenda et al. used MCBJ charge transport in π -stacked dimers and observed mechanically controlled QI.⁸¹ The molecules were an oligophenylene-ethynylene (OPE3) with either one (S–OPE3) or two (S–OPE3–S) thiol anchoring groups (Figure 4h). They acquired breaking traces of S–OPE3 and S–OPE3–S, and their two-dimensional conductance–displacement histograms are shown in Figure 4i. For S–OPE3–S, a single region of high counts was observed ($\sim 10^{-4} G_0$). In contrast, the conductance histogram of S–OPE3 displayed two characteristic regions with high probability, which indicated the existence of two π -stacked conformations of S–OPE3 with different binding energies, consistent with theoretical calculations. One exhibited a high-conductance state at approximately $10^{-5} G_0$ and the other lower one was at approximately $10^{-7} G_0$.

3.2. σ – σ Stacking

σ – σ stacking is a newly discovered class of nonbonding interactions expected to form complex systems with diverse structures and functions. σ – σ stacking has received less attention than π – π interactions because it exhibits lower charge transport and underestimated intermolecular interactions.⁸⁶ However, recent theoretical studies have indicated that σ – σ and π – π stacking interactions may have equal significance in stacked aromatic rings.^{87–89} Inspired by theoretical calculations, Feng et al. discovered that σ – σ stacking interactions between adjacent nonconjugated cyclohexanethiol or single-anchored adamantane molecules were efficient enough for charge transport.⁹⁰ During STM-BJ measurements, cyclohexanethiol exhibited two distinct conductance clouds in two-dimensional histograms (Figure 5a),

which were similar to those of benzenethiol (Figure 5b). 1-Adamantanethiol was used as a model to verify the possibility of charge transport via σ – σ stacked molecular junctions formed between nonconjugated cyclohexane rings. Three distributions were observed in the conductance histograms, indicating the formation of molecular junctions with three different configurations (Figure 5c). The shortest plateau with the high-conductance (G_H) state was close to the length of a single adamantane molecule, and the longest plateau with the low-conductance (G_L) state was approximately twice the length of the shortest one. Therefore, the G_H state was associated with only one 1-adamantanethio junction. The G_M and G_L states were determined to be stacked molecular junctions, formed by σ – σ interactions between two adamantane cages. The G_M state corresponded to a “side-to-side” interaction, while the G_L state corresponded to a “head-to-head” interaction (Figure 5d). Flicker noise analyses indicated that through-space coupling dominated charge transport, suggesting that σ – σ stacking could serve as a charge transport channel between two nonconjugated molecules. Although σ bonds are common in chemistry, the σ – σ stacking, as a weak nonbonding interaction, is currently only characterized by STM-BJ measurements. It is expected that further experimental evidence will be provided in the future to comprehensively decipher the nature of σ – σ interactions and realize the diverse functions based on them.

3.3. Hydrogen Bonding

Hydrogen bonding is a noncovalent interaction ubiquitous in biological and chemical systems. Molecular recognition and self-assembly based on hydrogen bonding are important in superstructures formed from building blocks. Charge transport via hydrogen bonding has been observed in single-molecule junctions.^{91–100} Nishino et al. found that it was more effective

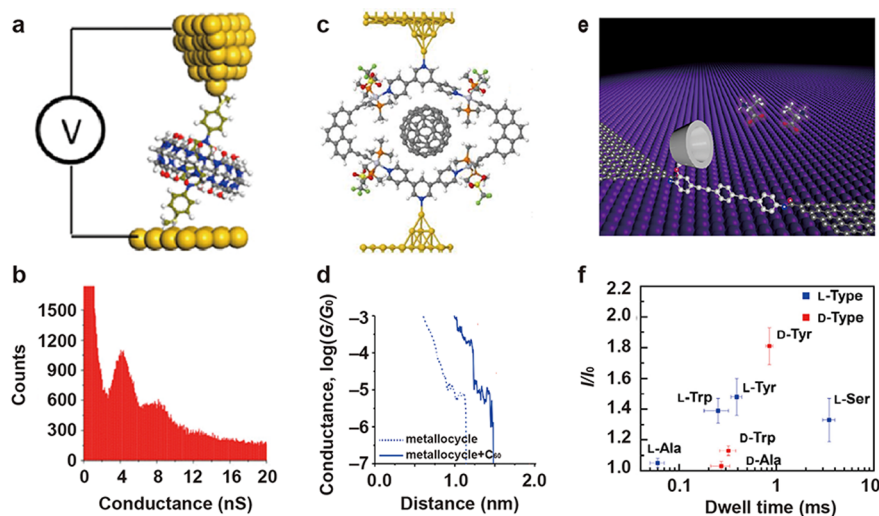


Figure 7. Host–guest interaction based on single-molecule junctions. (a) Schematic of viologen-CB[8] complexes. The guest molecule (viologen here) acts as a conducting bridge. (b) Conductance histogram of complex shown in (a). Reprinted from ref 106. Copyright 2016 American Chemical Society. (c) Schematic of metallocycles-C₆₀ junction. The host molecule (metallocycles here) acts as a conducting bridge. (d) Representative conductance versus distance traces of metallocycle and metallocycles-C₆₀ junction. Reproduced with permission from ref 107. Copyright 2019 Springer Nature. (e) Schematic of a PM-β-CD-based GMG-SMJ. The PM-β-CD that is covalently bonded to the molecular bridge acts as an additional local gate. (f) Recognition of different amino acids and their enantiomers. Reprinted with permission from ref 101. Copyright 2021 AAAS.

for charge transport than short-range σ bonds.⁹⁹ However, conductance in hydrogen bonding rapidly decayed for paths longer than 13 Å, reflecting the distance dependence of hydrogen bonding. Moreover, the formation and strength of hydrogen bonding are strongly affected by solvent conditions. Single-molecule junctions formed via hydrogen bonds tended to exist in aprotic, nonpolar, or low-polar solutions because the presence of strong proton donors or acceptors could interfere with the formation of target hydrogen bonds. Ge et al. investigated the single-molecule conductance of regioisomers BIT-zwitterion and BIT-neutral in aprotic and protic solvents, and found that a protic solvent enabled manipulation of hydrogen bonding, switching the conductance between CQI and DQI.⁹² Theoretical calculations predicted that, in the absence of a solvent, transport through the BIT-zwitterion was controlled by CQI, whereas that for BIT-neutral was controlled by DQI (Figure 6a). STM-BJ was used to measure the conductance of BIT-zwitterion and BIT-neutral under different solvent environments. Figure 6b compares individual conductance traces of BIT-Zwitterion in 1,2,4-trichlorobenzene (TCB), and a mixed solvent of propylene carbonate (PC) and ethanol (EtOH). The conductance of BIT-zwitterion in PC:EtOH was lower than that in TCB. Hence, relative to the aprotic solvent, the protic solvent decreased the BIT-zwitterion conductance because of the formation of intermolecular hydrogen bonds that induced a twist in the BIT-zwitterion. In contrast, the protic solvent increased the conductance of BIT-neutral because it induced a transformation from DQI to CQI with a change from planar to folded conformations. In addition, the BIT-neutral conductance was further increased via another through-space transport path between the two folded moieties. Characterization of hydrogen-bonding dynamics can be performed via static junctions. On the basis of a GMG-SMJ, Zhou et al. probed the bonding dynamics of a quadruple hydrogen bond supramolecular system in real time (Figure 6c).⁹¹ They performed solvent- and temperature-dependent measurements

of a quadruple hydrogen bond dimer using ureido pyrimidine-dione. Both experimental and theoretical results consistently had multimodal distributions (Figure 6d) originating from the stochastic rearrangement of the hydrogen bond structure, mainly via intermolecular proton transfer and lactam–lactim tautomerism. Charge transfer and dynamic characteristics of hydrogen bonds at the single-molecule level enable identification of molecules using hydrogen bonds, such as nucleic acids and amino acids, thereby achieving accurate sequencing.

3.4. Host–Guest Interaction

In the host–guest interaction, a host recognizes and specifically binds to a guest, creating supermolecules with specific functions. These interactions are increasingly complex and have been used for multiple functions in single-molecule junctions, such as biosensors¹⁰¹ and logic operations.¹⁰² By intensively studying host–guest interactions at the single-molecule level, we can more confidently cope with complex interacting systems on a larger scale. Three strategies have been developed to investigate these interactions in single-molecule junctions.

In the first strategy, the guest combined with a host (usually a macrocycle) is integrated into the electrodes on both sides, i.e., the guest molecule acts as a conducting bridge.^{103–106} For example, Zhang et al. constructed single-molecule junctions with a viologen conducting bridge and a cucurbit[8]uril (CB[8]) host.¹⁰⁶ They analyzed the conductance of three different viologen-based wires and the supramolecular viologen–CB[8] complexes (Figure 7a). When passing through CB[8], the conductance of viologen derivatives increased (Figure 7b), which was interpreted as a Marcus-type electron transfer attributed to the reduced reorganization energy of the outer sphere.

In the second strategy, the host is the conducting bridge and accommodates the guest.¹⁰⁷ Tang et al. used STM-BJ to measure the conductance of three supramolecular metallocycles and their complexes with a C₆₀ guest (Figure 7c).¹⁰⁷

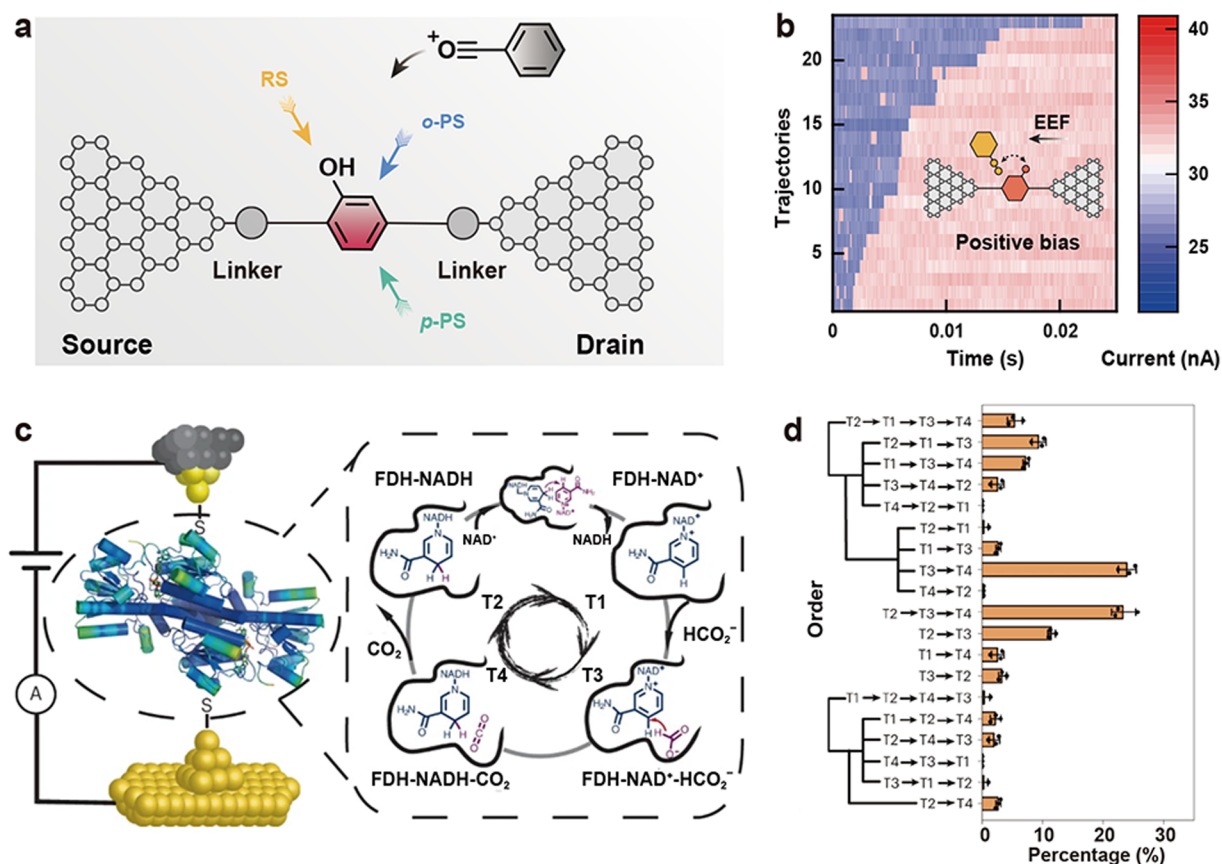


Figure 8. Characterization of substrate–substrate interactions based on single-molecule junctions. (a) Schematic of the phenol-centered GMG-SMJ with multiple binding sites to monitor the interactions between acyl moiety and phenol. (b) Mapping of I - t curves in single-substrate-molecule measurements. Reprinted with permission from ref 111. Copyright 2022 Wiley-VCH. (c) Schematic of the single-enzyme reaction measurements and the updated catalytic cycle for formate dehydrogenase. (d) Statistical analysis of the continuous dynamic individual trace library. Reprinted with permission from ref 112. Copyright 2023 Springer Nature.

The conductance of the metallocycles was enhanced by an order of magnitude upon complexation with the C_{60} (Figure 7d). The conductance switched back to the free-host level when the metallocycle- C_{60} junction was mechanically stretched, releasing the C_{60} guest from the metallocycle. With mechanical stretching, the metallocycle hosts with different shapes and cavity sizes showed varying degrees of flexibility to accommodate the C_{60} guest. This indicated that host-guest interactions could modulate molecular conductance.

In the last strategy, the host is covalently linked to a molecular bridge to form an additional gate.^{101,108–110} The guest can manipulate the carrier density via host-guest interactions, causing current spikes in real-time electrical measurements. This technology enables the direct observation of host-guest interactions at the single-molecule level, which will enhance our understanding of the interactions in complex biological systems. Liu et al. reported on a single-molecule technique for the direct differentiation of different proteinogenic amino acids and their enantiomers through precise dynamic measurements of the host-guest interactions using GMG-SMJ.¹⁰¹ The molecular bridge integrated with the electrodes had a rigid conjugated organic molecular backbone and a permethylated beta-cyclodextrin (PM- β -CD) side arm for the recognition function (Figure 7e). They observed real-time electrical recognition of amino acids with different structures and chirality within a few microseconds. Both the

electrical and theoretical results were consistent in showing that the PM- β -CD recognized various charged states of the amino acids. This was based on the current fluctuation range and the thermodynamic and kinetic parameters. From the statistical results, four amino acids and their corresponding enantiomers at different pH values were distinguished (Figure 7f). This provided a universal tool for the recognition of many other important environmental or biological molecules, as well as a deep understanding of biological processes at the molecular level.

4. INTERACTIONS IN CHEMICAL REACTIONS

Interactions are the basis of chemical reaction networks. Understanding the interaction mechanisms at the single-molecule level may explain the emergent complexity in chemical reaction networks. An accurate understanding of chemical reaction interactions necessitates a comprehensive description in both time and space via real-time tracking of reactions (time) and breaking the limits of ensemble averaging (space). Single-molecule junctions enable both perspectives. In particular, static junctions, have been used for studying intrinsic reaction mechanisms and interactions because of their high temporal resolution, in situ real-time monitoring of reaction trajectories and intermediates, and ability to decipher correlations between different events. The following summarizes cases where single-molecule junctions have been used to detect chemical reaction interactions.

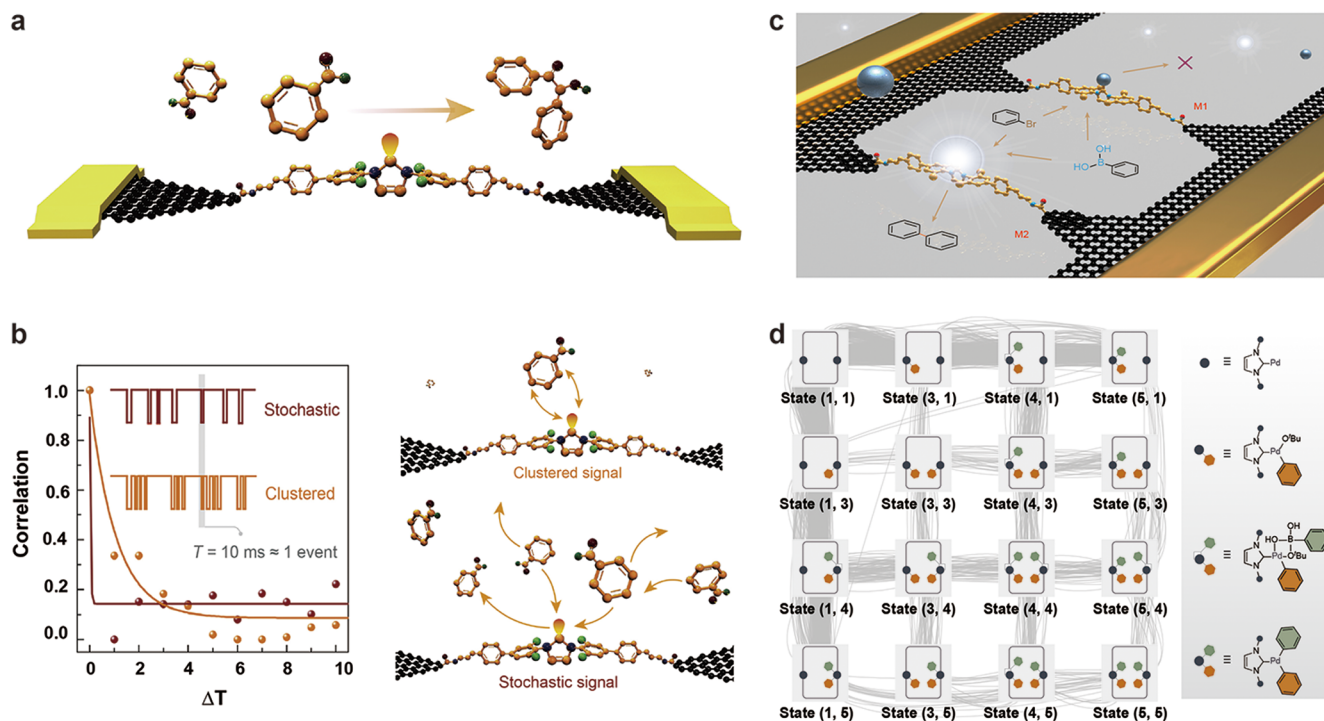


Figure 9. Characterization of substrate–catalyst interactions and catalyst–catalyst interactions based on single-molecule junctions. (a) Schematic of the NHC-catalyst-centered GMG-SMJ. (b) Left panel: Autocorrelation function of adjacent reaction events at low (orange) and high (red) concentrations. Right panel: Schematic of the interactions between one catalyst and substrates at low (top) and high (bottom) concentrations, respectively. Reprinted with permission from ref 113. Copyright 2021 Elsevier. (c) Schematic of the parallel two-catalyst device. (d) Conversion sequence mapping among the 16 states of the catalytic reaction network. Reprinted from ref 114. Copyright 2023 American Chemical Society.

4.1. Substrate–Substrate Interaction

Substrate–substrate interactions are a prerequisite for most chemical reactions, and are significant building blocks for complex reaction networks. Detailed single-molecule characterizations could elucidate reaction mechanisms, and create new functions. For example, Guo et al. used a GMG-SMJ to track Fries rearrangement reaction pathways in real time and their specific intramolecular/intermolecular interaction patterns. This elucidated the controversial reaction mechanisms and was used to fabricate a single-molecule memristor.¹¹¹ Specifically, divergent mechanistic pathways of the Fries rearrangement were proposed after inconsistent macroscopic crossover experiments. These included completely intramolecular, completely intermolecular, and partially intra- and intermolecular mechanisms. Guo et al. integrated a molecular bridge with a phenol center in the graphene electrodes, and monitored the interaction between the acyl moiety and the phenol (Figure 8a). Single-substrate measurements, where only one substrate was located at the center of the molecular bridge, indicated that several reaction events were detected before the acyl group finally left the reaction cage (Figure 8b). Reversibility was attributed to thermodynamic preference in the reaction coordinate and the π -cation interaction. Furthermore, eigenvalues of the events describing the reconfiguration of the acyl moiety were obtained from multiple sets of trajectories. This illustrated the inherent static energy profile and dynamic behavior of the Fries rearrangement. The numbers of interactions between the acyl moiety and the phenol to form reactant and product were $0.66 \pm 0.04 \text{ s}^{-1}$ and $0.36 \pm 0.04 \text{ s}^{-1}$, respectively. This reflected the acyl-phenol affinity, which was also demonstrated via the interaction time from the beginning of the reaction to the departure of the acyl

group. In the first and second elementary reactions, the interaction times were 15.1 ± 4.0 , and 7.0 ± 1.0 ms, respectively. The events and times reflected the inherent strength of the acyl-phenol interaction. In addition, these derived values were affected by the focused elementary reactions. More energy preferences for the reactant over the product resulted in longer interaction times between the reactant and acyl. Meanwhile, the lower energy of the intermediate with respect to the reactant also resulted in a higher number of interaction events. The observation of reaction trajectories in single-substrate measurements revealed the acyl-phenol interaction at a single-event level, enabling subsequent studies in more complex reactions.

Interactions between coenzymes at the single-molecule level are significant for complex biological processes. From single-enzyme conductance measurements and multiscale simulations, Zhang et al. proposed an updated catalytic cycle for formate dehydrogenase and elucidated the coenzyme-coenzyme interactions (Figure 8c).¹¹² To identify the catalytic pathways of the five intermediate states, a hover model of STM-BJ was used with the distance between the two fixed electrodes to detect real-time conductance fluctuations of single-enzyme reactions (Figure 8c). Despite the large number of monitored trajectories, Zhang et al. could not capture the apoenzyme state (T5) involved in the formate dehydrogenase (FDH) catalytic pathway (Theorell–Chance mechanism), (Figure 8d), suggesting that T5 might be bypassed in the catalytic cycle. Computational studies indicated that fresh nicotinamide (NAD^+) could easily diffuse into the proximity of NADH in FDH, causing strong π – π stacking interactions between NAD^+ and NADH. Nascent NADH could then be converted to NAD^+ via an in situ hydride transfer reaction with

fresh NAD^+ . Both experiments and calculations demonstrated that the enzyme-binding affinity of NADH was much stronger than that of NAD^+ , suggesting that the direct position exchange via the apoenzyme state was strongly disfavored. Therefore, probing enzyme-catalyzed reactions from single-molecule interactions could reveal complex biological processes.

4.2. Substrate–Catalyst Interaction

A comprehensive understanding of a catalytic reaction mechanism is of great importance in chemistry, biology, environmental issues, and energy. An in-depth investigation of dynamic substrate-catalyst interactions would be crucial for catalytic optimizations. Single-molecule junctions focus on reaction trajectories and kinetics of individual catalysts, enabling clarification of catalytic mechanisms and complex behaviors. Yang et al. reported a universal single-molecule electronic spectroscopy to reveal the intrinsic mechanism of the benzoin reaction, and the substrate–catalyst interactions.¹¹³ They used a N-heterocyclic carbene (NHC) catalyst with an unsaturated backbone as the center of the molecular bridge between the electrodes (Figure 9a), and monitored the homocondensation of benzaldehyde, and the cross-condensation of benzaldehyde and octyl aldehyde, to obtain real-time reaction trajectories and detailed thermodynamic/kinetic information. The substrate-concentration-dependent measurements revealed repeated interactions between the catalyst and substrates at low concentrations. Scattered or clustered signals (conversions between NHC and BI) appeared at low concentrations, while dense stochastic signals appeared at high concentrations. To quantify these characteristics, they recorded the reaction events at given intervals and analyzed correlations of adjacent intervals with an autocorrelation function (Figure 9b). At low concentrations, the reaction had a certain correlation, while it was completely random at high concentrations. This indicated repeated interactions between catalyst and substrate at low concentrations, attributed to the electron-rich catalyst and the electron-deficient aromatic substrate ring, as well as to π – π stacking between the molecular bridge and the aromatic aldehyde. This demonstrated characterization of chemical reaction interactions at the single-molecule level, in addition to identifying various intermediates and visualizing complex reaction processes.

4.3. Catalyst–Catalyst interaction

A catalytic system is not merely a sum of individual catalytic cycles. An increasing number of catalysts contribute to a complexity that cannot be disregarded. Therefore, the study of catalyst-catalyst interactions is needed to improve catalytic performance. Multiple-molecule junctions can analyze interactions between two adjacent catalytic reactions. Guo et al. discovered anticorrelation behaviors over the time scale of two individual catalysts in close proximity in two parallel molecular junctions (Figure 9c).¹¹⁴ Synchronous electronic characterization of Suzuki–Miyaura cross-coupling catalyzed by two catalysts revealed conversion-sequence mapping among the 16 states of the catalytic reaction network (Figure 9d). According to this mapping, the anticorrelation of the catalytic behaviors of one catalyst with those of the other (stopping at $\text{Pd}(0)$) was found with a large occupancy that suppressed the surrounding catalyst (causing it to stay at $\text{Pd}(0)$). The destructive interference between the two catalysts was caused by long-range electric dipole–dipole interactions induced by the

solvent. This destructive behavior could also decrease the turnover frequency in macroscopic experiments. These reaction dynamics measurements of multiple molecules with single-event resolution could be used to analyze emergent complexity in the transition from single molecule to ensemble, and to build a bridge between them.

5. CONCLUSIONS AND OUTLOOK

This Perspective highlighted advancements in single-molecule junction techniques for studying complex molecular systems, including intramolecular orbital interactions, weak intermolecular interactions, and interactions in chemical reactions. The behavior of molecules and interactions at the single-molecule level will enable an understanding of how macroscopic collective behaviors and functions emerge. Therefore, single-molecule techniques are crucial steps to ensemble analysis, bridging the gap between the individual and the whole.

Given the challenges of complexity science, we propose four directions for future single-molecule junction techniques to study complex interacting systems. The first recommendation is to redefine and formulate macroscopic concepts, such as fundamental thermodynamic and kinetic parameters, from a single-molecule perspective. At present, a series of thermodynamic/kinetic models for microscopic systems have not been established for the single-molecule level. To better describe the quantum-mechanical properties and to clarify correlations between single molecules and an ensemble, new models should be established from the single-molecule perspective. For example, the inadequacy of single-molecule systems to meet statistical requirements has necessitated the redefinition of concepts such as temperature, entropy, and pressure. This has opened up new possibilities for single-molecule theories. The second recommendation is to exploit intramolecular and intermolecular quantum effects, such as coherence, superposition, entanglement, and tunneling. In addition to chemical processes, biological processes such as photosynthesis, respiration, and vision all exhibit quantum phenomena.¹¹⁵ For example, long-lived quantum coherence has been found in electronic energy-transfer processes in photosynthesis.¹¹⁶ Hence, single-molecule junction techniques should continue to explore subtle quantum effects in molecules and their role in overall function. The third recommendation is to develop multimode single-molecule characterization methods. Electrical, optical, mechanical, magnetic, and other signals during interactions could contribute to a complete picture of complex interacting networks. Ultrahigh temporal and spatial resolution techniques that integrate these various physical property measurements should thus be developed to realize multidimensional and multimodal characterization. The fourth recommendation is to introduce computational modeling tools for visualization of data and complex behaviors in chemical systems, such as reaction nodes and correlations between products in networks.⁴ Modeling of the multiscale emergence of complex molecular systems is a challenging task that would require appropriate theory and the development of simulations for multiple time and spatial scales. Artificial intelligence for processing single-molecule experimental data for complex systems could be used to summarize the laws of emerging complexity, and thus provide guidance for experiments. Finally, an explanation or even a prediction of emergent phenomena at the single-molecule level would require the integration of chemistry, physics, biology, and computer science. Single-molecule junction techniques are a promising

tool in emergent complexity, with the potential to investigate collective behaviors.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We acknowledge primary financial supports from the National Key R&D Program of China (2021YFA1200101, 2021YFA1200102, and 2022YFE0128700), the National Natural Science Foundation of China (22173050, 22150013, 21727806 and 21933001), the New Cornerstone Science Foundation through the XPLOER PRIZE, the Natural Science Foundation of Beijing (2222009), Beijing National Laboratory for Molecular Sciences (BNLMS202105), the Fundamental Research Funds for the Central Universities (63223056), “Frontiers Science Center for New Organic Matter” at Nankai University (63181206).

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