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Parallel imaging MS/MS TOF-SIMS instrument

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The authors have developed a parallel imaging MS/MS capability for the PHI *nanoTOF* II time-of-flight secondary ion mass spectrometry (TOF-SIMS) instrument. The unique design allows a 1 Da wide precursor mass window to be extracted from a stream of mass separated secondary ions while all other secondary ions are detected in the normal manner at the standard TOF-SIMS detector. The selected precursor ions are deflected into an activation cell where they are fragmented using high energy collision induced dissociation and mass analyzed in a separate linear TOF mass spectrometer. This TOF-TOF approach allows MS/MS to be accomplished at a high speed maintaining the primary ion beam repetition rates used in TOF-SIMS. The new MS/MS capability enables molecular identification to be extended to higher mass ions where the mass accuracy of TOF-SIMS is not sufficient to unambiguously identify molecular structure. The ability to acquire TOF-SIMS and MS/MS data simultaneously from the identical analytical volume is a powerful new method for mass spectrometry imaging. © *2016 American Vacuum Society*.
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I. INTRODUCTION

The time-of-flight secondary ion mass spectrometry (TOF-SIMS) has become a well-established technique for surface analysis due to its unique attributes such as high sensitivity, high mass resolution, submicron spatial resolution, and ability to provide both elemental and molecular information. The widespread adoption of new cluster primary ion beams over the past decade has significantly improved the ability to sputter and detect intact molecular ions at higher mass.[1–3] This increase in sensitivity has translated directly into better spatial resolution molecular imaging as the minimum pixel size with an acceptable signal intensity has become correspondingly smaller. The use of a bismuth liquid metal ion source provides cluster primary ion beams (e.g., Bi_3^{+2}) with a beam size of 70 nm at low mass resolution and 500 nm at high mass resolution, which are both significantly smaller than the probe diameter of other imaging mass spectrometry techniques such as matrix assisted laser desorption/Ionization (Ref. 4) or nanospray desorption electrospray ionization mass spectrometry.[5] The developments in cluster primary ion beams have resulted in TOF-SIMS making increasingly important contributions to the understanding of complex molecular distributions in biological tissues and cells and for surface and thin film analysis of polymers and other engineered organic materials.

The ability to detect higher mass ions using cluster primary ion beams has made the challenge of peak identification more problematic. The mass accuracy in commercial TOF-SIMS instruments is not sufficient to provide unambiguous high mass peak identification. A VAMAS round-robbin study by Gilmore *et al*. concluded that using an optimized procedure for mass calibration, a 10 ppm mass accuracy could be achieved only up to 140 m/z.[6] This makes it impossible to distinguish CH_2 from N or NH_2 from O when trying to identify the chemical structure of higher mass peaks based on the exact mass measurement.

It has been recognized for many years that MS/MS is needed in TOF-SIMS in order to be certain of high mass peak identifications, especially for complex biological samples. This prompted the development of MS/MS on SIMS instruments based on a DC primary ion beam and a pulsed TOF mass spectrometer by research groups led by Winograd[7] and Vickerman.[8] The instrument presented here differs from these previous instruments in two ways: (1) the primary ion beam is pulsed rather than DC; and (2) the entire TOF-SIMS spectrum (except the precursor ions) is detected simultaneously with the MS/MS spectrum. In our implementation, no secondary ions are discarded while operating in the MS/MS mode of analysis. We refer to this as "Parallel Imaging MS/MS TOF-SIMS" because secondary ions are recorded at the standard TOF-SIMS detector at the same time that MS/MS fragment ions are recorded at the linear TOF detector. Because there are two mass spectrometers and two spectra are acquired within a single acquisition, we use the following nomenclature for clarity:

$$\mathrm{MS1} = \text{the TOF analyzer used for TOF} - \text{SIMS},$$

$$\mathrm{MS2} = \text{the linear TOF analyzer used for MS/MS},$$

$$\mathrm{MS}^1 = \text{the secondary ion mass spectrum},$$

$$\mathrm{MS}^2 = \text{the MS/MS fragment ion spectrum}.$$

The secondary ions detected in MS1 and MS2 are produced from the same primary ion pulses striking the sample surface. The x-y position of the primary ion beam is recorded for every count detected in both MS^1 and MS^2 spectra. In this way, images produced from MS^1 and MS^2 are in perfect registration and are from the identical analytical volume of the surface.

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II. INSTRUMENT DESIGN AND PERFORMANCE

We have developed a parallel imaging MS/MS spectrometer based on the commercial PHI *nanoTOF* II TOF-SIMS instrument.[9] The stigmatic imaging optics of the TRIFT analyzer, which has been described in detail previously,[10] produces a cross-over after the third ESA that provides an ideal location to deflect a spatially focused and mass resolved packet of ions into a second mass spectrometer for MS/MS. A precursor selection device has been positioned at this cross-over location, which can be pulsed at a specific time delay from the primary ion beam pulse in order to select the desired precursor ion mass for the MS/MS analysis. The selected precursor ions are deflected by 45° into an activation cell with a kinetic energy of 1.5 keV for collision-induced dissociation (CID). For the experiments reported here, argon was used as the collision gas. Only argon and neon has been used as a collision gas to date and they gave qualitatively very similar results. The selected precursor and fragment ions that emerge from the activation cells are bunched and further accelerated prior to entering the field free drift region of the linear TOF analyzer. A schematic of the new MS/MS spectrometer is shown in Fig. 1.

With the precursor selector off, the PHI *nanoTOF* II functions exactly as before with no change in TOF-SIMS performance specifications. The precursor selector and the CID cell are the only significant additions to the original *nanoTOF* II mass spectrometer. A new vacuum chamber was designed with ports for adding a turbopump and an x,y,z manipulator for the precursor selector optics. Minor shielding and mechanical changes were made to allow the MS/MS ions to cut across the entrance of ESA 1 and enter into the buncher and acceleration optics.

For the purposes of demonstrating the performance of the new MS/MS capability, a thin film of crystal violet was prepared by dissolving the powder (Ted Pella, Inc.) in methanol and pipetting it onto a piece of silicon and allowing it to air dry. A 30 keV Bi_3^{+2} primary in beam was used for all the measurements reported here. The positive TOF-SIMS spectrum of crystal violet produces a strong molecular ion from $C_{25}N_3H_{30}^+$ with a mass of 372.244 m/z, which was selected for the MS/MS analysis. The two spectra shown in Fig. 2 were acquired in a single acquisition. The TOF-SIMS spectrum (MS^1) is simply the spectrum of crystal violet minus the precursor ions that were selected for the MS/MS analysis. The MS/MS spectrum (MS^2) shows the precursor at 372 m/z and the fragments created by high energy CID. It is interesting to note that the three highest intensity MS/MS fragments (at 356, 340, and 328 m/z) are also the three largest fragments in the TOF-SIMS spectrum. In general, the ability to identify peaks in common between MS^1 and MS^2 is very helpful in the interpretation of both spectra. Most MS/MS fragments can be assigned from single bond cleavages of the precursor ion with several examples shown on the molecular structure in Fig. 2 inset.

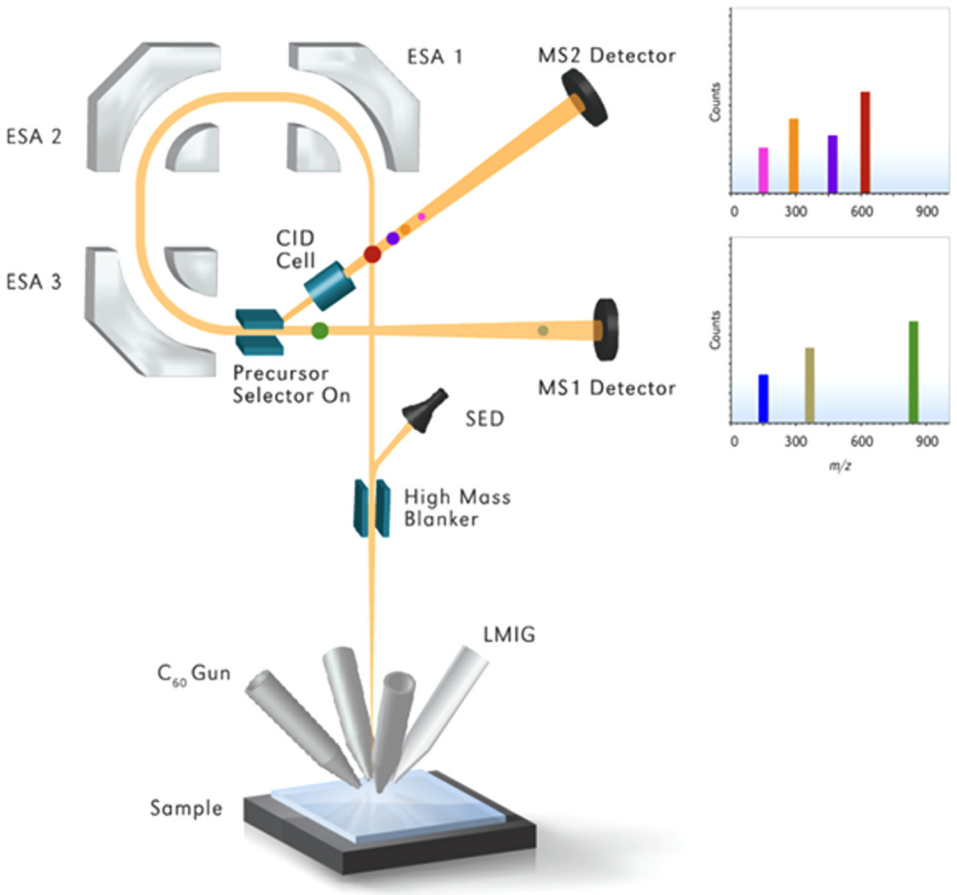

FIG. 1. (Color online) Schematic of the PHI *nanoTOF* II with MS/MS. Illustration courtesy of Physical Electronics.

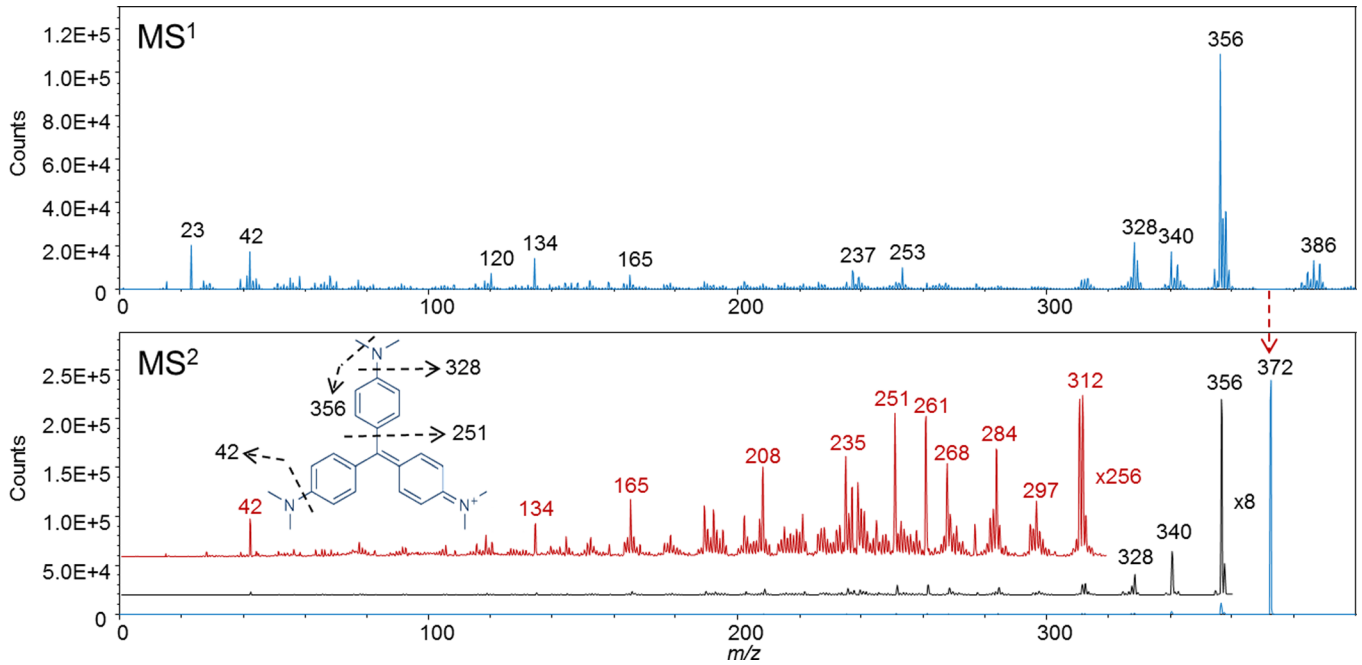

FIG. 2. (Color online) TOF-SIMS (MS^1) and MS/MS (MS^2) spectra of crystal violet acquired simultaneously.

The mass resolution of the precursor selector is 500 (m/Δm, fwhm). By limiting the precursor to a single mass, we have greatly simplified the complexity of the MS^2 spectrum. The 1 Da precursor window minimizes the number of interferences and even allows us to eliminate the spectral complexity due to ^{13}C isotopes, as is illustrated in Fig. 3. By choosing 372 m/z as the precursor ion, all peaks containing ^{13}C are eliminated, and the fragment ion at 134 m/z is a singlet. By choosing 373 m/z as the precursor ion, we know the molecule contains one ^{13}C atom. The MS^2 spectrum shows a doublet at 134 and 135 m/z. Since nine of the original 25 carbon atoms are in the fragment ion, there is a 36% change that the ^{13}C atom will be in the fragment ion and it will have a mass of 135 Da. There is a 64% chance that the ^{13}C atom will be in the neutral loss fragment, which creates a fragment ion with a mass of 134 Da. This ratio is verified experimentally in the data shown in Fig. 3. The high mass resolution in the precursor selection is especially beneficial when analyzing the complex biological samples where many similar molecules are detected very close in mass.

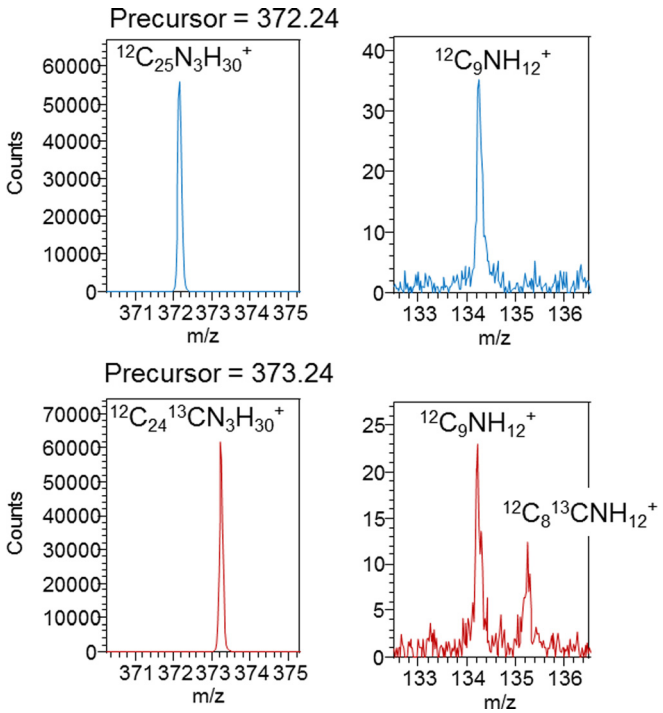

FIG. 3. (Color online) Demonstration of the 1 Da wide precursor selection window; (top) a precursor ion without a ^{13}C atom; (bottom) a precursor ion with one ^{13}C atom.

The mass resolution of the precursor in MS^2 is typically ~3000 (m/Δm, fwhm). This is much better than that expected from a linear TOF due to the time focusing effect of the buncher, which is located after the CID cell. One important feature is that the mass resolution in MS^2 is independent of the mass resolution in MS^1. This is illustrated in Fig. 4 where a MS^1 spectrum was acquired of crystal violet with the Bi_3^{+2} primary ion beam in the bunched and unbunched modes. In the bunched mode, the primary ion beam pulse is compressed in time, resulting in a high mass resolution in MS^1 (12 000 m/Δm, fwhm at >100 Da) and a moderate image resolution (500 nm). In the unbunched mode, the primary ion beam is not compressed, resulting in a low mass resolution in MS^1 (500 m/Δm, fwhm) and an excellent image resolution (70 nm). While the mass resolution in MS^1 is directly dependent on the primary ion beam pulse width, the mass resolution in MS^2 is unchanged. For peaks with sufficient intensity, this would allow the use of the unbunched imaging for ultimate spatial resolution, and separation of isobaric interferences in MS^2.

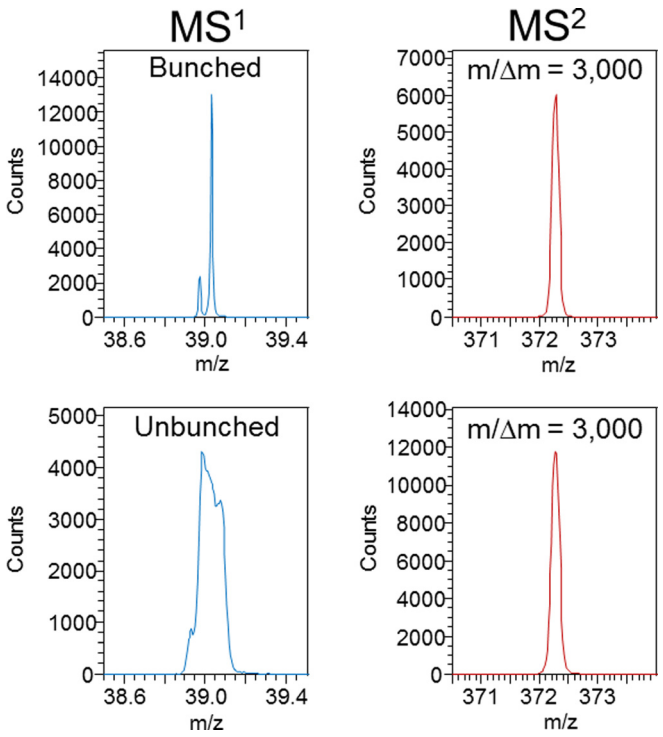

FIG. 4. (Color online) Mass resolution in MS^2 is independent of mass resolution in MS^1.

III. CONCLUSIONS

MS/MS greatly improves the power of TOF-SIMS for molecular identification, especially for peaks above 150 m/z. When analyzing the complex organic surfaces, such as biological tissues or engineered polymer products, the ability to select and fragment a 1 Da mass window literally moves the TOF-SIMS analyst from guessing what the structure is to knowing what it is. The prospect of a rapid spectral matching against MS/MS databases promises to be much more successful than trying to spectral match the pure known spectra to MS^1 spectra, which are a convolution of secondary ions from all elements and molecules on the surface. The TOF-TOF tandem mass spectrometry design presented here is unique in that it allows standard TOF-SIMS analysis and verification of selected molecular structures all within a single analysis. The TOF-TOF method with high energy CID is done at high repetition rates typically used in TOF-SIMS and is fully compatible with 2D or 3D imaging experiments without a significant increase in acquisition times.

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