Single-Molecule Sensors Based on STM Break Junction Measurements

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Single-molecule recognition and detection with the highest resolution measurement has been one of the ultimate goals in science and engineering. Break junction techniques, originally developed to measure single-molecule conductance, recently have also been proven to have the capacity for the label-free exploration of single-molecule physics and chemistry, which paves a new way for single-molecule detection with high temporal resolution. Scanning tunneling microscopy-break junction (STM-BJ), invented to measure electron transport by repeatably forming single-molecule junctions in a nanogap between two electrodes, has also been a unique platform for exploring the intrinsic properties of materials and the interaction of individual molecules at a single-molecule level. The tunneling currents in the molecular junctions are sensitive to molecular structure and configuration, interfacial coupling between the anchoring group and electrode, external stimulus and the surroundings.

single-molecule sensor STM break junction ionic detection pH detection

1. Introduction

Single-molecule sensors with extreme detection limits and the ability to reveal heterogeneity and stochastic processes [1][2], have attracted widespread attention [1] in chemical, physical, and biological sciences. During the past decades, some emerging methods have been developed to allow single-molecule measurements with sufficient speed and statistical accuracy, such as nanopore [3][4][5], microfluid [6][7], and single-molecule fluorescence microscopy [2][8]. It has been found that molecular counting might be the most accurate method for single molecule detection and analysis [9].

Recently, scanning tunneling microscopy-break junction (STM-BJ) [10][11], invented to measure electron transport by repeatably forming single-molecule junctions in a nanogap between two electrodes, has also been a unique platform for exploring the intrinsic properties of materials and the interaction of individual molecules at a single-molecule level [12][13][14]. The tunneling currents in the molecular junctions are sensitive to molecular structure and configuration, interfacial coupling between the anchoring group and electrode, external stimulus and the surroundings [15][16]. Therefore, the transduction features of tunneling current, single-molecule conductance peak and values can also be applied in designing a single-molecule sensor [15]. Compared with traditional single-molecule detections based on optical, physical and chemical methods, such as fluorescence [17][18], surface-enhanced Raman spectroscopy [19][20][21][22], and nanopores [23][24], the electrical sensors based on single-molecule conductance measurements can be complementary and has unique advantages with integrating the STM technique: (1) It is a label-free real-time electrical detection that requires only a small amount of sample. (2) It is not

limited by the working environment. STM can efficiently work in vacuum, atmosphere, solution and other different environments. (3) Dynamic and static molecular information at the interfaces, such as molecular adsorption and surface reaction, can be detected in a real space.

2. pH Detection

With single-molecule break junction techniques, numerous investigations have systematically studied the molecular structure, anchoring groups and electrode materials of metal–molecule–metal junctions over the past two decades [25][26][27][28][29]. Gradually, researchers have turned to tune electron transport in single-molecular junctions under an external stimulus for functional electronic components, such as switch [30][31], rectifier [32] and transistor [33][34]. The pH, as one of the most widely used chemical stimuli, has also been studied in the single-molecular junctions [35][36]. It has been found that the conductance peaks and values of pH-sensitive molecular junctions display very different features in acidic and basic solutions, which paves a new way for designing single-molecule pH sensing.

To be capable of responding to the environment pH stimuli, commonly, it requires the constructions of molecular junctions with pH-sensitive molecular structures. Li et al. used two dye molecules of malachite green (MG) and pararosaniline (PA) as molecular pH sensing units [37]. The molecules can undergo reversible structural transformation between a conjugated form in slightly acidic solution and a nonconjugated form in a basic solution. The theoretical calculation reveals that changing the hybridization of the central C atom from sp^2 at pH = 5.5 to sp^3 at pH = 13.6 can significantly enlarge the HOMO-LUMO gap, which results in the single-molecule conductance in the basic solution being about 100 times less than that in the acid solution. This proves the concept of single-molecule pH electrical sensor based on the pH-induced conjugation and electronic change of dye molecules.

Peptides contained pH-sensitive amino and carboxyl groups have also been explored at the single-molecule level by break junction techniques. In 2004, Xiao et al. constructed the molecular junctions of three cysteine peptides and measured the conductance upon the environment pH with the STM-BJ technique. Interestingly, a sigmoid-like titration curve is found for the pH-dependent conductance of the peptides with an amine group when the pH of the solution increases. The maximum change of the single-molecule conductance is at the pH of 7 close to the pK_a of the amine group measured in the bulk solution, while the conductance of the peptide with an amine and a carboxyl group significantly varies both at the pH close to the $pK_a \approx 8$ and 3. Such pH-dependent conductance is originated from the resultant effect of protonation/deprotonation of the amine and carboxyl groups, which increases the tunneling barrier at high pH and leads to a lower conductance [38]. Similarly, Nichols and collaborators have also proven that the single-molecule junctions of peptide sequence $H(EL)_5C$ (where H stands for histidine, E for glutamic acid, L for leucine, and C for cysteine) is sensitive to the environment pH with the STM-BJ technique. The single-molecule conductance decreases from 1.7 nS at pH = 2 to below 0.10 nS at the pH above 6.9. This change is attributed to the $H(EL)_5C$ bridge which exists in a more compact α-helical state at a low pH, while deprotonation at a high pH leads to the electrostatic repulsion between charged carboxylate groups of glutamate residues, promoting more extended conformation [39]. These discoveries laid a foundation for the application of peptides in pH single-molecule sensors.

Except the biological molecules, supramolecules [40][41][42] have also been proven for the design of single-molecule pH sensors. For example, cucurbit[n]uril (CB[n]) is commonly used due to its unique properties of good biocompatibility. In 2020, Ai et al. used Cucurbit[7]uril (CB[7]) as the host molecule to measure the conductivity properties of CB[7] and its host–guest complex melphalan@CB[7] (Mel@CB[7]) at different pH with STM-BJ technique [40]. They performed conductance measurements in PB solutions at pH = 1, 4, and 7, respectively, and found that the conductance decreased with increasing pH. At the same pH, the conductance value of CB[7] is larger than that of Mel@CB[7]. This arises from more protons interacting with the carbonyl group of CB[7] in acidic conditions, which can enhance the electron transfer in these molecular junctions, while the addition of Mel decreases the bonding stability of CB[7] to the gold electrode. This provides a new idea for designing pH single-molecule sensing. These results prove a pH-responsive host–guest system for single molecule detection through single-molecule conductance measurements.

Recently, the molecular junctions with nitrogen heterocyclic molecules, such as pyridine [43] and spiropyran derivatives [44], have also been proven to be pH responsive because the nitrogen atom in these molecules can (de)protonate under acidic (basic) conditions. This protonation or deprotonation can significantly change the electronic structure of the molecules and mechanism of charge transport, resulting in conductance switching. For example, Tang et al. reported that a molecular junction containing the pyridine nitrogen constructed by STM-BJ could interact with cationic reagents of trifluoro-methanesulfonate (MeOTf) to form protonated pyridinium, displaying a conductance increase of more than one order of magnitude [43]. With a flicker noise analysis, it is interestingly found that the electron tunneling is primarily through space changes to through bond for the protonated pyridinium. Theoretical analysis shows that this protonation leads to the interchange of frontier orbitals and converts destructive quantum interference (QI) into constructive QI for electron transport in the molecular junctions.

Similarly, other nitrogen heterocyclic molecules, imidazole [45][46] and pyrazole [47][48] have been proven as attractive molecules for forming molecular junctions. They can also provide pH-activated connections between Au electrodes and molecules. Kamenetska and co-researchers investigated the binding mechanism of imidazole in the molecular junctions with an Au electrode by STM-BJ [49]. They measured the conductance of imidazole in solutions with different pH values ranging from 3, 7, 9 to 12. Interestingly, it is found that the conductance peak between 10^{-2} G_0 and 10^{-1} G_0 can only appear in basic solutions when the pH is larger than 7. This determines that this molecule bridges the electrodes in its deprotonated form, providing a type of molecular material for single-molecule pH sensing.

In addition to the molecular backbones, pH-sensitive anchoring groups in molecular junctions can also respond to the external stimuli of environmental pH. For instance, pyridine as one of the most used anchoring groups can be protonated to a cation in acidic environments. Brooke et al. used electrochemical STM-BJ techniques to construct the molecular junctions of Ni|4,4′-vinylenedipyridine (4,4′-VDP)|Ni and measured the conductance at different pH and applied potential [50]. It was found that the molecular junctions changed from a high conductive state at a high pH of the solution or positive potentials of electrodes, to a low conductive state at a low pH of the solution or negative potentials of electrodes, vice versa. These arise from the pH or potential induced protonation of two

pyridyl moieties in the molecules. Furthermore, the relationship between the pH and potential for protonation occurs is obtained by statistically counting the conductance versus distance traces for determining the relative probability of high (P_{high}) and low (P_{low}) conductive states. The potential E' versus MSE for P_{high}/P_{low} = 1 against the pH shows a good linear relation. The gradient of the fitted line δ can be used to calculate the charge retained by a protonated 4,4′-VDP molecule adsorbed to Ni electrodes. These dual-response molecular junctions upon the pH and potential can be not only applied in a pH-sensitive switch, but also prove a prototype of a three-terminal sensor with inputting the gate potential to determine the local pH.

The pH-sensitive carboxylic acid group is also one of the most used anchoring groups for forming molecular junctions [51][52][53]. Single-molecule conductance measurement reveals its binding mechanism based on the -COO^--Au bond. Thus, the formation probability of molecular junctions strongly relies on the population of deprotonated carboxylic acid molecules, which provides a unique platform for designing a single-molecule pH sensor. Zhou and co-researchers used the STM-BJ techniques to probe the acid−base chemistry of SAM of 4-(methylthio)benzoic acid (4-MTBA) on the Au(111)/aqueous solution interface [54]. With changing the pH of solution from 0 to 5, the conductance peaks at about $10^{-2.90}$ G_0 ascribed to the formations of single-molecule junctions become intense. The normalized peak intensity versus pH fits well in a sigmoidal curve, due to the increased dissociation of carboxyl groups in less acidic solutions. Furthermore, the quantitative analysis of the conductance peak intensity is used to estimate the interfacial pKsurfa

value. The fractional surface coverage (θ) ratio of θ_{-COO-} /θ_{-COOH} is proportional to $(I - I_{min})/(I - I_{max})$, where I is the normalized intensity of conductance peak at a pH, I_{min} and I_{max} are the minimum and maximum at the current range of pH, respectively. With the Henderson–Hasselbalch type equation, the $\log[(I - I_{min})/(I - I_{max})]$ versus pH is found to be a good linear relation. A similar phenomenon can also be observed at the molecular junctions of terephthalic acid (TPA) and 3-methylthiopropionic acid (MPA). In addition, the interfacial pKsurfa of MTBA can be also quantitatively evaluated at 6.6, comparable to the reported 7.0 for of 4-mercaptobenzoic acid (4-MBA) immobilized on an Au surface. Therefore, this advances the application of break junction techniques in interfacial acid−base chemistry at the single-molecule level and provides a feasible way to design the single-molecule pH sensor.

3. Ion Detection

Appropriate amounts of some metal and non-metallic ions dissolved in aqueous media play important roles in the metabolism of plants, animals and humans. However, high concentrations of these ions can lead to many adverse health effects [55]. In addition, some ions, such as Hg^{2+}, Cd^{2+}, Pb^{2+}, and As^{3+}, are toxic, which can cause serious debilitating illnesses [56][57][58]. Therefore, it is significantly important to develop highly selective and sensitive methods for detecting ions [59][60][61]. It is highlighted the principles and strategies used in break junction measurements for qualitative and quantitative detection of ions at a single-molecule level [1][2][10][11][15].

An early break junction experiment for the prototype of metal ion detection was carried out by Tao and co-researchers in 2004 [62]. They used STM-BJ to construct single-molecule junctions of peptide and measured the

conductance and I–V characteristics with Au electrodes. Upon metal ions of Cu^{2+} or Ni^{2+} in the solution, the peptide can be a host for the metal ion guest. Due to the specific binding of peptides with the metal ions through deprotonated peptide bonds, it significantly changes the configuration of the molecular junctions and thus increases the tunneling current. Therefore, the electrical characteristics difference in the molecular junctions before and after the binding of metal ions paves a way to study the molecular recognition of metal ions at a single-molecule level.

Another host−guest strategy based on the molecular junctions of crown ether is also used for metal ion recognition. In 2020, Yan et al. designed and synthesized a conjugated oligo-(phenyleneethynylene)(OPE) molecule with the a substituted 15-crown-5 ether moiety at the central benzene ring (compound 1) [63]. The rigid and well-defined OPE backbone can suppress the conformational distortion, and the crown ether moiety can coordinate with various alkali metal cations. Furthermore, a good linear relation is found between the conductance values and the ionic effective charge (ze/r) for Li^+, Na^+ and Rb^+. While the conductance value of the molecules coordinated to K^+ does not follow the trend, it is approximately improved 4-fold larger than that in blank. Controlled experiments with OPE-based 18-crown-6 derivative (compound 2) and DFT calculations reveal that a 2:1 sandwich-type supramolecular junction is formed for K^+, which leads to increase the conductance. Hence, these findings not only advance the understanding of molecule-metal ion interaction and their electron transport in crown ether molecules, but also provide a unique opportunity to develop ion-induced conductance switching and single-molecule sensing device.

Except for metal ions [64], a single-molecule sensor for the non-metal ion of fluoride has also been proposed based on the Lewis acid–base interactions of boron–fluoride coordination in molecular junctions [65]. Two types of organoborane molecular junctions have been successfully constructed by the STM-BJ techniques with Au electrodes. With the present of fluoride ions in solution, a covalent B–F bond can be formed due to the strong Lewis acid–base interactions, which break the original boron-containing-conjugated system. This can change the tunneling mechanism from LUMO to HOMO for electron transport through the 2,5-dimesitylboryl group disubstituted OPE molecules, thus an about four times lower conductance value is observed in the conductance histograms. Such an organofluoroborate can generate a destructive quantum-interference effect in the dithienoborepin (DTB) molecular junctions, which leads to a conductance switch ratio up to four orders of magnitudes [66]. The significant conductance variation before and after capturing a fluoride ion shows a promising potential application in the design of single-molecule sensors.

Toward a practical single-molecule ion sensor, it is crucial to move from the above-mentioned ion recognition to accurately and quantitatively determine the target analytes. Recently, Hong and co-researchers reported a single-molecule conductance ratiometric strategy for quantitatively determining Ag[I] and nicotinamide adenine dinucleotide (NADH) [67]. The 3,3 ′,5,5 ′-tetramethylbenzidine (TMB) is used as the molecular probe for two reasons: (1) TMB can be oxidized to oxTMB by Ag [I], while oxTMB can be reduced to TMB by NADH; (2) single-molecule break junction experiments clearly show that the conductance of TMB (114.6 nS) is approximately 13 times that of oxTMB (8.7 nS), showing significant conductance peak difference to serve as a ratiometric conductance probe. In the presence of different concentrations of Ag[I] or NADH, the relative proportions of their peaks change accordingly.

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