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Structural Transition Dynamics in Carbon Electrode-Based Single-Molecule Junctions

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What is the most favorite and original chemistry developed in your What is the most important personality for scientific research? research group? Three aspects: interest, persistence and industriousness. The first key to Single-molecule device fabrication and detection. the success should be diligence. How do you get into this specific field? Could you please share some How do you keep balance between research and family? experiences with our readers? It is hard to balance the time. It is very important to have understanding and support from the family. I love them. I started to pursue this field during my PhD period. The promise of molecular electronics that might breakthrough the development bottleneck What's vour hobbies? of current microelectronics inspired my great interest. This interest Driving and watching movies. drives me to persist in the pursuit of practical molecular electronic devices as perfect as possible. Birth: Feb, 1975; Sichuan, China **Education: Xuefeng Guo** 1994–1998, BSc, Beijing Normal University 1998-2001, MSc, Beijing Normal University Professor at College of Chemistry 2001–2004, Ph.D., Institute of Chemistry, Chinese Academy of Sciences and Molecular Engineering, Peking Experience: University 2004–2007, worked as a postdoc at the Columbia University Nanocenter E-mail: guoxf@pku.edu.cn 2008-Current, worked as a professor at Peking University Awards: 2019, the EXPLORER PRIZE; 2017, The First Prize of MOE Science and Technology Homepage: Award; 2016, Top 10 Scientific and Technological Achievements from Chinese Universities; http://www.chem.pku.edu.cn/guoxf/ 2016, China Top Ten Scientific Progress. Interests: Nano/molecular electronics; Single-molecule dynamics and detection;

Organic/flexible electronics; Chemo/biosensors

Keywords

Structural transition | Photoisomerism | Molecular electronics | Noncovalent interactions | Stereoelectronic effect

Abstract



Monitoring the structural transitions of individual molecules is of great significance because it helps to in depth explore the properties of molecules and provide diverse possibilities for molecular applications in the fields of chemistry, biology and material science. This review summarizes the strategy of using single-molecule electrical approaches to study molecular structure transitions at the single-molecule level in real time. Specifically, through the use of stable single-molecule devices for real-time electrical monitoring, the process of molecular structure transitions of a single molecule can be investigated, which helps to explore the nature of molecules in chemical and biological systems. In particular, the detection methods have been extended to the investigation of biological macromolecules for monitoring the conformational changes of nucleotide chains in different systems, such as double helix DNA, aptamer and DNA enzyme. In the end, we discuss the future challenges of probing structural

transitions of single molecules, and provide prospects for further breakthroughs in this field.

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1. Introduction

In general, the molecular structure determines the physical, chemical and biological properties of molecules.^[1-2] The structural transitions of molecules are extremely important because they provide diverse possibilities for molecular applications in the fields of chemistry, biology and material science. Therefore, the structural transitions of molecules, especially rotation of chemical bonds, rearrangement of chemical bonds and interaction of non-covalent bonds, have attracted great attention. $^{\left[3-5\right] }$ For example, the configurational changes of photo/electro-isomeric molecules can be applied to molecular switches, digital storages and other fields.^[6-7] The conformational transitions, especially the stereoelectronic effects, are critical to chemical reactions and provide new functions for molecular devices.^[8-9] The conformational changes of biological macromolecules, such as the nucleotide chains, can be used to disease diagnosis and drug discovery.^[10-11] Therefore, monitoring the structural transitions of single molecules is extremely important, which can reveal the laws of subtle changes of molecular structures that determine the molecular applications.

In fact, several approaches have been developed to investigate the characteristics and transitions of molecular structures, including traditional characterization methods and single-molecule detection methods. The traditional characterization methods mainly include optical methods, such as ultraviolet-visible spectroscopy,^[12] infrared spectroscopy,^[13] Raman spectroscopy,^[14] fluorescence spectroscopy, and other methods such as nuclear magnetic resonance spectroscopy.^[15] In comparison with traditional characterization methods, single-molecule detection can investigate the structural transition of a single molecule rather than a collection of a large number of molecules and thus the ensemble average can be avoided.

Due to the advantages of single-molecule detection, various single-molecule optical and electrical methods have been developed to investigate the structural transitions of molecules in chemical and biological systems. Specifically, optical methods mainly include single-molecule Raman spectroscopy,^[16-17] single-molecule fluorescence spectroscopy^[18-19] and so on. For the single-molecule Raman spectroscopy, due to its weak signal intensity, additional enhancements are usually required to achieve singlemolecule characterization, such as surface-enhanced Raman scattering. The single-molecule fluorescence spectroscopy usually needs the introduction of external fluorophore modification to achieve the investigation of biological macromolecules. While the single-molecule electrical technology provides a quite different research perspective and can directly detect molecular properties related to conductance, such as spatial electronic structure or orbital energy level of molecules. $^{\left[20-21\right]}$ In addition, the electrical method also has the advantages of high time resolution and compatibility with various systems. The detection of structure and structural transitions of single molecules has been realized by using different electrical methods, such as nanotube^[22] or nano-wire based field effect devices,^[23-24] nanopore-based sensors,^[25]

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scanning tunneling microscope $^{\left[26\right] }$ and single-molecule junctions. $^{\left[27-28\right] }$

Among these methods, single-molecule junctions with carbon electrodes are particularly promising.^[27,29] They can covalently integrate a single molecule into the electronic nanocircuit and use it as a conductive channel. Thus, real-time and reliable monitoring of molecular conductivity can be achieved. The technology has proven to be a powerful single-molecule electrical detection platform, which can detect the structural transitions of single molecules and their dynamic processes at the single-event level. Moreover, the electrical detection platform has the advantages of high temporal resolution, high sensitivity and high signal-to-noise ratio, so it can be applied to many fields, such as photo-induced configurational change,^[30] temperature-dependent rotation of chemical bonds,^[8] and hydrogen bond or other non-covalent interactions.^[31]

In this account, we aim to summarize the strategy of using stable single-molecule devices to study molecular structure transitions from small molecules to bio-macromolecules. Through the electrical characteristics monitored by single-molecule devices, the processes of molecular structure transitions can be explored in real time at the single-molecule level, which helps to understand the nature of molecules in chemical and biological systems.

2. Carbon Electrode-Based Single-Molecule Junctions

In recent years, single-molecule junctions using single molecules as conductive cores have attracted much attention. It can provide a highly sensitive platform to study the laws of physics and chemistry at the single-molecule level. Due to the simplest chemical composition, atomic bond configuration, large surface area and good electrical conductivity, single-walled carbon nanotube (SWCNT) and graphene are ideal materials for constructing carbon electrode-based single-molecule junctions. There are several methods to fabricate single-molecule junctions based on carbon electrodes, including cross-plane fracture junction technology with graphene electrodes,^[32] feedback-controlled electroburning technology with nanogapped single-layer graphene electrodes,^[33] etc. And we have also successfully developed two types of single-molecule junction systems based on SWCNT^[34] and graphene^[29] electrodes through continuous development and improvement in the past 20 years. Furthermore, due to the strong chemical covalent bond connection between the carbon electrode and the molecule, the constructed single-molecule junctions are stable enough to reliably monitor the structural transitions of the connecting molecules.

Specifically, by locally oxidizing and cutting SWCNTs, SWCNT electrodes with nano-gaps matching the molecular size can be formed.^[35] Due to the strong oxidation during the fabricating process, the SWCNT electrodes have carboxyl groups at the end. Then, a single molecule with amine terminal groups on both sides is bridged to the carboxylic acid terminal of electrodes to form stable amide bond connections. The constructed single-molecule junction is sufficiently robust so that various external environments and conditions can be applied.

Similarly, graphene-based single-molecule junction is formed by covalently connecting a single molecule with graphene point contact electrodes, which are prepared by using the dash-line lithography (DLL) method.^[36] Specifically, graphene sheet is prepared on a silicon substrate by chemical vapor deposition and further transfer process or by a peeling technique, and then a polymethyl methacrylate (PMMA) layer is spin-coated. Then, by electron beam lithography, a design CAD file with a 5 nm wide dashed line is used to form an array with small holes less than 10 nm in the PMMA mask layer. Finally, through oxygen plasma etching, a graphene point contact array with a gap of less than 10 nm can be fabricated, which is terminated with carboxyl groups. And the carboxyl groups at the end of graphene point contacts will react with terminal amino groups of molecules to assemble together, thereby forming robust single-molecule junctions with high yield (maximum yield up to 50%).^[36]



Figure 1 Schematic diagram for carbon electrode-based single-molecule junctions. (a) SWCNT-based single-molecule junctions. Reprinted with permission,^[35] Copyright 2006, American Association for the Advancement of Science. (b) Graphene-based single-molecule junctions. Reprinted with permission,^[36] Copyright 2012, Wiley-VCH.

3. Configurational Changes of Azobenzene

Azobenzene as a typical photochromic molecule has attracted widespread attention. It has been widely used in polymers,^[37] liquid crystals^[38] and nanostructures,^[39] resulting in a variety of

novel applications including digital storage^[40] and on-command drug delivery. Due to its photo-induced cis-trans isomerism effect, it can transform from trans configuration to cis configuration under UV light, while the opposite is realized for visible light (Figure 2a). The trans isomer is almost planar, but the cis isomer adopts a bent configuration. The single-molecule junctions provide a feasible mean for exploring the configurational changes of azobenzene. One method is to bridge a single azobenzene molecule between molecular-scale graphene point contacts (Figure 2b).^[41] In this structure, the configurational change of azobenzene molecule occurs directly in the backbone. When azobenzene is exposed to UV light, the configuration changes from trans to cis, accompanying a change of conductance from high to low. Conversely, the reverse photo-isomerism occurs under the visible light, and the conductance almost recovers to the original value.^[36] This is because the *cis* form has a larger highest occupied molecular orbital (HOMO)-lowest unoccupied molecular orbital (LUMO) energy gap and poorer energy level alignment with the Fermi level of the electrodes. Another way is to use azobenzene molecule as side group of the bridging molecule, which undergoes configurational changes under light stimulation (Figure 2c). The cis/trans configurations of the azobenzene molecule show different dipole moments, which are opposite in the direction of the terphenyl backbone with values of ~6.59 D and ~1.22 D for cis and *trans* states, respectively (Figure 2d).^[42] Correspondingly, this significantly different configurational asymmetry leads to changed conductance of the single-molecule junction.



Figure 2 Configurational changes of azobenzene. (a) Structures of *trans* and *cis* isomers of azobenzene. (b) Chemical structures of azobenzene based molecules connected between the electrodes. Reprinted with permission,^[41] Copyright 2013, Wiley-VCH. (c) Schematic of azobenzene as side group of bridging molecules in the junction. (d) Dipole projection on the molecular backbone for charge transport. The arrow denotes the direction of the dipole projection. Reprinted with permission,^[42] Copyright 2019, Springer Nature.

4. Configurational Changes of Diarylethene

Diarylethene is mainly composed of two aromatic heterocycles bonded at both ends of a carbon–carbon double bond. It also has photoisomerization characteristics (Figure 3a).^[43] When diarylethene is exposed to ultraviolet light, it will switch from the non-conjugated open state to the conjugated closed state, thus leading to the change of molecular orbital energy levels. On the contrary, when the diarylethene is irradiated with visible light, it can return to the non-conjugated open state. In terms of configuration structure, the closed isomer is almost planar, but the open isomer adopts a bent configuration with its thiophene rings twisted about 61° out of the plane of the cyclopentene ring.

Diarylethene with different substituents at the X position (Figure 3b) is connected to the nano-gapped SWCNT electrodes.^[29] It is found that under UV light, the configuration of pyrrole-based molecule can change from the open state to the closed state. Due

to steric hindrance effect, the molecule can switch back to the closed state due to heat. However, the thiophene-based molecule junction can only achieve the transition from the low state to the high state by UV light stimulation. This means that the molecule in the junction can only achieve the transition from open state to closed state, but cannot return, so reversible configuration changes cannot be achieved.^[44] The reason is that the orbitals between the molecule and the electrode is highly hybridized, which causes the electrode to quench the photoexcited state of the diarylethene molecule in the closed state.

To tailor the energy level alignments at the moleculeelectrodes interface, the electrode material of the junction is changed to graphene. At the same time, by rationally designing the side groups and anchoring groups (Figure 3c), the diarylethene backbones are modified to explore the effects of energy level alignment and interface coupling. Specifically, the first way is to substitute the hydrogenated cyclopentene by the fluorinated units. The electron-withdrawing effect of fluorinated unit can reduce the electron density on the central alkene unit, resulting in a decrease in the energy level. The second way is to further introduce a methylene group (CH₂) between the terminal amine group and the functional center on each side. Since the CH₂ groups can cut off π -electron delocalization, the electronic interaction between molecule and electrode is largely decoupled. The energy band and electronic structure obtained by theoretical simulation prove that the tunable molecule-electrode coupling strength and adjustable energy levels can be achieved by molecular engineering (Figure 3d). These specially designed diarylethene molecules are respectively connected to graphene electrodes to make single-molecule junctions, but the reversible configurational changes of diarylethene molecules between the open and closed states still could not be realized.^[45]

To further explore the relationship between interfacial coupling and the realization of molecular structure transition, the diarylethene molecule with three methylene group as the spacer is covalently assembled to nano-gapped graphene electrodes (Figure 3e), which leads to low state density between the diarylethene backbone and the electrodes. In this way, the reversible conductance switching of the single-molecule junction proves that the reversible photoisomerization properties of diarylethene can be realized in the single-molecule junction (Figure 3f). This proves that the addition of three methylene groups reduces the molecule-electrode interfacial coupling to a certain extent, thereby avoiding the quenching of the molecular excited state by the electrodes, so that the diarylethene molecule can display the inherent characteristics.^[46]

5. Chemical Bond Rotation-Induced Stereoelectronic Effect

cules can be explored at the single-molecule level through single-

molecule junctions. The diarylethene molecule with three

As mentioned above, the configurational changes of mole-

(a) (b) Non Open Conjugated 1 x = S2 x = NMeConjugated Closed (C) 1 (d)E (eV) 3 Closed Open LUMC 3.86 IOMO HOMO (e) (f) 0.4 Off Off On Off In (nA) 0.2 0.0 UV Or On On 100 200 300 400 O 500 600

Figure 3 Configurational changes of diarylethene in single-molecule junctions. (a) Photoisomerization of diarylethene. (b) Diarylethene connected to SWCNT electrodes. Reprinted with permission,^[44] Copyright 2007, American Chemical Society. (c) Structures of three specially designed diarylethene molecules. (d) Calculated molecular energy levels and related molecular orbital diagrams of molecule 3. Reprinted with permission,^[45] Copyright 2013, Wiley-VCH. (e) Single-molecule junction of diarylethene molecule with three methylene groups between the diarylethene backbone and the terminal groups. (f) The photo-switching effect of diarylethene molecule with three methylene groups. Reprinted with permission,^[46] Copyright 2016, American Association for the Advancement of Science.

methylene groups covalently assembled into the nano-gapped graphene electrodes not only has the function of photo-switching, but also has the property of random switching in a certain temperature range. This random switching is derived from the stere-oelectronic effect caused by the rotation of the chemical bonds between the aromatic heterocycle and benzene ring (Figures 4a and 4b).^[47] The stereoelectronic effect brings out electron-phonon coupling, which leads to incoherent transport in molecular junctions. In addition, for the two conformations of reversible molecular photoswitch with different energy levels, the activation energies of incoherent transports are different. Through temperature-dependent experiments, the relationship between the activation energies of charge transport and the energy levels of molecule in different conformations can be explored with single-molecule junction.^[47]

Stereoelectronic effect involving changes of the molecular structure can also be observed in other molecules.^[8] In fact, stereoelectronic effects are the basis of reaction chemistry, because they reflect the influence of the relative spatial orientation of the electron orbits on the properties and reactivity of molecules. Here, the concept of stereoelectronic effect is narrowly defined, which means the conformational transitions caused by the rotation of chemical bonds, thereby switching between different conductance states. For example, as the elementary unit of organic functional materials, biphenyl has the stereoelectronic effect, that is, the variation of twisting angles and corresponding π - π overlaps between phenyl rings, which can significantly affect the structure and photophysical properties of organic functional molecules. To reveal the inherent stereoelectronic effect of the aromatic chain, the hexaphenyl aromatic chain was connected to the graphene electrodes (Figure 4c). According to the investigation of the current-voltage (I-V) characteristics of hexaphenyl aromatic chain single-molecule junctions, stochastic switching between two distinct conductance states occurs, because the twisting of the phenyl group in the aromatic chain molecule will produce different degrees of conjugation (Figure 4d). Specifically, there are two different dihedral angles between the two outer benzene rings at each end of the terphenyl unit: one is zero, and the other is almost twice that between the benzene rings in the biphenyl. The former is strongly conjugated, while the latter is weakly conjugated (Figure 4c).

6. Rearrangement of Hydrogen Bonds

Hydrogen bonds, which widely exist in nature, play a key role

in chemical, physical and biological processes.^[49] However, it is extremely difficult to directly detect the rearrangement of hydrogen bonds at the molecular level in real time. Through the construction of single-molecule junctions, the monitoring of isomerism caused by hydrogen bond rearrangement at the single-molecule and single-event level can be achieved.

By covalently bonding the quadruple hydrogen bond dimer based on ureido pyrimidine-dione (UPy) into the nano-gapped graphene electrodes, a stable supramolecular-assembled singlemolecule junction can be established.^[50] Based on the change of device conductance, the hydrogen bond rearrangement process related to solvent and temperature can be detected in real time. Moreover, the quadruple hydrogen system shows a multimodal distribution, which is mainly due to the stochastic rearrangement of the hydrogen bond structure caused by intermolecular proton transfer and lactam-lactim tautomerism (Figure 5e). Specifically, the tautomerism from structure 1 to 2 is caused by the migration of the hydrogen atom from the position of blue O to the position of red N in the molecule. The tautomerism from structure 4 to 5 is the opposite process, and the hydrogen atom migrates from red N to blue O. The conversion between the three structures of 2, 3 and 4 can be achieved by proton transfer, that is, the intermolecular hydrogen atoms migrate between the nitrogen atoms at different positions. Since different structures have different molecular energy levels, multiple conductance states can be observed in the single-molecule junction.^[50]

7. Host-Guest Interaction

Host-guest interaction is a process in which host molecules and guest molecules are selectively combined through non-covalent interactions to form host-guest complexes with specific functions under the conditions of structural complementarity and energy matching.^[51] With the characteristics of mild reaction conditions and reversible reaction process, the host-guest interaction has been applied to molecular machines and other fields.^[52] Therefore, it is meaningful to monitor the processes of host-guest interaction.

By covalently integrating a conjugated molecule wire with a pendant crown ether into graphene point contact electrodes, the pseudorotaxane formation processes between the electron-rich crown ether and a dicationic guest can be converted into realtime electrical signals (Figures 6a and 6b). When the guest molecule passes through the host molecule ring, there will be two



Figure 4 Stereoelectronic effects of different molecules. (a, b) Schematic of the charge transport mechanism transition and activated vibration modes of the diarylethene molecule. Reprinted with permission,^[47] Copyright 2017, American Chemical Society. (c) Schematic of conformational transition of terphenyl units between strongly conjugated and weakly conjugated states and corresponding hexaphenyl aromatic chain single-molecule junction. (d) Electron energy diagram and corresponding transition states for three stable conformations of the hexaphenyl molecule. Reprinted with permission,^[48] Copyright 2017, American Chemical Society.



Figure 5 Hydrogen bond rearrangement. (a) Schematic illustration of the electrical measurement setup. (b) Chemical structures for single-molecule junctions. (c) Phenomenon of multiple conductance states of the device. (d) A single-exponential decay fitting the corresponding states with different lifetimes. (e) Schematic diagram of each transition process between the five structures. Reprinted with permission,^[50] Copyright 2018, Springer Nature.

processes of association and dissociation, resulting in two states of high conductance and low conductance. Among them, high conductance state can be attributed to the association of the guest molecule with the host in the single-molecule junction, forming a host-guest complex. By analyzing the conductance of single-molecule junctions, a non-destructive method for quantitatively determining the binding force and rate constant can be achieved. Based on temperature-dependent experiments, the activation energy of the host-guest interaction in a specific solvent environment can also be obtained.^[53]

In addition, the detailed dynamic process of random motion of a single molecular machine can also be stably detected, which has host-guest interaction between the alkyl chains with different charges on both sides and the permethylated α -cyclodextrin. Specifically, the single-molecule junction is constructed by covalently assembling a pseudorotaxane featuring permethylated α -cyclodextrin into nano-gapped graphene electrodes (Figures 6c and 6d). The state fluctuations of the single-molecule junction are detected by in-situ long-term electrical measurements. To study the effect of charge on the structural transition of the host molecule, the two ends of the alkyl chain of the guest molecule are modified with negative and positive charges, respectively. When the negative end of the guest molecule is located in the cavity of the host molecule, the perturbed highest occupied molecular orbital (p-HOMO) of the pseudorotaxane is close to the Fermi level of the electrodes, thus achieving a high conductance state. On the contrary, when the positive end of the guest molecule is located in the cavity of the host molecule, the p-HOMO of pseudorotaxane moves away from the Fermi level of the electrodes, thereby reducing the conductance. When the alkyl chain of the guest molecule is in the cavity of the host molecule, the conductance is in an

intermediate state (Figure 6e). Furthermore, the entire change process of the above-mentioned conductance states is highly dependent on temperature changes.^[54]

8. Conformational Changes of Nucleotide Chains

Nucleotide chains are the constituent units of many biological systems, including double-helix DNA, aptamer, DNA enzyme, *etc.*, and play a key role in biological heredity, life development and the realization of biological functions.^[55] Due to the importance of nucleotide molecules, it is particularly important to monitor the conformational changes of nucleotide chains at the single-molecule level. It has great potential for applications in different fields ranging from gene mutation detection to disease diagnosis and drug discovery.^[56-57]

In fact, the nucleotide chain itself has many configurations, and many factors affect its conformational changes. Electrical characterization based on single-molecule junctions can explore the conformational changes of nucleotide chains of different configurations. For example, in the combination of the well-known double-helix DNA structure and the metal complex system, the double-helix DNA is bridged between the nano-gapped SWCNT electrodes (Figure 7a). Through the electrical properties of the single-molecule junction, it can be observed that the device conductance decreases during the removal of the Cu²⁺ ion from the metal base pair. This is because, on the one hand, the removal of Cu²⁺ ion reduces the conductive channel. On the other hand, the removal of Cu²⁺ ion leads to a metal-free duplex DNA structure and conformational changes, thereby preventing charge transport through the π -stacked DNA and reducing the device conductance.^[58] In addition to the metal complex induced binding,



Figure 6 Host-guest interaction at the single-molecule level. (a) Schematic representation of guest molecules passing through the host molecule ring in the single-molecule junction. (b) Structures of host molecule wire with pendant crown ether and dicationic guest. Reprinted with permission,^[53] Copyright 2016, American Association for the Advancement of Science. (c) Device structure and electrical characterization of the cyclodextrin single-molecule junction. (d) Structures of host molecule wire with permethylated α -cyclodextrin and charged alkyl chain guest. (e) Real-time current recording of the shuttling processes. Reprinted with permission,^[54] Copyright 2019, WILEY-VCH.

the effect of molecular intercalation on the conformation of DNA molecules can also be measured with single-molecule junctions. Taking DNA intercalation by individual ethidium bromide (EB)/ SYBR green I (SG) as an example, single-molecule junction is constructed with functionalized DNA molecule between nano-gapped graphene electrodes (Figure 7b). The charge transport through the DNA junction undergoes significant stepwise changes, which indicates that the distortion of the DNA conformation during molecular intercalation can be finely displayed at the single-event level.^[59] In addition to the double-helix DNA configuration with the nucleotide chain, the conformational changes of the

aptamer configuration with the nucleotide chain can also be monitored by the single-molecule device. By assembling a single DNA aptamer to nano-gapped SWCNT electrodes (Figures 8a and 8b), aptamer single-molecule junction has been constructed to detect the effect of protein-aptamer binding with conformational changes at the single-event level. When the target protein thrombin binds to the aptamer, its G4 conformation becomes more rigid, which promotes tight π -packing, thereby increasing the electrical conductivity of the single-molecule junction.^[60] According to the same principle, the influence of cocaine on the conformational change of the aptamer can also be investigated by the change in the electrical properties of the single-molecule junction. Specifically, the single-molecule junction is constructed by covalently linking single aptamer molecule between nano-gapped graphene electrodes (Figures 8c and 8d). Real-time electrical signal recording can realize the investigation of the conformational change process of the aptamer during the binding with cocaine molecule.[61]



Figure 7 Conformational changes of nucleotide chains in double-helix DNA. (a) Schematic representation of the sensing process of metallo-DNA-bridged device. Reprinted with permission,^[58] Copyright 2011, Wiley-VCH. (b) Schematic representation of DNA-functionalized molecule junction used for detecting the effect of EB or SG intercalations, and the molecular structures of EB and SG. Reprinted with permission,^[59] Copyright 2015, The Royal Society of Chemistry.

Besides, the system can be extended to the nucleotide chainbased enzymes, while single DNAzyme is integrated into graphene-molecule junction (Figures 8e and 8f). The action of metal ions such as Cu^{2+} causes the conformational changes of the DNAzyme, thereby increasing the conductivity. Therefore, the single-molecule junction can be used to detect the influence of metal ions on the conformational changes of the nucleotide chain.^[62]



Figure 8 Conformational changes of nucleotide chains in other configurations. (a, b) Schematic diagram and mechanism of the single-molecule junction for detecting the influence of protein interaction on conformational changes of the aptamer. Reprinted with permission,^[60] Copyright 2011, Wiley-VCH. (c, d) Schematic representation and interaction mechanism of the cocaine-aptamer device. Reprinted with permission,^[61] Copyright 2019, SIOC, CAS, Shanghai, & WILEY-VCH. (e, f) Schematic representation and mechanism of the DNAzyme junction for detecting metal ions. Reprinted with permission,^[62] Copyright 2015, The Royal Society of Chemistry.

9. Summary and Outlook

In conclusion, the single-molecule electrical detection methods with robust single-molecule junctions based on carbon electrodes are developed for directly measuring charge transport and corresponding structural transitions of different molecules. Due to the high sensitivity of molecular electrical properties, the transitions in molecular structure at the single-molecule level and singleevent level can be real-time monitored by electrical measurement of molecular conductance. Specifically, the configurational changes of photoisomeric molecules, such as azobenzene and diarylethene, have been monitored at the single-molecule level through electrical characterization. The specific effects of chemical bond rotation and non-covalent bond interaction on the conformational transitions of molecules have been investigated at the singleevent level. For example, the stereoelectronic effects caused by the rotation of chemical bonds have been observed. For the hydrogen bond dimers and host-guest interaction systems, it is also possible to monitor multiple conductance states caused by multiple conformations. Moreover, the detection methods can be extended to biomolecular systems, and the conformational changes of nucleotide chains in different systems, such as double-helix DNA, aptamer and DNA enzyme, have been monitored at the single-molecule level. This has broad application prospects in different fields from gene mutation detection to disease diagnosis and drug discovery. $^{[56,63]}$

Despite these significant achievements, there is still a need to expand the research systems and improve research methods. In specific, the configuration and conformation changes of more molecular systems and corresponding dynamic processes should be investigated. The research system should also be extended to the structural transitions of supramolecules, biological macromolecules, etc. To improve the detection resolution and obtain more details of the molecular structures, super-resolved imaging and ultrafast spectroscopy techniques can be combined with sin-gle-molecule electrical detection.^[64-65] When the time resolution is improved to the femtosecond level, it can be expected to observe the detailed processes of rearrangement and rotation of single chemical bonds, which will help to understand the processes of molecular structure transitions. These investigations will improve the understanding of molecular structures and provide more possibilities for molecular applications in biology, chemistry and materials.

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