Label-Free Dynamic Detection of Single-Molecule Nucleophilic-**Substitution Reactions**

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Supporting Information

ABSTRACT: The mechanisms of chemical reactions, including the transformation pathways of the electronic and geometric structures of molecules, are crucial for comprehending the essence and developing new chemistry. However, it is extremely difficult to realize at the single-molecule level. Here, we report a single-molecule approach capable of electrically probing stochastic fluctuations under equilibrium conditions and elucidating time trajectories of single species in non-equilibrated systems. Through molecular engineering, a single molecular wire containing a functional center of 9-phenyl-9fluorenol was covalently wired into nanogapped graphene electrodes to form stable single-molecule junctions. Both experimental and theoretical studies consistently demonstrate and interpret the direct measurement of the formation dynamics of individual carbocation intermediates with a strong solvent dependence in a nucleophilic-



substitution reaction. We also show the kinetic process of competitive transitions between acetate and bromide species, which is inevitable through a carbocation intermediate, confirming the classical mechanism. This unique method creates plenty of opportunities for carrying out single-molecule dynamics or biophysics investigations in broad fields beyond reaction chemistry through molecular design and engineering.

KEYWORDS: Single-molecule detection, reaction dynamics, molecular electronics, nucleophilic substitution

Revealing the dynamic processes of detailed molecular transformations of chemical reactions is crucial for comprehending the essence and developing new chemistry.¹⁻³ Previous reports proved that the pathway of chemical reactions seemed to be more complex than we imagine. For instance, even for a simple bimolecular nucleophilic substitution $(S_N 2)$ reaction, the mechanism is complicated and not fully understood.^{2,3} In general, it is extremely hard to access the detailed reaction pathways in macroscopic experiments because the ensemble always shows thermodynamic quasi-equilibrium conditions. In contrast, single-molecule analysis of chemical reactions can effectively avoid ensemble-average effects, encourage the discovery of new phenomena and species, and reveal the chronological reaction processes.⁴ To date, discrete single-molecule detection technologies, including optical methods⁵⁻⁷ and nanopores,⁸⁻¹⁰ have been developed to achieve the dynamic investigation of biological macromolecules. However, these techniques seem to be unsuitable for the

detection of general organic molecules and their reaction trajectories, mainly limited by the challenges including the lack of precise molecular immobilization, the requirement of fluorescent labeling, and low temporal resolution. Therefore, the development of robust single-molecule detection platforms with label-free capability is invaluable to offer plenty of room for probing molecular mechanisms of basic chemical reactions.

In this regard, the electrical approach may be a suitable choice.^{11,12} In particular, electrical platforms based on singlemolecule junctions (SMJs) are potentially attractive because these platforms might overcome the major challenges mentioned above. In the past two decades, different approaches to building SMJs,¹³ particularly mechanically controllable break junctions¹⁴ and conductive scanning probe microscopes,^{15–17}

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were developed that have made remarkable contributions to investigate the electronic properties of particular molecules. In our previous studies, we developed a reliable methodology to build a new type of SMJs based on graphene electrodes¹⁸ in which amine-terminated molecular wires can be immobilized in the nanogap between carboxylic acid-terminated graphene electrodes through covalent amide bonds. Such molecular nanocircuits benefit from the unique coupling modes and robust contacts at the electrode-molecule interface, resulting in the strong stability during long-term conductance measurements. Because a single molecule sandwiched between source and drain electrodes is the key contributor to the device conductance, the conductance of SMJs is generally ultrasensitive to the electronic structures of molecules. Through molecular engineering, specially designed molecules were integrated into SMJs to construct molecular electronic devices with specific functions such as rectifiers,^{19–21} field-effect transistors,²² switches,²³ and memories.²⁴ These examples demonstrate the capacity for in situ modulating the electronic structure (and thus the conductance) of SMJs by external stimuli, such that the rearrangement of the molecular electronic structures caused by chemical reactions can be deemed as possible external stimuli.²⁵ On the basis of this strategy, SMJs have been specially designed through structure-function relationships and have successfully detected chemical reactions such as complex formation²⁶ and nucleophilic addition.²

In the present study, for the first time, we test the potential of the utilization of SMJs as an electrical platform for direct dynamic measurement of a reversible unimolecular nucleophilic substitution $(S_N 1)$ reaction at the single-molecule level. As a well-known organic reaction, the classical pathway of a S_N1 reaction involves two steps. The first is heterolysis, in which a leaving group separates from the reactant to form a carbocation intermediate. The second is recombination, which the carbocation intermediate combines with a nucleophile to form a product. The reaction potential energy surface is shown in the top-right panel of Figure 1. Therefore, carbocation, as a short-lived but common intermediate, has attracted great interest in the field of organic chemistry, in which Olah et al. have made great contributions.^{28,29} We expect that the carbocation intermediate can be distinguished from the reactant and product electrically due to the conductance increase caused by the transition from sp^3 to sp^2 hybridization,



Figure 1. Schematic of a graphene–molecule–graphene single-molecule junction that shows the formation dynamics of a 9-phenyl-9-fluorenyl cation in an S_N 1 reaction.

which has been reported previously.³⁰ By real-time monitoring SMJs with a 9-phenyl-9-fluorenol center, we found that the conductance of SMJs was faithfully synchronous to the chemical reaction, through which we observed the reversible S_N1 reaction and its closely following competitive reactions, respectively. Statistical analyses in the time domain further revealed significant information about the reaction kinetics, which also provides useful guidance to other chemical reactions.

In particular, 9-phenyl-9-fluorenol was applied as a reactant to investigate the acid-catalyzed S_N1 reaction in the mixed solution of acetic acid (HAc) and trifluoroacetic acid (TFA). Such a mixed-acid solution can provide a high-proton environment in which to stabilize the carbocation intermediate, which is favorable for further detection. This particular reaction was first investigated by a series of macroscopic experiments. Gas chromatography-mass spectrometry confirmed the complete consumption of the reagent and observed a reversible transition between a 9-phenyl-9-fluorenyl cation and a 9phenyl-9-fluorenyl acetate in the solution. The kinetic and thermodynamic properties of the reaction were determined by UV-vis experiments and flash photolysis (see section 1 of the Supporting Information). Through molecular engineering, we covalently integrated a molecular wire with a functional center of 9-phenyl-9-fluorenol into nanogapped graphene electrodes to form stable graphene-molecule-graphene single-molecule junctions (GMG-SMJs) (Figure 1). The details of molecular synthesis are provided in section 2 of the Supporting Information. To confirm the formation of GMG-SMJs, the current-voltage (I-V) curves of the devices at different stages were measured, as shown in Figure S9a. We found that the current decreased to zero after precise oxygen plasma etching and recovered to some extent after molecular immobilization, indicating the success of the device fabrication. Under optimized conditions, the connection yield was found to be ~15%; that is, 25 of 169 devices on the same silicon chip showed the increased conductance. These working devices showed similar electrical properties in the following experiments, demonstrating the reproducibility. On the basis of these data, statistical analysis demonstrated that charge transport through the junction mainly resulted from single-molecule connection (see section 3 of the Supporting Information).

High-temporal-resolution electrical characterization was carried out to monitor the conductance of GMG-SMJs in real time (Figure 2; constant bias voltage of 0.3 V and sampling rate of 57.6 kSa/s). GMG-SMJs were initially measured in the air, and then anhydrous HAc/TFA solutions with different proportions were gradually added to GMG-SMJs with the aid of a polydimethylsiloxane (PDMS) solvent reservoir (Figure S9b). Panels a and b of Figure 2 show the representative current-time (I-t) trajectories. In comparison to the I-ttrajectory in the air, which was dominated by the flicker (1/f)noise, random telegraph signals (RTSs) appeared when acid solutions were added. Correspondingly, in the current distribution histograms (Figure 2c), we observed largeamplitude two-level conductance states: a large-numbered, narrowly broadened low-conductance state (shown in blue) and a less-numbered, widely broadened high-conductance state (shown in red). This observation demonstrated that GMG-SMJs had two stable states in acid solutions. A previous report demonstrated that the current itself might lead to the reconnection of graphene electrodes at high bias voltages (~1.2 V for ~3 nm nanogaps, similar to the condition in this work).³¹ To rule out this possibility, we fixed an optimized bias



Figure 2. Real-time conductance measurements of a representative GMG-SMJ among five different devices. (a) Representative I-t trajectories in different conditions (from top to bottom: in the air, pure HAc, 25% TFA/75% HAc, 50% TFA/50% HAc, and 75% TFA/25% HAc (vol/vol)). (b) Partial I-t curves of the corresponding parts in panel a. Insets show the enlarged views of the peaks as indicated by red arrows. (c) The corresponding histograms of panel a. The blue and red lines show the Gaussian-shaped fit for the low- and high-conductance states, respectively. Insets show the enlarged views in the high-conductance regions. Source-drain bias voltage ($V_{\rm D}$) of 0.3 V, gate voltage ($V_{\rm G}$) of 0 V, and sampling rate of 57.6 kSa/s.

Figure 3. Theoretical simulations of GMG-SMJs. (a) Calculated energy levels of the molecular wire in the three forms: R = (+) (carbocation, red), R = Ac (acetate, blue), and R = Br (bromide, orange). The dashed line shows the Fermi level of graphene electrodes: $E_F = -4.8$ eV. (b) Corresponding calculated frontier molecular orbitals (FMOs) of the molecular wire in the three forms. (c) Transmission spectra of GMG-SMJs in the three forms around the Fermi level of graphene at a zero-bias voltage.

voltage at 0.3 V (much lower than 1.2 V used in the literature) to maintain a stable conductance as well as a high signal-noise ratio. Under such a condition, we proved that the RTS did not appear in the air and the RTS behavior was highly related to the acid solution, demonstrating that RTS signals are solventdependent, rather than the behavior of graphene electrodes. To further rule out other potential artifacts, three different chargetransporting systems were established as control devices: (i) macroscopic uncut graphene ribbons, (ii) partially cleaved graphene nanoconstrictions, and (iii) SMJs bridged by a molecular wire containing an acid-inert sexiphenyl core, which has similar molecular length and conductance to the 9-phenyl-9-fluorenol core. These were applied to exclude the possibility of conformation-induced switching or the other systemic interference between the solvent and SMJs. Under the same testing conditions used in Figure 2, RTS fluctuations did not appear in all of the I-t trajectories (see section 4 of the Supporting Information), proving that the observed RTSs only originated from the chemical reaction happening on the 9phenyl-9-fluorenol core.

To attribute the conductance states to the corresponding molecular forms, the molecular electronic structures and quantum transport properties were theoretically analyzed. As shown in Figure 3a,b, the first-principles calculations performed by Gaussian package (see section 5 of the Supporting Information) showed totally different electronic structures between acetate and carbocation forms due to the variation of the hybridization types of the central carbon atom: sp^3 hybridization in the former and sp^2 hybridization in the latter. As a result, the valence electrons are much more conjugated in the carbocation, yielding the conclusion that the energy gap between the frontier molecular orbitals (FMOs) is significantly decreased to ~1.34 eV (Figure 3a). Different energy gaps and orbital distributions can be verified by the different UV-vis spectroscopic behaviors in Figure S15. According to the transition voltage spectroscopy (TVS) model and the theoretical approach by Bâldea et al., $^{32-34}$ the decreased FMO gap of the carbocation form can largely lower the tunneling barrier height and increase the tunneling current, leading to a higher conductance. We further calculated the charge-transport properties of these molecules in combination with graphene probes by using the density functional theory (DFT) within the nonequilibrium Green's function (NEGF) technique (see section 5 of the Supporting Information). As shown in Figure 3c, compared to the acetate form, for the carbocation form, the perturbed lowest unoccupied molecular orbital (p-LUMO) and perturbed highest occupied molecular orbital (p-HOMO) have transmission peaks with energy much closer to that of the unbiased electrode chemical potentials $(E_{\rm F})$. In the resonant tunneling mechanism described by the Landauer-Büttiker formalism, the energy gap between the p-FMOs and the $E_{\rm F}$ plays a crucial role in the current calculation under a low bias voltage: the smaller the gap, the more electrons can enter the Fermi window in the bias range explored.^{23,35,36} In addition to the p-FMOs, we also notice that for the carbocation form the p-HOMO-1 is also close to the $E_{\rm F}$ with a distinguished transmission peak, which can contribute to a large conductance. Therefore, with the same results analyzed by the above-mentioned two methods and the quantum transport calculations, we can conclude that the carbocation form should have a higher conductance than the acetate form under a low bias voltage. The calculated scattering states of these critical transmission p-FMOs are consistent with the

FMOs (Figure 3b), indicating that the transmission channels are mainly derived from the electronic orbitals of the molecules (Figure S16). It was found that carbocation conductance varied along with solution conditions. Recent studies reported that the dipole-dipole interaction between the measured molecule and solution molecules might affect molecular conductance.^{21,37} Considering the fact that HAc and TFA have the big difference in dielectric constant (\sim 6 for acetic acid and \sim 39 for TFA), the different polar intermolecular interactions should affect electron transport of molecular junctions to some extent, thus causing the conductance variation. Another possibility is that different solutions could influence the lifetime of carbocation. Due to the measurement limit of the instruments used, the transition between the carbocation and acetate forms could be too fast to follow without fully reaching the conductance platform of carbocation, as demonstrated in Figure 2 in mixed solutions (pure HAc and 25% TFA/75% HAc).

To analyze the reaction dynamics, RTSs in *I*–*t* trajectories were idealized into a two-level interconversion by using a QuB software (Figure 4a). In this analysis, the lifetimes (τ_{low}/τ_{high}) of

Figure 4. Statistical analyses of the GMG-SMJ device used in Figure 2. (a) Measured I-t trajectories (black dots) of a GMG-SMJ in the solution of HAc-TFA (25%/75%, vol/vol). The red line shows the idealized two-level interconversion by using a QuB software. (b, c) Plots of time intervals of the (b) low- and (c) high-conductance states derived from I-t trajectories of a GMG-SMJ in the solution of HAc-TFA (25%/75%, vol/vol). The distributions were fit well by a singleexponential decay function (blue lines). Insets show the corresponding reaction pathways. (d) Activation energies of the symmetric S_N1 reaction derived from macroscopic (dash lines) and single-molecule (solid lines) experiments. (e) Combination constants of carbocation (pK_{R+}). Column: pK_{R+} values derived from GMG-SMJs. Solid columns represent the respective pK values, and striped columns represent the generalized acid function J_0 in the corresponding solutions. The blue and black dashed lines show the J_0 -TFA% relationship and the pKR+ values derived from bulk experiments, respectively.

the acetate and carbocation forms are derived from the probability distributions of the dwell times $(T_{\rm low}/T_{\rm high})$ of the low- and high-conductance states. By taking the device in Figure 2 as an example, both of the probability distributions of $T_{\rm low}$ and $T_{\rm high}$ in the solution of 75% TFA/25% HAc (v/v) were well fit by a single exponential decay function, as shown in panels b and c of Figure 4, which produce the values of $\tau_{\rm low} = 5320 \pm 790 \ \mu s$ and $\tau_{\rm high} = 2540 \pm 200 \ \mu s$, respectively, according to a hidden Markov chain model. On the basis of this

Figure 5. Competitive reactions between carbocation and different nucleophiles. (a) Schematic representation of competitive reactions of carbocation with Ac⁻ and Br⁻. (b–e) Representative *I*–*t* trajectories and corresponding enlarged views of a GMG-SMJ, which was submerged into a HAc/Br⁻/TFA ternary solution (25% HAc/75% TFA (v/v); Br⁻, 10 μ mol/L). Ac, Br, and C+ represent the acetate form, the bromide form, and the carbocation form, respectively.

fact, we initially assumed that the reversible reaction could be regarded as a simple Poisson process. Their rate constants (k_d and k_c), corresponding to the heterolytic dissociation of the acetate form $(k_d = 1/\tau_{low})$ and the combination of the carbocation form with acetic acid ($k_c = 1/\tau_{high}$) (insets in panels b and c of Figure 4), were derived to be $(1.88 \pm 0.28) \times 10^2$ and $(3.94 \pm 0.29) \times 10^2 \text{ s}^{-1}$, respectively. More data in different conditions are shown in section 6 of the Supporting Information. Figure 4d (solid lines) shows the corresponding activation energies $(E_d \text{ and } E_c)$ calculated from the Eyring equation $E = RT \ln(k_{\rm B}T/hk)$, where R = 8.314 J/(mol·K), T is the temperature, $k_{\rm B}$ is the Boltzmann constant, and h is the Planck constant. These values show the same tendency in comparison with the macroscopic results measured by UV-vis experiments and flash photolysis (dash lines). It was worthy noticing that these statistics resulted from a long-term observation of one molecule rather than the observation of the ensemble, and thus, the results were defined in a time domain, which should be comparable to the macroscopic results due to the equivalence between time average and ensemble average.

Single-molecule "thermodynamic functions" should be redefined based on kinetic constants derived from GMG-SMJ experiments. The equilibrium constant (K) is defined as the division of the rate constants of the dissociation/combination reactions $(K = k_d/k_c)$. In the solution containing TFA proportions from 0% to 75%, the pK values (p indicates the -10-base logarithm) were calculated to be 3.57 ± 0.11 (0%) TFA), 2.55 ± 0.21 (25% TFA), 1.73 ± 0.06 (50% TFA), and 0.32 ± 0.20 (75% TFA), respectively. The combination constants (K_{R+}) between the carbocation form and acetic acid were derived from the pK values normalized by a carbocationbased generalized acid function (J_0) (Figure 4e, blue line and striped columns), which was measured by an indicator overlap method: $pK_{R+} = J_0 + pK$. The pK_{R+} values were calculated as -4.10 ± 0.11 (0% TFA), -8.11 ± 0.21 (25% TFA), $-9.46 \pm$ 0.06 (50% TFA), and -9.72 ± 0.20 (75% TFA) (Figure 4e, solid columns), respectively. In comparison with the macroscopic results, $pK_{R+} \approx -10.50$ (see section 1 of the Supporting Information), it seems that GMG-SMJs may improve the stability of the carbocation state more or less. A pair of possibilities could explain this finding: (i) in comparison with isolated molecules, graphene electrodes extend the conjugation range of carbocation, which obviously lowers the Columbic potential of carbocation; and (ii) electrostatic catalysis may take effect in GMG-SMJs, such that the strong electro-static field between graphene electrodes ($E_{\rm s} \approx 0.3$ V/nm) increases the stability of charge-separated intermediates. In brief, the dipole (μ) of molecules is more likely to array parallel to the electrostatic field, thus generating a field-induced stabilization energy $\mu \times E_s^{,38,39}$ Because the carbocation-anion pair is charge-separated and much more polar than the acetate, there is no doubt that the electrostatic field generates more stabilization energy in the carbocation intermediate. Considering that the external electric field can be "counteracted" by the directional alignment of solution molecules, the effect of electrostatic catalysis depends on the polarity of solution. Because TFA is much more polar than HAc, it is reasonable that the effect of electrostatic catalysis becomes stronger along with the decrease of TFA proportion (Figure 4e), thus leading to the higher pK_{R+} value at 0% TFA.

We further investigated the feasibility of observing the competitive reactions between different nucleophiles (Figure 5a). To do this, bromide anions were introduced to the solution to act as another nucleophile. Specifically, 10 μ mol/L cetyltrimethylammonium bromide was introduced to a HAc/ TFA solution (25%/75%, vol/vol). We measured the conductance changes of functioning GMG-SMJs in the HAc/ Br⁻/TFA ternary solution in real time. In addition to the RTSs observed previously, a third conductance state was occasionally detected in the I-t trajectory (Figure 5b-e), which did not exist before. The appearance of this novel conductance state is probably related to a new competitive product: the bromide form (Figure 5a). To understand its origin, in Figure 3, we compared the electronic structures and transport properties of the bromide form with the formers (the carbocation form and the acetate form). The calculated results showed that the bromide and acetate forms have much more similarity compared to the carbocation form. This is mainly because both bromide and acetate forms have an identical sp^3 hybridization type in the central carbon atom, leading to the close FMOs energy values in Figure 3a and similar conjugated

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orbital distribution in Figure 3b. The transmission spectrum in Figure 3c also shows that the transmission peaks (p-FMOs) of these two sp^3 -hybridized structures are close, while those much further away from E_F compared to the sp^2 -hybridized carbocation form. Furthermore, we noticed that there is a minor transmission difference between these two structures as shown in Figure 3c and the p-HOMO (which dominates the conductance) of the bromide form is a bit closer to E_F compared to the acetate form. According to the models and the quantum transport analysis discussed above, it is reasonable to conclude that the bromide form and the acetate form should correspond to the experimentally observed two similar low-conductance states, and the conductance of the bromide form is slightly higher than the acetate form.

Therefore, we attribute these three conductance states (from high to low) to the carbocation form (C+, red), the bromide form (Br, orange), and the acetate form (Ac, blue), respectively. On the basis of the attribution, we can elucidate the reaction pathway of individual molecules in GMG-SMJs from real-time conductance recordings, which are faithfully synchronous to the chemical reaction. By taking Figure 5e as an example, we witnessed the transformation pathway of Ac-(C+)-Br-(C+)-Ac-(C+)-Br-(C+)-Br-(C+)-Ac, which nicely includes the similar reaction processes of Ac-(C+)-Br-(C+)-Ac in Figure 5c and Ac–(C+)–Ac–(C+)–Br–(C+)–Ac in Figure 5d. Reproducibly, we found that the carbocation form is an inevitable intermediate in the transition between the bromide and acetate forms, which confirms the classical S_N1 mechanism. It should be mentioned that the carbocation form was less populated when the bromide anion was added, which is consistent with the bulk experiments (Figure S6). In addition, the kinetics of competitive reactions were analyzed according to the statistical approach used above. The rate constants, involving the heterolytic dissociation process of the acetate/ bromide forms (k_d) and the combination process of the carbocation form with acetic acid and bromide (k_c) , were calculated as $k_{\rm d} = (1.16 \pm 0.18) \times 10^2 \, {\rm s}^{-1}$ and $k_{\rm c} = (2.73 \pm 10^{-1})^{-1}$ $(0.16) \times 10^3 \text{ s}^{-1}$ (Figure S18), respectively. Compared to the condition without the addition of the bromide anion, the rate of heterolytic dissociation barely changed while the rate of combination increased. Such results also confirm the classical S_N1 mechanism; that is, the heterolytic dissociation process (first step) is only related to the reactant, and the combination process (second step) is related to both the reactant and the nucleophile at the same time.

In conclusion, this work demonstrates a single-molecule way to overcome the difficulty of realizing label-free, real-time electrical measurements of fast reaction dynamics with singleevent sensitivity and high temporal resolution and reveal the molecular mechanisms of classical chemical reactions. Both experimental and theoretical results demonstrated the reversible acid-catalyzed S_N1 reactions at the single-molecule level, including acidity dependence and nucleophilic competitive reactions. On the basis of these results, more details in S_N1 reactions, such as racemization and intramolecular rearrangement reactions, are feasible to investigate in the future. By rationally integrating target functional groups into molecular bridges via molecular engineering, this approach offers a promising tool for revealing the fundamental mechanisms of general chemical reactions as well as deeply understanding the basic processes of life at the molecular level and developing accurate molecular diagnostics.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.nano-lett.8b00949.

Additional details on macroscopic experiments, molecular synthesis, device characterization and analysis, characterization of control devices, detailed theoretical analysis, dynamic analysis, and additional experimental results. (PDF)

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Notes

The authors declare no competing financial interest.

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