In Situ SIMS Analysis and Reactions of Surfaces Prepared by Soft Landing of Mass-Selected Cations and Anions Using an Ion Trap Mass Spectrometer

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Mass-selected polyatomic cations and anions, produced by electrosonic spray ionization (ESSI), were deposited onto polycrystalline Au or fluorinated self-assembled monolayer (FSAM) surfaces by soft landing (SL), using a rectilinear ion trap (RIT) mass spectrometer. Protonated and deprotonated molecules, as well as intact cations and anions generated from such molecules as peptides, inorganic catalysts, and fluorescent dyes, were soft-landed onto the surfaces. Analysis of the modified surfaces was performed in situ by Cs^+ secondary ion mass spectrometry (SIMS) using the same RIT mass analyzer to characterize the sputtered ions as that used to mass select the primary ions for SL. Soft-landing times as short as 30 s provided surfaces that yielded good quality SIMS spectra. Chemical reactions of the surfaces modified by SL were generated in an attached reaction chamber into which the surface was transferred under vacuum. For example, a surface on which protonated triethanolamine had been soft landed was silylated using vapor-phase chlorotrimethylsilane before being returned still under vacuum to the preparation chamber where SIMS analysis revealed the silyloxy functionalization. SL and vapor-phase reactions are complementary methods of surface modification and in situ surface analysis by SIMS is a simple way to characterize the products produced by either technique. (*J Am Soc Mass Spectrom* 2009, 20, 949–956) © 2009 American Society for Mass Spectrometry

Interactions of ions with surfaces play an important role in fundamental research relevant to disciplines such as materials science, microelectronics, and nanotechnologies, and in characterization and imaging methods based on mass spectrometry, electron spectroscopy, and laser spectroscopy [1, 2]. Controlled tailoring of chemical and physical properties by hyperthermal ion/surface collisions is integral to the preparation of specifically modified surfaces for biological research [3], the development of new heterogeneous catalysts [4], and fundamental understanding of the nature of ion/surface collisions [5]. Soft landing (SL)—the capture of intact polyatomic ions at a condensed phase interface—is a promising approach to the modification of surfaces in a controlled fashion [6], especially when the version of the process known as reactive landing (RL) is used; this involves chemical

reactions with the substrate, as illustrated most compellingly in recent work by Laskin et al. [3] on the binding of peptides to functionalized self-assembled monolayer (SAM) surfaces. It is normally assumed that the landed ion will retain its charge(s) but neutralization accompanying deposition/binding is also well known. Laskin has done much to elucidate the process of charge loss during and after the SL event [7]. The SL procedure not only alters the surface, but it also offers a new approach to preparative scale molecular separation and to molecular-level understanding of the interactions between molecules/ions and substrates relevant to biological, catalytic, and other applications [8, 9]. Since the introduction of the basic concept of SL [6], the method has been applied to small molecules, clusters, peptides, proteins, oligonucleotides, and even viruses, with deposition onto different substrates [10–15]. Although the first successful surface modification was reported in 1983 [16], applications aimed at on the preparation of unique surfaces are more recent [17–19]. SAMs provide a particularly convenient and flexible platform for creating materials with specific chemical properties and they have been used extensively for studying ion/surface collision phenomena, including SL experiments

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To Julia Laskin, in appreciation of her incisive contributions to mass spectrometry and especially ion/surface interactions.

[10, 20–22]. The past few years have seen new instrumental realizations of the SL process, as well as new discoveries in ion/surface interactions.

Among the newer instruments designed to implement SL, two of the more interesting have come from Pacific Northwest National Laboratory (PNNL). The first was a custom-built Fourier transform ion cyclotron resonance mass spectrometer (FT-ICR MS) in which a beam of mass-selected ions of variable kinetic energy was used to modify surfaces via SL [7]. In situ analysis of the modified surfaces was achieved by 2 keV Cs^+ secondary ion mass spectrometry (SIMS) with FT-ICR detection of the sputtered secondary ions (FT-ICR-SIMS). A second instrument used for SL experiments in this same laboratory consisted of an electrospray ionization (ESI) source, a quadrupole mass filter, a bending quadrupole, and a vacuum lock system for introducing surfaces into an ultra-high vacuum analysis chamber without breaking vacuum [23]. Laskin, Futrell, and colleagues recently reviewed the current understanding of the fundamental factors that affect SL of biomolecular ions onto inert and reactive SAMs [13]. SAMs are good substrates for SL because they can trap ions by dissipating kinetic energy and this was reflected in a dramatic increase in the ion yield in in situ SIMS analysis [7]. It is also interesting to note that a significant fraction of soft-landed peptide ions retain their charge, even after exposure of the surface to the ambient atmosphere, confirming a noteworthy earlier result [12]. This was demonstrated by ex situ time-of-flight (TOF)-SIMS analysis in the cases of SL on fluorinated and hydrogenated self-assembled monolayer (FSAM and HSAM, respectively) and COOH-SAM surfaces [25]. Peptide ions deposited onto these surfaces, with kinetic energies in the range 0 to 150 eV, retain at least one proton for long periods after deposition [26].

Applications of SL-modified surfaces are expected to be relevant to the development of novel biosensors and as substrates for improved molecular and even cellular adhesion [27, 28]. Covalent linkage of peptides to the solid substrate is an essential step in peptide adhesion experiments. Reactive SL [3] provides a new approach for efficient covalent linkage of peptide ions to *N*-hydroxysuccinimidyl ester terminated alkylthiol-SAM surfaces through the amino group in the lysine side chain. This method introduces exceptional selectivity and specificity into the surface preparation [5] and, by generating a covalent modification, ensures its chemical ruggedness. The efficiency of covalent immobilization of peptides was thoroughly investigated by considering factors such as charge state, nature of the reactive amino group, the collision energy of the projectile ion, and the properties of the SAM [24]. Very recently, Laskin et al. [8] further demonstrated, using SL, the preparation of conformationally selected peptide arrays, selecting a singly protonated Ac-A15K peptide as a model system. Infrared reflection absorption spectroscopy (IRRAS) confirmed the α -helical conformation of the soft-landed peptide. Previous surface-enhanced Raman spectroscopy (SERS) studies of soft-landed protein surfaces

proved that substantial biological functionality is retained in the hyperthermal collision event during SL [18]. Soft-landed biological or polyatomic organic molecules can be probed by fluorescent imaging, scanning electron microscopy, atomic force microscopy, and X-ray photoelectron spectroscopy (XPS) [5, 18, 29]. Clearly, controlled deposition of organic and biomolecular ions onto surfaces represents a new approach for obtaining molecular level understanding of the interactions of these molecules/ions with a variety of hydrophobic and hydrophilic substrates.

Recently, we reported the design and characterization of a relatively simple instrument, using a rectilinear ion trap (RIT) as mass analyzer, for the controlled deposition of mass-selected polyatomic ions [4]. The system included an elongated RIT (10 cm) preceded by a 90° bent-square (in rod cross section) quadrupole, the latter serving both as an ion transport system and, when needed, as an independent—albeit low-resolution—mass analyzer. Three methods of mass analysis have been implemented; (1) the bent-square quadrupole can be operated as a continuous radiofrequency (rf)/dc mass filter, (2) the RIT can be operated as a quadrupole mass filter in a continuous mass filtering mode [30], or (3) it can be operated as a standard quadrupole ion trap in the ion trapping mass-selective instability mode. This instrumentation was designed for high throughput and it provides a non-mass-selected ion current of more than 1 nA and mass-selected currents of up to 500 pA. In addition, a second earlier instrument, consisting of an ESI ion source, a linear ion trap mass analyzer, and a surface loading and positioning system, is being used for comparative SL studies [31]. Fascinating results—including the creation of prototype protein microarrays, chiral enrichment of octameric serine cluster ions, and purification of peptides—have been achieved using these instruments [12, 32–34].

Post-landing analysis of the soft-landed species must take into consideration the type of surface used, the material being analyzed, and the type of information sought. Analysis can be performed ex situ using various analytical methods after removing the substrate from the vacuum system. Ex situ methods available to investigate modified soft-landed surfaces include matrix-assisted laser desorption/ionization (MALDI) and nanoESI mass spectrometry [4, 18]. In these experiments, the material is rinsed off the surface for further analysis. On-surface ex situ investigations of soft-landed species can use SERS, fluorescence, and bioassays, as well as microscopic techniques [4, 18]. Other ex situ techniques also reported include IRRAS, temperature-programmed desorption (TPD), and SIMS [8, 34, 35]. During ex situ analysis, characterization of the landed material is performed after exposure of this surface to the ambient atmosphere. In situ analysis has many advantages: the landed sample can be analyzed without exposure to air, the surface species is in its original environment, and the surface concentration is unaffected.

In this study, in situ analysis of modified soft-landed surfaces using a custom-built RIT-SIMS instrument is implemented. The modified surfaces were probed by 2–9 keV Cs^+ primary ions and the secondary ions so formed were directed into the same RIT mass analyzer used to analyze the primary ion beam before SL. The new in situ SIMS capability provides an opportunity for rapid characterization of modified surfaces and eliminates possible contamination and signal loss associated with ex situ analysis. The resulting instrument is a simple high-throughput device. Successful cationic and anionic SL and chemical modifications of the modified surface are reported.

Experimental

Instrumentation

A new SIMS probe and reaction chamber were added to a custom-built and previously described [4] SL instrument (Figure 1). A syringe pump was used for direct infusion of the sample at a flow rate of $2 \mu\text{L}/\text{min}$ into an electrosonic spray ionization (ESSI) source. Efficient transmission of ions into the vacuum system was achieved using an electrodynamic ion funnel [36–38]. After emerging from the ion funnel, ions are transmitted through a bent-square quadrupole operated in the rf-only mode; they are turned through 90° to avoid contamination of the landing surface by neutral species

emerging from the ion source. Ions guided by the bent quadrupole pass through a skimmer and then into an electrostatic ion guide consisting of a set of three tube lenses. After exiting the last tube lens, ions are directed into the RIT mass analyzer. This is operated in the usual mass selective instability mode, with orthogonal electron multiplier detection, when recording a mass spectrum (the API mode in Figure 1). Alternatively, during the SL phase of the experiment (Figure 1d), the RIT is operated as a mass filter [30] with a constant rf voltage and using rf/dc mass-selective transmission (SL mode, Figure 1). When performing SL, the emerging ion beam is further focused by another set of electrostatic ion lenses before reaching the landing surface. The last tube lens behind the RIT electrostatic ion guide is mounted onto the RIT assembly and the front and back endcap electrodes of the RIT as well as the trap itself are grounded. The collision energy of the ions was selected by changing the dc offset applied to the bent quadrupole. The vacuum in the soft-landing region was 5.0×10^{-6} Torr.

Ion Kinetic Energy, Operating Conditions, and the Reaction Chamber

The kinetic energy of the ions was measured using the retarding potential method by systematically varying the potential on the surface and monitoring the ion

Figure 1. (a) Schematic of the RIT-SL-SIMS mass spectrometer used for SL experiments. (b) Schematic showing SL chamber and reaction chamber. Time sequence used for (c) atmospheric pressure ionization (API) mode; (d) SL mode; (e) SIMS analysis mode. Abbreviations: t1, ion injection time; t2, ion isolation time; t3, ion cooling time; t4, ion ejection time.

current. When the potential applied to the bent quadrupole was 5 V, the ion kinetic energy peaked at 4 eV with a full width at half-maximum (FWHM) of 1 eV. When the bent quadrupole voltage is set to 15 V, the ion kinetic energy maximum was 12 eV with FWHM of 4 eV, a broader distribution of kinetic energies of the landed ions compared to the 5 V distribution. The magnitudes and distributions of ion kinetic energies are affected by ionic collisions with background gas in the bent quadrupole. Unless otherwise specified, the following experiments used the 5 V applied potential for a nominal 4 eV SL collision energy. The SL spot size was measured as about 4 mm² by direct optical imaging of the surface after SL.

Figure 1d shows the experimental timing sequence used to achieve mass-selected SL; the dc offset of the RIT was kept at 0 V throughout the experiment. The potentials on dc_x (dc bias potential applied to the x electrode) and dc_y (dc bias potential applied to the y electrode) were opposite in sign and the absolute value of dc_x was higher by 5 V than that of dc_y . The time sequence used in the SIMS experiments is given in Figure 1e. The potentials on the tube lens were adjusted to optimize the SIMS signal. During operation in the SIMS mode, the front endcap of the RIT was kept at +30 V, whereas the back endcap were kept at +3 V. Identical voltages but with the opposite signs were applied to the endcap electrodes when mass spectra were recorded using the mass-selective instability ion scan rather than the rf/dc mass-selective stability experiment used during ion SL.

The instrument was modified by attaching an additional reaction chamber directly to the main vacuum chamber and connecting the two chambers by an isolation valve. A simple mechanical transport system was used to move the sample linearly from the main chamber, where SL occurred, into the reaction chamber. This arrangement allowed the soft-landed surface to be examined before and after being subjected to chemical reactions without exposure to the ambient atmosphere. To prepare a soft-landed surface for in situ reaction, a 1.0×10^{-4} M triethanolamine solution in 49/49/2 methanol/H₂O/HOAc was electrosprayed at a rate of 2 μ L/min and mass-selected ions were soft-landed onto a cleaned Au surface for 1 h. The modified surface was then transferred to a reaction chamber (~ 0.5 L) by a magnetically controlled rod. A glass tube with 100 μ L chlorotrimethylsilane was connected to the gas line through a leak valve and the gas line connected to the reaction chamber. When the leak valve was opened, the chlorotrimethylsilane was vaporized by adiabatic expansion, and the chlorotrimethylsilane vapor was introduced into the chamber via a leak valve. The typical vapor pressure of reaction was about 5 Torr and the gas exposure continued for 1 h. After this, the substrate was retracted into the main chamber for SIMS analysis.

In Situ Analysis of Modified Surfaces

Primary Cs⁺ ions, generated from a Cs⁺ gun (HeatWave Labs, Inc., Watsonville, CA, USA), were accelerated through an 8-mm-diameter hole in the last element of the tube lens, directed at 45° incident angle, and allowed to collide with the landing surface held in its original position. Static SIMS conditions (total ion flux of $\sim 6.2 \times 10^{10}$ ions/cm², current 5 nA, spot size 0.5 cm²) were achieved when the following potentials were applied to various focusing elements: Cs⁺ gun floating voltage, +5 kV; Cs⁺ ion gun shield, +4900 V. Data acquisition was accomplished using a Finnigan LCQ data station (Thermo Fisher Scientific, Pittsburgh, PA, USA). The modified surface was subjected to in situ SIMS analysis after various landing times.

Materials

Gold-coated silicon wafers were purchased from International Wafer Service, Inc. (Colfax, CA, USA). Both FSAM and bare Au surfaces were used as SL targets. The FSAM on Au surface was prepared using reported procedures by exposing the Au surface for 24–36 h to perfluorodecanethiol (Sigma–Aldrich, St. Louis, MO, USA) in ethanol solution [10]. The surface was then removed from the ethanol solution, ultrasonically washed in ethanol for 5 min, and dried under nitrogen gas before being introduced into the SL instrument. Rhodamine B, Jacobsen's catalyst (*N,N'*-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanedi-*amino*manganese(III)chloride), the tetrapeptide Met-Leu-Phe-Ala (MLFA), chlorotrimethylsilane, and triethanolamine were all purchased from Sigma–Aldrich and used as received. Using a Milli-Q water purification instrument (Millipore Corp., Billerica, MA, USA), deionized water was purified to 18 m Ω . All other solvents was purchased from Sigma–Aldrich and used without purification.

Results and Discussion

To test the performance of the modified instrumentation, we chose to soft land a fluorescent dye, Rhodamine B, onto a polycrystalline Au surface. For the SL experiment, a 1.0×10^{-5} M solution of Rhodamine B in 49/49/2 methanol/H₂O/HOAc solvent was electrosprayed at 2 μ L/min and landed at nominal 4 eV kinetic energy onto the polycrystalline gold substrate. The ion current after mass selection was about 150 pA. Figure 2a shows the SIMS mass spectrum of the surface recorded after SL of the Rhodamine B cation at 4 eV kinetic energy for 30 min. Prominent fragment ions included those at m/z 399 (loss of CO₂), 355 (loss of C₂H₆N from m/z of 399), and the sequential fragment ions at m/z 326 (loss of C₂H₅) and 282. The same set of ions that occurs in the SIMS spectrum of the soft-landed surface also occurs in the ESI MS/MS spectrum of Rhodamine B recorded using a commercial LTQ linear ion trap mass spectrometer (Thermo Fisher Scientific). The analogous

Figure 2. SIMS spectra (Cs^+ ions 5 keV) after SL for 30 min onto an Au surface (a) Rhodamine B (m/z 443) in positive-ion mode (b) sodium dodecylbenzenesulfonate (m/z 325) in negative-ion mode.

mass spectra from SIMS and direct ESI MS/MS confirm the successful soft landing of intact Rhodamine B onto the Au surface, and demonstrate the capability of SIMS for in situ characterization of soft-landed surfaces.

The in situ analysis and SL capabilities of the modified instrumentation were tested in the negative-ion mode by mass selecting and SL the anion of sodium dodecylbenzenesulfonate (m/z 325) onto an FSAM surface for 10 min at 4 eV kinetic energy. In this experiment, a 1.0×10^{-4} M solution in 50/50 methanol/ H_2O was ionized by ESSI, using a sample solution flow rate of $2 \mu\text{L}/\text{min}$. In this case, the ion current after mass selection was about 200 pA. The negative-ion SIMS spectrum of the landed surface was recorded by reversing the polarity of the lens voltages. Figure 2b is a typical negative-ion mode SIMS spectrum of the modified surface. The intact molecular anion represents the major organic peak. Other prominent ions are the Au and Au_2 dimer anions.

To test the performance of the SL and in situ analysis system for collection of biomolecule ions, we chose the tetrapeptide MLFA as a model compound. A solution (1.0×10^{-4} M) of the peptide in 49/49/2 methanol/ $\text{H}_2\text{O}/\text{HOAc}$ was electrosprayed at a rate of $2 \mu\text{L}/\text{min}$. Figure 3a shows SIMS spectra obtained before and after deposition of 150 pA of the singly protonated peptide (m/z 481) onto an FSAM surface for 30 min. In addition to common FSAM-related peaks, the SIMS spectrum of the modified surface displays a single-fragment ion because of protonated LFA (m/z 330), together with Cs^+

(m/z 133) and Au^+ (m/z 197) signals. Interestingly, no $[\text{MLFA} + \text{H}]^+$ was detected in this spectrum or the SIMS spectrum of the pure peptide on gold. To determine whether this dissociation could be avoided using different SIMS conditions, evolution of the mass spectrum was followed as a function of the Cs^+ acceleration voltage in a series of SL experiments. Using a voltage of just 1 kV, the only significant peaks were those attributed to Cs^+ and Au^+ ; other clusters occurred in lower intensity. With increasing accelerating voltage, the intensity of the Au^+ signal increased and the LFA fragment had significant intensity. The peptide fragment signal was at optimum at an accelerating voltage of 5 kV. With further increases in the Cs^+ ion energy, neither secondary ion intensity nor resolution was improved further.

It is known that charge retention and neutralization during the SL process show different behaviors on FSAM and bare Au surfaces [26]. These effects were examined further by landing Jacobsen's catalyst on the two surfaces. Corresponding data are given in Figure 4 for SL 1.8×10^{-5} M solution of the catalyst in 49/49/2 methanol/ $\text{H}_2\text{O}/\text{HOAc}$ onto FSAM and onto a bare Au surface using ESSI ionization in both cases. The landing current was around 150 pA. For both surfaces, the intensity of SIMS secondary ions increased rapidly at the early stages of SL and reached saturation after 30 min. In their work on protonated ion of Gramicidin S, Laskin and colleagues demonstrated similar behavior [39]. The signal did not reach saturation in their exper-

Figure 3. SIMS after soft-landing of protonated peptide MLFA (m/z 481) onto FSAM surface for 30 min using Cs^+ ion kinetic energies (a) 2 keV and (b) 9 keV.

Figure 4. Ion intensity versus time of soft landing of Jacobsen's catalyst onto bare Au and FSAM surfaces. Inset: Cs^+ SIMS spectrum of Au surface after SL of Jacobsen's catalyst (m/z 600) for 30 s.

iments because the SL ion current (~ 16 pA) was an order of magnitude lower than that used here. It should be noted that the two curves in Figure 4 are different. During the first few minutes, the ion intensity recorded from the FSAM was higher than that recorded at the Au surface; a few minutes later, the ion intensity reaching the Au surface was greater. The saturation intensity for the Au surface is a little higher than that on the FSAM surface. The difference is tentatively attributed to higher charge retention on the FSAM. We speculate that at the beginning of the SL process, ions are more easily landed and the charge is retained on the FSAM surface as the result of its insulating and hydrophobic nature. After a certain time, the degree of charge accumulation on the FSAM surface is such that incoming ions are less likely to be successfully landed compared to those arriving at the Au surface. The lower saturated ion intensity on the FSAM can also be attributed to better charge retention.

In our previous experiments [4], the soft-landed material was analyzed by nanoESI or desorption electrospray ionization mass spectrometry (DESI-MS) after being rinsed off of the surface. Good signal-to-noise ratios were recorded only when the landing time was at least 1 h. In a welcome contrast, *in situ* SIMS analysis provides spectra with good signal-to-noise ratios even

after 30 s landing time with 150 pA ion currents (Figure 4). This result arises from the extremely high sensitivity of *in situ* SIMS analysis coupled with the absence of sample dilution and loss during its removal and *ex situ* analysis.

Heterogeneous chemical reactions of the soft-landed surface represent a promising approach to effect further surface modification. In pursuit of this goal, silylation was carried out using vapor-phase chlorotrimethylsilane on a bare Au surface previously soft landed with protonated triethanolamine (see Scheme 1).

The entire process of soft-landing, SIMS verification of SL, heterogeneous phase reaction, and SIMS verification of the final product was conducted *in situ*. The landing current of protonated triethanolamine (m/z 150) was about 150 pA. The exposed surface area was about 4 mm² and the total ion dose was 3.4×10^{12} ions, corresponding to an ion flux of around 8.5×10^{11} ions/mm². One expects a saturated surface coverage of 1.0×10^{12} molecules/mm², assuming a molecular size of 1 nm. Figure 5 shows the SIMS spectra of the triethanolamine-modified Au surface before and after the silylation reaction. The peak at m/z of 150, before silylation, corresponds to the singly protonated ethanolamine cation. A major new peak occurs at m/z of 366 in the spectrum recorded after silylation; the mass of this ion, together with its isotopic distribution, confirms it as $\text{HN}^+[\text{C}_2\text{H}_4\text{OSi}(\text{CH}_3)_3]_3$. This indicates that all three hydroxyl groups reacted with chlorotrimethylsilane and that reaction was complete almost instantaneously. It can be also noted that the product ion intensity (m/z 366) is several times higher than that of the reactant ion (m/z 150), suggesting that the silylated product is much easier to re-ionize and release from the surface than the reactant triethanolamine during SIMS analysis. This is likely attributable to the weaker forces binding the molecule to the surface.

Conclusion

In this study, we have described a simple and convenient SIMS system that allows *in situ* analysis of modified surfaces after mass-selective deposition of particular ions. The same mass analyzer is used for both the SL and SIMS phases of the experiments. Detailed investigations on various modified surfaces reveal intriguing differences in charge retention at different surfaces. The

Scheme 1. Reaction of triethanolamine with chlorotrimethylsilane showing m/z values of ions examined.

Figure 5. SIMS spectra of (a) Au surface modified by SL of mass-selected triethanolamine cation (m/z 150) and (b) the modified surface after reaction with chlorotrimethylsilane vapor for 1 h to give the tris(trimethylsilyl) derivative (m/z 366); M is $\text{HN}^+[\text{C}_2\text{H}_4\text{OSi}(\text{CH}_3)_3]_3$.

ability to chemically modify the soft-landed surface in situ is demonstrated with a simple silylation of deposited triethanolamine. These studies and this new instrumentation could be an additional gateway to detailed investigations of the factors that uniquely affect ion/surface interactions in the cases of catalysis or biological applications. Future work will focus on generation and landing of catalytic-active inorganic species and on continued studies of charge retention at the surface. Modified surfaces will continue to be analyzed ex situ using various surface analytical methods, including XPS, Raman spectroscopy, and DESI-MS, as a complement to the internal examination by SIMS and heterogeneous reactivity.

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