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A Revolutionary Approach for Molecular Imaging with TOF-SIMS Parallel Imaging MS/MS

John S. Hammond[1], Gregory L. Fisher[1], Paul E. Larson[1] and Scott R. Bryan[1]
[1.] Physical Electronics USA, Chanhassen, Minnesota, USA

At the time of introduction in the 1980's, TOF-SIMS was a surface analysis research instrument providing elemental ion and limited molecular fragment ion spectra and images of the outer layer of solid materials. Since the initial successes, TOF-SIMS has evolved into a more powerful technique based on several important instrumentation advances. These advances, listed in chronological order, are listed below:

- Improved mass resolution up to 16,000 m/Δm
- Improved depth of field up to 200 μm for analysis of many real world samples
- Enhanced higher mass fragment ion sensitivity using cluster ion probe beams, i.e. Bi_n^{q+}
- Organic depth profiling, with minimal chemical damage, using cluster ion sputter sources
    - SF_6^-
    - $Glycerol^+$
    - C_{60}^+
    - $Coronene^+$
    - Ar_n^+ Gas Cluster Ion Beam (GCIB)
- 3D Imaging, FIB-TOF and 3D Tomography

All of these advances have expanded the breadth of applications, most notably the use of TOF-SIMS for analyzing organic contamination, tissue cross sections and polymer surfaces with sub-micron spatial resolution. The limitation of organic molecular fragment compositional peak assignments, based on the mass resolution up to 16,000 m/Δm and the mass accuracy of ~10 to 20 ppm for current state-of-the-art TOF analyzers, has obviated some of the benefits of the listed advancements. Routine analysis can produce ion spectra and ion images over 2,000 m/z. For many molecular ion fragments, unambiguous peak assignments cannot be achieved over a mass of ~ 200 m/z (for either positive or negative polarity ions). Clearly a paradigm shift is needed in the data acquisition of higher mass molecular ion fragments for TOF-SIMS to reach its potential for sub-micron spatial resolution analyses. This is particularly important for cellular and sub-cellular biological tissue analysis, as well as micro-features on polymers, biomaterials, and other organic materials.

To provide this needed paradigm shift, a new TOF-SIMS Parallel Imaging MS/MS instrument has been designed and a review of results from this instrument will be presented. The newly developed TOF-TOF tandem imaging mass spectrometer allows conventional TOF-SIMS (MS^1) analysis and product ion (MS^2) analysis to be acquired simultaneously and in parallel. Secondary ions for MS^1 and MS^2 analysis are produced from the same area of the surface by a pulsed and digitally raster-scanned primary ion nanoprobe. Activation of the precursor ions, defined by a 1 Da precursor selection window, is accomplished by 1.5 keV CID using Ar gas. Lateral resolutions produced in both MS^1 and MS^2 images are demonstrated in the present research to be < 200 nm. The MS^2 fragment spectra from pure Crystal Violet demonstrates that the 1 dalton wide precursor selection window can eliminate or select ^{13}C containing precursor peaks, providing enhanced MS/MS data from samples with complex mixtures of additives on the surface. This data also bodes well for imaging of lipids and metabolites from tissue samples. The MS^2 fragment spectra also demonstrate better than 10 ppm mass accuracy for the identified peaks. The conversion efficiency of precursor ion peaks to the spectrum of fragment ion

peaks is, on average, ~10%.

The PHI *nanoTOF* II imaging MS/MS schematic is shown in Figure 1. The system design allows simultaneous MS and MS/MS imaging up to 8.3 kHZ. Figure 2 shows the MS/MS spectrum of the Erucamide polymer additive negative polarity precursor molecular ion. The spectrum allows the structural identification of the double bond location. Figure 3 shows the MS images for a heat treated polyethylene terephthalate film and the MS/MS images from the positive polarity 577 m/z precursor ions. The simultaneous MS^1 and MS^2 imaging of the heat treated PET sample confirmed that the crystal structure on the surface of the PET is a cyclic trimer structure. The MS^1 images and MS^2 images derived from the CID activation of the positive polarity 577 m/z precursor show that the crystal images are in exact registry with one another. Line scans (80% to 20% intensity) show <200 nm spatial resolution for both modes of imaging.

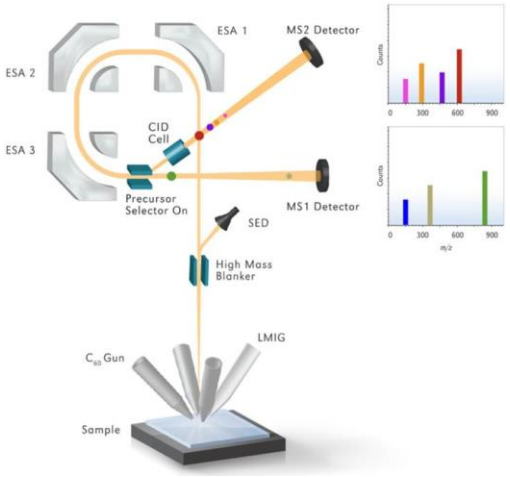

Figure 1. TOF-SIMS Imaging MS/MS

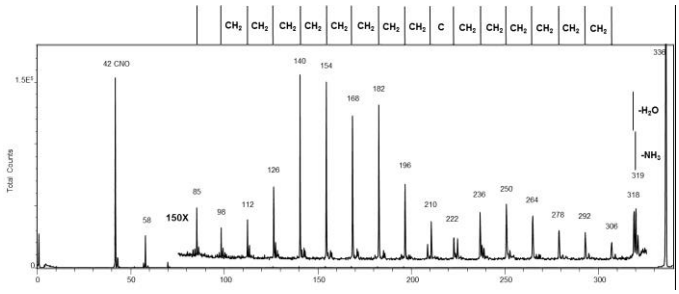

Figure 2. MS/MS spectrum of -336 m/z Erucamide precursor ion

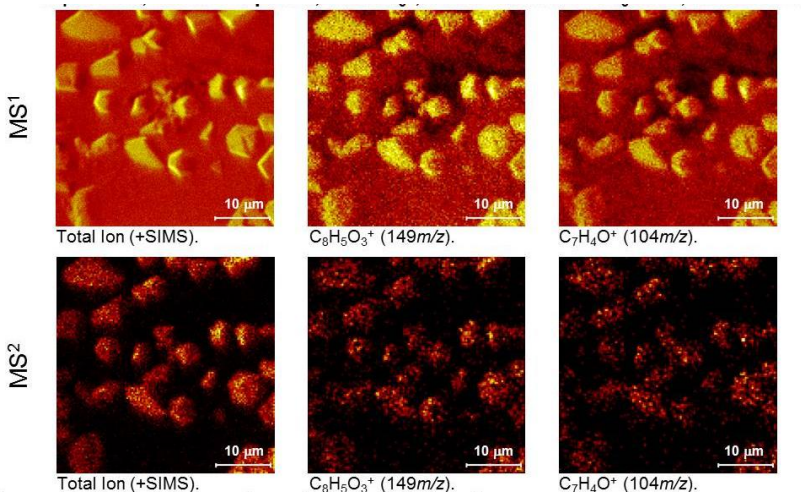

Figure 3. MS^1 images, and MS/MS images from positive polarity 577 m/z precursor ions, from heat treated PET

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