Tip-enhanced ablation and ionization mass spectrometry for nanoscale chemical analysis

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Spectroscopic methods with nanoscale lateral resolution are becoming essential in the fields of physics, chemistry, geology, biology, and materials science. However, the lateral resolution of laser-based mass spectrometry imaging (MSI) techniques has so far been limited to the microscale. This report presents the development of tip-enhanced ablation and ionization time-of-flight mass spectrometry (TEAI-TOFMS), using a shell-isolated apertureless silver tip. The TEAI-TOFMS results indicate the capability and reproducibility of the system for generating nanosized craters and for acquiring the corresponding mass spectral signals. Multi-elemental analysis of nine inorganic salt residues and MSI of a potassium salt residue pattern at a 50-nm lateral resolution were achieved. These results demonstrate the opportunity for the distribution of chemical compositions at the nanoscale to be visualized.

INTRODUCTION

Among current commercial mass spectrometric techniques, only secondary ion mass spectrometry (SIMS) and atomic probe tomography (APT) can offer nanoscale lateral resolution of chemical imaging. However, SIMS suffers from severe spectral interference and matrix effects (1, 2), and sample preparation is very cumbersome in highly specialized APT (3). Laser-based mass spectrometry imaging (MSI) technologies are a prominent choice because of their usability and reliability (4–7), but nanoscale analysis is still challenging due to the diffraction (8) and detection (9) limits. Unceasing efforts have been made to bring the lateral resolution of laser-based MSI from the microscale to the nanoscale. Using novel optics, atmospheric pressure matrix-assisted laser desorption/ionization (MALDI) MSI achieved its best lateral resolution of 1.4 μm in tissue analysis (10). At the cost of using an extreme ultraviolet laser and elaborate optics, a lateral resolution of 75 nm was achieved by analyzing polymers (11). By introducing near-field optics into MS systems, nanoscale lateral resolutions were achieved using an aperture-type near-field probe (12, 13). On the premise of obtaining MS signals, the optimal crator size was approximately 200 nm (14, 15). Furthermore, submicrometer lateral resolutions have been obtained using a nanotip for thermal desorption when analyzing molecules with low melting points, such as caffeine and pigment (16, 17). Alternatively, because of the localized surface plasmon resonance (18), the near-field effect locally amplifies and highly confines the incident optical field at the apex of apertureless tip or nanoparticles, enabling the lateral resolution to go beyond the diffraction limit in Raman (19–21), infrared (22), and fluorescence spectrometry (23). Moreover, the apertureless tip can also endure much higher irradiance than the aperture-type probe (24). Near-field ablations at the nanoscale have been performed using nanoparticles (25) and apertureless tips (26–29), but the idea of using the near-field effect of apertureless tips as a direct ionization source for MSI has not been fully explored.

RESULTS AND DISCUSSION

Tip-enhanced ablation and ionization

The performance of TEAI is demonstrated in Fig. 1 (D to I). In this case, a 10-nm-thick Ti layer was coated on the Au (111) substrate (Au@Ti). The surface roughness of the sample remained at ±1 nm (fig. S4, A and C). The laser irradiation (1.7 × 1010 W cm−2) was under the damage threshold of the sample (30, 31). A shell-isolated silver tip coated with 2 nm of SiO2 (fig. S1B) was used in the near-field experiment. The shell-isolated tip had an apex diameter of 80 nm (fig. S1A). When the tip was lifted to a position of 30 μm above the sample surface (the retracted mode), no surface damage was observed after 200 pulses of fs-laser were applied to the area of interest (Fig. 1D). Consistent with this result, no MS signal was detected (Fig. 1F). However, when the tip was kept at 5 nm from the surface of the sample (the approached mode), a crater with a diameter of approximately 50 nm was generated by performing the same 200 pulses of fs-laser (Fig. 1E). The absence of an ablated rim around the crater perimeter is in accordance with the typical mechanism of fs-laser ablation (32), in which the thermal effect is minimized. The MS signal of the ablated and ionized material from the nanosized crater was simultaneously acquired. Peaks of Ti and its isotopes could be seen in the spectra, and no silver ions were detected (Fig. 1G).

An experiment was performed on Au@Ti to demonstrate the reproducibility of the system. After 200 laser pulses were applied to the area of interest in the approached mode, a 2 × 2 array of craters was achieved with diameters ranging from 50 to 80 nm (Fig. 1H). Signals

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of Ti are shown in the corresponding mass spectra, with the intensities matching the sizes of the craters (Fig. 1I).

Electromagnetic simulations showed that the magnitude of the Poynting vector was localized and enhanced at both the tip apex and the surface due to the near-field enhancement (Fig. 1C). This contributed to the small size of the crater in near-field ablation. The maximum enhancement factors of electromagnetic power were 42 near the apex and 15.8 near the sample surface. The localized energy triggered the change of temperature and the generation of plasma, resulting in ablation and ionization. The intensity of the mass spectra was relatively low due to the low experimental ablated atom number (~2.2 × 10^5; table S2).

The formation of craters by tip-enhanced ablation

The formation of near-field craters was studied on Au@Ti. Figure 2A was acquired in the retracted mode after firing 1600 laser pulses on the sample, revealing that the sample was not damaged by the incident laser. Results of Fig. 2 (B to H) were obtained in the approached mode after performing different numbers of laser pulses ranging from 40 to 1600. The diameters of the ablated craters were maintained within the range of 40 to 50 nm, with a growing number of pulses up to 800 (Fig. 2, B to F). This is because the laser energy mainly heats the electrons to high temperatures and is weakly transferred to the lattice during the fs-laser–induced near-field ablation, reducing damage to adjacent surfaces (33). By performing more than 800 pulses of fs-laser, the diameters of the craters became slightly enlarged until it reached about 80 nm (Fig. 2, G and H). The corresponding MS signals of the craters were acquired (Fig. 2I). The intensity of MS signals first increased and then stabilized as the cumulative number of pulses increased.

Comparison of TEAI-TOFMS and SIMS

A comparative study of TEAI-TOFMS and SIMS for multi-elemental analysis was carried out by analyzing a residue mixture of nine inorganic salts (Fig. 3, A and B). The area of interest was the central region of the coffee ring, where the tunneling current can be detected (Fig. 3C). The inset in Fig. 3E suggests that no signals were obtained in the retracted mode. In the near-field experiments, nine metal elements and their isotopes were observed (Fig. 3, D and E). Compared with those obtained from SIMS (Fig. 3, F and G), the results of TEAI-TOFMS are more explicit with less interference from the substrate.
**MSI with nanoscale lateral resolution**

A proof-of-principle MSI experiment with a nanoscale lateral resolution was achieved by scanning a $1 \times 1 \text{mm}^2$ area of interest on a micro-patterned potassium iodine residue (Fig. 4A), which was prepared by electrohydrodynamic jet printing (fig. S3A). Figure 4B was acquired using fs-laser–based TEAI-TOFMS. It exhibits the distribution of $^{39}\text{K}^+$ corresponding to the potassium iodide residue with a lateral resolution of 50 nm, which coincides with the morphological image (Fig. 4A). However, the MS signal of iodine was not detected because of its high ionization potential (Fig. 4C).

**Simulation result of near-field enhancement**

The simulation model, in accordance with the experimental conditions, consists of an Ag tip above the Au@Ti. The finite-difference time-domain (FDTD) method is introduced to calculate the near-field enhancement for the tip located above the Ti surface.

The magnitude of the Poynting vector was recorded and imaged in both the XZ (Fig. 5A) and XY (Fig. 5B) planes. The physical significance of the Poynting vector is the electromagnetic power density. Given an experimental fs-laser irradiance value of $1.7 \times 10^{10} \text{ W cm}^{-2}$ on the ellipse irradiated area of the surface and the relationship between Poynting vector and electromagnetic fields, the corresponding electric field amplitude was calculated to be $3 \times 10^6 \text{ V cm}^{-1}$ and set to the model. After FDTD calculation, the power densities are $7.2 \times 10^{11} \text{ W cm}^{-2}$ near the apex and $2.7 \times 10^{11} \text{ W cm}^{-2}$ near the sample surface, which are 42 and 15.8 times higher than the incident laser power density, respectively.

**Simulation results of ablation process, plasma initiation, expansion, and ionization**

Using the enhanced laser power above as the energy input, a three-dimensional (3D) “two-temperature” model was used to simulate the femtosecond pulsed laser–solid interaction process (34–36). With this model, the sample temperature distribution (Fig. 6A) and ablated pit morphology (Fig. 6B) can be calculated. All the necessary data for the calculation were acquired from previous studies (37–40). Note that the time points are selected to be 3000 fs, when the bulk temperatures reach their highest values from one laser shot. The high-temperature area, with its highest value of 9371 K, is highly confined to the central part of the sample surface and hardly penetrates downward, leaving the inner part of the bulk almost unaffected. With the ongoing heating of the sample surface, a material phase transition takes place. The ablation crater progressively evolves and finally becomes steadily formed when the surface cools down, as shown in Fig. 6B by one laser shot. It has been reported that fs-laser ablation is so fast that the irradiated solid directly turns into the gas phase (sublimation) hardly with the process of melting (41, 42). The diameter of the ablated crater is about 50 nm, which is in accordance with the experimental observation in Fig. 2B. The crater has a distinct boundary in the case of the fs-laser–induced near-field enhancement, with minimal thermal effect on the surrounding area. The total ablated volume during one laser shot is found to be 132 nm$^3$, which corresponds to 7472 Ti atoms.

As for the plasma initiation, expansion, and ionization processes, a model has been developed, which takes into account the vaporization/sublimation equations (43, 44), the 1D planar fluid mechanics equations...
Fig. 4. Results of MSI with a lateral resolution of 50 nm. (A) SEM image of the KI residue on a Si substrate coated with a 10-nm layer of Au. The area inside the red square represents the area of interest. (B) Image of $^{39}$K$^+$ distribution obtained by fs-laser–induced near-field MSI with a lateral resolution of 50 nm by scanning an array of 20 × 20 spots at 50-nm spot intervals with 40 shots per spot. The color scale shows the normalized intensity of $^{39}$K$^+$. (C) Typical mass spectrum in an MSI experiment.

Fig. 5. FDTD-simulated distribution of Poynting vector. (A) Magnitude of Poynting vector in the vertical XZ panel ($Y = 0$ nm). (B) Magnitude of Poynting vector in the horizontal XY panel ($Z = 0$ nm).

Fig. 6. Simulation results of tip-enhanced ablation, plasma initiation, expansion, and ionization processes. (A) 3D bulk temperature (at 3000 fs) from one shot. (B) Final ablation crater by one shot. (C) Plasma temperature from one fs-laser shot at 3000 fs. (D) Total/ionized particle number density from one shot at 3000 fs.
(concerning the conservation of mass, momentum, and energy) (45, 46), the conservation laws of matter and charge (47), and a series of plasma state equations (43). After solving these equations, the plasma temperature (Fig. 6C) and particle number density (Fig. 6D) at the central point of the ablated area (at 3000 fs) can be calculated. Note that this time point is when the surface temperature reaches its maximum value during one laser shot and, correspondingly, when the highest plasma ionization efficiency occurs. The highest plasma temperature is 15,900 K. Using the total/ionized particle number densities, the plasma ionization efficiency can be calculated by integrating the ionized particle data over the whole plasma length and then dividing them by the corresponding value of the total number of particles. The calculated ionization efficiency is 3.9%.

In summary, we have developed a TEAI-TOFMS system and demonstrated its capability and reproducibility for ablation and ionization using near-field enhancement. The TEAI is capable of sampling a nanoscale area of interest. The shell-isolated tip has desirable features of robustness, anti-contamination, and a long lifetime (fig. S7). Furthermore, salt mixture residues were analyzed, indicating the rapid multi-elemental analysis capability and explicit spectral feature. MSI of robustness, anti-contamination, and a long lifetime (fig. S7). Future work will focus on exploring the possibility of analyzing chemical species with high ionization energies by introducing a post-ionization source into the TEAI-TOFMS system, and MSI of the chemical composition of nanodevices, single cells, and even cell organelles is expected to enlarge the scope of its applications.

**MATERIALS AND METHODS**

**Chemicals**
Perchloric acid (70%), anhydrous ethanol, and 10 different inorganic salts [NaCl, MgCl2, Al(NO₃)₃, KCl, CaCl₂, CrCl₃, FeCl₃, CuCl₂, CsCl, and KI] were purchased from Sinopharm Chemical Reagent Co. Ltd. (analytical grade) and used without further purification. Silver wire (0.25 mm in diameter, 99.9985%) and two types of gold wires (1 mm in diameter, 99.99%; 0.25 mm in diameter, 99.999%) were purchased from Alfa Aesar. Copper foil (polycrystalline) was purchased from Hefei Kejing Materials Technology Co. Ltd. The ultrapure water was used throughout the experiment.

**Experimental setup**
The schematic diagram of the TEAI-TOFMS system is shown in Fig. 1. The system was designed and built in-house. A frequency-doubled (515 nm) laser (s-Pulse HP, Amplitude Systèmes) with a pulse width of 500 fs and p-polarization was used. The laser beam was focused by a plano-convex lens (f = 230 mm) onto a spot diameter of 400 μm.

The laser irradiation intensity was below the damage threshold of the sample. The pulse-to-pulse energy stability of fs-laser was better than 5% (relative SD). The TOF mass analyzer was designed according to the previous experience in constructing MS instruments in our group (48–50). The mass analyzer and the ion source were kept in the same high-vacuum chamber to keep the loss of ions at minimum. To verify the potential in ablation and ionization from the near-field enhancement, no post-ionization source was used in our experiments. The time-lag focusing technique and a dual-stage reflectron were introduced into the TOF system to improve the mass resolution (51). A digital storage oscilloscope (42Xs, LeCroy) was used to acquire mass spectral signals. The data were processed by an in-house–compiled program written in LabVIEW (National Instruments Inc.). The detailed operating parameters were listed in Table S1.

A silver tip fabricated by electrochemical etching was fixed and mounted on a tip holder. The tip holder was connected to two level plates and a step motor. The step motor was controlled by the STM system (MicroNano STM-II, Shanghai Zhulun MicroNano Equipment Co. Ltd.). A 2D closed-loop piezo scanner (SLC-17, SmarAct GmbH) provided precise control of movement of the sample on the XY plane. In the Z direction, the coarse adjustment of the sample was controlled by a manipulator. A scanning tube was connected to the STM system and mounted on the piezo scanner, enabling precise movement of the sample in the Z direction. The distance between the tip and the surface of the sample was kept by adjusting the coordinated movements of the step motor and the scanning tube. The tunneling current between the sample and the tip was measured automatically by the STM detection system. All the movements of the tip were controlled by computer software. An in-house–built vibration damping system was used to minimize the vibration. Observation of the coarse position between the tip and the sample was achieved by a charge-coupled device (CCD) camera (SN-300/130, Shenzhen Sannuo Co. Ltd.). All the atomic force microscopy (AFM) images were obtained from Cypher S AFM (Asylum Research) operated in tapping mode. Near-field enhancement simulations are performed using the commercial software of FDTD Solutions (Lumerical Solutions Inc.).

Secondary ion mass spectra were obtained using a TOF secondary ion mass spectrometer (TOF-SIMS 5) from IONTOF GmbH. A 30-kV Bi⁺ analyzing gun combined with a 500-eV O₂⁻ sputtering gun was applied to analyze the metal salt solution on silicon wafer under interlaced mode with a target current of 68 nA. The analyzed area was 100 × 100 μm for Bi⁺ gun, and the sputtered area was 300 × 300 μm for O₂⁻ gun. The final spectrum was the sum of 200 scans (128 × 128 pixels per scan and 1 shot per pixel).

**Procedure for controlling the distance between the tip and the surface of the sample**
Initially, the tip was far from the surface of the sample with a distance of approximately 30 μm. To attain the working position, the tip was kept near the surface of the sample, which was driven by a step motor, until it reached a position of 1 μm from the surface. Then, the sample was moved toward the apex of the tip driven by a piezo scanning tube until the tunneling current was detected by the STM system. To avoid the mechanical contact between the tip and the surface caused by thermal expansion (52), the sample was quickly withdrawn to 5 nm from the surface by the piezo scanning tube after reaching the tunneling position, and then the lasers were operated at low frequency in the experiment. All the movements of the stepper motor and the piezo scanning tube were controlled by the feedback loop of the STM system. After performing pulses of laser to the gap between the surface and the tip, the tip was removed 30 μm from the surface. Then, the sample was moved to the next location for sampling. The laser was turned off at the interval between two consecutive sampling actions.

**Preparation of shell-isolated silver tip**
The silver tip was fabricated from a 0.25-mm silver wire by electrochemical etching (53, 54). A mixture of perchloric acid and ethanol with a volume ratio of 1:4 was used as the electrolyte. A gold ring was fabricated from a 1-mm gold wire and served as the counter electrode.
The silver wire was placed vertically in the center of the gold ring, and an approximately 3-mm-long silver wire was immersed in the electrolyte. An automatic cutoff etch circuit was introduced to the etching system to control the cutoff time of the applied voltage as the lower part of the silver wire dropped off, preventing over-etching (55). A dc voltage of 8.9 V was applied to the etch circuit as a starting voltage. The total etching time of a single silver tip was within 2 min. After etching, the upper part of the tip was retracted. It was immersed in deionized water for 5 min and then rinsed three times in ethanol. The silver tips with an apex diameter of 80 nm (fig. S1A) were easily acquired by adjusting the starting voltage. The shell-isolated tips were fabricated by depositing a 2-nm-thick layer of SiO₂ on the silver tip apex (fig. S1B) using an atomic layer deposition system (R-200 Advanced, Picosun). The shell-isolated tips were characterized by a transmission electron microscope (JEM-2100, JEOL).

Preparation of the metal coating sample

The single crystalline Au (111) substrate was fabricated by the Clavilier method (56). Briefly, a single crystalline bead with a diameter of approximately 3 mm was formed by melting one end of a 0.25-mm gold wire in a hydrogen-oxygen flame. The bead was mounted on a gold disc, with one of the (111) facets facing upward, and served as the substrate. Then, the gold surface was cleaned by electrochemical polishing and flame annealing in sequence. A metal layer of Ti with a thickness of 10 nm was coated on the Au (111) (fig. S2) by a magnetron sputtering device (Explorer-14, Denton Vacuum) in the Pen-Tung Sah Institute of Micro-Nano Science and Technology of Xiamen University.

Preparation of residues on copper substrate

By modifying a previous method (57), we prepared the inorganic salt residues (fig. 3, A and B). Briefly, nine different inorganic salts were dissolved in ultrapure water with an identical concentration of 1 mM. By evaporating 10 μl of the solution on a Cu substrate, residues were prepared. Then, 10 μl of ethanol was added to the center of the residues. After the ethanol was evaporated, the residue surface became smoother in the central region such that the bump on the substrate can be avoided during the tip lateral movement. The residues were coated with a 2-nm-thick layer of gold before analysis.

Preparation of the micropatterned KI sample

The micropatterned KI sample was prepared by the electrohydrodynamic jet printing (58). Glass pipettes with an inner diameter of 2 μm were fabricated using a laser-based micropipette puller (P-2000, Sutter Instrument). The outer pipette wall was coated with a layer of gold by a sputter coater (MCM-200m, SEC Co. Ltd.). The solution of 1 mM KI was drawn to the pipette by capillary forces from the nozzle. The micropipette was then placed on a piezo motor from the pipette apex. A single-crystal silicon plate coated with a Cr/stratex, a Taylor cone was generated and droplets of ink were ejected after applying a 300-V dc voltage between the pipette and the substrate. The pipette and the substrate were separated at a distance of 5 m.

Lateral resolution analysis

To determine the lateral resolution of MSI based on the 16 to 84% criterion (59, 60), three scanning lines were selected in fig. S6A. Figure S6B shows the normalized MS signals extracted from three scanning lines of fig. S6A. Therefore, we believed that the lateral resolution of the MSI was ~50 nm. It took ~6 hours for the elemental image following the previously reported procedure (61, 62). The corresponding mass spectral data were processed to construct the elemental image using a self-developed LabVIEW program. The results of MSI presented infig. 4B and fig. S6A were reconstructed with automatic interpolation using Surfer 9 (Golden Surfer Inc.).

SUPPLEMENTARY MATERIALS

Supplementary material for this article is available at http://advances.sciencemag.org/cgi/content/full/3/12/eaaq1059/DC1

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