Visualization of the intermediates in organic catalytic reaction by singlemolecule electrical spectroscopy

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The capture and characterization of highly reactive and short-lived intermediates in organic catalytic reactions are challenging yet are very important for mechanism elucidation. Recently in *Matter*, Guo and co-workers employed single-molecule electrical spectroscopy (SMES) to detect the key intermediate and analyze the mechanism of *N*-heterocyclic carbene (NHC) catalyzed benzoin reactions.

Investigation of the catalytic reaction and understanding the catalytic mechanism are essential for the design and development of efficient chemical catalysts. The structural information of intermediates can be obtained by *in situ* real-time monitoring during the catalytic process. Identifying the relationship between different intermediates and analyzing the reaction trajectory can help us establish the thermodynamic and kinetic model of the process, which is of great significance in understanding the catalytic reaction mechanism.

The conventional investigation of the chemical reaction mechanism mainly deduces the transformation process of the reaction by characterizing the change of species concentration with time, which reflects the overall averaged ensemble results. However, as a basic unit in the reaction, the acquisition of information on structural change from a single molecule provides fundamental insight into the reaction mechanism. Single-molecule electrical detection offers a new promising approach for detecting the structural changes of the individual molecules in the singlemolecule junctions.^{1–4} In situ monitoring of the electrical signals of a single molecule can reflect the change of molecular structure in real-time during the reaction and therefore provides a highly time-resolved reaction kinetic model at the single-molecule scale.

For instance, Aragonès observed the Diels-Alder reaction between the dienophile and furan diene by using the scanning tunneling microscopy breakjunction technique. By analyzing the frequency of electrical signal blinking that indicates the formation of product molecule junction, it is demonstrated that the electrostatic-field stimulus can accelerate the Diels-Alder reaction.¹ The break junction technique was also used to study the selective catalysis of single-molecule reaction caused by the oriented external electrical fields⁵ and to probe the photothermal reaction of dihydroazulene-vinylheptafulvene.⁴ Using their unique graphenemolecule-graphene construction technology, Guo's group deciphered a series of chemical reaction processes at the single-molecule level, including reversible photoinduced reaction,² host-guest complex,⁶ nucleophilic-substitution reaction,⁷ and nucleophilic addition reaction.⁸

In the recent work published in *Matter*,⁹ Guo and co-workers focus on the *N*-heterocyclic carbene (NHC) catalyzed benzoin reaction. Benzoin is an important intermediate in drug synthesis and industrial processes. NHC is able to catalyze umpolung benzoin condensation reaction from conveniently available aldehydes. With the advantages of high efficiency and low pollution, NHC has replaced cyanide and become the most



used catalyst for benzoin condensation reaction. Breslow et al. reported a detailed study on NHC-catalyzed benzoin reaction earlier and proposed a four-step mechanism.¹⁰ NHC, which has strong nucleophilic property, can undergo nucleophilic addition to an aldehyde to form an transient intermediate. This intermediate can then be converted to a more stable Breslow intermediate (BI) through proton migration. The enaminol-type BI can attack another aldehyde molecule and finally form a benzoin product. The reaction mechanism has been widely accepted so far, but the reaction trajectory has not been experimentally investigated from the molecular level. To solve this problem, Guo et al. set out to analyze the catalytic reaction process by employing single-molecule electrical spectroscopy (SMES) technology. Through chemical modification, they placed an NHC catalyst as a molecular bridge between two graphene electrodes to construct a monolayered graphene junction (Figure 1A). The change of the conductance of the molecular junction can reflect the structural change of the catalyst molecule. By applying bias voltage on the molecular junction and recording the current through the molecular junction in realtime, the structural changes of a single catalyst molecule during the course of the catalytic reaction can be monitored.

When the molecular junction encounters the reactant, the catalytic process begins. From SMES, it can be observed that NHC catalyst periodically shows different conductance states going through the catalytic cycle of benzoin condensation. The transmission curves of various possible intermediates were calculated to infer the attribution of these conductance states. At room temperature (298°K), the catalyst is



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Figure 1. Schematic diagram of the single-molecule junction and catalytic reaction (A) Schematic diagram of the graphene-NHC-graphene single-molecule junction. (B) Schematic of NHC-catalyzed benzoin reaction.

BI

captured in three states: the free NHC, BI, and the intermediate (INT3) from second addition. However, according to mechanism proposed by Breslow, the first addition intermediate (pre-BI) should also exist in the reaction process (Figure 1B). In hopes of capturing the highly reactive pre-BI, the authors lowered the reaction temperature. At 238°K, a new conductance state attributed to pre-BI appears. Thus, a complete reaction scenario is presented. The temperature-dependent measurements also give the time intervals of the four intermediates at various temperatures. The thermodynamic and kinetic parameters were calculated from these results using the Arrhenius/van Hoff equation.

To further reveal the potential of the single-molecule spectroscopy method, the authors carried out measurements for cross-condensations. Unlike the homocondensation, four kinds of reaction trajectories in the cross-condensation of benzaldehyde and octylaldehyde were characterized, which shows that SMES is remarkably reliable for the analysis of different catalytic reactions. Next, the concentration-dependent experiments were designed and performed to evaluate the advantages of SMES over the ensemble method in deciphering dynamics. Referring to the kinetic characteristics of the enzyme, they calculated the relationship between product formation rate and concentration using the Michaelis-Menten equation. The results show that the single-molecule behavior based on statistics is consistent with that of ensemble catalysis, providing a new strategy to semiquantitatively analyze the interaction between substrate and catalyst.

Understanding the kinetic mechanism of the physicochemical reaction is a long-term goal for scientists to explore the law of chemical transformation. This study presented an unprecedented method to decipher the NHC-catalyzed benzoin reaction and demonstrated



that SMES not only captures highly reactive catalytic intermediates but also establishes new kinetic and thermodynamic models. It has proved that the SMES technique, together with other single-molecule electrical detection techniques, will become unique and promising platforms for investigating reaction mechanisms and bridge the research areas of single-molecule electronics and catalysis.

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