The Expanding Frontiers of Tip-Enhanced Raman Spectroscopy

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Abstract
Fundamental understanding of chemistry and physical properties at the nanoscale enables the rational design of interface-based systems. Surface interactions underlie numerous technologies ranging from catalysis to organic thin films to biological systems. Since surface environments are especially prone to heterogeneity, it becomes crucial to characterize these systems with spatial resolution sufficient to localize individual active sites or defects. Spectroscopy presents as a powerful means to understand these interactions, but typical light-based techniques lack sufficient spatial resolution. This review describes the growing number of applications for the nanoscale spectroscopic technique, tip-enhanced Raman spectroscopy (TERS), with a focus on developments in areas that involve measurements in new environmental conditions, such as liquid, electrochemical, and ultrahigh vacuum. The expansion into unique environments enables the ability to spectroscopically define chemistry at the spatial limit. Through the confinement and enhancement of light at the apex of a plasmonic scanning probe microscopy tip, TERS is able to yield vibrational fingerprint information of molecules and materials with nanoscale resolution, providing insight into highly localized chemical effects.

Keywords
Raman spectroscopy, scanning probe microscopy, nanoscale, tip-enhanced Raman spectroscopy, TERS, single-molecule spectroscopy, surface science

Introduction
With the growth of nanotechnology and methods of bottom-up assembly, true single-molecule and even single-atom control has become possible.1–4 In instances where a surface is used as a template to allow thin films or two-dimensional (2D) materials to form, interactions between the building blocks themselves and between the building blocks and the surface become fundamental to the growth process and the ultimate properties of the new nanostructures.5 Therefore, characterizations of these chemical and physical interactions are of fundamental importance. The ideal technique would possess the ability to define the chemical system at the atomic scale.

The implementation of a single analytical technique typically results in tradeoffs. Optical spectroscopy, such as infrared and Raman spectroscopy, can be used for chemical identification, based on characteristic vibrational fingerprints. Additionally, the molecular vibrations that result in a spectrum are critically sensitive to intermolecular interactions and the local chemical environment.2,6 The net result is a technique that can identify and characterize a chemical system as well as describe the interactions that define it. However, most optical spectroscopies are limited by a fundamental resolution limit, a physical phenomenon that is fundamental to the wave-like nature of light.7 As a consequence, these techniques become blind to isolated local chemical environments as the spectrum generated corresponds to an ensemble measurement. On the other hand, since their invention, scanning probe microscopy (SPM) systems have been proven capable of atomic-scale...
resolution of interfaces. The two most common SPM techniques are atomic force microscopy (AFM) and scanning tunneling microscopy (STM). Although the mechanisms of these two microscopies are quite distinct, both have proven to be capable of achieving sub-molecular resolution of flat-lying adsorbates on surfaces as well as atomic resolution of the surface itself. Recent work with noncontact AFM described the ability to distinguish the bond order of individual carbon–carbon bonds, and in a separate study, individual surface atoms were chemically identified. However, these experiments necessitate extreme conditions of ultrahigh vacuum (UHV) along with extremely low temperatures. In order to obtain chemical information, most groups rely upon a combination of spectroscopic techniques and SPM to fully characterize a chemical system. This can result in a mismatch between the two techniques where the spectroscopic ensemble measurement is a statistical interpretation while SPM may reveal local chemical effects that cannot be sufficiently defined.

Spectroscopy where the signal only comes from the tip-sample junction offers the ability to circumvent this issue with direct chemical identification of individual adsorbate molecules with real-space knowledge of its location via SPM. Scanning tunneling microscopy inelastic electron tunneling spectroscopy (STM-IETS) is one such method where vibrational spectra are obtained by monitoring tunneling electrons which lose energy when they excite vibrations of the adsorbates. This technique allows for direct identification of single molecules adsorbed on a surface via vibrational fingerprints. Although studies involving STM-IETS are truly impressive, showing single bond sensitivity, this technique requires extreme mechanical stability and cryogenic temperatures. For a more thorough overview of this technique, we refer you to a review of its applications in single-molecule chemistry. Meanwhile, optical spectroscopy has enjoyed applications across numerous fields as an analytical technique yielding chemical information with a low barrier to entry but at the cost of spatial resolution. A tandem technique of SPM with optical spectroscopy offers the potential for chemical information with spatial resolution, ideally with an experimental setup that is more easily accomplished.

Tip-enhanced Raman spectroscopy (TERS) ideally fits these requirements, offering a Raman spectrum that as a result of light highly localized, confined, and enhanced at the tip apex can correspond to a single molecule. Since it was experimentally realized in the year 2000, TERS has attracted attention across the scientific community for its ability to provide vibrational fingerprints with nanoscale spatial resolution. Subsequently across the years, it has found applications in ambient, liquid, and even UHV conditions. With routine detection of single molecules and unique characterizations of nanoscale features of low-dimensional materials, TERS has drawn interest broadly from the scientific community. The applications of TERS in the study of localized chemical effects will be discussed with a focus on newer work, in areas such as materials, surface science, biochemistry, and electrochemistry.

**Brief History**

**First Experiments**

To a large degree, the history and development of TERS began with the discovery of surface-enhanced Raman spectroscopy (SERS). Another focal point review of SERS in this special issue describes the technique as well as its growth. In brief, an enhancement of Raman scattering was first discovered for pyridine adsorbed on roughened silver electrodes in 1974 by Fleischmann and coworkers, but the enhancement was ascribed to an increase in surface area of the electrode. In 1977, Albrecht and Creighton, and Jeanmaire and Van Duyne both independently identified the enhancement mechanism as resonant Raman effects from interactions with the substrate or an electric field enhancement at the surface, respectively. While the discovery of SERS was the result of attempts to explain an experimentally observed phenomenon, the first TERS experiments were efforts to realize an earlier proposed theory.

The theory behind TERS was first introduced in 1985, but it was not until 2000 that it was truly experimentally realized. In 1985, Wessel described a new concept called surface-enhanced optical microscopy (SEOM). This method relies upon a strong field associated with the plasmon resonance at a particle surface as well as a lightning-rod effect that results from further field enhancement in regions of high surface curvature. Significantly, he acknowledged its similarities to STM which at the time was recently developed by Binnig, Rohrer, and coworkers at IBM Zürich, in which tunneling current between a probe tip and a conductive sample is monitored as the probe is scanned across the surface yielding the three-dimensional topography of surfaces at the atomic scale. Wessel also identified similarities with another technique that allowed spectroscopy below the diffraction limit through near-field optical-scanning microscopy where a tip with a built-in aperture is used. It is also possible to use the scanning probe tip as a near-field scattering source when illuminated with focused light. Scanning-type scanning near-field optical microscopy enables the study of light-matter interactions below the diffraction limit of light. In 1986, the modification of an STM to measure the motion of a cantilever beam and subsequently capture interatomic forces on a sharp tip led to the discovery of the AFM. The stage was set for the implementation of Wessel’s proposed SEOM, since the principles of STM or AFM enabled the control of the optical probe particle relative to the sample surface. However, it would be 14 years before SEOM theory was experimentally proven, albeit with a different name, tip-enhanced Raman spectroscopy.

In the year 2000, four separate groups published the first TERS experiments achieved by coupling an inverted optical microscope with primarily an AFM where the probe tip was...
Pettinger et al. reported TERS enhancements of CN– ions primarily relied upon improvements to tip and sample stability. Early efforts to improve the spatial resolution of TERS partially resolved measurements and prevented longer duration experiments. In order to address this issue, Steidtner and Pettinger developed a unique instrument capable of acquiring measurements at cryogenic temperatures. The first TERS experiment with liquid nitrogen temperature provided sufficient stability for remarkable results, it is possible to still further stabilize the system by using liquid helium.

Through supreme sample stability, TERS performed at cryogenic temperatures offers the capability for fundamental studies of the vibrational modes of isolated single molecules on a surface. The first TERS experiment with liquid helium cooling of the sample was used to examine the adsorbate–substrate interactions of the rhodamine 6G (R6G)/Ag(111) system. Through comparison of TERS spectra with theoretically calculated spectra, the authors identified the localization of molecule–substrate interactions within the R6G chemical structure. In this work published in 2014 by the Van Duyne group, they observed significant narrowing of peaks due to low temperature, as shown in Fig. 1c, up to instrument-limited resolution, that correspond to vibrational modes of the adsorbate molecule along with new vibrational characteristics resulting in the identification of the localization of molecule–substrate interactions to the xanthene moiety and its ethylamine substituents. In a similar manner, just last year the vibrational modes of a single molecule, Co(II)-tetraphenylporphyrin (CoTPP) were visualized on a Cu(100) surface by the Apkarian group. We will discuss the details of this experiment later in this review. Overall, the progressive improvements in the spatial resolution of TERS have largely been attributed to supreme mechanical stability that has enabled the precise control of the tip-sample junction at the atomic scale. Due to the strong relationship between the enhancement and confinement of light with the tip-sample distance, the most recent works involving cryogenic UHV TERS that show intramolecular resolution rely upon the ability to
maintain subatomic separation between the terminal tip atom and a molecule. Although the conditions for these studies are extreme, the ability to study chemistry spectroscopically at the sub-nanoscale offers unprecedented access to visualizing the inner workings of a molecule.

The history of TERS is relatively short, but rich in developments over the course of its nearly 20 years. Through improvements to its spatial resolution, it has become possible to spectroscopically characterize low-dimensional materials and materials with sub-nanoscale resolution. Advances in supplementary technologies and the ability to integrate TERS within other fields of research have led to consistent growth as its applications in various fields have been proven over time. Twenty years since the first TERS experiments, proof-of-concept experiments have largely been accomplished. Recent research with TERS is turning towards critical chemistry questions that can only be answered with spectroscopic information at the ultimate spatial limit.

**Technique Development**

As an analytical technique, it is paramount to consider the development of TERS over the course of its history in order to gain a thorough understanding of the systems that have been examined as well as appreciate the various directions of the technique within a larger context. As previously mentioned, the history of TERS relied upon advancements in instrumentation to allow new and improved combinations of SPM with enhanced optical spectroscopy. Within this framework, it is crucial to consider the optical setups used to introduce the light source to the tip-sample junction as well as the tip and sample individually.

**Optical Setups**

One of the key components of a successful TERS experiment is the ability to efficiently introduce the excitation light to the tip-sample junction while also collecting the Raman scattered light. Some early SPM-TERS experiments occurred in ambient conditions with back illumination used to introduce the laser light to the tip-sample junction, as shown in Fig. 2a. Unfortunately, this required a transparent sample, since the excitation light and Raman scattered light had to pass through the sample. Alternative methods include side-illumination and top-illumination in terms of lens setups. However, a parabolic mirror can also be used with opaque samples to simultaneously focus the laser light and collect the enhanced Raman signal. Ultimately, the potential to implement TERS with multiple optical setups allows the flexibility to integrate the
technique with different types of samples as well as within a variety of experimental contexts.

In order to implement TERS in UHV, there must be optical access to the tip-sample junction and the optical components must be successfully aligned to bring the tip apex into focus for optimal excitation and collection.49 Traditionally surface science carried out in vacuum systems relies upon metal single crystals as the sample surface or substrate. These samples are solid and opaque. This property prevents the use of transmission mode TERS, where the excitation light is incident on the back of the sample and travels through the transparent substrate to the tip-sample junction. But the other optical setups have found success in recent years. An alternative method using a parabolic mirror instead of a lens to focus and collect light has also been realized by other research groups, as shown in Fig. 2b.38,48,53 Ultimately, optical setups are chosen to maximize for the tightest excitation focus, while also maintaining a maximally large collection angle or numerical aperture in order to optimize the signal-to-noise ratio.

As Raman spectroscopy measures the shift in energy between a scattered photon and the incident photon, it is possible to use a range of laser wavelengths as the illumination source and still obtain a characteristic Raman spectrum. This ability to vary the incident wavelength enables a unique type of Raman spectroscopy known as resonance Raman spectroscopy. Resonance Raman scattering occurs when the wavelength of the incoming photons coincides with an electronic transition of the molecule or material being studied.54 This results in a significant increase in the intensity of the peaks corresponding to vibrational modes that are observed in the Raman spectrum. Specifically, in the case of surface-enhanced resonance Raman spectroscopy of rhodamine 6G (R6G), an overall Raman enhancement of $10^6$ was observed.55 Although the most significant enhancement arises from the highly confined and enhanced electromagnetic field caused by the localized surface plasmon resonance (LSPR) at the tip apex, additional enhancement from molecular resonance Raman effects can be used to further improve the signal quality in TERS studies.34

Since many TERS studies rely upon the combination of enhancements due to the tip’s LSPR and resonance Raman effects, certain incident laser wavelengths are commonly observed in experiments. Gold and silver nanostructures exhibit LSPRs that occur in the visible to near-infrared region of light.56 As most TERS tips are Ag or Au, this results in the near exclusive use of laser wavelengths that lie in the visible to near-infrared regime, depending on the molecule or material being investigated. Additionally, in order to use molecular resonance Raman effects, many enhanced Raman studies rely upon molecules that absorb light strongly in a range that corresponds with the LSPR of the plasmonic tip or substrate. As a result, organic dye molecules were extensively used in early SERS- and TERS-based experiments, where a laser wavelength is carefully chosen to align with both a molecular electronic transition and the tip’s LSPR.57 New theoretical and experimental developments have shown that resonance Raman effects are not inherently necessary for TERS imaging, even for intramolecular Raman images.43 The development of theoretical mechanisms to explain the extreme levels of enhancement and sub-nanoscale spatial resolution will be the next focus.

**Theoretical Developments**

Although TERS was initially the realization of a theoretical proposal to confine light, ongoing technique developments that have resulted in unprecedented angstrom scale spatial resolution have also necessitated new theoretical approaches. Similar to the two possible enhancement mechanisms proposed for SERS, a range of theoretical explanations have been suggested to explain the high enhancement and fine lateral resolution of TERS. Here we seek to provide a brief overview of these theoretical approaches.

Theoretical explanations to explain the source of high spatial resolution TERS imaging have followed the trend
towards the angstrom scale. Early work approximated the tip as a sphere, where the experimental radius of the tip significantly determined the confinement of the near-field enhancement.\textsuperscript{58} However, the first demonstration of a lateral resolution for TERS at the subnanometer limit necessitated an innovative approach. One such method relies upon an optomechanical approach, where the nonlinear enhancement arises from dynamical backaction amplification of molecular vibrations.\textsuperscript{59,60} In a similar manner, it has also been proposed that the near-field self-interaction of the molecule in the plasmonic nanogap due to multiple elastic scattering events results in the tremendous enhancement of observed Raman scattering and the experimentally reported subnanometer resolution of TERS.\textsuperscript{61–63} More recently, theoretical approaches have focused on the role of atomic-scale protrusions and their ability to form “picocavities” that confine light on the atomic scale,\textsuperscript{64–68} with the potential for a lightning rod effect that further enhances the local field.\textsuperscript{69} Building upon this explanation, another group has proposed that the localization of the near-field by an atomic protrusion results in significant field-gradient effects in the intramolecular TERS images that have been observed for individual molecules.\textsuperscript{70–73} Overall, theoretical studies into the physical origin of high-resolution TERS are still ongoing. Experimental demonstrations of new levels of lateral resolution have inspired the proposal of new physical mechanisms in theoretical studies. And the synergy between theoretical and experimental TERS studies enables the growth and expansion of the technique.

\section*{Optimization Methods}

\subsection*{Substrate Selection}

Although the reliable fabrication of tips with a stable and high TERS enhancement effect remains an ever-present technical challenge, some groups have turned towards manipulating the sample to optimize the enhancement through an alternative method. The most common method involves selecting a substrate material that matches the plasmonic metal of the tip, typically Ag or Au. This enables gap mode TERS which usually results in a significantly higher enhancement than if a dielectric or otherwise non-plasmonic material is used.\textsuperscript{58,74–76} In some cases, this can result in strong coupling of a single molecule to the plasmonic cavity,\textsuperscript{77} where hybrid light-matter states become accessible, a potential avenue for TERS studies.\textsuperscript{78,79} Beyond this, efforts have been made to manipulate the substrate to further improve the TERS signal. Nanoscale roughness was found to increase the signal by an order of magnitude,\textsuperscript{80} while fabrication methods to create a Fabry–Perot cavity substrate were found to result in a $5 \times$ enhancement.\textsuperscript{81} The tip may be the primary means to generate the enhanced electromagnetic field, but it is clear that carefully selecting the substrate can result in a further enhancement of the TERS signal.

\subsection*{Tip Fabrication and Modification}

The eponymous tip used in TERS experiments is paramount and as such, extensive research has been conducted into fabrication methods and quite a few reviews have focused on these developments.\textsuperscript{82–88} A review focused on the role of a TERS tip as a nanoantenna is also available.\textsuperscript{89} As a result, we will focus our evaluation of tip-related developments to a broad survey of the current state of methods alongside a focus on novel or atypical advances. Tips used in TERS experiments are frequently Au\textsuperscript{90–95} or Ag\textsuperscript{96–101} with a tapered tip formed during an electrochemical etching process that ideally results in a reproducible and controllable tip apex radius, as depicted in Fig. 3a, 3b, and 3d. Synthetic methods to grow a TERS tip have also been explored\textsuperscript{102} with a popular method being deposition of plasmonic metals onto an otherwise plasmonically inactive tip finding practical and widespread use in AFM measurements performed under ambient conditions.\textsuperscript{103} Electrochemical etching and plasmonic metal deposition have become some of the most common methods to fabricate TERS tips.\textsuperscript{83}

Some UHV-TERS groups have found success in post-processing electrochemically etched tips with special Ar\textsuperscript{+} ion sputtering or focused ion beam milling (FIB) in vacuum. Both methods have been used to smooth the tip or fabricate nanostructures on the tip with reports that both conditions improve the TERS enhancement. Notably, Tallarida et al. use field-directed sputter sharpening to produce nanoscopically smooth silver tips, as shown in Fig. 3c.\textsuperscript{104} In this process, a positive bias applied to the tip results in a repulsive potential and localized electric field enhancement at the apex, preserving and sharpening the tip apex therefore smoothing and reducing the tip radius of curvature.\textsuperscript{105} Alternatively, Yang et al. used an ion-beam sputtering technique that they developed to fabricate a tip apex decorated with a nanoneedle array, using a “Tip-on-Tip” structure to enhance TERS signal beyond their self-reported measurement with an Ag-coated tip of rhodamine 6G (R6G).\textsuperscript{106}

Meanwhile, FIB enables the design of intricate nanoscale features allowing for unique experimental setups. Grooves and gratings milled into the body of the tip allow the unique manipulation of the plasmonics of the tip that cause the TERS enhancement. It has been found that a single groove in the shaft of the tip can modulate STM-induced luminescence as a result of interactions between localized and propagating surface plasmon modes.\textsuperscript{107} Conversely, linear nanoslits gratings have been found to result in an optical antenna of sorts where far-field excitation incident on the grating results in a surface plasmon polariton that propagates towards the tip apex resulting in nonlocal excitation at the tip apex, as seen in Fig. 3e.\textsuperscript{108,109} Since the
laser is incident on the grating on the tip body as compared to the sample, this method of nonlocal excitation has been found to result in a decrease in background observed far-field Raman signal during TERS measurements. In a similar manner, Fig. 3c shows a tip where a silver nanoparticle or nanostructure affixed to the tip body was used to enable remote-excitation. Although most groups rely upon conventional methods of electrochemical etching to fabricate tips, current research into post-processing suggests that there are improvements to be made to the fabrication process to allow a higher degree of TERS enhancement and ideally improve system compatibility.

As a relatively young tandem technique, work is ongoing in the development of the experimental techniques and instrumentation that enable TERS experiments. As the technique matures, a variety of optical setups have developed, facilitating the characterization of new types of samples. At the same time, improvements in substrate selection or design and most importantly tip fabrication have pushed the spatial resolution of TERS to the subnanometer regime in recent studies. The diversification of TERS research into numerous fields such as biology, materials, and even fundamental surface science has resulted in a vibrant technique where ongoing discoveries are actively pushing spectroscopy studies to new levels of spatial resolution.

**Study Objectives**

As an analytical technique, TERS has found extensive employment in the interrogation of the vibrational properties of adsorbed molecules, low-dimensional materials, and biological macromolecules on metal surfaces. Some research has also found applications in the study and manipulation of chemical reactions at the nanoscale. This section of the review covers the development and applications of TERS towards these various systems under ambient conditions (such as solid–gas, solid–liquid, and electrochemical interfaces) with a focus on recent works in this field.

**Biological Molecules**

In recent years, Raman spectroscopy has found extensive applications in the study of biological materials as a noninvasive technique that yields biochemical and structural information via vibrational spectroscopy. Raman microspectroscopy provides a degree of spatial resolution that allows for the generation of point spectra and the identification of the localization of certain biochemicals within larger biological structures. However, improved spatial resolution holds promise for fundamental knowledge of the chemistry and structural factors that drive biological systems.
Tip-enhanced Raman spectroscopy spread to biological studies early on during its development. Following the initial proof-of-concept experiments, the spatially resolved spectroscopic technique was applied to the study of biological molecules under ambient conditions. The detection of TERS of Watson–Crick base pairs such as adenine, guanine, thymine, and cytosine on Au(111) was reported, and the hydrogen bonding between adenine and thymine was investigated with TERS later. These studies provide evidence and validation of TERS towards biological problems, allowing a pathway to precisely monitor DNA sequencing, as shown in Fig. 4.

In a similar manner, TERS has been applied to the study of other biological macromolecules. TERS enabled the nanoscale study of segregated lipid domains as well as large peptide fragments such as β-amyloid(1–40). Recently, TERS has shown promising results in characterizing the electron transport process of the copper protein Azurin bound to a gold surface. Through tuning the bias voltage applied by the STM and simultaneously acquiring TERS spectra, it was possible to track subtle differences in the vibrational fingerprint. Therefore, it is found that the protein’s vibronic response directly affects the electron transport process. Other proteins have also been investigated, such as albumin and hemoglobin, along with viruses and bacteria. Significantly, in very timely work, a modified TERS technique allowed the direct differentiation between influenza and picornavirus.

This has by no means been an extensive review of the applications of TERS in the study of biological systems, with new applications being discovered in the study of viruses, such as albumin and hemoglobin, along with viruses and bacteria. Significantly, in very timely work, a modified TERS technique allowed the direct differentiation between influenza and picornavirus.

![Figure 4](image_url)

**Figure 4.** (a) Schematic for tip-enhanced Raman scattering of single-stranded DNA (ssDNA) molecules ($\lambda_{es} = 532$ nm). (b) to (e) DNA sequencing of a sample containing 1.0 pmol of M13mp18 DNA. (b) TERS image of a single ssDNA segment with a step size of 0.5 nm. The plots show the integral intensities of the spectrum from 1630 to 1650 cm$^{-1}$. The numbers marking the map indicate the order of the sequences. (c) The “on strand” TERS spectrum of Pixel 7 and the “off strand” spectrum one step above Pixel 7 in panel (b). (d) A bar chart shows the probabilities $P_i$ from the spot 1 to 24 labeled in panel (b). (e) The probabilities $P_i$ from the spot 25 to 31. Two strands in panel (b) are separate by 1 nm. The different sequences of spots 13 to 19 and spots 25 to 31 provides evidence that TERS imaging can distinguish two parallel DNA molecules only separated by 1 nm. Figure and caption reprinted (adapted) with permission. Copyright 2019 American Chemical Society.
viability of applying nanoscale spectroscopy to the study of biological macromolecules. Although TERS offers unique nanoscale characterization of biological samples, it is crucial to mention the possible complications that may arise during an experiment that uses an enhanced spectroscopy. Although TERS is regarded as a noninvasive and nondestructive technique, biological samples are generally soft leading to potential damage by the SPM tip or the focused laser. This is commonly addressed with low laser intensities or lower acquisition times for point spectra in an effort to minimize sample damage. Although this results in lower signal for the identification of vibrational modes, the enhancement of TERS allows for spectroscopic characterization. It is also significant to note the complicated chemical nature of biological samples. A Raman spectrum of such a sample can be complicated by numerous features that correspond with the functional groups and backbones of multiple macromolecules. However, it is apparent that through careful examination of spatially resolved spectra it is possible to use Raman spectroscopy to study these systems.

Low-Dimensional Carbon and Nanomaterials

In the past decade, low-dimensional materials have become one of the hottest fields in physics, chemistry, and materials science since the discovery of graphene in 2004, the first 2D material.132 The impressive rise and success of graphene sparked scientists to explore other novel 2D crystals. In cases where these new materials are meant to function as part of a larger device, relatively easy and robust fabrication methods are mandatory. This simultaneously drives a need for characterization methods. Raman spectroscopy has proven to nondestructively provide relatively facile characterization of materials.133 And as such, TERS has found applications in this field, providing nanoscale Raman spectroscopy. We will provide a brief overview here, but once again we refer to a more thorough review focused on this area of TERS applications.134

The investigation of carbon-based materials, such as graphene and carbon nanotubes (CNTs), is ideally suited for TERS-based experiments. Initial work into single-wall CNTs was performed by the Novotny group.135–137 Later, single- and multi-wall CNTs were independently probed using TERS by a few research groups.138,139 It was possible to manipulate CNTs on the surface with an AFM tip, inducing localized strain, which could then be localized based on TERS mapping of a specific vibrational mode.138 Furthermore, TERS mapping of CNTs has been used to measure the spatial resolution of TERS in ambient conditions. The Kawata group documented a spatial resolution of 1.7 nm for TERS with simultaneous STM imaging, finding that the defect activated D-band only exists at the junction of two CNTs.140 Ultimately, TERS of carbon-based materials allows the identification of highly localized chemical effects.

Recently, TERS has also found applications in the characterization of 2D covalent monolayers. It is possible to probe nanoscale defects in 2D covalent monolayers, as shown in Fig. 5a and 5b, by utilizing surface selection rules which dictate that out of plane modes will be more enhanced compared to in-plane modes.141 The authors incorporated an alkyne (–C≡C–) group in the precursor molecule which shows Raman signal in an interference free region of a spectrum allowing analysis with high precision. The locations of nano-defects were identified by spatially mapping the 2220 cm\(^{-1}\) (\(v_{\text{C=C}}\)) since the alkyne groups orient perpendicular to the surface in defect regions, while they remain planar in the larger 2D network. The TERS map appears in Fig. 5d, while representative spectra corresponding to designated pixels appear in Fig. 5c. TERS has also shown great potential as a tool to measure the local crystallinity of a sample, providing a means to validate fabrication methods prior to more application-based studies.142–144

With the growth of research into new 2D materials, new applications for TERS are continuously being discovered. Transition metal dichalcogenides, with a general formula of MX\(_2\) (M = Mo, W, V, Nb, Ta, Hf, Pt, and X = S, Se, Te) are a very broad family of layered materials which have earned tremendous attention because of their diverse physical properties and a variety of potential applications.145–147 This intriguing type of 2D material, including MoS\(_2\) and WS\(_2\), is primarily prepared by chemical vapor deposition and micromechanical/liquid exfoliation, with metals, such as Ag, Au, and Cu, serving as supporting substrates.148,149 Through TERS, it becomes possible to characterize nanoscale defects in MoS\(_2\), such as local strain,150 edges, and grain boundaries.151–153 The Zhang group has also investigated the interactions of copper phthalocyanine molecules with MoS\(_2\).154,155 Additionally, TERS has proven capable of probing spatial phonons in monolayer and few-layer gallium sulfide.156 Ultimately, TERS is an extremely powerful tool to understand the nanoscale properties of new low-dimensional materials as well as their interactions with adsorbates when they are used as substrates.

Surface-Adsorbed Species

From its discovery, TERS has been used for the study of molecules adsorbed on surfaces. In this section, we will briefly mention some studies that demonstrate TERS applications in ambient conditions that examine molecular conformations and interactions. In order to maintain stability of the adsorbed molecules on the surface, thiol functional groups are commonly used to bind the self-assembled monolayer (SAM) molecules to the substrate via a strong S–Au covalent bond. The molecules that compose the SAM can exhibit flexibility in their chemical structure, which can be probed with TERS.157,158 Furthermore, TERS has proven useful in cases where a molecule can adopt two
configurations through a switching mechanism. The Zenobi group monitored the photo-induced switching of a self-assembled thiol-azobenzene molecule, using the vibrational mode that occurs at 1525 cm$^{-1}$ for the cis isomer, whereas it is absent in the TERS spectrum of the trans isomer.$^{159}$ Beyond the typical flat surface, TERS has also been applied to study the interactions of molecules with nanoscale features.$^{160}$ The nanoscale investigation of molecular orientation and intermolecular interaction has been proven possible with TERS in ambient conditions.$^{161}$

Investigations of Reaction-Based Systems

So far, we have limited TERS to the implementation of surface-adsorbed species in a static environment and considered it as a relatively noninvasive technique. In this manner, it is possible to use TERS to monitor the progress of a catalytic reaction with spatial resolution. However, it is known that a plasmon can induce a reaction.$^{162-164}$ Since TERS relies upon a localized plasmon, it is possible to probe as well as directly induce a reaction.$^{165}$ Ultimately, TERS can be used as a passive observing technique or as the means to drive the reaction. We will consider both methods in this section.

The spatial resolution of TERS enables the identification of catalytic active sites based on the chemical species that are observed on different substrate sites. With a tip coated in an ultrathin layer of alumina film to deactivate its plasmonic reactivity, TERS was used to chemically map the plasmon-induced reaction of \textit{para}-aminothiophenol (p-ATP) to dimercaptoazobenzene (DMAB) on a silver film.$^{166}$ Also recently, the Ren group fabricated a bimetallic surface—consisting of a sub-monolayer of Pd on a Au(111) surface—and used a probe molecule, phenyl isocyanide (PIC); PIC interacts with substrates via its N=C bond which is highly dependent on the local chemical environment. The authors showed that the N=C frequency weakens when the molecule was adsorbed on Pd step edges as opposed to terraces, with a TERS line profile showing 3 nm spatial resolution.$^{167}$ The same group further examined the bimetallic surface for the local generation and diffusion of active oxygen species (AOS). It was found that the AOS (reactive -OH radical) generated from H$_2$O$_2$ oxidizes a surface-adsorbed thiolate molecule, as shown in Fig. 6, with STM and TERS line profiles. With TERS imaging, the authors located the formation of -OH radicals to the Pd surface with an increase at the Pd step edge where they would then diffuse across the surface to react with the thiolate molecules.$^{168}$ The same group has also examined Pt nanoislands/Au(111) with TERS in an effort to understand the localization of bimetallic properties.$^{169}$ As previously mentioned, it is possible to use the tip plasmon to trigger a chemical change and use TERS spectra
to recognize it simultaneously. In 2012, the first reported TERS study of a chemical change triggered and observed the catalytic change of para-nitrothiophenol (p-NTP) to p,p'-dimercaptoazobenzene (DMAB) supported on a gold nanoplate,170 a reaction earlier discovered with SERS.171 Recently, the Zenobi group investigated seven different molecules with a thiol group self-assembled on a gold substrate. They observed the formation of cross-linked products during the course of TERS measurements. These products mirrored what would be expected through electron-beam or X-ray induced surface chemistry.172 Additionally, a nanoscale dehydrogenation reaction driven by a TERS-induced plasmonic field has been observed.173

Although the full potential of TERS in analyzing chemical reactions under ambient conditions is yet to be realized, initial work has documented its applications as a technique to study dynamic systems at the nanoscale.174,175 Future work using TERS both as a noninvasive tool and in the context of plasmon-induced reactions holds promise to provide fundamental knowledge of these new reaction systems.176

Single-Molecule Study

The utmost goal of any analytical technique is to identify and detect a single molecule. Such high sensitivity enables the analysis and interrogation of local chemical properties. However, in ambient conditions, single-molecule resolution with SPM is difficult, resulting in the historical need for a means to validate single-molecule resolution. In 2007, the first TERS experiment of a single molecule, BCB, adsorbed on an atomically flat gold surface was reported.97 In this work, the authors relied upon a series of factors to validate the asserted single-molecule sensitivity of their measurements. Extremely dilute samples were used, spectroscopic fluctuations characteristic of single-molecule behavior were observed, and discrete signal losses corresponding to the degradation of a single molecule were observed. At a similar time, another group reported Raman spectra of malachite green dye in an ambient environment with single-molecule sensitivity, facing criticism of their assertion of single-molecule sensitivity that required response.177–179 Later, the Van Duyne group examined rhodamine 6G (R6G) molecules and argued the detection of single-molecule spectra based upon an isotopic substitution experiment. R6G-d0 and the deuterated dye R6G-d4 were co-deposited on a silver film. Multiple spectra showed vibrational fingerprints of only one isotopologue, with TERS clearly able to distinguish between the two, as shown by the shift in a vibrational peak shown in Fig. 7, resulting in the conclusion that single molecules were being observed with TERS.180

A somewhat different method relied upon attaching a single molecule to the tip and monitoring variations in the...
line shape and peak position of vibrational modes in a TERS spectrum that correspond to conductance at the tip-sample junction. This technique is referred to as fishing mode TERS (FM-TERS). Based on the conductance of the tip-sample junction (ON) state and detached (OFF) state, single-molecule sensitivity was verified. Ultimately, efforts to prove single-molecule sensitivity become complicated when the SPM technique being used cannot image isolated single molecules.

Non-Ambient Measurement Conditions

Although the ideal scenario would be to visualize a single molecule with SPM and acquire the corresponding TERS spectrum simultaneously, the lack of stability in ambient conditions prevents the easy visualization of a single molecule on a surface with SPM. Due to this difficulty, groups performing TERS in ambient conditions turn to alternative methods to define the single-molecule nature of TERS measurements. However, another means relies upon improving the stability of the sample and measurement significantly, we will mention UHV-LT-TERS in a later section as an avenue to test the spatial resolution of TERS.

Liquid TERS

At the same time as the move towards UHV-TERS, there has also been efforts to apply TERS to more in situ conditions. The solid–liquid interface is ubiquitous, appearing in biological systems, catalysis, and electrochemistry, with nanoscale characterization difficult due to the surrounding solvent. Of note are studies that have investigated the application of TERS in liquids, with the intent to apply TERS to electrochemistry and other reaction-based systems in an effort to understand reactions at solid–liquid interfaces. Recently, a few groups have published research using electrochemical TERS (EC-TERS).

In 2009, as a proof-of-concept experiment the Zenobi group first demonstrated TERS at a solid–liquid interface. Interestingly, the presence of pure solution actually helped the detection of TERS signal as the authors noticed fewer photo-decomposition products.
Fujinami group utilized TERS to investigate phospholipid bilayers in an aqueous medium.\textsuperscript{187} In order to achieve stability under aqueous condition, they developed alumina and silver coated tungsten tips. Although preliminary efforts have been made to apply TERS to liquid systems, there remains significant work to further demonstrate its applications and refine the methods so that it may find more widespread adoption.\textsuperscript{188}

**Electrochemical TERS**

Electrochemical interfaces can be widely found in electron transfer processes, energy conversion, and storage which are extremely significant in solar cells, electrochemical reactions, storage devices, and so forth. Recently, TERS has been employed in electrochemical systems utilizing both STM\textsuperscript{185} and AFM\textsuperscript{189} by the Ren group and the Van Duyne group, respectively. The Ren group developed EC-TERS, using a side illumination EC-TERS set-up. They used TERS to monitor the configurational change in 4-(pyridin-4-yl)biphenyl-4-yl)methanethiol (4-PBT) as it depends on the applied electrochemical potential, the experimental setup, as well as a representative TERS spectrum appear in Fig. 8a to 8d.\textsuperscript{185} More recently, the Ren group introduced a new side-illumination EC-TERS technique that uses a water immersion objective, as shown in Fig. 8e to 8g, to minimize the mismatch of refractive indices, resulting in the study of non-resonant molecules with improved sensitivity.\textsuperscript{190} The Van Duyne group also used EC-TERS to measure the redox behavior of Nile blue (NB) molecules during cyclic voltammetry (CV) measurements, using an inverted TERS set-up with oil immersion objectives.\textsuperscript{189}

These preliminary studies provided evidence for the potential applications of EC-TERS. It became apparent that the solutions used in an electrochemical experiment are beneficial due to their ability to dissipate the abrupt local temperature that is generated at a plasmonic hot spot, therefore leading to a stable environment for TERS. Recently, the Van Duyne group demonstrated the first nanometer scale detection of the electron transfer reaction of NB molecules that were covalently bonded with Au(111) electrode with in-situ TERS.\textsuperscript{191} A potential swap between +0.109 V and –0.241 V caused the appearance and disappearance of characteristic TERS spectra that directly related to the oxidized or reduced form of the molecule. In this study, TERS intensity decreased as the NB was reduced reversibly. In a similar manner, the same group also investigated a molecular system, i.e., self-assembled...
cobalt–phthalocyanine (CoPc). However, the self-assembly formation at the solid–liquid interface highly depends on molecule–substrate, molecule–molecule, and solvent–substrate interactions.186 Recently, the Kim group has also published their first EC-TERS experiments involving benzothiol (PhSH) SAMs on Au(111).192 In an effort to characterize electro-active surface sites under reaction conditions, the Domke group used EC-TERS to map the electrochemical oxidation of gold nanodefects of a Au(111) single crystal electrode with about 10 nm spatial resolution.193 The growth of EC-TERS is an ongoing process as more research groups learn the potential of EC-TERS to uniquely study nanoscale electrochemical reactions.

The current state of work in EC-TERS demonstrates impressive potential in monitoring electrochemical redox processes and solution phase electron transfer. Furthermore, it is possible to investigate other systems such as photocatalysis and plasmon-induced electron reactions. We have only provided a brief impression of EC-TERS as a burgeoning technique. With the apparent opportunities for growth, we expect this field will remain active.

**UHV Conditions**

Few groups are currently capable of UHV TERS experiments as it requires specialized experimental knowledge across multiple broad fields, ranging from fundamental vacuum technologies, to surface science, to optics. However, the promising results accomplished thus far are attracting interest to the field and new approaches to answering chemistry questions at the spatial limit. As new research groups adapt the technique for their research focus, the growth of UHV-TERS promises to be dynamic and varied with new applications.

**Fingerprint Identification**

Raman spectroscopy has found extensive use as an analytical tool, providing chemical information and identification.194–196 TERS has been proven to provide vibrational fingerprint identification of chemical species below the diffraction limit of light.197,198 From its beginning, the sample and tip stability inherent to UHV-TERS experiments have allowed exceptional levels of spatial resolution. STM imaging of a molecule can be combined with a TERS map, where the intensity of a Raman mode is plotted on a color gradient against the x and y position of the tip, essentially generating a 2D real-space image where the color of a pixel is a representation of the intensity of a Raman mode at that particular tip position. Mapping as well as line profiles remain a staple in the TERS toolkit as a means to test and use the extreme spatial resolution alongside each full spectrum, which corresponds to a vibrational fingerprint, that is acquired at each individual pixel. The stability found in UHV conditions allows for these types of experiments, but the further improvement by moving towards low temperatures allows for further stability of the tip-sample junction and subsequently high-quality spectra with multiple vibrational modes apparent and longer acquisition times for each spectrum become possible.

As mentioned earlier, the first UHV-STM-TERS experiment that observed multiple vibrational modes, equating to a vibrational fingerprint, with molecular resolution STM images was published by the Van Duyne group. UHV-TERS spectra of CuPc on Ag(111) acquired concurrently with molecular resolution STM imaging were compared with SERS spectra of CuPc on a silver film over nanosphere substrate (Fig. 9a and 9b).30 TERS spectra allowed the quantitative identification of eight different vibrational modes. Significantly, in this study, all aspects of sample preparation were completed in UHV. This work would set the stage for the study of individual large polyatomic molecules on the surface as well as their intermolecular interactions and the interactions of molecular adsorbates with specific binding sites on a substrate in UHV.

In more recent works, vibrational fingerprints obtained with TERS have been used to differentiate adjacent regioisomers that are nearly identical in their structures. The Jiang group employed UHV-TERS at low temperature to chemically and structurally characterize regioisomeric porphodilactone molecules. In comparison with the molecular resolution RT-STM images seen in Fig. 9a, it is clear that the stability found at low temperatures allows for improved STM imaging (Fig. 9c). The improved system stability also allows for spatially resolved studies of these molecules when they are co-adsorbed on a surface. Even though they are isomers, alternating the lactone moieties causes significantly different vibrational fingerprints. In this work, Mahapatra et al. validated that TERS can achieve single-molecule sensitivity by performing a line profile with a spatial resolution of 8 Å across the boundary of regioisomeric assemblies.199 Then the authors characterized this two-component organic heterojunction with large-scale TERS mapping (Fig. 9d). The TERS image shown in Fig. 9e unambiguously shows the position of trans- and cis-porphodilactones, via identification of their individual vibrational fingerprints which are overlaid over the respective self-assemblies. Low-temperature TERS enables the identification of individual molecules on a surface via vibrational fingerprint analysis. Subsequently, a new type of spectroscopic study focused on a single molecule at a time becomes possible.200–202

**Single-Molecule Studies with Intramolecular Resolution**

Shortly after the initial studies combining UHV techniques with STM-TERS, one of the most often-mentioned UHV-LTTERS work was published in 2013. In this work meso-tetrakakis(3,5-di-tertiarybutylphenyl)-porphyrin (H$_2$TBPP) was
investigated on a Ag(111) substrate at a temperature of 80 K. TERS maps of a single H$_2$TBPP were recorded with the results of mapping multiple vibrational modes revealing the localization of specific vibrational modes within the molecule, allowing for the central cavity of the porphyrin core to be resolved and compared against the corresponding STM image. Importantly, they made use of resonance Raman effects to further enhance Raman scattering. Furthermore, the effects of the adsorption configuration of a molecule were observed. The TERS spectrum of a single molecule was compared to that of a molecule within a molecular island and the tilt of a molecule adsorbed on a step edge could be ascertained by comparison with a series of DFT calculated TERS spectra for a molecule at different tilt angles. Ultimately, the structure and conformation of a single molecule was achieved via spectroscopic chemical identification with subnanometer resolution. This study opened the door for further work exploring the limits of intramolecular resolution for TERS of a single molecule.

Continuing with the trend of the previously mentioned work, in 2019 the Apkarian group investigated CoTPP on Cu(100) at a temperature of 6 K. The authors stated that through scanning with the STM tip in a close approach, the CoTPP molecule could be flattened on the surface. Once the molecule was manually flattened, they were able to image the vibrational normal modes of the planar molecule by maintaining the tip within the atomistic contact limit, closer than previously published TERS studies. An illustration of this experiment appears in Fig. 10a, with images of...
various vibrational modes adjacent in Fig. 10b. Significantly, it is only possible to keep the tip this close to the molecule due to the extreme stability of the flattened molecule on the Cu substrate and the low temperature of the system. Ultimately, individual vibrational modes are visualized within a single molecule, including the localization of C–H bonds on a peripheral phenyl group, where the apparent spatial resolution was found to be 1.67 Å. In an effort to drive TERS towards molecular characterization at the ultimate spatial limit, the Dong group investigated a single magnesium–porphine molecule adsorbed on a Ag(100) substrate in liquid helium cryogenic conditions (7 K), shown in Fig. 10c and 10d.44 In a first of its kind study, the authors report the ability to construct the chemical structure of a single molecule by mapping specific vibrational modes that are established to correspond to specific chemical groups. It then becomes possible to establish the chemical structure of the molecule, once the building blocks are known, in a process that the authors liken to assembling LEGO. As seen in Fig. 10e, when taken together and assembled into a single color-coded image, the vibrational modes corresponding to a C–H group, pyrrole, pyridine, and Mg–N bond result in a merged image showing the complete molecular structure of a Mg–porphine molecule with lateral resolution down to 1.5 Å.

The most recent TERS work that shows intramolecular resolution was published at the beginning of this year, 2020. Copper napthalocyanine (CuNc) was investigated on a three-monolayer-thick insulating NaCl film supported on a Ag(111) substrate as well as on the bare silver surface, as shown in Fig. 11.204 Different vibrational modes of a CuNc molecule were considered via TERS mapping resulting in intramolecular resolution of the molecule when adsorbed on the NaCl insulating layer. A tunable laser was used to vary the excitation wavelength to match an electronic transition of the molecule and achieve resonance Raman conditions. In this manner, vibrational modes with three kinds of vibrational symmetries were investigated for a single CuNc molecule on NaCl. The D₄h molecule resulted in Raman active modes with A₁g, B₂g, and B₁g symmetry as observed in the TERS image.

Single-molecule TERS studies that offer intramolecular resolution of vibrational modes have been few and far between. Atomic-scale control appears paramount, where everything from substrate and molecule selection to atomic asperities on the tip plays a role in confining light to the subnanometer scale. When the conditions are correct, the generated TERS images are truly impressive and create new fundamental knowledge of chemical bonds and molecular vibrations. The focus on intrinsic vibrational features of individual molecules has pushed the spatial resolution of TERS towards lower and lower limits. However, there remains much to be learned through considering other chemical systems that do not need such intramolecular...
resolution. Intermolecular and molecule–substrate interactions are tremendous opportunities for study via Raman spectroscopy with nanoscale resolution.

Molecule–Substrate Interactions

Traditional Raman spectroscopy is well documented to show sensitivity to molecule identity, chemical environments, and intermolecular forces.205 Meanwhile, the surface selection rules found in enhanced Raman techniques such as SERS and TERS result in the orientation characterization of molecules adsorbed on the surface.206 When taken together with the spatial resolution of a technique such as TERS, it becomes possible to identify adjacent molecules on a surface, probe adsorption configurations, characterize molecule–substrate and intermolecular interactions, and even differentiate and define between adjacent molecules that adopt different adsorption configurations on a surface. Simultaneous high-resolution SPM imaging with atomic-scale spatial resolution allows the correlation of vibrational information with highly localized chemical environments. A survey of these studies will now become our focus.

Since TERS spectra rely upon molecular orientation, it is possible to unambiguously determine the tilt or orientation of molecules on a surface. Due to the selection rules for TERS and SERS, vibrational modes that are perpendicular to the surface and parallel to the tip and enhanced EM field are the most strongly enhanced.207 This is commonly experimentally proven through the combination of STM imaging, simulations, and finally, TERS spectra that have a unique fingerprint for molecules adsorbed in a particular orientation. In 2017, Jiang et al. examined a dynamic molecular domain boundary of N-N’-bis(2,6-diisopropylphenyl)-1,7-(4-t-butylphenoxo)perylene-3,4:9,10-bis(dicarboximide) (PPDI) molecules adsorbed on a Ag(100) surface using UHV-TERS. A stable island of PPDI adjacent to a diffusing phase was visualized with STM imaging at room temperature. However, a description of the orientations of the molecules within each phase was only possible through the combination of TERS with tilt angle dependent Raman simulations, with a planar orientation found in the stable island and perpendicular adsorption orientations identified within the diffusing phase.208

Two more recent works used UHV-TERS to compare the orientation of molecules that bound a self-assembled island with molecules that lie within the interior. As shown in Fig. 12a and 12b, the Dong group identified multiple orientations of 4,4’-bipyridine (44BPy) molecules. They found that 4BBPY molecules positioned along an island edge adopt a more perpendicular orientation compared to molecules that lie in the interior of the self-assembly.209 The Jiang group characterized the binding configurations of rubrene that result in multiple self-assemblies on a Ag(100) substrate. Through the combination of TERS and density functional theory calculations, Schultz et al. identified multiple orientations of rubrene on a Ag(100) surface where perpendicular orientations were preferentially adopted within one-dimensional chains and at the boundary of islands composed of planar rubrene molecules, as depicted in Fig. 12c to 12f.210 For similar non-planar molecules, the spatial resolution of STM is not as high as the resolution.
when the planar molecules lie parallel to the surface. The Jiang group reported 5 Å resolution shedding light on the application of TERS for orientation characterization, when it is not easily accessible via solely STM. Adsorption orientation is critical to catalytic processes as well as device fabrication via bottom-up assembly. The sensitivity of TERS to molecular orientation combined with its spatial resolution allows the unambiguous identification of multiple orientations and their dependence upon highly localized chemical environments.

Porphyrin-like molecules are known to adsorb onto surfaces with multiple configurations possible as the peripheral functional groups distort in response to molecule–substrate interactions. TERS studies of this type of molecule allow clear characterization of the binding configurations, where a change in substrate can drastically change the adsorption configuration of the molecule.211,212 In another impressive study of multiple binding conformations on one surface, the Van Duyne group reported a TERS line profile across H2TBPP molecules on Cu(111) where adjacent “bowl-up” and “bowl-down” configurations were distinguished with 2.6 Å resolution depicted in Fig. 13a to 13c.213 In cases of self-assembled molecular islands such as this, intermolecular interactions become involved in determining the local chemical environment. In other cases, it even becomes possible to distinguish the strength of the molecule–substrate interaction in mediating binding configurations, as shown in Fig. 13d and 13e.52,214 Once again, TERS is capable of providing nanoscale information of these interactions at the nanoscale; it has also been used to reveal the lifting of a degenerate vibrational mode of a molecule as a result of intermolecular interactions.215 Spectroscopic characterization of molecular interactions and binding configurations becomes possible at the nanoscale with TERS.

**New Research Areas for UHV-TERS**

As previously mentioned, Raman spectroscopy readily pairs with materials science as a means to characterize low-dimensional materials. Fundamental characterization of materials relies upon measurements of the pristine material to determine its intrinsic properties. To these ends, measurements of materials in UHV are an ideal method to understand a material’s nanoscale properties and subsequently its utility for potential applications. In this section, we highlight some recent applications of UHV-TERS towards the study of typical 2D materials. Since the study of graphene, numerous 2D crystals have been fabricated with a growing and diversifying library. The most obvious
analogues of graphene are from the elements close to carbon in the periodic table, i.e., silicon, boron, and germanium. Silicene, a 2D silicon-based counterpart of graphene epitaxially grown on supporting substrates, such as Ag(111), Ir(111), and Ru(0001), has attracted extensive interest. Although Raman spectra of silicene have been intensively studied from both the theoretical and experimental sides, TERS with high spatial resolution is the most ideal tool to probe silicene’s structural and vibrational properties due to the complex formation of diverse Si phases on Ag(111) that depends on growth temperature. In 2017, the Wu group reported TERS of a silicene sheet on Ag(111) with an enhancement factor of \( \sim 10^9 \), and a reported spatial resolution of 0.5 nm, which could be considered the first UHV-TERS study of 2D materials.

The authors observed considerable tip-enhancement of two peaks, so-called \( A^1 \) and \( A^2 \) modes, which represent dominating out-of-plane vibrations of the Si atoms in the silicene layer. In contrast, an insignificant \( E \) mode results from its nature of in-plane vibrations under a vertical electric field between the Ag tip and the Ag substrate. The high tip-enhanced signal and spatial resolution enabled the researchers to characterize various structural phases of silicene and thus chemically distinguish them by directly comparing the TERS spectra. In addition, the high sensitivity of TERS to the structural properties of materials facilitates the investigation of local vibrational properties of defects or domain boundaries in silicene, shedding light on the interaction between silicene and the Ag substrate.

Figure 13. (a) High-resolution STM image before the TERS imaging experiment. The dotted green line indicates the points where TERS spectra were obtained. (b) Vertical waterfall plot of H2TBPP TERS obtained along the green dotted line in panel a (0.25 nm per step). (c) Top: Schematic of H2TBPP porphyrin rings on Cu(111) buckled up/down, middle: simultaneously acquired STM line scan, bottom: TERS line scan of the integrated 1502 cm\(^{-1}\) mode (\( \lambda_{\text{ex}} = 561 \) nm). Figure and caption reprinted (adapted) with permission. Copyright 2016 American Chemical Society. (d) STM image showing submonolayer coverage of molecular islands of SubPc on a Ag(100) substrate. The molecular superstructure can be discerned, as well as the presence of bright spots corresponding to SubPc molecules in a “chlorine-up” configuration. (e) Experimental UHV TERS (black line = tip retracted, red line = tip engaged) and UHV SERS (pink line) vibrational spectra of SubPc compared to calculated (blue line) vibrational modes. Adjacent, 701 cm\(^{-1}\) vibrational mode model as calculated by DFT (\( \lambda_{\text{ex}} = 561 \) nm). Figure and caption reprinted (adapted) with permission. Copyright 2018 American Chemical Society.
Following the above-mentioned work, the same group employed TERS in studying the vibrational properties and the electron–phonon coupling of borophene,\textsuperscript{228} a new 2D boron allotrope experimentally fabricated on metal surfaces recently.\textsuperscript{229–231} They demonstrated the Raman spectroscopic fingerprints of two well-known phases of the borophene structure supported on Ag(111), i.e., $\beta_{12}$ and $\gamma_{3}$, after measuring the far-field Raman spectrum for comparison. In addition, as shown in Fig. 14, TERS was performed to prove that the smooth $\beta_{12}$ phase and striped $\beta_{12}$ phase are the same structure in nature but with different borophene–Ag(111) registries, which is related to the commensuration and strain in a metal-supported 2D layer.

The above studies enable us to gain insight into the structural and vibrational properties of silicene and borophene sheets, which paves the way for future investigations of their physical and electronic properties and potential applications. There are many new 2D materials to be explored via TERS. For example, germanene, a planar germanium allotrope akin to graphene and silicene, is another group-IV elemental 2D crystal. The growth of germanene on Au(111) has been reported,\textsuperscript{232,233} following the first synthesis on Pt(111) by molecular beam epitaxy in UHV.\textsuperscript{234} However, experimental studies were rarely reported on Raman characterization of germanene, although its vibrational properties have been investigated by means of first-principles calculations.\textsuperscript{235,236} Recently, germanene sheets have been epitaxially prepared on Ag(111) films supported on Ge(111)\textsuperscript{237} and on hexagonal (h)-AlN grown on Ag(111),\textsuperscript{238} affording researchers the opportunities to perform TERS studies on its vibrational properties and interactions with the underlying substrates.

Metal-supported ultrathin oxide films have been intensively studied in the field of physical chemistry and model catalysis.\textsuperscript{239–241} Liu et al. reported tip-enhanced resonance Raman spectroscopy (TERS) of graphene-like ZnO layers grown on a Ag(111) surface, where the TERS intensity showed a strong dependence on the local electronic states as demonstrated by performing TERS combined with scanning tunneling spectroscopy on different ZnO/Ag interfaces, as shown in Fig. 15.\textsuperscript{242} They also revealed that the spatial resolution of TERS is dependent on the tip-surface distance which is related to the strong electromagnetic field confinement between the Ag tip and the sample. With ongoing discoveries of new materials and new uses for existing materials, UHV-TERS promises to be a reliable characterization method to understand the unique properties of pristine low-dimensional materials.\textsuperscript{243–245}

**Figure 14.** TERS spectra of $\beta_{12}$ borophene. (a) Gap distance dependent TERS spectra. (b) TERS intensity of $B_{3g2}$ mode as a function of the gap distance. The data points can be fitted well with an exponential decay. The inset is an STM image with the tip at the labeled position for TERS measurement, the scale bar is 10 nm. (c) STM image of 0.5 ML borophene on Ag(111) surface. (d) TERS spectra with the tip on the terrace and at the edge of the borophene island labeled in (c), respectively. (e) TERS intensity map of the $B_{3g2}$ mode of the area marked by a red box in (c), with a step of 0.64 nm. (f) TERS intensity profile along the black arrow line in (c), which was measured with a step size of 0.3 nm ($\lambda_{ex} = 532$ nm). Figure and caption reprinted (adapted) with permission. Copyright 2019 American Chemical Society.\textsuperscript{228}
Conclusion

Twenty years after the first experiments, the development of TERS is still ongoing. Improvements and refinements to the technique and instrumentation have positioned TERS uniquely to characterize chemical systems with spatial resolution, which in some cases is below the size of a molecule. The combination of vibrational spectroscopy with SPM has attracted the interest of other research fields, resulting in the growth of TERS into new areas. In this review, we highlighted the history and development of the technique with recent work chosen to highlight the diverse applications of TERS. Nanoscale factors determine the properties of chemical reactions, materials, and biological macromolecules. The capability of TERS to characterize these systems with nanoscale resolution has resulted in growth of the technique, as it becomes possible to address questions old and new.

Tip-enhanced Raman spectroscopy has enjoyed significant success as a novel technique with a growing number of applications. Meanwhile, improvements in experimental conditions and theories allow improvements to its spatial resolution. As previously mentioned, the primary difference between TERS and SERS, is that TERS relies upon a single hot spot located at the apex of the SPM tip, while SERS benefits from countless hot spots that altogether give a tremendous enhanced Raman signal. Since TERS depends only on a single hot spot, the proper tip structure and condition are critical in order to generate any enhanced Raman signal. Research is still ongoing into the most reliable means to fabricate a TERS active tip, with individual research groups identifying their own methods to first fabricate and process the tip, and then condition the tip during the course of the experiment. New theories to explain the lateral resolution suggest that beyond the microscale structure of the tip, an atomic-scale protrusion is necessary at the tip apex to achieve sufficient confinement of the enhanced field for angstrom scale measurements. Control of the tip apex at the atomic level remains troublesome, with true characterization of the tip structure at the same degree exceedingly difficult. It also merits mentioning that TERS excels with specific chemical systems. Due to the nature of the enhanced field that generates TERS signal, polyatomic molecules with vibrational modes normal to the substrate produce the cleanest spectra with the most enhanced vibrational peaks. This is apparent in molecules that were selected for the UHV-TERS studies that demonstrate intramolecular resolution. Simultaneously, some groups use resonance Raman to further enhance the signal, limiting the selection of molecules to ones that absorb light in the visible range. The published work that demonstrates angstrom scale resolution for TERS relies upon the unique selection of factors to optimize the chemical system as well as the experimental conditions. It is not an easy task to confine light to such a degree.

As a growing field, TERS has not asserted itself as a universal technique, but it is clear that its promises of spectroscopic characterization at the nanoscale are attracting increasing interest. Thus far, technique development appears to be largely accomplished to the point that it is now possible to address interesting and unique chemistry and materials questions. Significantly, some efforts have...
been focused on integrating nonlinear spectroscopic approaches with TERS. TERS offers the ability to examine the consequences of local chemical effects at individual sites, allowing mechanistic studies of molecular interactions and reactions of an individual molecule on a surface. Newer work has shown that a larger variety of molecules are able to be considered, ranging from CO to smaller molecules that do not absorb light in the visible range. TERS research is expanding beyond porphyrin-like or dye molecules towards molecules relevant to catalysis and the fabrication of 2D materials. The potential of TERS is attracting interest from new fields, resulting in overall growth of the technique down novel avenues. And integrated instruments have recently become commercially available, significantly lowering the barrier to entry. This has allowed researchers from diverse scientific backgrounds to apply nanoscale spectroscopy to their own fields. However, to an extent, the challenge of fabricating and maintaining a reliable tip remains. A TERS experiment itself is not quite turnkey yet, requiring user knowledge across relevant scientific areas. In order for TERS to continue to grow in a positive direction, it is paramount for open communication between early adopters and those arriving to the technique more recently.

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