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Could Microplasma Ionization and Ultra-high Mass Resolution Alleviate Chemical Separations for Elemental and Isotopic Analysis?

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Abstract: At the extremes, all analytical spectrometric measurements are limited by the resolution of the spectrometer system. Spectral overlaps, isobars in the case of mass spectrometry, can lead to the implementation of complex and time-consuming chemical separations to alleviate those interferences. In the area of elemental/isotopic mass spectrometry, use of sector-field instruments can provide a mass resolution of ~10,000, but still necessitate chemical separations. Described here is the coupling of the liquid sampling-atmospheric pressure glow discharge (LS-APGD) microplasma to ultra-high resolution Orbitrap mass analyzer systems to yield mass resolution values ranging from 70k to 1M. Resolution of this order, with commensurate improvements in precision and accuracy, holds the promise to affect elemental/isotopic determinations without the need for chemical separations.

Keywords: Elemental analysis · Isotope ratio mass spectrometry · Microplasma · Ultra-high mass resolution

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1. Introduction

Regardless of the type of particles (α, β, γ, UV/VIS/IR, or ions) being detected in a given assay, the quantitative limits of any determination are ultimately set by the available spectral resolution and the sensitivity of the detection mechanism. As an example, the case of radiochemical determinations, the potential for high levels of portability and rapid analyses are clear advantages in the realms of nuclear safeguards and forensics. But primary limitations lie in the lack of spectral resolution between different emitting species, originating from either direct overlaps or contributions from spectral background/continua. As such, entire research programs are dedicated to the development of chemical separation strategies/technologies to isolate species of interest from analytical host matrix interferences,[1] be they for field deployable or laboratory-based determinations. This concept is universal across all forms of analytical spectrometry.

Of course, chemical separations are only practical in a targeted -analysis strategy where methods are directed at specific species, at the potential expense of missing other entities that may be of high information value. While generally viewed as limited in terms of sample turnaround times, expense, and operational overheads, mass spectrometry (MS) provides sensitive and comprehensive levels of information across the periodic table. That said, high-fidelity quantitative and isotope ratio (IR) measurements may require very complex chemical separations.[2] Beyond time and cost considerations, extensive processing can result in the loss of chemical information (*e.g.* speciation), much less the loss of valuable analyte material. At the extremes, though, mass spectrometers of ultra-high mass resolution, as demonstrated in this laboratory, may effectively mitigate the need for complex chemical pre-processing. An MS system with sufficiently high mass resolution and accuracy and employing an ion source that allows for rapid elemental and molecular species determinations, would address many analytical challenges in terms of minimizing separations and also providing elemental/isotopic information of diverse species.

This laboratory, in collaboration/support from the Pacific Northwest National Laboratory (PNNL) and the Oak Ridge National Laboratory (ORNL), has developed a novel set of MS capabilities based on the interfacing of a liquid sampling-atmospheric pressure glow discharge (LS-APGD) microplasma ionization source with a commercial Orbitrap mass spectrometer (MS) platform,[3] with applications to date in the areas of nuclear forensics and safeguards. The coupling has proven itself to be a highly effective means of performing ultrahigh resolution isotopic analysis of uranium, in particular.[3b-e] More recent IR efforts have extended measurements to Pu, Nd, and Sm.[3f]

The microplasma has also been shown to be highly effective as a combined atomic and molecular (CAM) ionization source,[4] capable of ionizing both atomic species to effect elemental/isotopic analysis while also yielding 'molecular' mass spectra from species ranging from amino acids to polyaromatic hydrocarbons (PAHs), polyfluorinated alkyl substances (PFAS), and proteins.[5] Importantly, mass spectra have been derived from intact actinides such as uranyl acetates.[5a] This diversity of analytes is comple-

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mented by the range of means of sample introduction, including infusion of solutions, liquid chromatography (LC), laser ablation,[6] and surface microextraction.[7]

Different from the case of the stalwart inductively coupled plasma (ICP) ionization source, which poses very high gas and thermal loads on MS sampling interfaces, the LS-APGD can be directly coupled to virtually any 'organic' MS platform as typically used with electrospray ionization (ESI) sources.[3a,8] To this end, the ultra-high resolution (UHR) provided by now-standard Orbitrap mass spectrometers has been applied here in the realm of elemental/isotopic mass spectrometry. We speak of minimum mass resolving powers (R = m/Δm) of R= 70,000 @ *m/z* = 200. As a reference point, the state-of-the-art in multicollector, sector-field (SF) instruments employed in ICP and thermal ionization (TI) mass spectrometry (ICP-MS and TIMS) provide a resolution of ~10,000. While these platforms deliver excellent performance, they require very extensive sample preparation/workup (*i.e.* TEVA (TEtraValent Actinides) and UTEVA (Uranium and TEtraValent Actinides) columns) for many sample matrices of interest in order to alleviate potential mass (isobaric) interferences in actinide determinations.[9] The respective attributes of the LS-APGD microplasma and Orbitrap mass spectrometry and their coupling have the potential to alleviate many complex chemical separations prior to mass spectrometric elemental/isotopic species determinations.

2. Experimental

Both the LS-APGD and its coupling to Orbitrap mass spectrometers have been described in detail in publications over the last 12 years and so only a cursory description is presented here. As depicted in Fig. 1, the components of the microplasma are fairly straight forward. In short, a discharge is struck between the surface of the electrically-grounded flowing electrolyte solution (which serves to carry solution-phase analytes) and the metallic counter electrodes of 1 mm diameter biased at a potential of ~+600 V. The solution is introduced *via* a syringe pump into the discharge region *via* ~100 mm diameter silica capillary. That capillary is seated within a stainless-steel capillary, with the space between flushed with a helium gas flow which serves to cool the inner capillary and also helps in solution nebulization. All of the plasma utilities are delivered/controlled by a single unit designed and produced by GAA Custom Electronics (Kennewick, WA, USA). Typical plasma operation characteristics are presented in the text box. In the majority of applications involving elemental/isotopic analysis, the electrolyte carrier stream is a 2% aqueous HNO_3 solution. In the case of molecular species determinations, methanol-water mixtures are employed.

While the microplasma source has been coupled to many different MS platforms and formats (ion traps, quadrupoles, *etc.*), the vast majority of the efforts to date have been carried out on a ThermoScientific QExactive Focus (San Jose, CA, USA) located at Clemson University, though early realization of the benefits of ultra-high resolution were performed on a ThermoScientific Fusion Lumos.[10] The Clemson instrument (*circa* 2010) was originally equipped with an electrospray ionization (ESI) source, as is commonly employed in the realm of 'organic' mass spectrometry. The low kinetic temperatures and gas loads realized by the microplasma allow direct coupling to the Orbitrap in the place of the ESI source, without any other modifications. The QExactive Focus provides for two means of collisional activation to remove waters of hydration and loosely bound salts from the plasma-generated ions, simplifying the product mass spectra to yield bare atomic ions for transition metals, metal oxides for rare earth elements (REEs), and dioxides for lanthanide/actinides. The base resolution (R = m/ΔDm) of the instrument is rated as ~70k at *m/z* = 200.

As the Orbitrap instrument is designed for applications in 'organic' mass spectrometry, there are some prominent limitations regarding applications in multielement and isotope ratio mass spectrometry. The first of these is the restriction of the applicable mass range to values of greater than *m/z* = 50. (In reality, performance is degraded below *m/z* = 70.) The second limitation occurs by virtue of the enhanced Fourier Transform (eFT) mode of signal transient processing, wherein the background signals do not 'average out' with successive acquisitions. Third, this effect is compounded by the fact that an automatic thresholding is performed at a value of ~0.007% of the base peak in the specific spectrum, effectively reporting values of '0' below that point. This process can greatly affect the recovery of low abundance signals and makes realistic measurements of signal-to-background (S/B) impossible. Fourth, in the inability to achieve improved signal-to-noise (S/N) characteristics, the successive accumulation of signal transients is limited to a value of 10. Finally, the practical dynamic range is limited to ~4 orders of magnitude, a major limitation in regard to quantitative analysis.

This laboratory has implemented an advanced, third-party data acquisition (DAQ) and processing system that circumvents each of the 'electronic/detection' shortcomings as they relate to elemental/isotopic analysis. The FTMS Booster X2T sold by Spectroswiss (Lausanne, CH) is a standalone unit which operates

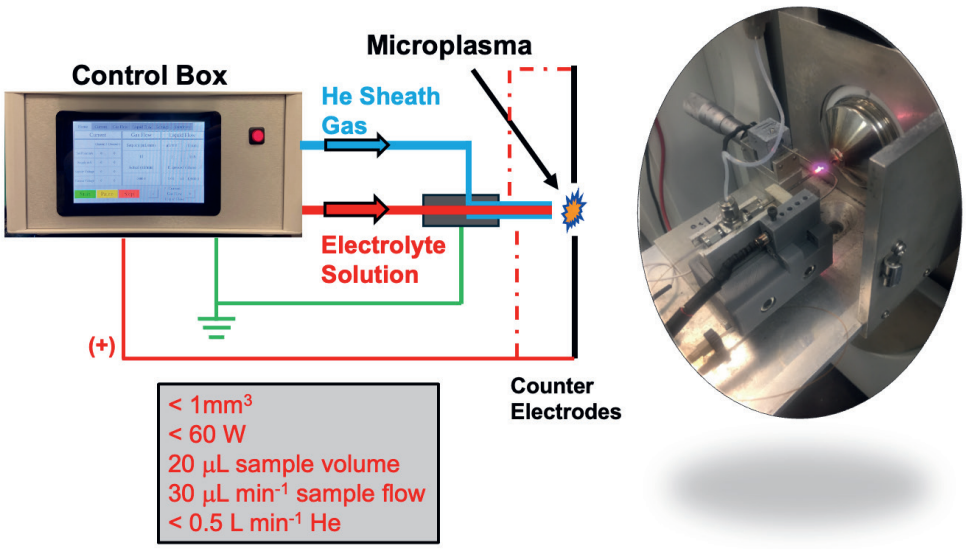

Fig. 1. Basic diagram of the LS-APGD source and picture of its coupling to an Orbitrap mass spectrometer.

in parallel with the Orbitrap OEM system, employing acquisition and processing methods which ultimately provide much higher spectral resolution, direct access to background signals, improved S/B and S/N, enhanced precision and accuracy, and a vast improvement in dynamic range. In simple terms, the system allows for acquisition of much longer signal transients (3500 *vs* 256 ms) than the base QExactive system, employing absorption-mode FT processing (aFT) and the ability to provide an infinite number of spectral co-additions (co-adds) versus the 10 for the base Orbitrap system. Processing transients in the aFT mode, as common in NMR spectroscopy, has long been demonstrated to improve performance in FTMS.[11] These capabilities combine to improve the spectral resolution up to ~1M and dynamic ranges that extend by ~7 orders of magnitude. While the base capabilities of the LS-APGD/Orbitrap coupling present many attractive capabilities, the further implementation of the FTMS BoosterX2T represents yet another function improvement in potential capabilities to achieve elemental/isotopic analysis without chemical separations.

3. Results and Discussion

The fundamental operating characteristics of the LS-APGD microplasma allow ready coupling to commercial, off-the-shelf (COTS) Orbitrap mass spectrometers. While the earliest efforts on 'base-level' platforms demonstrated resolution benefits versus SF instruments, greater performance can be further realized. Described below are efforts which illustrate the benefits of extended transient acquisition/processing in terms of higher resolution, improved isotope ratio precision and accuracy, and measurement sensitivity. Ultimately, these qualities are projected to allow measurements in complex systems, perhaps to the point of alleviating the chemical separations required when utilizing other MS platforms.

3.1 *^{87}Sr/^{87}Rb Resolution on High-Field Orbitraps*

There are many cases where direct isobaric interferences are encountered in isotopic measurements, for example the geochronological-significant ^{87}Sr:^{87}Rb dating pair.[12] Rb-Sr dating is employed across a very broad range of applications due to the long beta-decay constant of ^{87}Rb ($t_{1/2} \approx 4.9 \times 1010$ yr) which forms the radiogenic ^{87}Sr isotope, forming the basis for the method. The mass resolution requirements to measure each entity is of the order of 290k, approximately 30x that of sector-field instruments. As a result, the practical chronometric measurement is the isotope ratio between the primordial ^{86}Sr and ^{87}Sr which contains both the primordial concentration and contributions due to Rb β-decay, following the tedious chemical removal of any Rb species. As an alternative, multiple approaches using dynamic/chemical reaction cells have been developed for use on multi-quadrupole ICP-MS instruments.

Orbitrap instruments are produced in two basic configurations, low- and high-field, reflective of the electrostatic potential applied to the orbitrap cell, the base-level instruments being of the low-field variety. In practice, higher fields provide greater ion coherence and thus longer transient times and mass resolution. Shown in Fig. 2 are the effects of improvements in mass resolution (transient times) for the ^{87}Sr:^{87}Rb pair, taken on a high-field ThermoScientific Fusion Lumos instrument housed at the University of Pau, France.[10a,10c] The evolution of the two isotopes as a function of the pre-set mass resolution is clearly seen, a capability surely appropriate for age dating.

Of equal relevance towards elemental/isotope ratio analysis is the improvement in the precision and accuracy in the ^{87}Sr/^{86}Sr pair commonly used in Rb/Sr dating, shown in Fig. 2b. Here, monitoring of longer transients provides great improvements in both of these metrics. Different from SF instruments, where higher resolution is realized by narrowing the slits, there is no penalty in quantitative performance in this case using a higher resolution

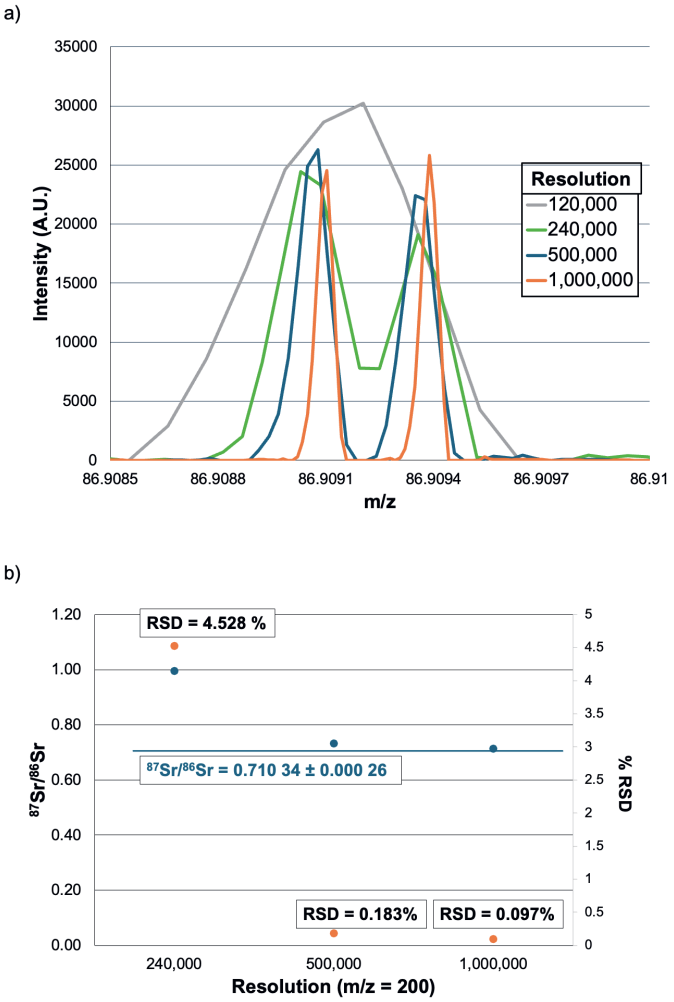

Fig. 2. a) Representative spectra of ^{87}Sr and ^{87}Rb using increasing resolving power to separate the two isotopes. b) Effects of resolution on isotope ratio measurement accuracy and precision.[10c]

on the Orbitrap platform. That said, the high-field instrument still imposes the automatic thresholding process of the other Orbitrap instruments and limited co-adds; limits in accuracy, sensitivity, and dynamic range.

3.2 *Implementation of an Enhanced Data Acquisition (DAQ) System*

As shown in the previous examples, while surely higher mass resolution, in general, is advantageous in multi-element/isotope analysis, there are also advantages in terms of IR precision and perhaps accuracy. A third-party vendor, Spectroswiss, has developed a parallel data acquisition and processing console which provides great enhancements in mass resolution on low-field instruments by virtue of longer transients, with the ability to perform any number of co-adds and direct access to the full dynamic range of the measurements including the spectral background.

Fig. 3 illustrates the basic attributes of applying the Spectroswiss FTMS Booster X2 on the Clemson QExactive Focus, low-field instrument.[13] It shows is the parallel capture of the standard 256 ms transients yielding R = ~70k and the Booster-captured 512 ms transient to yield R = ~140k (as will be seen subsequently, transients of multiple seconds are possible using the Booster). The resultant mass spectra are displayed for the OEM data system in red and the Booster in black. First, an improvement in the mass resolution is seen *via* the individual peak profiles. Next, and highlighted for the response of the $^{234}UO_2$ ion, is the recovery of the

analyte signal in the presence of what would be a very appreciable isobaric interference in the case of the external DAQ, from what is simply a spectral baseline with the OEM data system. Finally, a standard response curve is presented, covering an elemental concentration range of 250 ng mL^{-1} to 10 mg mL^{-1}, for the respective $^{234}UO_2$, $^{235}UO_2$, and $^{238}UO_2$ isotopes. Excellent correlation is seen in the log-log function across 7 orders of magnitude. Ultimately, an isotopic detection limit of <13 pg mL^{-1} is seen for 20 mL injections. As was seen for the high-field instrument, conditions leading to high mass resolution resulted in appreciable improvements in isotope ratio precision and accuracy.

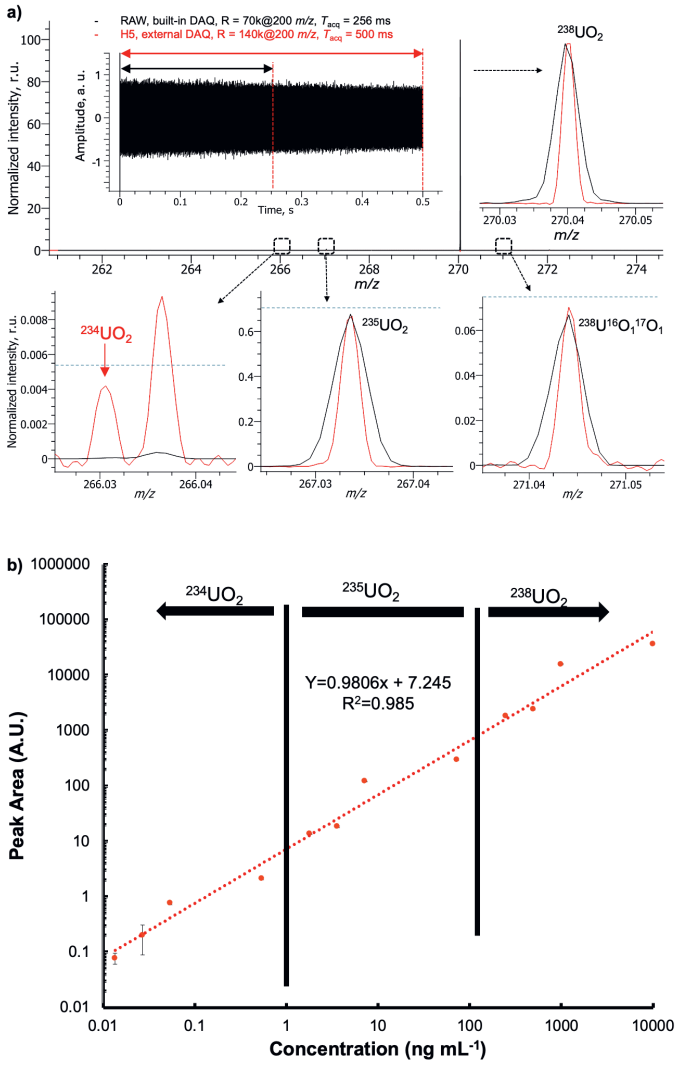

Fig. 3. a) Representative transients and spectra based on OEM (black) and external (red) DAQ acquisitions, 70k *vs* 140k resolution. b) Isotopic response curves obtained using the external DAQ using 20 mL injections.[13]

3.3 *Alleviation of Common ICP-MS Interferents in Uranium Analysis*

As most of the early efforts relating to the microplasma/Orbitrap coupling have dealt with uranium isotopes, it is natural to consider to what extent the methodology provides practical improvements over widely-applied SF ICP-MS methods. In this case, isotope ratio analyses are greatly affected by the presence of contaminant metals that tend to form oxides and hydroxides which are isobaric with the target uranium atomic ions. Common interfering species are related to Pb, Pt, Ta and W, present in the primary analytical samples.[14] In the case of multi-quadrupole instruments, diverse reaction cell strategies must by employed for the more simplified case of uranium quantification.[15] As a result, high precision/accuracy uranium IR analyses necessitate very laborious and time consuming chemical separations prior to the ultimate mass spectrometric determinations.

To be clear, the product mass spectra derived from the LS-APGD are very different in composition from the use of an ICP source, metal oxides for transition metals and dioxides for actinides. Likewise, the ability to affect different levels of collisional activation effect the spectral composition. Lastly, it would be expected that that the ultra-high resolution provided by Orbitrap instruments may in itself alleviate potential isobaric interferences. An evaluation of the extent of potential isobaric interferences was performed on the standard QExactive Focus instrument at Clemson University with the base mass resolution of ~70k and the OEM processing package.

The workflow of this targeted evaluation included the acquisition of the raw (no collisional dissociation) mass spectra for each of the test elements (Pb, Pt, Ta and W) at a concentration of 10 mg mL^{-1} and the product spectra following CID and HCD processing.[3h] The impact of excesses of these elements on potential overlaps with the uranium isotopic responses was evaluated though interrogation of the mass spectra with the 'contaminants' present at concentration excesses of 1000 – 5000x.[13] Those efforts demonstrated that each of the target UO_2 ions was free from any appreciable interferents, that would surely have been observed on instruments of lower mass resolution. Ultimately, with reference to the performance of uranium isotope ratio measurements, the obtained ratios for a neat low-enriched uranium sample (IRMM-2028) were compared to a solution spiked with the 'common' elements which present interferences *via* ICP-MS. Shown in Fig. 4 are average $^{235}U/^{238}U$ ratios obtained from the neat solutions (solid blue line) and in the presence of the common interferents. Whether by virtue of the types of ions produced by the microplasma or by the high mass resolution of the Orbitrap, there is statistically no difference in the IR values. If this observation holds true in 'real world' samples, the need for extensive chemical separations in these determinations will be dramatically reduced if not alleviated.

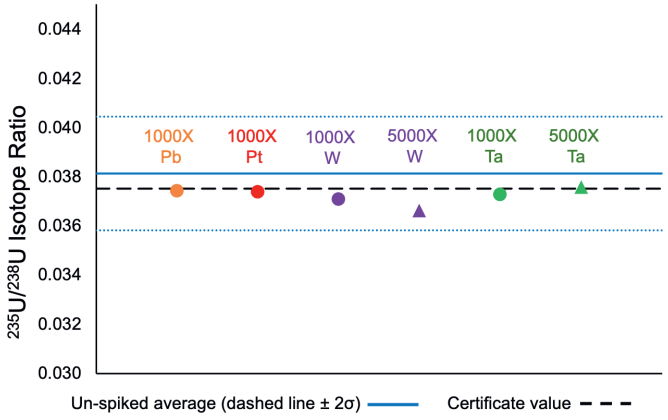

Fig. 4. Uranium isotope ratios obtained for IRMM-2208 (10 ng mL^{-1}) as a neat solution and in the presence of the noted excesses of potential contaminant elements.[3h]

3.4 *Complete Isotopic Separation Across the Nd/Sm Envelope*

The analysis of rare earth elements (REEs) is of interest to a variety of communities, including geological, nuclear, and critical material analysis. Regarding the nuclear chemistry application space, REE characterization can be indicative of nuclear mate-

rial origin[16] or provide information on spent nuclear fuel.[17] Nd in particular is a valuable test element. Among the Nd isotope ratios, $^{143}Nd/^{144}Nd$ is particularly significant for age dating of geological and archaeological samples.[18] It can be an equally valuable signature in nuclear forensics as trace amounts of Nd can be present in nuclear fuel samples.[19] Brennecka and co-workers have recently presented the use of $^{143}Nd/^{144}Nd$ ratios in assessing the provenance of uranium ore concentrates.[20] Additionally, Nd isotopes are also generated as fission products in the different stages of nuclear fuel cycles and so can be used as burn-up indicators.[21]

As both Nd and Sm isotope ratios play important roles in geological dating and as nuclear forensic signatures, the overlap of the respective 144, 148, 150 Nd/Sm isobars must be addressed, requiring prior separations to be performed before analysis on typical MS platforms. These include multiple approaches to separate the isotopes of interest from isobaric interferences; in the Nd[16a,22] and Sm[23] isotopic systems, for example. If high precision quantification of the REEs is necessary, typically an isotope dilution approach is considered; however, this also requires laborious separations due to isobaric interferences.[16c,17a] Beyond this, alternative designs of MC-ICP-MS instruments have been recently investigated,[24] and could be applied to REE, but these still remain in their infancy. These MC-ICP-MS based instruments include the use of a double-Wien filter[24a] and a collision/reaction cell,[25] employed to overcome isobaric interferences through element-specific mass shifts.

Implementation of the LS-APGD/Orbitrap coupling, augmented by the Spectroswiss Booster X2T, provides sufficient resolution to fully resolve the entire Nd:Sm isotopic envelope.[26] Even in the case of equal concentrations, the resolution provided alleviates the need for chemical separations and/or gas phase manipulations. Shown in Fig. 5a are the product mass spectra measured at increasing resolution (longer transient times) on the QExactive Focus instrument. As seen, only in the case of resolution values greater than ~200k are each of the isotopes revealed. Needless to say, none of these pairs is resolved using quadrupole instruments, and $^{150}Nd/^{150}Sm$ is only resolved using the 10k resolution common to MC-ICP-MS. Fig. 5b illustrates the alleviation of the isobaric interferences for the respective Nd and Sm isotope ratios realized by increasing the resolution of the base QExactive (~80k) using the Booster X2 (~230k). The horizontal line is representative of the baseline IR values (p-value = 1) for the neat elemental solutions, with the red-dotted values obtained at the lower resolution and the circles representing the values obtained at high resolution for the mixture. As can be seen, use of high resolution yields a quantitative recovery of the correct IR values.

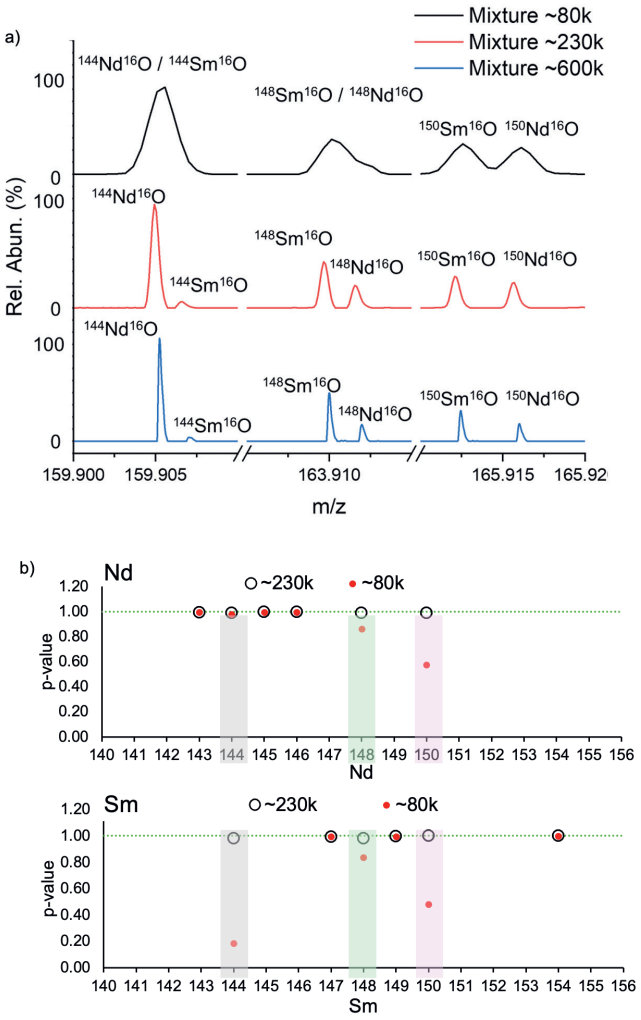

Fig. 5. a) Overlay of the acquired Orbitrap mass spectra for the 1:1 Nd:Sm mixture (1 mg mL^{-1}) at mass resolution values of ~80k (black), ~230k (red) and ~600k (blue). b) Isotope ratios determined from individual solutions and the 1:1 Nd:Sm mixture.[26]

4. Conclusions

The major impediments to high quality elemental and isotope ratio measurements lie in the extent of isobaric interferences experienced by the target species. While well-established methods of chemical separation have existed for decades towards addressing the most important of these challenges, higher-order mass spectrometric methods including reaction cells on quadrupole and SF instruments must be implemented. Even then, the resultant 'resolution' can still be insufficient while still being effort, time, and money consuming. The LS-APGD/Orbitrap coupling, particularly when coupled to the enhanced DAQ offered by Spectroswiss, provides a 'brute simplicity' approach to alleviation of isobars; frankly at a cost and instrumental complexity far below the most advanced commercial ICP-MS platforms. While there will surely be limitations, this approach does indeed hold promise towards the alleviation of chemical separations in elemental and isotopic analysis.

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Author Contributions

RKM was the sole contributor to this manuscript.

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