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Investigating Nanoscale Electrochemistry with Surface- and Tip-Enhanced Raman Spectroscopy

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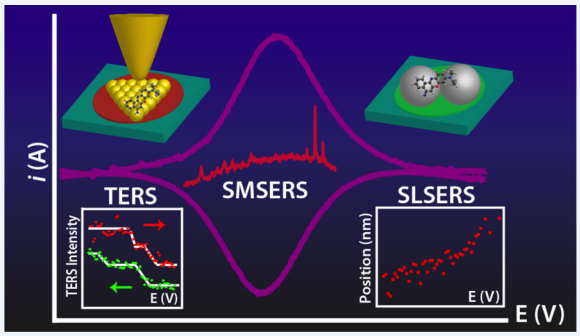
CONSPECTUS: The chemical sensitivity of surface-enhanced Raman spectroscopy (SERS) methodologies allows for the investigation of heterogeneous chemical reactions with high sensitivity. Specifically, SERS methodologies are well-suited to study electron transfer (ET) reactions, which lie at the heart of numerous fundamental processes: electrocatalysis, solar energy conversion, energy storage in batteries, and biological events such as photosynthesis. Heterogeneous ET reactions are commonly monitored by electrochemical methods such as cyclic voltammetry, observing billions of electrochemical events per second. Since the first proof of detecting single molecules by redox cycling, there has been growing interest in examining electrochemistry at the nanoscale and single-molecule levels. Doing so unravels details that would otherwise be obscured by an ensemble experiment. The use of optical spectroscopies, such as SERS, to elucidate nanoscale electrochemical behavior is an attractive alternative to traditional approaches such as scanning electrochemical microscopy (SECM). While techniques such as single-molecule fluorescence or electrogenerated chemiluminescence have been used to optically monitor electrochemical events, SERS methodologies, in particular, have shown great promise for exploring electrochemistry at the nanoscale. SERS is ideally suited to study nanoscale electrochemistry because the Raman-enhancing metallic, nanoscale substrate duly serves as the working electrode material. Moreover, SERS has the ability to directly probe single molecules without redox cycling and can achieve nanoscale spatial resolution in combination with super-resolution or scanning probe microscopies.



This Account summarizes the latest progress from the Van Duyne and Willets groups toward understanding nanoelectrochemistry using Raman spectroscopic methodologies. The first half of this Account highlights three techniques that have been recently used to probe few- or single-molecule electrochemical events: single-molecule SERS (SMSERS), superlocalization SERS imaging, and tip-enhanced Raman spectroscopy (TERS). While all of the studies we discuss probe model redox dye systems, the experiments described herein push the study of nanoscale electrochemistry toward the fundamental limit, in terms of both chemical sensitivity and spatial resolution. The second half of this Account discusses current experimental strategies for studying nanoelectrochemistry with SERS techniques, which includes relevant electrochemically and optically active molecules, substrates, and substrate functionalization methods. In particular, we highlight the wide variety of SERS-active substrates and optically active molecules that can be implemented for EC-SERS, as well as the need to carefully characterize both the electrochemistry and resultant EC-SERS response of each new redox-active molecule studied. Finally, we conclude this Account with our perspective on the future directions of studying nanoscale electrochemistry with SERS/TERS, which includes the integration of SECM with TERS and the use of theoretical methods to further describe the fundamental intricacies of single-molecule, single-site electrochemistry at the nanoscale.

1. INTRODUCTION

Electrochemical reactions are typically monitored and described as ensemble experiments, averaging the response over many surface site and molecule−substrate interactions. However, electrochemical reactions occurring at different surface sites will have a different formal potential, E^0, and heterogeneous rate constant, k^0; these single-site characteristics are masked in bulk measurements. Therefore, it is necessary to look to single-molecule, single-site nanoelectrochemistry in order to understand how nanoscale surface features and molecular orientation affects fundamental electrochemical properties.

Electrochemical single molecule detection was first achieved using scanning electrochemical microscopy (SECM).[1−3] While

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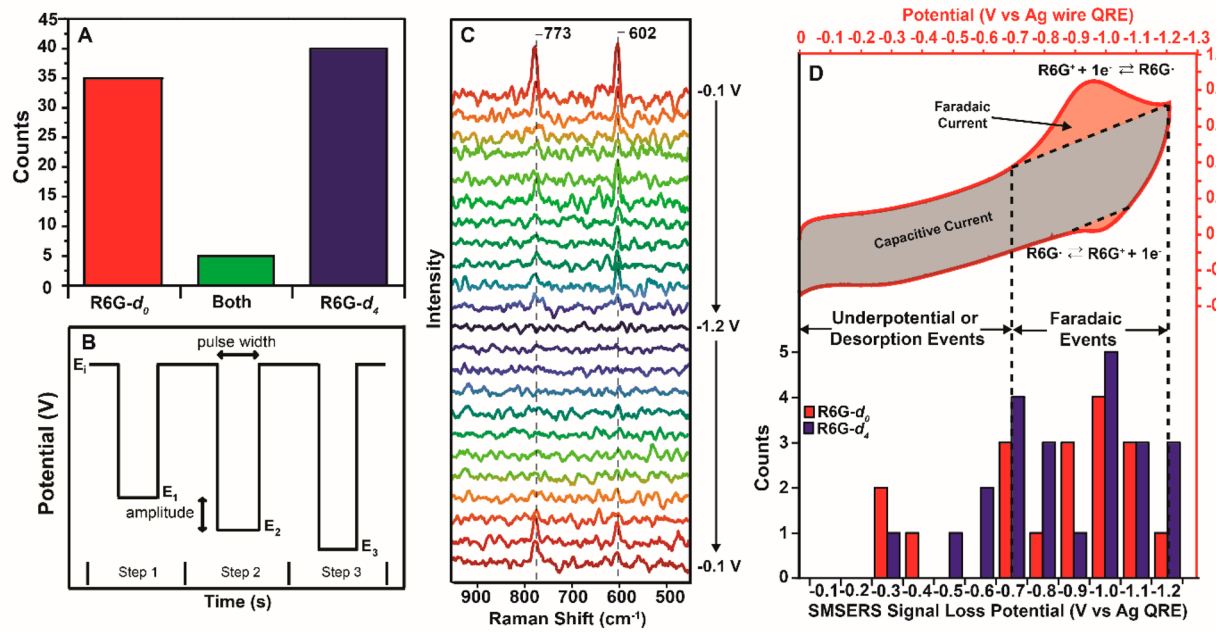

Figure 1. (A) Histogram displaying SMSERS events assigned by the identity of the SERS-active probe(s). (B) Representative potential step function applied in EC-SMSERS measurements, where E_i = 0 V, E_1 = −0.1 V. The pulse width is equivalent to the spectral acquisition time. (C) Representative SMSERS spectra from a single AgNP aggregate labeled with R6G-d_0 versus applied potential. The SMSERS signal is lost at −1.2 V (center, dark blue trace) and returns at −0.2 V (bottom, red trace). (D) Surface CV of R6G on a Ag disc electrode in 100 mM tetrabutylammonium perchlorate in acetonitrile (top) compared to the histogram of potentials at which SMSERS signals turn off (bottom). Figure adapted with permission from ref 21. Copyright 2015 American Chemical Society.

other electrochemical methods such as lithographic nanogap electrodes[4] and nanopipettes[5] have been implemented to study nanoscale electrochemistry, there has been a recent burst of interest in investigating nanoscale electrochemistry with optical spectroscopy.[6−8] The appearance or disappearance of an optical signal from a molecule during an electrochemical reaction requires a molecular system in which either the reduced or oxidized form is optically active. Using optical spectroscopy to study nanoelectrochemistry is advantageous over electrochemical detection techniques in that single-molecule detection is readily attainable and the signal does not need amplification. Detecting single-molecule and single-nanoparticle electrochemical events via optical spectroscopy has been achieved through fluorescence microscopy,[9−13] electrogenerated chemiluminescence,[14−16] and single-molecule SERS (SMSERS).[17−22]

SERS is an ideal method to study nanoelectrochemistry because it provides information on the structural changes of a redox couple in close proximity to a nanostructured metallic surface without quenching of the optical signal.[23] SERS was discovered due to the observation of a million-fold Raman enhancement of pyridine on a roughened Ag electrode.[24] However, it was not until 20 years after the inception of SERS that SMSERS was experimentally realized,[25,26] for which rigorous statistical proof took an additional decade.[27,28] SMSERS was first used to study electrochemistry in 2010.[18] Later work demonstrated that electrochemical SMSERS (EC-SMSERS) can provide insight into nanoscale potential-dependent charge transfer dynamics[19] and the heterogeneity in redox potentials of Nile Blue (NB) on Ag nanoparticles.[18,20] More recently, the Van Duyne group investigated single-electron transfer with EC-SMSERS, and the Willets group has implemented superlocalization electrochemical SERS (EC-SERS) to understand site-specific nanoelectrochemistry with 5−10 nm spatial precision.[17,21,22] The high chemical information content of SERS can be combined with the sub-5 nm spatial sensitivity of scanning probe microscopy (SPM) through tip-enhanced Raman spectroscopy (TERS). TERS uses a plasmonic SPM tip, typically Au or Ag, as the source of plasmonic enhancement and nanometer-scale spatial resolution.[29−31] While still in its infancy, recent pioneering work demonstrates the potential power of using EC-TERS to study site-specific nanoelectrochemistry.[32,33]

The implementation of EC-SERS/EC-TERS provides the ability to monitor molecular behavior on the nanoscale in parallel with fundamental electrochemical properties (e.g., E^0 and k^0). In this Account, we discuss recent progress in the field, focusing on EC-SMSERS, superlocalization EC-SERS, and EC-TERS. We then describe substrates and molecular systems of interest in order to gain maximum insight from these experiments. Lastly, we comment on novel directions for studying nanoelectrochemistry with EC-SERS/EC-TERS.

2. RECENT ADVANCES IN EC-SERS/EC-TERS

2.1. Electrochemical Single-Molecule SERS

The ability of EC-SMSERS to directly monitor single, heterogeneous electrochemical events provides insight into site-specific behavior at the nanoscale. Recently, the Van Duyne group implemented EC-SMSERS to study single electron reduction events of the dye molecule rhodamine-6G (R6G).[21] Because single electron transfer can be altered by the presence of water and oxygen, a custom spectroelectrochemical cell was designed for dry solvent transfer under vacuum and measurements in a nonaqueous environment.

SMSERS events were validated by the isotopologue proof,[27] where a sufficiently low concentration of an equimolar mixture

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of nondeuterated and deuterated forms of R6G are adsorbed on Ag nanoparticles. Isotopologues have the same electronic properties and binding affinities and unique SERS spectra, and the statistical distribution of recorded SMSERS spectra follows a binomial Poisson distribution (Figure 1A). The spectroelectrochemistry of single R6G molecules was observed by stepping the potential of the indium tin oxide (ITO) working electrode, functionalized with SERS-active Ag nanoparticles, from 0 V to −1.2 V in −0.1 V steps (Figure 1B,C). A SMSERS signal loss event indicated the reduction of R6G. As displayed in Figure 1D, the distribution of SMSERS signal loss events was broader than the surface CV of R6G adsorbed on Ag, demonstrating underpotential reduction events in the non-Faradaic region. These events were hypothesized to originate due to variations in the Ag nanoparticle binding sites where the R6G molecule is adsorbed. Observing single electron transfer with EC-SMSERS strongly demonstrates the electrochemical heterogeneity of nanoparticles and highlights the importance of site-specific heterogeneous electrochemistry.

2.2. Superlocalization SERS

One challenge with the experiments described in the previous section is relating the measured single molecule reduction potentials to the position of the individual molecules on the nanoparticle electrode surface. Optical microscopy techniques are obstructed by the diffraction limit, which restricts resolution to roughly half of the emission wavelength (∼250−350 nm) and makes it difficult to gain insight into how electrode structure and local environments affect electrochemistry on the nanoscale. One strategy to defeat the diffraction limit and localize diffraction-limited emission from a single emitter (e.g., a nanoparticle labeled with a spectroelectrochemical probe) with sub-10 nm precision is to fit the emission to a model function in order to relate the spatial origin of the signal with the reduction potential of the probe.[34] The most common model function is a two-dimensional Gaussian, where the peak position of the fit is approximated as the emitter position. Wilson and Willets applied this strategy, known as SERS superlocalization,[35] to NB physisorbed onto Ag colloidal nanoparticle (NP) aggregates, where the SERS intensity modulates off and on with reduction and oxidation.[17] Figure 2 shows the integrated EC-SMSERS intensity originating from a diffraction-limited spot as a function of applied potential (Figure 2A) and the associated spatial origin of the SERS emission as determined by Gaussian fitting (Figure 2B). The SERS intensity rises and falls in a single digital step upon oxidation and reduction, indicative of a single NB molecule on the nanoparticle electrode surface. The loss of SERS intensity caused by reduction during the two potential cycles occurs at distinct potentials (Figure 2A, R1 and R2), which correspond to unique positions of the molecule (Figure 2B, i and ii). This observation suggests that there is a spatial dependence associated with the potentials at which a molecule undergoes ET on a nanoparticle electrode. While intriguing, these single molecule electrochemical measurements are limited by small sampling of the electrode area, the limited number of potential cycles that the molecule remains emissive, and the inability to discriminate between a reduction and photobleaching event.

Figure 2C shows the integrated SERS intensity from a AgNP aggregate labeled with multiple NB molecules in response to an applied potential. Here, the SERS intensity gradually rises and falls during oxidation and reduction, indicative of few-molecule behavior. Because of the higher NB coverage, when the

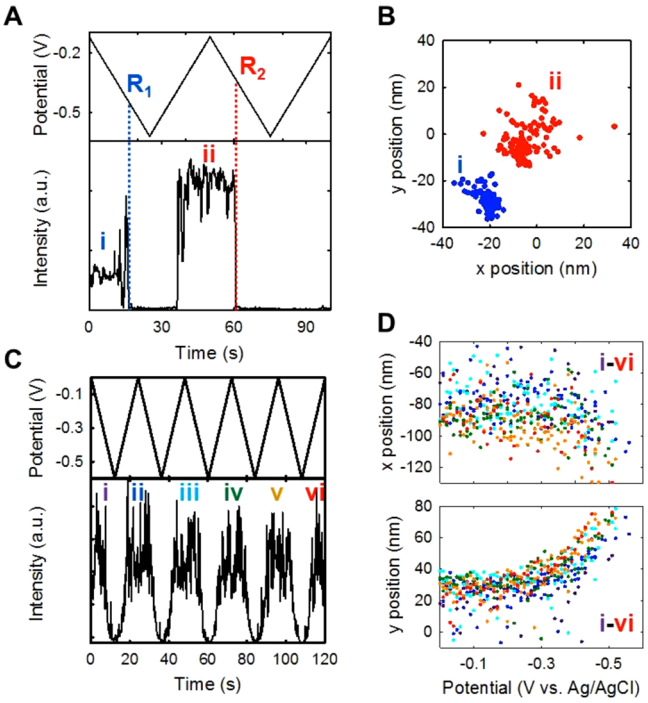

Figure 2. (A) Single-molecule and (C) few-molecule integrated SERS intensity trajectories modulated by electrochemical reduction and oxidation waveforms, as shown. (B) Localized SERS emission corresponding to the two emission events in panel A. (D) Localized SERS emission voltammograms corresponding to the events in panel C. Adapted with permission from ref 17. Copyright 2014 American Chemical Society.

diffraction-limited SERS emission is fit to a two-dimensional Gaussian, the calculated position represents an intensity-weighted superposition of all molecules in the oxidized state.[36] The spatial origin of the SERS emission reproducibility shifts as the potential is swept, suggesting that individual molecules are being oxidized or reduced at unique potentials based on their location on the electrode (Figure 2D). This observation further supports the conclusion of site-specific redox potentials for NB on AgNPs.

To understand the relationship between site-specific redox potentials and NP structure, Weber et al. covalently immobilized NB on spherical AuNPs and performed superlocalization EC-SERS imaging followed by correlated scanning electron microscopy (SEM).[22] The NB is tethered to the surface to prevent diffusion along the surface of the nanoparticle(s) as well as desorption. These correlated studies revealed that at the most negative potentials, the SERS emission is localized to junctions between NPs. At the most positive potentials, where all molecules are expected to be oxidized, the SERS emission is localized near the geometric center of the aggregates. Hence, these observations indicate that more (less) energy is required to reduce (oxidize) molecules in nanoparticle junctions, consistent with the model of site-specific redox potentials on nanoparticle electrodes.

2.3. Electrochemical TERS (EC-TERS)

EC-SMSERS and superlocalization EC-SERS provide valuable insights into potential distributions of single-molecule electrochemistry but are typically performed on nanoparticle aggregates with poorly defined or heterogeneous geome-

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tries.[17,18,20−22] Correlating electrochemical behavior with specific sites on an electrode surface requires both a controllable, well-defined hot spot and nanoscale spatial resolution or characterization. Such complete information can be achieved by EC-TERS. Recently, the Van Duyne group was the first to demonstrate EC-TERS of NB at the few-molecule level.[32] A Au-coated atomic force microscope (AFM) tip was used to acquire EC-TERS spectra of NB spontaneously adsorbed to an ITO working electrode as a function of applied potential. Figure 3 shows selected TERS spectra (A) acquired

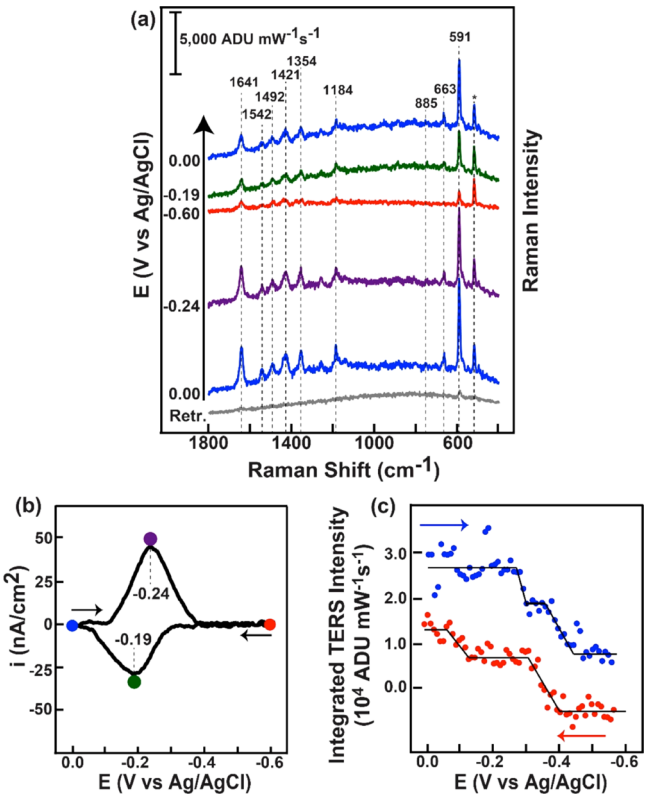

Figure 3. (A) EC-TERS of NB acquired at the indicated potentials in the surface CV of NB on ITO (B). (C) TERS CV showing the amplitude of the 591 cm^{-1} band of NB versus applied potential. The cathodic trace (blue) and anodic trace (red) are offset for clarity. Adapted from ref 32. Copyright 2015 American Chemical Society.

at various potentials along the CV (B). Upon sweeping the potential from 0 to −0.6 V vs Ag/AgCl at 10 mV/s, oxidized NB (NB_{OX}), electronically resonant at the incident wavelength, was reduced to the nonresonant product (NB_{RED}). The TERS intensity therefore decreases as NB_{OX} is reduced to NB_{RED} and is restored along the anodic wave as NB_{RED} is oxidized. The total charge passed during the CV was used to determine that, on average, fewer than 10 molecules were probed.[37] Few-molecule behavior consistent with this calculation was observed in some EC-TERS spectra. Figure 3C shows one example of the integrated 591 cm^{-1} peak intensity of NB_{OX} versus potential, with step-like features that suggest the presence of only a few molecules. TERS CVs acquired in different locations on the same ITO surface revealed different local coverages of NB, with some TERS CVs containing steps and others resembling smooth, sigmoidal ensemble behavior. This work demonstrates the power of EC-TERS in monitoring few-molecule electrochemistry and probing variations in local coverage otherwise inaccessible by SERS and is a strong starting point for further development of EC-TERS.

3. EXPERIMENTAL CONSIDERATIONS FOR EC-SERS/TERS

3.1. Molecular Systems: Surface Adsorption, Redox, and Optical Properties

Ideal molecular systems for directly monitoring nanoscale electrochemical processes using SERS/TERS must have both large Raman cross sections and well-characterized and well-behaved electrochemistry. Additionally, the binding affinity of the molecular system to the electrode is of extreme importance, and we will discuss it in a later section. The most common class of molecules used to optically monitor electrochemical processes are redox-active dyes, such as NB, which show changes in their electronic resonances associated with changes in their redox states. Several SERS and TERS studies in the past decade have exploited the well-characterized electrochemistry of NB using 633 nm excitation to monitor the disappearance of NB_{OX} signal upon reduction to the nonresonant NB_{RED}.[17,18,20,22,32,38]

Adapting EC-SERS/EC-TERS to nonaqueous systems will greatly expand the list of candidate molecules for studying nanoelectrochemistry spectroscopically. As described above, the Van Duyne group has demonstrated the first nonaqueous EC-SMSERS study using R6G, which undergoes a reversible one-electron transfer in acetonitrile.[21] The most significant experimental challenge in monitoring single one-electron transfer events is careful removal of oxygen and water from the system, which can alter the mechanism. For SMSERS measurements, a gastight cell was used to study one-electron transfer reactions;[21] however, an analogous cell for TERS has not yet been developed due to the challenge of creating an airtight seal around the head of the scanning probe microscope.

Ultimately, the fields of EC-SERS/EC-TERS will benefit from studying molecules with practical applications instead of model dye systems. Porphyrins, for example, have large resonance Raman cross sections adequate for single-molecule detection and have extensive applications in solar cells and conductive polymers.[30,31] Typically, charge transfer dynamics of porphyrins are studied using single-molecule fluorescence[11] but only SERS/TERS can give detailed structural information at the single-molecule level,[19] highlighting the advantage over fluorescence to study nanoelectrochemistry.

3.2. Substrates

Substrates for EC-SERS require nanoscale features, which support a localized surface plasmon resonance (LSPR) to enhance Raman signals. Lithographic nanohole and nanopore arrays are well-suited for EC-SERS due to their reproducibility and ease of making electrical contact.[39,40] Alternatively, periodic particle arrays prepared by nanosphere lithography have a tunable LSPR, can be prepared on an optically transparent electrode such as ITO, and have highly enhancing triangular features that allow for SMSERS detection.[41,42] Colloidal AgNP and AuNP aggregates offer highly enhancing hot-spots that can be optically isolated, but aggregates are commonly polydisperse involving varied cores and suffer from variations in morphology and surface structure and functionalization.[27,28]

Unlike EC-SERS substrates, EC-TERS substrates do not have to support a LSPR and can be extended to more materials such as ITO and well-defined surfaces such as single crystals (e.g., Au(111)). The choice of EC-TERS substrate is ultimately

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limited by illumination geometry, and the discussion below will highlight EC-TERS substrates according to two types of TERS illumination geometries.

EC-TERS experiments in a bottom illumination geometry require optically transparent electrodes, such as ITO[32] or thin (e.g., <10 nm) Ag island films.[43] However, the surfaces of these electrodes are polycrystalline, and it is therefore challenging to correlate a TERS response with electrode morphology. Alternatively, a well-defined Au(111) single crystal substrate can be used for EC-TERS studies, as recently demonstrated by the Ren group.[33] Future EC-TERS studies can also implement large (0.1−5 μm edge lengths), thin (<20 nm), atomically flat Au(111) nanoplates[44] supported on optically transparent electrodes, which provide an easy to fabricate, well-defined surface for correlating TERS spectra, electrochemical behavior, and surface morphology.

When side illumination is employed, studying opaque samples is possible. Bulk single crystal electrodes such as Au(111) and Ag(111) have been extensively studied with molecular resolution with TERS[31,33,45,46] and electrochemical scanning tunneling microscopy (EC-STM).[47,48] Thus, EC-STM TERS can potentially be used to study the electrochemistry of single molecules adsorbed at atomic-scale features (e.g., step edges, kinks, vacancies, and adatoms), providing a direct correlation between the electrochemistry of a single molecule and its adsorption site. Vibrational information obtained using TERS can be used to elucidate molecule−surface binding through site specific shifts in vibrational energies, painting a complete electrochemical, structural, and vibrational picture of a single molecule−single surface site pair.

3.3. Substrate Functionalization

Molecule immobilization is important to prevent desorption and diffusion of analyte molecules, which can limit the information obtained from EC-SERS/EC-TERS experiments. Immobilization can provide a better survey of the entire electrode surface and enable targeted labeling. There are many strategies to attach optically active redox molecules on substrates, but we will highlight three used for EC-SERS/EC-TERS: spontaneous adsorption, self-assembly of thiolated reporter molecules, and carbodiimide cross-linking. Each strategy has advantages and disadvantages and requires careful characterization in order to properly interpret the nano-electrochemistry.

Spontaneous adsorption of molecules onto nanoscale noble metals has been widely used since the discovery of SERS to the observation and application of SMSERS/SMTERS.[18,24,25,32,49] Major advantages of this labeling strategy are that a wide range of molecules can be used and the number of adsorbates on a substrate can be controlled by changing the solution concentration. Limitations include preferential adsorption, surface diffusion, and spontaneous desorption, all of which complicate the correlation of nanoscale electrochemical properties to optical signal changes. One strategy to overcome these shortcomings is to implement a thiol-containing redox probe, which can react with plasmonic metals to form a covalent sulfur−metal bond. For example, SERS- and redox-active viologens can be thiolated and subsequently self-assembled into a monolayer on gold electrodes[50] to detect three Raman-distinct redox states.[51] The electrochemistry of a monolayer of self-assembled molecules needs to be carefully characterized because intermolecular interactions and variable molecule−electrode distances can change the electrochemical behavior and resultant SERS/TERS signals.[52,53]

Alternatively, SERS/TERS-active molecules can be covalently bound to an electrode using a chemical reaction with a self-assembled monolayer (SAM) on the electrode surface. For example, the well-known 1-ethyl-3-(3-(dimethylamino)propyl)-carbodiimide/*N*-hydroxysulfosuccinimide (EDC/NHS) pair can be used to couple a carboxylic acid terminated alkanethiol SAM with a primary amine.[22,54] A disadvantage of this immobilization strategy is that the efficiency of EDC/NHS coupling is generally low and variable, yielding submonolayer coverages. Moreover, the act of coupling a molecule to a surface can impact its electrochemical properties, as shown for surface-tethered NB in Figure 4.[55,56] Voltammograms obtained using

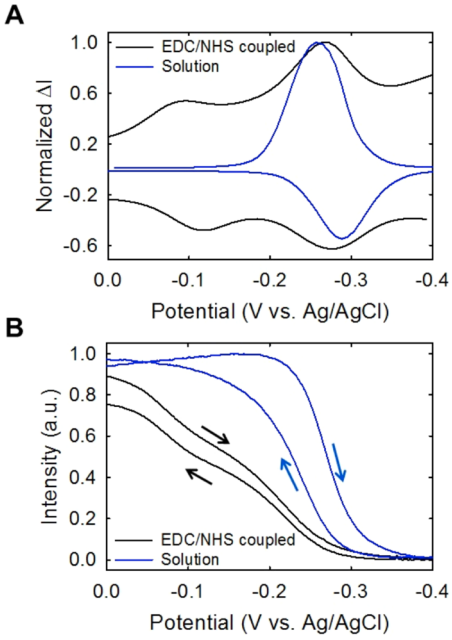

Figure 4. Covalent attachment of redox probes to substrates can change their electrochemical and EC-SERS behavior relative to solution-phase electrochemistry: (A) Differential pulse voltammograms of EDC/NHS coupled NB (black) and solution phase NB (blue) on a gold disc electrode coated with 8-mercaptooctanoic acid reveals a change from a two-electron, two-proton transfer (solution) to two one-electron, one-proton transfers (tethered). (B) SERS intensity as a function of applied voltage shows differences in intensity modulation consistent with the change in the voltammetry experiments from panel A. Samples are EDC/NHS coupled NB (black) and solution phase NB (blue) on a 7 nm gold island film on ITO electrode. Arrows indicate the direction of the potential scan.

both differential pulse voltammetry (DPV, Figure 4A) and EC-SERS (Figure 4B) are markedly different between NB in solution and NB EDC-coupled to a gold surface.[56] Notably, the DPVs convert from a single redox reaction for NB in solution to two distinct peaks when tethered to a gold disk electrode (Figure 4A). The single peak in the DPV of the solution NB corresponds to a single inflection point in the rise/fall of the NB EC-SERS intensity, while two inflection points are observed in the EC-SERS of the tethered species, overlapping with the two peaks in the DPV (Figure 4B). These studies reveal the importance of coupling nanoscale electrochemical studies with traditional bulk characterization tools, in order to

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understand how the properties of the optically active redox probes change upon tethering to an electrode surface.

4. CONCLUDING REMARKS

The work presented in this Account highlights the power of EC-SERS and EC-TERS toward understanding nanoelectrochemistry. This field is expanding from proof-of-concept experiments with model systems to scientifically relevant molecular systems. We highlight progress from single or few molecule studies on polycrystalline surfaces, which will be crucial toward understanding processes in areas including electrocatalysis, energy storage, and plasmon-driven chemistry.

The EC-SERS and EC-TERS experiments discussed in this Account only monitor signal loss of reactant because excitation for these experiments was chosen based on the electronic resonance of the molecule. Gaining information about molecular structure using EC-SERS/EC-TERS can be fully exploited in these measurements by monitoring the vibrational signatures of both redox states. The use of dual excitation wavelengths that overlap with the electronic resonances of the redox states of a molecule can further elucidate single-molecule structural changes throughout the course of a reaction, which can be correlated with electrode structure and fundamental redox properties. For example, porphyrins can be probed with molecular resolution on single crystal electrodes,[48,57] which makes them excellent candidates for high resolution EC-TERS studies. Selective excitation of the Soret band and Q bands amplifies particular vibrational modes of the porphyrin, enriching the chemical information provided by EC-SERS/EC-TERS.[58] The ability to fully characterize the structural changes of single molecules as they undergo redox processes and correlate with redox behavior and electrode structure represents the ultimate goal of electrochemical Raman experiments and would revolutionize our understanding of single-molecule electrochemistry.

To correlate the spectra of single molecules with nanoelectrochemical reactivity, optical approaches can be integrated with SECM. SECM monitors current generated by a redox mediator cycling between the SECM probe, typically a micro- or nanoelectrode, and the substrate to map sample morphological and reactivity variations with few-nanometer resolution.[59,60] TERS is an ideal complement to SECM, because TERS provides chemical identification of a redox mediator as it undergoes an electrochemical reaction to correlate with the topology and reactivity of the specific surface sites probed by SECM. Thus, SECM−TERS would allow for structural interrogation of short-lived intermediates present only in the tip−sample junction.[61,62]

In addition to experimental strides toward understanding nanoelectrochemistry, implementing theoretical methods would provide a tool for predicting and explaining experimentally observed phenomena. While recent theoretical work has focused on modeling electrocatalytic reactions on metallic nanoparticles using DFT,[63] there have not yet been theoretical efforts toward describing the behavior of electrochemical reactions of optically active molecules. Using DFT would aid in predicting the fundamental redox properties and site-specific vibrational fingerprint for specific surface site/molecule motifs, further describing the intricate relationship between nanoscale electrode features and molecular configuration and their effects on nanoelectrochemical behavior.

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Notes

The authors declare no competing financial interest.

Biographies

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Andrew J. Wilson was born in 1986 in Elk Run Heights, IA. He received his B.S. degree at The University of Iowa followed by his Ph.D. from The University of Texas at Austin under the supervision of Katherine A. Willets. Currently he is a postdoctoral researcher in the same lab at Temple University. His research interests are in using light to study and drive electrochemical reactions.

Michael Mattei received his B.S. in Chemistry from Bucknell University in 2013. He is currently pursuing his Ph.D. in the Van Duyne Group at Northwestern University. His research interests include electrochemical TERS on AFM and SECM platforms.

Xu Chen studied physics at Nanjing University, China, and received his diploma in 2013. Since 2013, he has been carrying out Ph.D. research at Northwestern University in the lab of Richard Van Duyne where he uses TERS and SECM to study nanoelectrochemistry.

Guillaume Goubert obtained his B.S. in optical engineering in 2008 at the Institute of Optics, Palaiseau, France, and his M.S. in physics in 2010 at Laval University in Quebec City, Canada. He received his Ph.D. in chemistry in 2014 at Laval University under the supervision of Prof. Peter McBreen studying asymmetric heterogeneous catalysis at the single molecule level. He is currently working in the laboratory of Richard P. Van Duyne at Northwestern University where he focuses on studying electrochemistry at the nanoscale combining Raman and SPM.

M. Fernanda Cardinal studied Chemistry at the University of Buenos Aires (Argentina) and obtained a Ph.D. in 2012 from the University of Vigo (Spain) working under the supervision of Prof. Luis M. Liz-Marzán and Prof. Jorge Pérez-Juste. Currently she is a postdoctoral fellow in the Van Duyne group, and her research focuses on the fabrication of plasmonic substrates for SERS and LSPR sensing by top-down methods or metal nanoparticles assembly.

Katherine A. (Kallie) Willets is the Robert L. Smith Early Career Professor of chemistry at Temple University. She received her Ph.D. from Stanford University in 2005, working in the lab of W. E. Moerner, then moved to the lab of Richard Van Duyne at Northwestern University as a postdoctoral researcher from 2005 to 2007. After beginning her independent career at the University of Texas at Austin in 2007, where she was promoted to associate professor in 2014, she moved to Temple University in 2015 where her lab uses single molecule optical imaging techniques to understand how nanoscale features of plasmonic nanostructures impact ligand binding, SERS, and electrochemical reactions at surfaces.

Richard P. Van Duyne is the Charles E. and Emma H. Morrison Professor of Chemistry at Northwestern University. He received his B.S. degree from Rensselaer Polytechnic Institute in 1967 and a Ph.D.

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in analytical chemistry from the University of North Carolina in 1971. He was elected into the US National Academy of Sciences in 2010. He is known for the discovery of SERS, the invention of nanosphere lithography (NSL), and development of ultrasensitive localized surface plasmon resonance (LSPR) spectroscopy nanosensors. His research interests include all forms of SERS, plasmonics and nanophotonics, nanoscale chemical/biological sensors, atomic layer deposition (ALD), NSL, AFM, STM, ultrahigh vacuum (UHV) STM, UHV-TERS, MALDI-TOF mass spectrometry, and surface-enhanced femtosecond stimulated Raman spectroscopy (SE-FSRS).

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