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SPECIAL FEATURE: TUTORIAL

Inductively coupled plasma mass spectrometry (ICP MS): a versatile tool

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Inductively coupled plasma (ICP) mass spectrometry (MS) is routinely used in many diverse research fields such as earth, environmental, life and forensic sciences and in food, material, chemical, semiconductor and nuclear industries. The high ion density and the high temperature in a plasma provide an ideal atomizer and element ionizer for all types of samples and matrices introduced by a variety of specialized devices. Outstanding properties such as high sensitivity (ppt–ppq), relative salt tolerance, compound-independent element response and highest quantitation accuracy lead to the unchallenged performance of ICP MS in efficiently detecting, identifying and reliably quantifying trace elements. The increasing availability of relevant reference compounds and high separation selectivity extend the molecular identification capability of ICP MS hyphenated to species-specific separation techniques. While molecular ion source MS is specialized in determining the structure of unknown molecules, ICP MS is an efficient and highly sensitive tool for target-element orientated discoveries of relevant and unknown compounds. This special-feature, tutorial article presents the principle and advantages of ICP MS, highlighting these using examples from recently published investigations. Copyright © 2007 John Wiley & Sons, Ltd.

KEYWORDS: inductively coupled plasma mass spectrometry; sample introduction; total element quantitation; element speciation; species identification

INTRODUCTION

Plasma source mass spectrometry (PS MS) has a long-lasting, unbroken and still increasing record of excellent performance. However, in most publications, MS automatically is associated with a 'soft', low-temperature ion source, as though MS would exclusively be performed by low-temperature ion sources for organic molecular ion formation and fragmentation. This is not justified, especially because the performance of PS MS is undoubtedly superior in useful aspects of analytical chemistry. Inductively coupled plasma (ICP) MS, the most widely applied PS MS, has played and is still playing an important role in many fields of applied science and research. The complementarity of ICP MS with other types of ion source MS (such as electrospray ionization MS) and the recent tremendous progress made in the development of these for bioinorganic analytical chemistry have been well documented in an excellent review.[1] The information that can be recovered from the application of the two types of ion sources is quite different[2] but ultimately complementary (Table 1), which is affirmed by the efforts to develop modulated ion sources capable of generating either elemental ions or molecular fragment ions within the same ion source device.[3]

Today, ICP MS is routinely deployed in diverse fields such as geochemistry, environmental and life sciences, industries (food, chemical, semiconductor, nuclear), forensic science and archaeology. After introduction of the first commercially available instrument in 1983, the technique[4] has continuously improved. Several manufacturers produce reliable and robust instruments with very low detection limits (ppt) and high spectral resolution (10 000) for multielement isotope detection.[5,6] On the basis of the broad range of applications and its indispensable role demonstrated in the investigation of numerous devastating health crises (such as nerve degeneration by methyl mercury, degeneration of male sexual organs in animals by organotin compounds, brain damage by organolead compounds, poisoning by arsenicals in drinking water, etc.), the technique is further expanding in life science research since it is well established in sensitive heteroelement detection and ease of quantitation. ICP MS has also become the method of choice in elemental speciation,[7,8] covering a broad field of covalently bound elements, coordinated metals, metalloids and organometallic metabolites.[9] A large number of proteins bearing heteroelements such as S,

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Table 1. Comparison of the ICP and ESI ion source

Applications	High-temperature atomizing ion source (ICP)	Molecular-ion-forming ion source (ESI)
Elemental composition	On whole samples	On organic molecules
Accurate quantification	Species-unspecific standards; CRM-validated isotope dilution	Specific reference compound required
Structure determination	By coupling to highly selective separation and reference compounds	By molecule fragmentation
Online LC detector	Eluent tolerant (salts)	Eluent intolerant (salts)

CRM, certified reference material.

P, Se natively binding metals (Zn, Fe, Mn, Cu, Ni, Mo, Cr) have been detected and quantified[10] by ICP MS, emphasizing its potential in life science research.[11] Parallel to proteomics research, the activity in bioinorganic speciation has rendered metallomics studies accessible,[12] a new research field linked to proteomics, since more than 25% of all proteins contain metals.

In the following, an overview is given on the specific role ICP MS plays in diverse research fields. Special or unique features are highlighted through recently published examples, rather than providing a complete review of the literature.[13,14]

ICP – A HIGH-TEMPERATURE ATOMIZING ION SOURCE

An ICP is the standard high-temperature ion source used almost exclusively in commercial instruments for PS MS.[5] Details of such an ion source and its interface are given in Fig. 1. It provides temperatures of approximately 5500 °C[15] that no material can withstand. Thus, it is the most versatile atomizer and element ionizer available. Contrary to low-temperature ion sources for molecular ions, in a plasma all bonds are broken irrespective of their chemical bonding. Hence, the data acquired from a plasma ion source corresponds to the total content of an element in the sample. The elemental response is independent of the different species containing the same element, enabling simple and accurate species-unspecific, multielement quantitation based on commercially available certified multielement standards and certified reference materials (CRMs).[16] Simple mass spectra in the mass-to-charge (m/z) range 5–250 are generated at the expense of multiple fragmentations and the loss of information on molecular mass and structure. Another unique property of a plasma is that it has the highest ion density (Ar^+ and e^-) and hence provides the highest collision rate available.[3] In combination with the high temperature, this drives the ionization of an element toward the physical limits set by the ionization potential of the element. Thus, much higher analyte ion densities and higher sensitivities are generated than by other ion sources.[3] Additionally, the ICP ion source is much less vulnerable to the salt and solvent loads introduced by a sample and tolerates, for example, 100 mmol/l salt concentrations. Salt and solvent tolerance restrictions, however, do exist, as these can induce clogging of the cone and ultimately contaminate the instrument. However, if the salts injected contain volatile elements that decompose in the plasma into gaseous components, hundreds of millimoles per liter are tolerated and no instrument contamination occurs. This is used to minimize the influence of the variable sample matrix by adding a high level of volatile acid (0.1–1 mol/l HNO_3) to the samples. Under such a regime, it is not surprising that sample matrix effects are much less severe than in any other type of ion source. The known matrix-dependent response in ICP MS (acid effect,[17–19] space charge effects,[20] general effects from concomitant ions,[21] organics on aerosol formation[22]) can be accounted for by matrix-adapted standards, standard addition to the matrix or isotope dilution. These outstanding properties make ICP

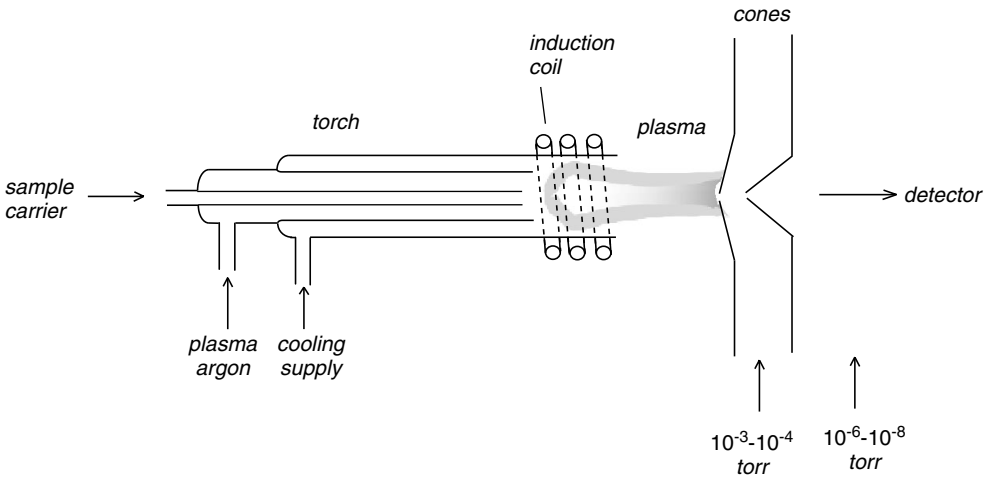

Figure 1. Ion source and interface in ICP MS. The plasma is at atmospheric pressure and range of pressures for the two interface vacuum stages is given in Torr.

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MS extremely useful, efficient and reliable in detecting, keeping track of, identifying and quantifying elements. Even molecules can be identified that contain at least one heteroatom if a reference compound is available. In this case, the instrument has to be hyphenated to a species–specific separation technique that has to provide sufficient selectivity to separate the compound for identification and quantitation.

DIVERSE SAMPLE INTRODUCTION SYSTEMS MAKING ICP MS VERSATILE

Contrary to large variations in mild ion sources (ESI, CI, FAB, etc.), in commercial instruments there is no variation of the plasma ion source. However, in addition to different types of nebulizers and desolvating systems, a large variety of sample introduction systems[23] have been developed for ICP MS. An overview of the basic types of introduction systems is shown in Fig. 2. Liquid solution nebulization is by far the most economical and most often used sample introduction technique. Many solid samples have to be digested and dissolved to obtain a homogeneous sample. For direct access to analytes in solids and on surfaces, laser ablation[24] (LA) is used with a spatial resolution on the micrometer scale (~1 μm), which is ideally suited for microsampling on surfaces and in-depth profile analysis.[25] In several fields, it is the preferred technique and in some cases the only avenue available. This is the case for the analysis of rock inclusions in geology,[26] tree rings and biological tissue sections[27] and for many other microsurface area samplings such as in material and forensic sciences[28] and for virtually nondestructing sampling on valuable antique and archaeological objects. LA of proteins directly from sodium dodecyl sulfate polyacrylamide electrophoresis (SDS-PAGE) gels after two-dimensional separation has become of general interest for life science studies and was used to determine metal distribution in a proteome,[29] a methodology that has been recently improved.[30] Electrothermal vaporization (ETV) allows *in situ* sample preparation (drying, decomposition of heat-labile matrix) and hence sample preconcentration.[31] Higher sample introduction efficiency is provided by high-efficiency nebulizers, namely, ultrasonic nebulizers (USN), LA and ETV. If available, no or low solvent-introducing systems are preferred such as dried aerosols, LA and ETV, since they generate fewer polyatomic ions and lower background levels. LA, ETV and solution nebulization have been compared for liquid samples, confirming enhanced reproducibility but lower detection limits for solution nebulization.[32]

SPECIES-INDEPENDENT TOTAL ELEMENT QUANTITATION BY ICP MS

The capability of gathering chemical information and other outstanding features of ICP MS are summarized in Table 2. Detecting and quantifying 85% of all elements down to concentrations not measurable by other techniques opens a broad analytical window, allowing a unique holistic approach. This means a true nontarget approach that semi-quantifies all detectable elements in a full mass scan, thereby discovering problems more reliably than by preselecting some elements and excluding the unexpected ones. Both

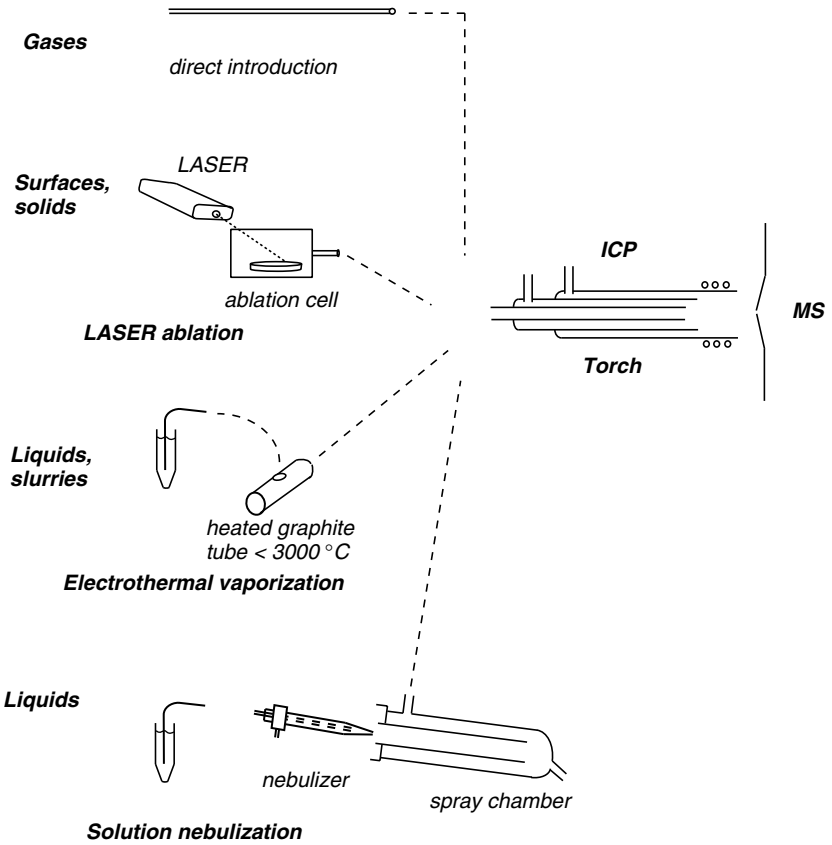

Figure 2. Principles of sample introduction in ICP MS.

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Table 2. Total elemental quantification by ICP MS

Basic-level chemical information on composition
Almost complete multielemental composition (holistic approach)
Selected elements – total content
Isotope ratios
CRM-validated quantifications
Outstanding advantages
Lowest detection limits (ppb–ppt)
High throughput
Low cost per parameter

CRM, certified reference material.

positive as well as negative findings are confirmed, which is a fundamental prerequisite to completely assess all element-related quality and compositional aspects of a sample. Besides this important aspect, ICP MS on its own provides chemical information on a basic level, such as total single elemental contents or elemental and isotope ratios. Here the technique has an outstanding record as a highly sensitive, high-throughput and, over its total life cycle, a fairly inexpensive analytical tool. When measuring on a routine basis dozens of parameters in a sample and thousands of samples per year, the costs calculated per parameter for an instrumental life cycle (~10 years) is in the same order of magnitude as the cost of a sample vial. This is an extremely good cost–benefit ratio despite a somewhat higher material and running cost (Ar consumption).

To cover the whole mass range for all elements, a simple quadrupole mass analyzer provides ample resolution ($R = 300$) to detect all the isotopes of an element differing by 1 atomic mass unit (amu). This isotope-specific detection is element specific, since each element has at least one isotope that differs from all others by 1 amu. Without preconcentration, detection limits are usually in the nanogram per liter range and below when detecting with a highly sensitive, high-resolution ICP MS instrument.[33] In fact, the simple access to isotope quantitation is the most utile feature of ICP MS. A large part of elements (80%) is composed of several isotopes. Naturally occurring stable isotopes are routinely measured, as well as unstable isotopes in nuclear research. Kinetically fractionated isotope ratios need higher-precision ICP mass spectrometers that are provided with multicollector detection units.[34] Highly concentrated elements can be measured using their low-abundance isotope(s) (less sensitive), thereby protecting the detector and increasing the instrument flexibility to measure high and low concentrated elements in the same run without diluting the samples. Furthermore, measuring at least two isotopes of the same element allows not only safe element identification but also recognition of the contributions from interfering masses by the deviation in natural isotopic ratios.[35] To deal with polyatomic interferences while reducing background levels, specialized devices such as reaction/collision cells[36] and high-resolution instruments[37] have been developed.

Sensitive single element determinations were very useful in many metal–protein binding studies, e.g. revealing metals in enzymes and other protein-binding sites.[10] Very recently, the *in vitro* specific affinity of Cd to the estrogen binding site in the estrogen receptor was demonstrated.[38] A much more detailed picture is obtained by determining multielement and multitraceelement compositions by ICP MS. It is a well-established technique applied in many diverse fields such as environmental science,[39,40] geology,[41] pharmaceutical and biomedical sciences,[42] bioinorganic analysis[1] and forensic investigations,[43] among many others. Elemental compositions are used not only to characterize and judge the quality aspects of a sample but are also often used to diagnose processes or reveal the history of the sample. Multielement ratios are an ideal tool to track processes or assign the provenance that leads to a particular composition of a sample; e.g. the geographic production area can be assigned by the elemental ratios in foodstuff[44] and wine.[45,46] Elemental cycling on a local or global scale and element accumulation in living organisms[47] can also be followed.

Isotope dilution experiments, that is, the addition of an enriched isotope of known content to a sample, are increasingly used for different purpose.[48] For quantitation it is the most accurate method since an internal standard of identical chemical behavior is measured.[49] The direct determination of heteroelements or exchanging these with enriched stable isotopes to tag molecules and proteins was established, as well as analysis of conjugated and labeled proteins.[50] Detection and, especially, quantitation of such multiple elemental tags and labels by ICP MS are highly advantageous in lifesciences.[51] Particularly, the high sensitivity of this approach will allow replacement of radioactive tracers by natural, stable isotopes.[51] Isotope dilution is also a very useful and elegant technique to investigate dynamic systems. The content and kinetics of an element-exchanging pool, ranging in size from micro to a large scale, can be determined by addition of enriched isotopes. For example, enriched ^{207}Pb was used to determine the Pb availability in contaminated soils.[52] Administration of isotope-enriched micronutrients and their dilution and quantitation after passage through the body is a common method in nutrition research to elucidate the uptake of minerals and nutritional mineral status.[53]

ICP MS HYPHENATED TO SEPARATION TECHNIQUES FOR SPECIES-SPECIFIC DETECTION AND IDENTIFICATION

The high salt or acid tolerance of the plasma makes ICP MS an ideal elemental detector for species-specific, high-performance separations techniques such as GC,[54] HPLC[55] and CE[56] (Fig. 3). ICP MS serves as a versatile and sensitive detector for compounds containing known or unidentified heteroelements including metals[39] and nonmetals.[57] The effluent of liquid chromatography is connected to a nebulizer to introduce the effluent as an aerosol into the plasma. Such hyphenated systems built for elemental speciation analysis[58] are again used in many applied research fields.[59] Depending on the separation window, a partial elemental distribution fingerprint or a complete elemental distribution for different compounds is obtained. The total content of an element determined before separation allows calculation of the portion missed by the separation technique used

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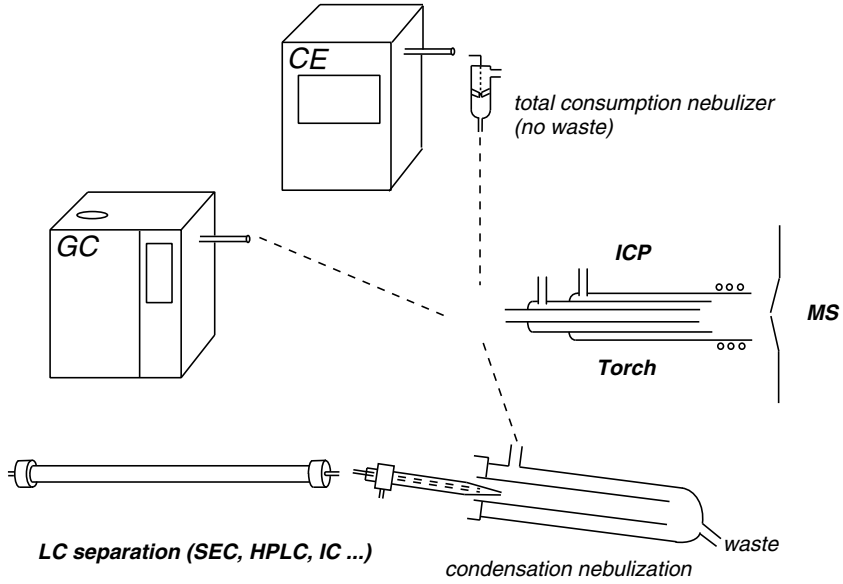

Figure 3. Separation techniques hyphenated to ICP MS. Gas chromatography (GC), if used without cryo-trapping, is directly connected to the torch. Liquids from LC and capillary electrophoreses (CE) are introduced via a nebulizer into the plasma. CE and micro-LC are connected via a total consumption nebulizer without condensation losses, whereas all higher-flow LC separation techniques are connected to a liquid nebulizer with condensation waste.

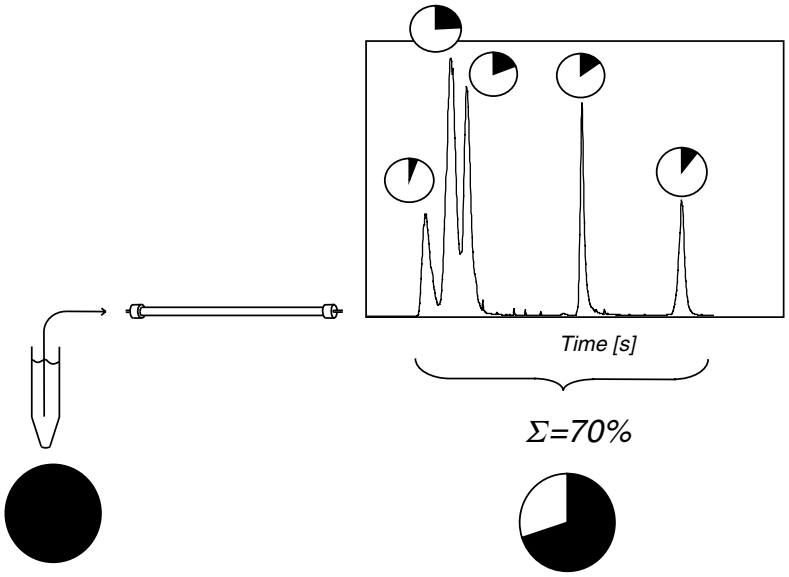

Figure 4. Element distribution and element balance over the separation step determined by ICP MS using non-species-specific calibration standards.

and the percentage of the individual peak recovered compared to the total amount (Fig. 4). It is a unique and outstanding advantage of ICP MS to easily provide quantitative control on elemental distribution on each step of an experiment. Under such quantitative control, only relevant unknown species are subsequently investigated by a molecular ion source MS for detailed structural assignment. Such an approach has been beneficial in many cases, and is typically chosen for discovering unknown compounds and studying metal–protein interactions by elemental speciation analysis.[8] A good example of this was given in a recently published investigation in which the higher Cd tolerance among plants was correlated for the first time with the structural differences in phytochelatins (PC) complexing Cd and thereby reducing its toxic effects.[60] Cd–PC extracted from cells have been separated by size exclusion (SE) and detected online by ICP MS. Cd-containing PC fractions were further analyzed by ESI ToF MS, revealing an additional cysteine that allowed the binding of more Cd and hence having a higher Cd tolerance. There is also a growing interest in identification and characterization of natural selenium-containing compounds since these have been demonstrated to inhibit tumor growth.[61] Several Se compounds were analyzed in water extract from selenized yeast by ion-pair reversed-phase HPLC ICP MS[62] and in nuts by SE ICP MS.[63] Subsequent accurate molecular mass

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determination by ESI-Q-TOF MS/MS identified several unknown Se-glutathione species[62] and selenopeptides.[63] Despite the emergence of liquid chromatography as an efficient alternative to separate proteins, gel electrophoreses is still the most widely used protein separation technique in life science disciplines. Adapting the gel to a column and coupling it online to an ICP MS[64] allowed DNA fragments to be separated and quantified by monitoring the phosphor signal with enhanced precision (<3%) compared to other conventional methods.[65] Two ICP MS-based methods for quantitative estimation of the phosphorylation level of a cellular proteome were introduced, which accessed the native proteome state without requiring the introduction of any label or derivatization.[66] Enriched ^{111}Cd isotope was administrated to fish in chronic concentration so that the change in natural isotope ratios (^{114}Cd/^{111}Cd) measured in metallothioneins by anion exchange ICP MS clearly showed accumulation and distribution of Cd including redistribution from liver to kidney.[67] Mercury, one of the largest threats to life, remains a problem because of ongoing emission and deposition of inorganic Hg.[68] In water and sediments, bacteria convert mercury into methylmercury, which accumulates in the food chain. Until now, the contribution of historical contamination and fresh deposition could not be differentiated, blocking measures against the emitting sources. Applying enriched ^{202}Hg to natural environment and mercury speciation by GC ICP MS revealed the distribution of mercury in environmental compartments and its transformation to methylmercury, thereby quantifying for the first time the amount of methylmercury derived from fresh anthropogenic mercury emission directly diverted to the food chain.[69]

MOLECULE IDENTIFICATION CAPABILITIES OF HYPHENATED SYSTEMS

In the course of element speciation, hyphenated ICP MS methods that can identify compounds in well-defined cases are emerging frequently. In combination with the aforementioned features, species identification makes hyphenated ICP MS a fascinating and powerful analytical tool. In the case where only one single element is detected from a molecule, identification capabilities depend entirely on its retention time (t_R) and the existence of a reference compound. The selectivity of the coupled separation device has to guarantee that no other species present in the injected sample and containing the same element appears at the same retention time. However, this can conveniently be achieved by modern high-selectivity separation techniques; at least by combining two or more of these (two- or multidimensional separation[70]) eliminates any ambiguity. Additionally, most often the matrix itself contains a drastically reduced number of possible species, or only a few are relevant (e.g. toxic); so, typically, a small number of all known species have to be separated from one sample. For stable and relevant species, CRMs are available,[71] which allow safe identification and accurate quantitation. This issue has recently become a subject of debate in the arsenic speciation literature. Today, over 60 As species of diverse polarity (apolar, anionic, cationic) have been identified. There is, however, no single procedure to individually separate these. Applying only one separation procedure inevitably results in As species coelution.[72] A safe identification of coeluting organic As species can be done only by means of selective detection as provided by electrospray tandem MS, requiring the compounds for accurate quantitation.[72] However, not many of these compounds are present in a particular matrix, and an even lower number of these present a real problem.[73] So the selectivity of two-dimensional separation procedures hyphenated to ICP MS is sufficient to identify these from most matrixes.[74] This is valid as well in bioinorganic speciation. SE chromatography is often used in combination with another more selective liquid separation technique, e.g. ion exchange. Many metal–protein interaction studies profit from the advantage of such LC techniques coupled to ICP MS since this detector is much less restrictive to salt concentrations in the mobile phases, providing a larger flexibility to adapt separation procedures. Investigating metallothioneins (MTs), Infante *et al*.[75] have revealed the dominant role of MT including single MT isoforms in sequestering Cd, Zn and Cu in fish living in contaminated waters. Separating the proteins from liver and kidney by SE gave a mixture of MT, which was compared to the total metal content in the tissue. The mixture was further separated by ion-exchange chromatography to obtain the metal distribution on single, separated MT isoforms. Species-unspecific calibration was used by online isotope dilution and detection by ICP ToF MS.

SPECIES IDENTIFICATION INCLUDING ELEMENTAL RATIOS BY HYPHENATED ICP MS

Using the multielement capability and the ability to detect more than one element in the same species provides elemental ratios as an additional criterion besides t_R to identify species. If no reference compound is used, the theoretical element ratio expected from the stoichiometry is assumed to be identical to the stoichiometry of the species under investigation. This might not be the case for complex and unstable structures, which need additional confirmation of the structural features under the actual experimental condition, e.g. by an exact molecular weight determination. A good example was given by Hann *et al*.,[76] who detected Cu/S in proteins after SE separation. Because of insufficient selectivity, the identification of a larger protein relied exclusively on assumed Cu/S stoichiometry, which was verified by ESI MS molecular weight determination. In this example, the Cu/S ratio was not found as theoretically predicted since an unexpected S-bearing cysteine was lost during the protein expression step. However, for smaller molecules, detecting several elements during high-efficiency separation drastically increases the reliability of species identification by hyphenated ICP MS and can even be independent of retention times. This has been demonstrated for chelators (e.g. EDTA, DTPA, CDTA, etc.), each forming several strong metal complexes. According to the variations in the metal ionic radius, each metal forms a structurally different complex with the same chelator, which was separated by high-performance gradient ion chromatography.[77] It has been shown that chelators

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found in the environment each gave a different metal separation pattern that was distinct from all other chelators bound to the same metal. Detection of a few metals allowed safe identification of each chelator according to its unique separation pattern independently of retention times.[78]

Sequentially detecting ICP MS instruments (all except ToF MS) are limited by the number of multielement ratios they can detect during a chromatographic run. The shorter the peak width, the lower the number of different m/z values that can be sequentially determined. This means that the better the chromatographic separation efficiency, the fewer the isotopes or elements that can be detected. Moreover, isotope and element ratios of sequentially detected transient signals (peaks) are skewed[3] and need to be corrected.[79] There is a need for the development of simultaneous MS detection to prevent the progress made in separation efficiency to increasingly restrict the applicability of MS in hyphenated systems. Currently, sequential MS detection is a bottleneck that is unable to measure in the same run all the multielement species that a high-performance separation is able to resolve. This brings detectors for mass spectrometry[80] into the focus of instrument developers; a mass spectrometer with a focal plane detector[81] capable of simultaneously accumulating signals has already been described.

CONCLUSIONS

Research on trace-level concentrations requires analytical techniques that are versatile, robust, of the highest sensitivity (ppt) and capable of providing accurate and reliable information on concentrations and species identity. With respect to most of these criteria, determination of trace elements by ICP MS is performing extremely well and is unchallenged by other MS techniques. Increasingly, by using heteroatoms to discover and analyze molecules, ICP MS coupled to high-performance separations is expanding its role into species identification. Besides the multielement composition of a molecule, an element detector requires reference compounds and high selectivity or multidimensional separations to identify species. Because the ionization is matrix dependent in molecular ion source mass spectrometers, they require a reference compound for accurate quantitation. On the other hand, it is a unique and outstanding advantage of ICP MS to use inexpensive, unspecific, certified element standards, allowing a quantitative control on elemental losses, species decomposition or contamination in each single step of an experiment. Whereas molecular fragmentation is used to determine the structure of unknown compounds, in a plasma, atomized elements provide convenient and efficient access to high sensitivity for target-element orientated quantitation and the discovery of relevant unknown compounds and in the same process quantifying their relative mass contribution to the total content. These two approaches should therefore be considered complementary. It is probable that in the future, offsprings of today's instruments will contain both types of ion sources, allowing researchers to work with only one combined analytical system and still satisfying the research needs.

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