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SHORT COMMUNICATION

Ultra-High Resolution Elemental/Isotopic Mass Spectrometry (m/Δm > 1,000,000): Coupling of the Liquid Sampling-Atmospheric Pressure Glow Discharge with an Orbitrap Mass Spectrometer for Applications in Biological Chemistry and Environmental Analysis

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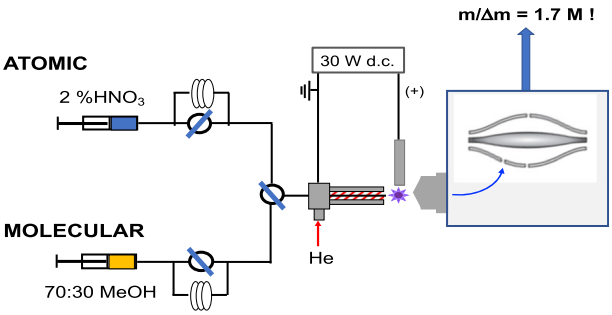

Abstract. Many fundamental questions of astrophysics, biochemistry, and geology rely on the ability to accurately and precisely measure the mass and abundance of isotopes. Taken a step further, the capacity to perform such measurements on intact molecules provides insights into processes in diverse biological systems. Described here is the coupling of a combined atomic and molecular (CAM) ionization source, the liquid sampling-atmospheric pressure glow discharge (LS-APGD) microplasma, with a commercially available ThermoScientific Fusion Lumos mass spectrometer. Demonstrated for the first time is the ionization and isotopically resolved fingerprinting of a long-postulated, but never mass-spectrometrically observed, bi-metallic complex Hg:Se-cysteine. Such a complex has been implicated as having a role in observations of Hg detoxification by selenoproteins/amino acids. Demonstrated as well is the ability to mass spectrometrically-resolve the geochronologically important isobaric ^{87}Sr and ^{87}Rb species (Δm ~ 0.3 mDa, mass resolution m/Δm ≈ 1,700,000). The mass difference in this case reflects the beta-decay of the ^{87}Rb to the stable Sr isotope. These two demonstrations highlight what may be a significant change in bioinorganic and atomic mass spectrometry, with impact expected across a broad spectrum of the physical, biological, and geological sciences.

Keywords: High resolution, Microplasma, Orbitrap, Isotope analysis, Metallobiochemistry, Mercury:selenoamino acid

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Introduction

The need to assess the isotopic composition of materials touches many fields of basic and applied sciences. Questions of the origins of the universe, atomic physics, geochronology, metabolism, nuclear forensics, and nutrition are just a few of the areas where the ability to determine or monitor isotopic compositions are of relevance. Mass spectrometry of one form or another is the method of choice for the determination of stable and long-lived radioisotopes. Methods to determine isotopic composition lie in the realm of atomic mass spectrometry, wherein the ultimate function of the ionization source is to produce monoatomic ions, usually to the exclusion

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of latent molecular information. Thermal ionization mass spectrometry (TIMS) and inductively coupled plasma mass spectrometry (ICP-MS) are the standard bearers in this genre.

Elemental signatures (usually metals) are becoming increasingly relevant as the roles of metals in biochemical and environmental systems become more evident. Herein lies the continuously expanding area of metallomics. The efficacy of a metal in any biological system, or its transport in the environment, is dictated by its chemical form. In this regard, it is not sufficient to identify the presence of a metal in a specimen, but more significant is the identification of its molecular form. Electrospray ionization (ESI) has been a workhorse in the ability to produce intact molecular species; so long as the chemistry of the entity is amenable to its ionization in a suitable solution phase.

In order to make maximum use of high-performance mass spectrometry platforms, ionization sources which are operationally compatible with the MS, while also capable of affecting the desired ionization functions, are required. The focus of the present communication is the demonstration of the use of a singular, combined atomic and molecular (CAM) ionization source, coupled to an ultrahigh resolution ThermoScientific Orbitrap Fusion Lumos 1 M mass analyzer towards important problems in bioinorganic chemistry and geochronology; the identification of an intact mercury:seleno amino acid complex and the direct mass spectrometric resolution of ^{87}Sr and ^{87}Rb. Both of these demonstrations are believed to be the first of their kind. Specifically, the liquid sampling-atmospheric pressure glow discharge (LS-APGD) microplasma [1, 2] is employed to efficiently ionize atomic species as well as organometallics, without changing the ionization source. The LS-APGD has previously been shown to provide very high precision measurements of uranium isotope ratios [3, 4], while also having the capability to ionize diverse organic species [5], from small molecules to proteins. The different "atomic" and "molecular" operation modes are affected by a simple change in delivery solvent (solution electrolyte), 5% HNO_3 in the former case, and 70:30 methanol:water in the latter. This differential level of information has been demonstrated explicitly for the case of uranyl acetate, where operation in nitric acid yields a spectrum dominated by U^+ and UO^+, with very minor amounts acetate-related species while the mixed solvent yields almost exclusively the ligated uranium [6]. Operation under mixed-solvent ($MeOH:H_2O$) conditions appears to yield a plasma with lower kinetic temperatures, producing spectra that are comparable to atmospheric pressure chemical ionization (APCI), composed predominately of protonated psuedomolecular ions $(M+H)^+$. Likewise, injections of caffeine (for example) under the acidic electrolyte case result in very low intensity, structurally complex spectra [5], reflecting a more kinetically energetic environment.

At present, the device has been coupled to over one-half dozen MS platforms; all of which were equipped with standard ESI interfaces. The Orbitrap Fusion Lumos 1M analyzer platform is designed to provide ultrahigh mass resolution ($m/\Delta m \approx$ 1,000,000 @ m/z = 200) in conjunction with ESI ionization towards applications in proteomics. The coupling of the CAM ion source with the Orbitrap Lumos provides unique capabilities in terms of diversity of analytes, ultrahigh mass resolution, and high precision isotopic analysis. The two demonstrations here highlight what may be a step function change in atomic and bioinorganic mass spectrometry, with impact expected across a broad spectrum of the physical, biological, and geological sciences.

Experimental

While the previous reports of the coupling of the LS-APGD to Orbitrap platforms have used essentially the same breadboard-based ion source assembly [3, 4], we employed here an ion volume cube (constructed from aluminum) to mount on the Fusion Lumos, along with a new, integrated utility control box. The combined atomic and molecular (CAM) microplasma is struck (10–40 mA; 100–1000 V d.c.) between the surface of the electrolytic solution containing the analyte solutes and a stainless steel counter electrode. The gap between the two electrodes is controlled with an adjustable micrometer, with the distance between the solution electrode and the entrance to the ion transfer capillary fixed at 0.5 cm. A helium sheath gas (0.2–0.5 L min^{-1}) surrounds the capillary delivering the test solution at flow rates of 10–30 μL min^{-1}. The sole difference in the operation of the CAM ionization source between the atomic and molecular implementations is that the former operating with 2%HNO_3 as the carrier (electrolyte) solution and the latter with a 70:30 mixture of methanol:water. With the microplasma operating in the constant-current mode, there was no discernible difference in maintenance voltage in changing between these solvents.

The ThermoScientific (San Jose, CA) Orbitrap Fusion Lumos 1M instrument was operated without any modifications [7], other than the replacement of the as-delivered ESI source cube with that of the LS-APGD. Beyond a much higher resolution rating, the Lumos has added functionality beyond the previous Exactive-series instruments, including higher-order collisional activation regions, which are not employed here. In these experiments, in-source collisional dissociation was implemented as a means of removing loosely bound solvent molecules, while high energy collisional dissociation (HCD) was employed for further activation prior to mass analysis in the Orbitrap cell. The overall Lumos operation was controlled under the TUNE functionality and data acquisition in the Excalibur environment. The specific operational parameters of the MS are provided with the figure captions.

Results and Discussion

Application of the CAM Source:Orbitrap Combination in Biological Chemistry

One of the primary drivers in the development of the CAM source is the potential for affecting both molecular and elemental/isotopic analyses with the same device. Previous efforts using the LS-APGD have demonstrated the concept for small organic molecules, polymers, and proteins [5]. Given the importance of metal-containing molecules in biochemistry, any progress in that direction across mass spectrometry is warranted. Mercury, particularly in the form of methyl mercury ($HgCH_3$) causes severe neurological illness in mammalian systems [8]. The concept of selenium detoxification of Hg in biological systems has been known, studied, and debated for over 50 years [9]. Since that time, a wide variety of biological, chemical, and ecological studies have indeed shown the chemical efficacious relationships across many forms of selenium [10–12]. With respect to biological systems, the formation of an Hg:Se amino acid (AA)/protein complex is not difficult to rationalize, by extension, as the affinity between sulfur and mercury is very high, inclusive of the sulfur-containing amino acids. In fact, computations have shown very clearly that the affinity of selenium for mercury is ~ 10^6× higher [12]. As such, while the fraction of sulfur-containing amino acids/proteins is far greater than the corresponding selenium forms, the degree of complexation of mercury with those species becomes the dominant avenue for detoxification. A number of mechanistic pathways have been proposed involving Se-AAs and Se-proteins [10, 11]. Ultimately, the formation of Hg-Se bi-metallic nanoparticles have been identified in some species [13, 14].

The analytical (i.e., instrumental) methods which have been used to implicate the existence of Hg:Se-AA/protein complexes has been recently reviewed by Krupp and co-workers [14]. The primary tools for assessing the association of Hg and Se-AA/proteins are gas or liquid chromatography, wherein changes in retention times and/or loss or gain of eluting species are noted as a function of the addition of $HgCH_3$ to model or living systems. Association of the two metals is suggested by the coupling of separation methods with ICP-MS, wherein both elements are seen to elute in the same chromatographic fractions. The proximity of Hg and Se in complexes has been implied by X-ray absorption methods (XANES and EXAFS). Nuclear magnetic resonance (NMR) has been employed to suggest the potential formation of an Hg:Se-AA intermediate by the shifting of the ^{199}Hg signature [15]. The complexation of Hg with S-containing amino acids and peptides has been confirmed through ESI-MS by a number of research groups to reveal the anticipated products [16, 17]. While a number of experiments involving ESI-MS detection have included the relevant Hg:Se-AA/peptide reactants, it does not appear that the intact complex is ionizable and/or remains intact under those conditions.

The capability of the CAM-Orbitrap combination to directly observe the long-postulated Hg:Se-cysteine complex was assessed by mixing equimolar amounts of methyl mercury (MeHg) and selenocysteine (Se-Cys) in the presence of the reducing agent dithiothreito, l and a 2% HNO_3 final diluent, with the mixture having a final molar concentration of ~ 3.3×10^{-6} M of each of the reactants. In this case, the use of acid as the final diluent was necessary for stability of the complex and enabled its observation. The mass spectrum presented in Fig. 1a indeed confirms the existence of a stable complex/molecule, with each of the ions observed having the molecular formula of Hg:Se-Cys with an added proton (H^+). A comparison of the Hg:Se isotopic distribution (Fig. 1b) shows good agreement with natural abundance ratios. It is believed that this is the first direct mass spectrometric evidence of a mercury:selenoamino acid complex. The level of agreement here is quite acceptable given the spectrum acquisition conditions employed, which are far less comprehensive (fewer microscan/scans) than used in previous isotope ratio determinations [3]. Importantly, and as expected, the spectra reflect the fact that the methyl group is lost from the Hg upon complexation with Se-Cys. It is this species that is implicated as the active agent in mercury neurotoxicity. The high level of efficiency of the reaction is demonstrated by the lack of any Hg and minor (but observable) level of SeCys (~ 15% relative to the complex), reactants in the spectrum.

The scale expansion in Fig. 1, revealing the nominally isobaric ^{202}Hg^{82}Se and ^{204}Hg^{80}Se pair ($m/\Delta m \approx 700{,}000$), demonstrates the high resolving power of the Fusion Lumos instrument, as a complete finger print of the expected isotopic combinations are seen. Indeed, the mass resolution is sufficient to also quantify the isotopic composition inclusive of the hydrogen, carbon, nitrogen, and oxygen components of the cysteine. While this level of mass resolution could prove invaluable across many areas, the same CAM ionization source experiment performed on a lesser-resolution instrument could allow the solving of many problems based simply on unit mass-resolved isotopic patterns.

Application of the CAM Source:Orbitrap Combination in Environmental Elemental/Isotopic Analysis

The isobaric Sr:Rb pair is one of the most broadly applied systems in geochronology, finding applications not only in geological dating, but also studies of human migration and food nutrition/provenance [18]. The basis of the dating method comes from the beta-decay of ^{87}Rb ($t_{1/2} \approx 4.9 \times 10^{10}$ year) which forms the radiogenic ^{87}Sr isotope whose concentration is given by

$$^{87}\mathrm{Sr} = {}^{87}\mathrm{Sr}_0 + {}^{87}\mathrm{Rb}_0 - {}^{87}\mathrm{Rb}_0 e^{-\lambda t} \quad (1)$$

where ^{87}Sr$_0$ and ^{87}Rb$_0$ represent the primordial isotope levels, and λ is the decay constant of 1.42×10^{11} year^{-1}. The long half-life of the Rb species makes it an attractive chronometric marker, but by the same token makes it very difficult to quantify the emitted β-particles with high efficiency. As such, the chronometric measurement is derived from the isotope ratio of ^{86}Sr and ^{87}Sr, the first being stable and the latter

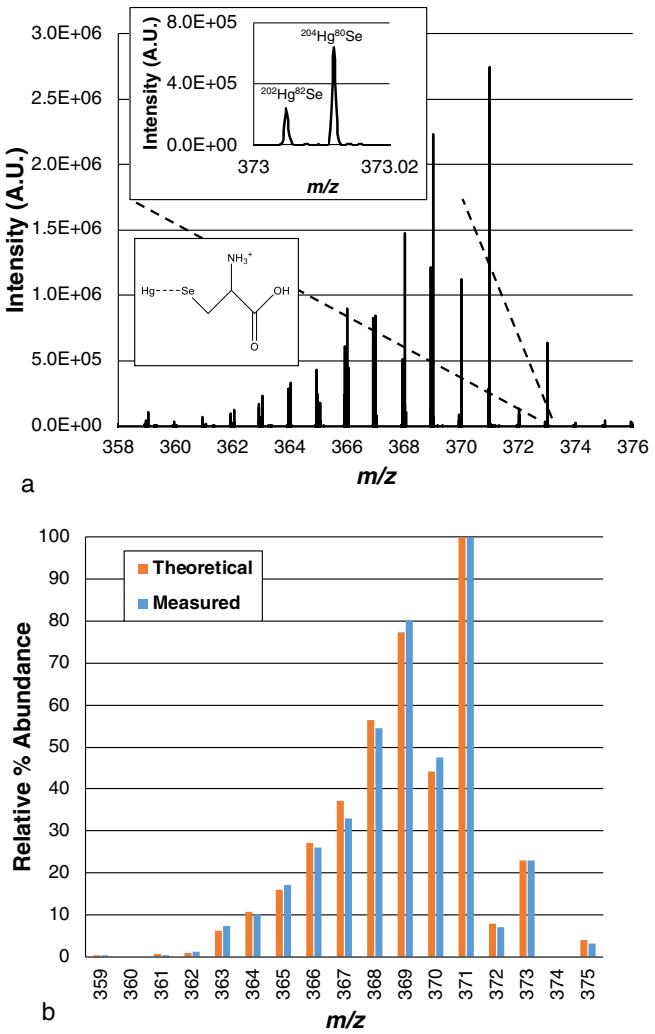

Figure 1. (**a**) LS-APGD mass spectrum obtained on an Orbitrap Fusion Lumos instrument and (**b**) plot of the theoretical and measured isotope patterns for Hg-SeMet. The theoretical pattern was generated using the Thermo Tune Software. Reactant concentrations: $[HgCH_3] = [Se\text{-}Cys] = \sim 3.3 \times 10^{-6}$ M. Solution (70:30 methanol:water) flow rate = 30 mL min^{-1}, He sheath gas flow rate = 0.5 L min^{-1}, and discharge current = 30 mA. MS acquisition parameters: resolution = 1 M @ mass 200, average of 10 scans of 10 microscans each. Solution preparation, 50 mg of dithiothreitol (as a reducing agent) into 2 mL of a 525 μg mL^{-1} (as Se) selenocystine in order to form selenocysteine. 20 μL of the Se-Cys solution was mixed with 80 μL of a 328 μg mL^{-1} (as Hg) monomethylmercury solution. The product solution was diluted 20× in 2% HNO_3 before analysis

being a measure of the primordial concentration and contributions due to Rb decay. A number of excellent reviews exist describing the use of $^{87}Sr/^{86}Sr$ isotope ratio measurements for chronometry across diverse disciplines [18–20]. The utility of the approach lies in the +2 valency of Sr, making it a valuable tracer in terms of uptake in bones, teeth, minerals, and plant materials.

While the rationale for applying Sr isotope measurements to achieve dating through the relationship with ^{87}Rb β-decay is sound, the measurement is challenged by the presence of remnant Rb. Specifically, the mass difference between the product ^{87}Sr and the parent ^{87}Rb is ~ 0.3 mDa (86.908877 vs. 86.909180 Da) [21], requiring a minimum mass spectrometric resolving power ($R = m/\Delta m$) of ~ 290,000; a factor of 30 greater than TIMS/ICP-MS instruments. Thus, the presence of background Rb in the mass spectrum from any source will positively bias the determined $^{87}Sr/^{86}Sr$ values. Many chemical approaches have been employed to deplete Rb from the desired Sr, usually via ion exchange chromatography [20]. Given the desire to measure the $^{87}Sr/^{86}Sr$ with accuracies and precision on the level of 0.01%, this could require extensive processing as the two elements are very commonly found together. Other approaches include the use of performing a mathematical correction based on an accurate determination of the total Rb. The most promising means of alleviating the Rb isobaric interference has been demonstrated by Vanhaeck and co-workers in a series of studies [22], wherein an ICP ionization source, coupled to multi-quadrupole mass spectrometers. Introduction of CH_3F as the reaction gas causes gas-phase Sr ions to form SrF^+ species with high efficiency.

The current, secondary measurement of $^{87}Sr/^{86}Sr$ as a reflection of ^{87}Rb, faces many challenges and relies on a number of inferences. Ideally, one could measure directly the $^{87}Sr/^{87}Rb$ ratio in the same experiment. Figure 2 presents the mass spectrum obtained from this unique coupling, yielding a completely resolved isotopic pair, with a calculated mass resolving power of ~ 1.7 M; a value not reported to date in the literature for any atomic mass spectrum. Significantly, the spectrum demonstrates complete resolution for a case where a lower mass resolution would yield an $^{87}Sr/^{86}Sr$ ratio in error by + 100% on a standard TIMS or ICP-MS mass spectrometer. A significant aspect of the microplasma approach is the fact that the total sample volume consumed in the acquisition of this spectrum is < 2 μL. Of note is a very low intensity satellite peak ~ 0.17 mDa higher than the ^{87}Rb isotope. This feature occurs for all Sr and Rb peaks in the spectrum, and was seen in earlier ICP-Orbitrap work [23] as well. At this point, there is no physical explanation for these features and it remains under investigation. Clearly, much work remains in elucidating the role of the relative isotopic signals on the ability to affect complete mass resolution of the two isotopes. Importantly, while there are means of chemically resolving Rb and Sr species in solution, they are not applicable in direct-solids analysis such as when laser ablation sampling is applied [24]. The present method is applicable in that instance, and indeed the LS-APGD has been employed as a secondary ionization when coupled to laser ablation sampling [2].

Conclusions

An effective mass spectrometry experiment requires the matching of an ionization ource capable of producing ions that accurately represent the analyte(s) of interests and a mass spectrometer having the sensitivity, functionality, and

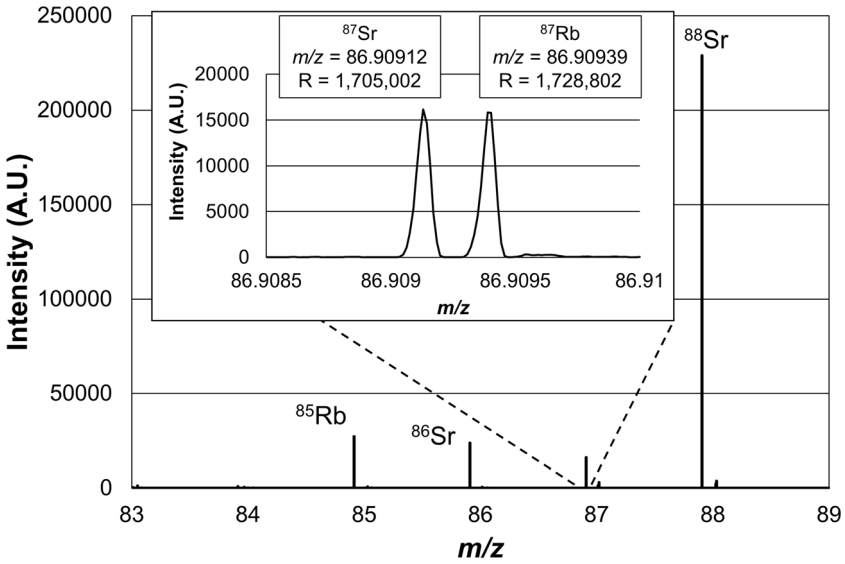

Figure 2. LS-APGD mass spectrum obtained on an Orbitrap Fusion Lumos instrument. [Rb] = 6 ng mL^{-1} (from $RbNO_3$) and [Sr] = 70 ng mL^{-1} (from $SrCO_3$) in 2% HNO_3. Solution flow rate = 30 µL min^{-1}, He sheath gas flow rate = 0.5 L min^{-1}, and discharge current = 30 mA. MS acquisition parameters: resolution = 1 M @ mass 200, average of 100 scans of 10 microscans each

resolution to glean the desired level of information. Described here was the coupling of a combined atomic and molecular (CAM) ionization source with a commercial mass spectrometer, the ThermoScientific Orbitrap Fusion Lumos, having the ultimate in mass resolution and MS functionality. Specifically, the liquid sampling-atmospheric pressure glow discharge (LS-APGD) microplasma is shown to be able to provide atomic mass spectra as desired for elemental/isotopic analysis, while also having the capability to ionize molecular species of biological relevance. The LS-APGD mounts to the mass spectrometer in place of its conventional ESI source, without modifications. The unique capabilities of these two components are demonstrated against what are well-document challenges in biological chemistry and elemental/isotopic analysis. The ability of the same source to effectively ionize the long-postulated Hg:Se-Cys illustrates a level of versatility that is quite remarkable. The mass resolving power of the commercial Orbitrap is specified as $m/\Delta m = 1{,}000{,}000$ at $m/z = 200$ Da, with a resolution of $> 1{,}700{,}000$ achieved for the ^{87}Sr:^{87}Rb pair; representing the loss of a beta particle. This level of resolution holds the possibility of alleviating much of the sample preparation (separation science) required forms of elemental/isotopic analysis. This capability complements the other LS-APGD/Orbitrap isotope ratio characteristics in comparison to commonly accepted methods [4], including very small sample volumes. Clearly, much work remains in extracting the ultimate information for these two chemical systems, but it is believed that this pairing has the potential to have pronounced impact across many areas of basic science.

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