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Review

Plasma-source mass spectrometry for speciation analysis: state-of-the-art

Steven J. Ray, Francisco Andrade, Gerardo Gamez, Denise McClenathan, Duane Rogers, Gregory Schilling, William Wetzel, Gary M. Hieftje*

Department of Chemistry, Indiana University, Bloomington, IN 47405, USA

Abstract

Current and emerging capabilities of plasma-source mass spectrometry (PS-MS) as it is employed for elemental speciation analysis are reviewed. Fundamental concepts and their advantageous aspects, experimental conditions, and analytical performance are described and illustrated by recent examples from the literature. Novel instrumentation, techniques, and strategies for inductively-coupled plasma mass spectrometry (ICP-MS), microwave-induced plasma (MIP) mass spectrometry, glow-discharge (GD) mass spectrometry, and electrospray ionization (ESI), among others, are described. The use of ionization sources that provide tunable ionization, others that can be modulated between different sets of operating conditions, and others used in parallel is also examined.

Keywords: Elemental speciation; Tunable ionization sources; Time-of-Flight mass spectrometry; Electrospray ionization mass spectrometry

Contents

* Corresponding author. Tel.: +1 812 855 2189; fax: +1 812 855 0958.
E-mail address: hieftje@indiana.edu (G.M. Hieftje).

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1. Introduction

It has been known for some time, but only now becoming widely appreciated, that the speciation of a particular element is of critical importance in many applications of plasma-source mass spectrometry (PS-MS). As a result, such analyses will likely constitute a major driving force in the future of atomic analytical spectrometry. Often vaguely defined, elemental speciation is simply the quantification of an element amongst its various chemical forms. These forms might be the oxidation states of an element, covalent bonds between it and organic or inorganic ligands, non-covalent complexes or associations, or the distribution of an element amongst various biological species. In contrast to more conventional PS-MS strategies, modern speciation analysis establishes both the identity of elemental associations and their absolute concentrations.

The importance of elemental speciation derives directly from the fact that the chemical form of an element governs many of its features. To be sure, determination of the identity and quantity of elements remains important; however, for many applications measurement of total metal content alone provides insufficient information, and in some cases leads to erroneous conclusions. The example of arsenic is often cited: the total As concentration in many types of seafood is dominated by arsenobetaine, which is not toxic. In contrast, inorganic arsenic is highly toxic, and to a degree that depends on its oxidation state. Generally, it can be stated that the chemical, physical, and morphological state of elements in a sample has a direct influence on their toxicity, bioavailability, bioactivity, transport, uptake, bio-geological distribution, and environmental impact. Thus, elemental speciation analyses have been employed in a wide range of disciplines including clinical and medicinal chemistry [1,2], environmental science, geology [3,4], and bioinorganic chemistry [5], among others. Elemental speciation represents a broad, multidisciplinary field of study, and a number of recent reviews and books provide an excellent reference to the role of various elements in these chemistries [6–9].

Overwhelmingly, current elemental speciation analyses employ hybrid techniques consisting of a chemical or physical separation method, such as high-pressure liquid chromatography (HPLC), in combination with a sensitive atomic spectrometric method such as inductively-coupled plasma mass spectrometry (ICP-MS). In such a strategy, chemical selectivity is supplied by the chromatographic separation, which establishes the chemical form of the element based upon retention time or peak shape. The atomic spectrometric procedure then confirms the identity and presence of a particular element or elements and offers highly sensitive detection and accurate quantification. As a consequence of the orthogonality of these two types of chemical information it follows that only those compounds containing the same target elements need to be resolved by the chromatographic separation, greatly simplifying analyses. Unfortunately, this arrangement establishes the identity of these chemical species indirectly by retention-time matching and through addition of standards, and thereby with a fidelity limited by the chromatographic resolution of the separation step and the availability of standard compounds.

From a historic viewpoint, the development of elemental speciation techniques is shifting from those focusing on screening for the presence of known, toxic (often anthropogenic) metal-containing compounds toward state-of-the-art speciation of much more complex multielemental systems. Nowhere is this trend more evident or more challenging than in the analysis of elements in biological systems, a field broadly termed metallomics. The role of various elements in cellular function, disease states, and in establishing protein structure and function is an area of current and increasing interest in the life sciences. These investigations require the survey of a vast number of unidentified species present at various, and often minute, concentrations in complex matrices.

Not surprisingly, the peak capacity of conventional separation-based speciation methods is quickly overcome, and retention-time matching is impractical when the sample contains large mixtures of unknown analytes. Further, overlapping peaks that contain the same element can be mistakenly quantified together, and any chemical conversion of species that might occur during the separation often go undetected. This latter situation is exacerbated by the fact that most detection methods for mass and emission spectrometry focus on one or a handful of elements to the exclusion of all others, thereby ignoring the total elemental composition of the molecule under study.

For these reasons, many investigators are currently pursuing strategies for improving plasma-source techniques for elemental speciation. In some instances, these efforts are aimed at enhancing the general performance of PS-MS itself, specifically in raising sensitivity or in mitigating matrix interferences that have historically hindered the determination of some elements. Other investigators are coupling PS-MS with chromatographic methods that possess greater separation efficiencies, are based on other mechanisms, that are better adapted to samples of ever-smaller quantity, or that are conventionally employed only for particular samples. Other strategies are aimed at modifying the plasma ionization source itself in order to gain specific benefits, to obtain more and different chemical information and thus more selective detection, or to scale plasma sources to better operate with separations of ever-decreasing physical dimensions. Here, several of the novel methods, instruments, and techniques currently being developed within PS-MS for elemental speciation are reviewed and contrasted, with examples provided from the authors' laboratory and the literature. This review is not intended to be exhaustive nor to focus upon the application of elemental speciation to a specific problem, but rather to highlight current areas of activity in speciation-based PS-MS and to illustrate the importance of elemental speciation.

2. Inductively-coupled plasma mass spectrometry

ICP-MS is the current method of choice in many speciation applications for reasons that are easy to recognize: ICP-MS offers high sensitivity and very low limits of detection for elements across the period table, a wide linear dynamic range, access to isotopic information in a simple spectrum with limited spectral overlaps, modest matrix effects, and convenient quantitative and semi-quantitative analyses of solid, liquid, and gaseous samples. A number of chromatographies have been coupled to ICP-MS for the purpose of speciation: HPLC [8,10], capillary electrophoresis (CE) [11,12], size exclusion chromatography (SEC) [5], ion chromatography (IC) [13], supercritical fluid chromatography (SFC) [14], gas chromatography (GC) [15], and multidimensional separations. A number of excellent reviews cover these topics in more detail [5,8,10].

The ICP is attractive for use in speciation in part because it is highly efficient and permits simultaneous analysis. Nearly all the elements in the periodic table (with the exception of some halogens and noble gases) can be ionized with an efficiency close to unity, and under similar operating conditions [16]. Thus, it might be expected that a simultaneous multielemental measurement technique would be the optimal means of exploiting the attributes of such a plasma source. Historically, however, ICP-MS instrumentation has been based upon quadrupole mass filters or double-focusing sector mass spectrometers. Although these spectrometers possess many attractive features, both are sequentially scanned in nature, and therefore have inherent limitations that can compromise multielement determinations [17]. With such systems only a single mass-to-charge ratio (m/z) is monitored at any given time, so the duty cycle (the number of ions analyzed/the number of ions presented to the mass analyzer) achievable for each m/z value decreases directly with the number of m/z values measured. The signal-to-noise ratio (S/N) and precision obtainable in a given time, as well as the mass resolution, are therefore a function of the number of elements and isotopes that are to be investigated.

In some instances, the consequences of low signals and ion statistics can be overcome simply by extending the length of the observation. However, when a transient signal is being studied the observation time is necessarily restricted. For example, the peak widths of eluting compounds are directly related to the resolution of a chromatographic separation. Because there is a fundamental limit to the rate at which successive measurements can be made with these instruments, a compromise is often made to limit the number of masses that are observed during each transient, or by approximating a steady-state situation by diluting a transient to extend its duration [18,19]. Recently, several investigators have accomplished quantitation of transient events in ICP-MS by collecting as few as three to four points across each transient profile, sacrificing peak-shape information in order to observe a greater number of m/z values [20–22]. The authors note, however, that care must be taken in applying this

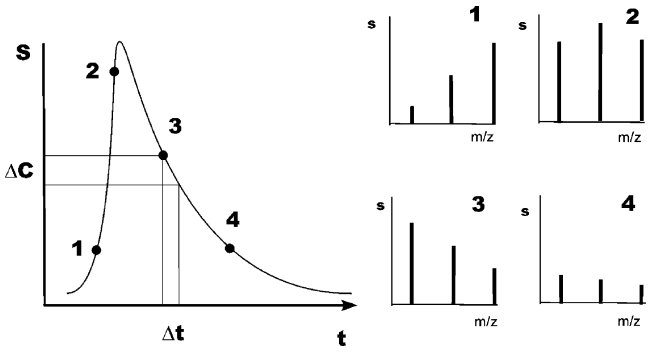

Fig. 1. Conceptual diagram illustrating the origin of spectral skew error. Transient profile (left) depicting signal (S) as a function of time (t) undergoes a change in concentration (Δc) during the time (Δt) required to complete one scanned spectral acquisition. The result (right) is a skewing of apparent intensity of three equally abundant m/z dependent upon the point (1–4) at which they were observed during the transient.

under-sampling technique, which is best suited to the analysis of relatively imprecise single-channel measurements and to transients with symmetric peak shapes [23]. In these instances, information is lost or analytical performance can be sacrificed in order to accommodate the scanning nature of the mass spectrometer. Further, analyzing fast transient signals in this manner can lead to a sampling error known as spectral skew.

Spectral skew refers to the distortion in relative abundances of peaks in a mass spectrum that results from scanning the spectrum during a time-dependent concentration change. This sort of error is fundamentally unavoidable when a scanning spectrometer is used to record a transient signal. A conceptual diagram illustrating spectral skew is shown in Fig. 1, where the concentration profile of a hypothetical transient event, such as an eluting peak from a chromatographic separation, is depicted as a function of time.

A sequentially scanning spectrometer (mass, wavelength, etc.) that initiates a spectral scan at some point (t_1) will require a finite period of time to complete the scan (t_2), where $t_1 - t_2 = \Delta t$ is the reciprocal of the spectral-generation rate. Because the concentration of the analyte in the sampled volume is continuously changing (Δc) during this interval (Δt), the recorded spectra will distorted. In Fig. 1, for example, if one were to scan across three m/z of equal abundance proceeding from low-to-high m/z, those m/z values observed at a point nearer the initiation of the scan (the point labeled 1 in Fig. 1) will appear artificially suppressed compared to those observed nearer the completion of the scan (Fig. 1, pane 1). Subsequent scans across the eluting peak will be similarly skewed with respect to the true mass-spectral abundances. This error can have serious implications in the measurement of short transient events and is of particular interest in chromatography, where chemical information is encoded in the retention time and peak shape of eluting compounds.

Sequential measurement of m/z values can also limit the precision with which ratio measurements can be made. PS-MS techniques often exhibit only modest precision; single-

channel ICP-MS measurements, for example, are usually limited to 1–5% R.S.D. The source of much of this variance comes from multiplicative phenomena; it affects all signals in the same manner, and by an amount proportional to the signal amplitude. In particular, the ICP is known to suffer from a source of correlated noise known as whistle noise, which typically occurs in the audible range, as well as flicker (1/*f*) and white noise [24–27].

Multiplicative sources of noise can be eliminated only by applying the arithmetic opposite, division, and thus ratioing techniques such as internal standardization and isotope ratio analysis are often used. However, because scanning instruments cannot measure all *m*/*z* values of interest at the same moment in time, the measurements become susceptible to low-frequency noise and drift. Several researchers have shown the isotope-ratio precision obtainable with quadrupole [26,28] and double-sector [29] ICP-MS instruments to improve as the time between successive *m*/*z* observations is reduced. Bjorn et al. [20] have also shown the isotope ratio precision to be a function of the order in which *m*/*z* are observed.

Naturally, the magnitude of the inaccuracy incurred during this sampling error depends critically on the sampling rate, the transient lifetime or frequency characteristics of the signal, and the type of information sought from the analysis. Spectral skew can be particularly pronounced in conventional GC-MS experiments, where the mass range to be examined is broad, in which a large number of molecular fragments of varying abundance must be observed, and where transient signals might possess a range of shapes depending upon tailing, loading, etc. [30]. Analogous effects are observed in PS-MS with chromatographic sample introduction or when sample-introduction sources such as electrothermal vaporization (ETV) are employed. A number of authors have studied experimentally and theoretically the effect of scan rate on the quality of information available from transient signals produced by ETV, flow injection analysis (FIA), laser ablation (LA), and various chromatographic separations [20–22,31,32].

Many have recognized that the aforementioned limitations can be overcome by simultaneous observation of all *m*/*z* of interest. Further, simultaneous detection of an entire atomic mass range offers several additional benefits; thus, quadrupole ion traps (QIT) [33,34], Fourier transform ion cyclotron resonance mass spectrometers (FTICR) [35], time-of-flight mass analyzers (TOFMS) [36], and multichannel mass spectrographs [37] have all been coupled to the ICP. To the authors' knowledge, however, the latter two are the only ones to have been used for elemental speciation.

3. Time-of-flight mass analyzers

A TOFMS possesses a number of attributes that make it attractive for use in PS-MS, and particularly for elemental speciation. Like other simultaneous mass analyzers, but unlike sequentially scanning instruments, TOFMS offers the same precision, sensitivity, and resolution regardless of the number of *m*/*z* that appear in the spectrum. Thus, all elements and isotopes can be monitored throughout a chromatographic separation, so unexpected or unknown compounds can be recorded as they elute, without adversely affecting S/N. Additionally, because every *m*/*z* can be detected with each extraction event, a TOFMS is capable of more efficiently utilizing those ions than its scanning counterparts. The lack of restrictive architecture within the instrument also offers greater transmission efficiency than that obtained with other mass spectrometers, thus promising excellent sensitivity.

Simultaneous extraction of all *m*/*z* from the primary ion beam also permits greater measurement precision to be achieved with TOFMS. Multiplicative noise can be overcome by internal standardization and isotopic ratioing, and the complete elemental and isotopic coverage of TOFMS means that all *m*/*z* are available during even short-lived transients. Vanhaecke et al. [38] reported that isotope ratios of various elements could be determined with a precision better than 0.05% R.S.D. after only 30 s observation of a 500 μg/L solution, and isotope ratios could typically be measured with precision <0.5% R.S.D. for FIA injections 6 s in duration (FWHM). Similar levels of isotope-ratio precision and accuracy have been achieved by quadrupole-based ICP-MS if only a limited number *m*/*z* values is examined [31]. Because sensitivity and precision are unaffected by the number of *m*/*z* monitored by ICP-TOFMS, such systems find greatest advantage in isotope-ratio determinations of short-lived transient events such as are often produced during elemental speciation.

The limiting rate at which successive mass spectra can be generated by a TOFMS is simply the inverse of the time required for the largest *m*/*z* of interest to traverse the drift region and be detected. Elemental speciation by PS-MS often examines only the atomic mass range (roughly from 7 to 238 amu), so PS-TOFMS instruments can produce a complete elemental mass spectrum in tens of microseconds, and can generate tens of thousands of such spectra every second when utilized with continuous ionization sources. These high spectral-generation rates, combined with the ability to provide complete multielemental and isotopic coverage with each mass spectrum, makes TOFMS well suited for use with pulsed ionization schemes or in conjunction with transient sample-introduction sources. The coupling of PS-TOFMS with chromatography for elemental speciation is particularly advantageous, as multielemental analysis can be conducted in the absence of spectral skew. TOFMS is also well known for its unlimited mass range. Although this attribute would seem to be of limited importance in inorganic mass spectrometry, it could be critical to elemental speciation, or in conjunction with a source capable of producing either atomic or molecular mass spectra.

Several reviews treat TOFMS instrumentation for plasma sources in detail [39–42]. Likewise, the utility of ICP-TOFMS as a detector for elemental speciation has been comprehensively reviewed [43–45], so only selected examples will be included here.

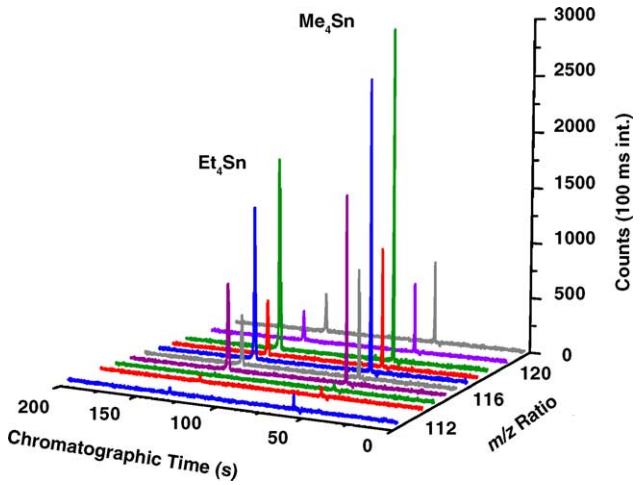

Fig. 2. Multi-isotope detection during the separation of tetramethyltin (Me_4Sn) and tetraethyltin (Et_4Sn). Injection contained 50 pg of tin per compound [reproduced from reference [47] with permission].

Several researchers have successfully coupled ICP-TOFMS to capillary-column GC for elemental speciation [15,46–49]. This hyphenated combination is particularly attractive since eluting GC peaks are often of single-second duration, during which time the ICP-TOFMS can provide several thousand complete atomic mass spectra and complete isotope-ratio information. Leach et al. [47] have recently employed GC-ICP-TOFMS for the speciation of organotin and organolead compounds. A chromatogram illustrating such a separation is reproduced in Fig. 2, where the isotopes of tin representing the separation of 5 pg tetraethyltin and tetramethyltin are shown. The authors reported limits of detection from 11 to 13 fg for several organic tin and lead compounds, with a linear dynamic range extending over six orders of magnitude. More than 80 measurements (each the average of 255 mass spectra) could be averaged across eluting peaks 1–2 s in duration, and $^{118}Sn/^{120}Sn$ isotope ratios were determined with an accuracy of 0.28% and precision of 2.88% R.S.D. based upon 10 replicate injections of 5 pg tetramethyltin as compound.

The ability to accurately and precisely measure isotope ratios during chromatographic separations is of importance when biological stable isotope tracers are employed, and when the biological and environmental fate of anthropogenic compounds is examined. Haas et al. [50] recently employed GC-ICP-TOFMS to determine volatile tin and antimony compounds in landfill gas samples as a means to examine the biovolatilization of metals in the environment. Here, the authors examined isotopic fractionation in biotransformed organometallic species, observing 30 isotopes of various volatile organometallic elements present in picogram quantities following cryotrapping and separation by GC. Such applications illustrate the increasing complexity of elemental speciation analyses, as “real-world” landfill samples might contain any number of volatilized elements, and require capturing isotopic information from eluting peaks that are only seconds in duration [51]. Antimony and tin isotope ratios ($^{118}Sn/^{120}Sn$, $^{121}Sb/^{123}Sb$) were determined for seven standard compounds with accuracies of 0.13–1.7% and precisions from 0.34 to 1.9% R.S.D. based on headspace GC analysis of several organometallic compounds present at 1 ng in 100 mL air. Many volatile organometallics present at concentrations from 2 to 50 ng/L were observed, and isotope ratios were determined with precision from 0.2 to 2.8% R.S.D. The fact that many of the observed metal-containing compounds did not correspond to known molecules illustrates another challenge facing modern elemental analysis. Although these compounds could be accurately characterized for metal content, little could be learned of their identity by such methods.

Recently, multicapillary (MC) GC columns have been coupled to ICP-TOFMS, permitting greater sample loading without appreciably sacrificing chromatographic resolution. Jitaru et al. [52] have characterized the speciation of mercury by MC-GC-ICP-TOFMS, reporting limits of detection from 16 to 257 fg/g for several organolead compounds in biological samples. These MC columns consist of (900) 40 μm i.d. GC columns bundled into a 1 m long array, permitting increased column loading, correspondingly lower limits of detection, and very rapid separations in situations requiring a modest number of theoretical plates. The authors achieved complete separation in 35 s with eluting peaks as narrow as 400 ms FWHM. Heisterkamp and Adams [46] have also recently coupled multicapillary GC columns to ICP-TOFMS for the speciation of organolead compounds, reporting that typical capillary GC separations 4 min in length could be completed in 20 s with peak widths as narrow as 180 ms FWHM.

Like GC, capillary electrophoresis can produce eluting peaks of single-second duration, and CE has also been successfully coupled to ICP-TOFMS for elemental speciation. Costa-Fernandez et al. [53] have separated nine aqueous metal and organometallic ions in 70 s, with peak widths ranging from 0.9 to 5.7 s FWHM. As in the previous examples, the use of ICP-TOFMS permits such profiles to be followed without peak distortion and in the absence of spectral skew. Fig. 3 illustrates one such CE separation, reflecting the injection of 100 pg of each species (as the metal), with the exception of arsenic which was present at 400 pg. The authors report limits of detection ranging from 1.6 to 21 pg for various nickel, chromium, copper, cobalt, arsenic, and vanadium ions.

Perhaps most challenging is elemental speciation in bioscience, where sample quantities are often very limited and where complex mixtures are encountered, often comprised of unknown species which may themselves be in flux. Infante et al. [54,55] determined metalloproteins in various biological cytosols by size-exclusion HPLC-ICP-TOFMS and anion-exchange HPLC-ICP-TOFMS. Fig. 4 illustrates the fractionation of free ions among several standards detected by SEC-HPLC-ICP-TOFMS, where chromatographic traces are shown for 16 selected isotopes of elements present at pg-levels in a 50 μL injection. The limited number of theoretical plates available makes the faithful reproduction of the

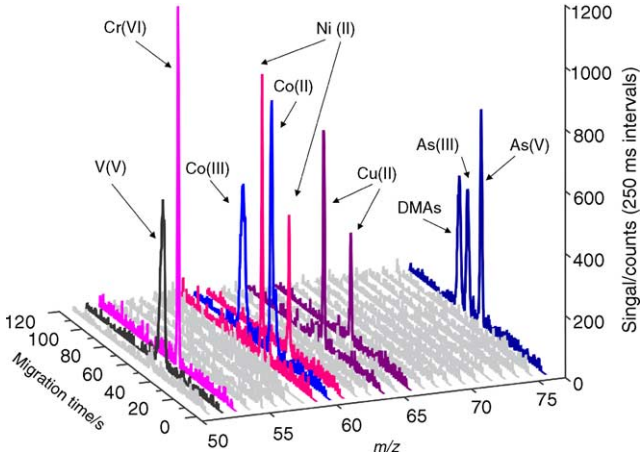

Fig. 3. CE-ICP-TOFMS separation and multielemental detection of V^{V}, Cr^{VI}, Co^{II}, Co^{III}, Ni^{II}, Cu^{II}, As^{V}, As^{III}, and dimethylarsenic (DMAs) cyanide complexes. Injection contained 100 pg of each metal analyte per compound (400 pg of metal per arsenic species) [reproduced from reference [53] with permission].

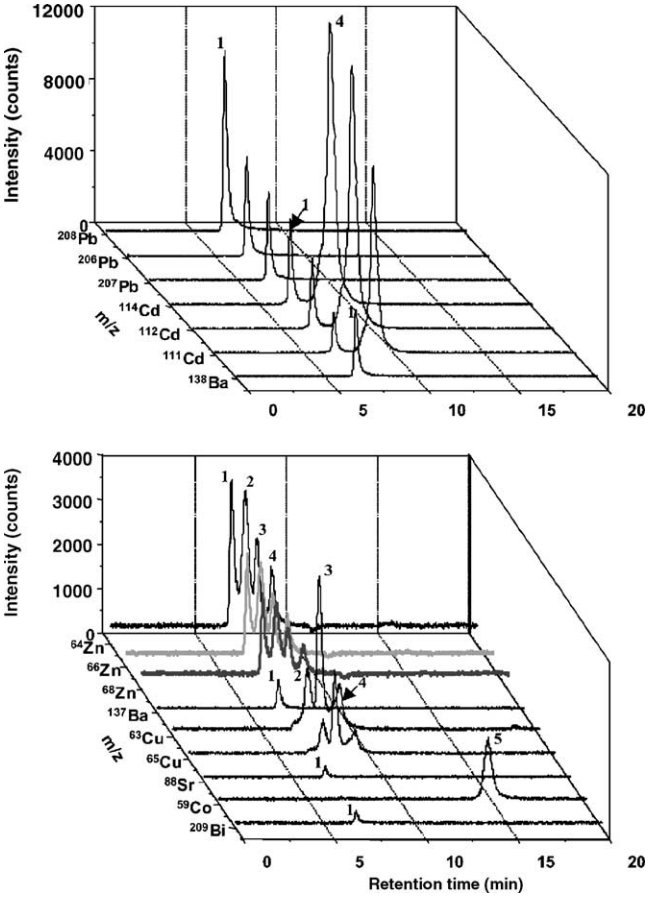

Fig. 4. Performance of the TOFMS spectrometer in transient signal mode using SEC-HPLC-ICP-TOFMS for a single injection (50 μL) of a gel-filtration standard mixture: (1) ferritin; (2) bovine albumin; (3) superoxidase dismutase (SOD); (4) metallothioneine (MT); and (5) Vitamin B_{12} [reproduced from reference [55] with permission].

peak shape important in this application. Limits of detection for the technique were 19–158 pg for several elements. The accumulation of toxic and heavy metals in fish tissue was studied by this method; over 30 *m/z* values were monitored and metallothionene-like fractions or isoforms saturated in several elements were found to be present at μg/g levels. It is noteworthy, however, that the only information the technique provided concerning the chemical identity of the biological species associated with each particular metal was the molecular weight fraction.

Applications of ICP-TOFMS to speciation are hindered by the somewhat lower sensitivity of such instruments compared to quadrupole mass filters. Detection limits reported for ICP-TOFMS instruments are often a factor of 5–20 worse than those achieved by quadrupole ICP-MS instrumentation [31]. However, a theoretical evaluation by Myers and Hieftje [36] suggests that both should offer similar levels of performance; the lower duty cycle of TOFMS (∼10%) when a single *m/z* is monitored should be quickly offset in multielement determinations by the need of a quadrupole filter to scan the mass range of interest. This scanning yields a duty cycle that is inversely related to the number of *m/z* being monitored. Still, although incremental improvements in ICP-TOFMS continue, sensitivity comparable to commercial quadrupole mass filters has not yet been realized.

4. Array detector atomic mass spectrometry (ADAMS)

Although TOFMS and quadrupole instruments offer many of the benefits of simultaneous multielemental, multi-isotope detection, they are often termed pseudo-simultaneous mass analyzers because they rely upon simultaneous sampling of the ion beam rather than truly concurrent detection. With each sampling event, all *m/z* values are extracted from the primary ion beam at the same moment. Therefore, as long as the ion population sampled by the mass spectrometer faithfully represents the composition of ions in the source at a given time, most of the features of simultaneous detection are retained. However, in situations in which ions have greatly divergent energies, or in which very small differences between ion populations are at issue (such as in highly accurate isotope ratio measurements), the distinction could become significant. Further, these instruments often yield duty cycles much less than unity, since no sampling can occur while a mass analysis is underway. For these reasons, several investigators have pursued means of continuous and simultaneous detection for mass spectrometry [56–59].

Recently, a collaboration among our laboratory, the University of Arizona, and Pacific Northwest National Laboratory has resulted in the development of a focal plane camera (FPC) coupled to a Mattauch-Herzog mass spectrograph as a means of simultaneous and continuous detection in atomic mass spectrometry. The double-focusing Mattauch-Herzog spectrograph is a particularly appropriate choice for such a

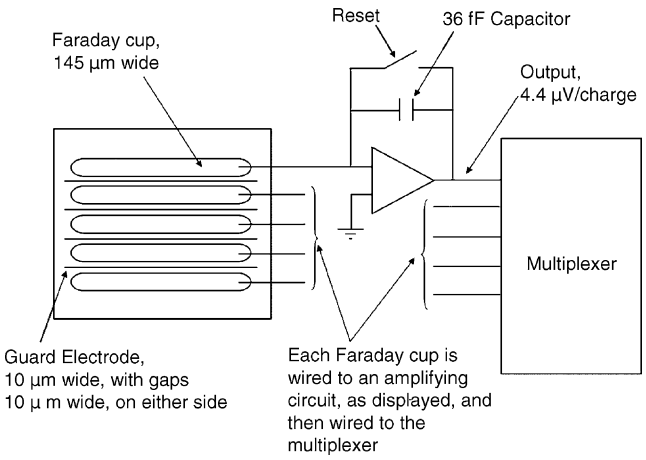

Fig. 5. Schematic diagram of the focal plane camera (FPC) used for simultaneous multichannel detection of mass spectra.

system, as it possesses a flat focal region along which the slit image corresponding to every *m*/*z* is simultaneously focused. Thus, a linear detector array positioned at this focal plane is capable of observing all *m*/*z* of interest at all times. Because Faraday cups respond to absolute charge measurements, produce no mass bias, and are capable of precise, low-drift amplification, they offer much greater precision than electron multipliers and were therefore chosen for use in the FPC.

In this case, the camera consists of a micro-array of gold Faraday collectors, each of which is electrically connected to its own high-gain charge-integrating amplifier. An illustration of the FPC is included as Fig. 5, and more detailed information can be found elsewhere [60]. The ion current from all individual Faraday collectors is integrated simultaneously and continuously, and the integrators can be repeatedly interrogated sequentially, or randomly, by means of a low-noise multiplexer unit. This reading process is non-destructive, so the finite noise involved in the reading operation can be reduced by multiple read events. When a given channel nears its saturation level, the integrating capacitor can be shorted, to reset the integrator and to allow it to continue accumulating charge. This combination of destructive and non-destructive readout expands the dynamic range of the system by allowing each channel to be integrated for an optimal length of time. The authors report that 4.4 μV is observed across the capacitor (36 fF) for each ion accumulated by the 145 μm wide detector element, and the limit of detection for the current FPC detector is estimated to be 20 ions with a linear range spanning more than seven orders of magnitude [60].

Scheidemann et al. [61,62] have described a system based upon a more traditional Faraday cup detector array, but employing a novel Mattauch-Herzog mass spectrograph. In a conventional magnetic-sector mass spectrograph, *m*/*z* varies quadratically with position along the focal plane, meaning that adjacent isotope peaks pack together at high *m*/*z*. Scheidemann et al. [63] have modified a magnet to generate a quadratic field that in turn causes *m*/*z* to be dispersed linearly along the focal plane, thus greatly simplifying the camera design. A commercial instrument based on this concept is being offered.

Barnes et al. [64–67] have evaluated their FPC mass spectrograph with both ICP and glow discharge (GD) ionization sources, and compared the results obtained with the FPC to those with conventional detectors. Their preliminary FPC design yielded GD-MS detection limits improved by more than three orders of magnitude over those obtained with a previous electro-optic array detector, and delivered performance comparable to that of conventional electron multiplier detectors. Limits of detection spanned the range from 1 to 100 μg/g (in the solid) for various metals for GD-MS, and 1–0.1 ng/L with the ICP. Observation of a range of *m*/*z* values simultaneously and continuously provided an improvement in isotope-ratio precision by more than two orders of magnitude over single-channel measurements. Isotope-ratio precision ($^{107}Ag/^{109}Ag$) was shown to be as good as 0.007% R.S.D. for an integration time of 3 min with ICP ionisation, and isotope-ratio accuracies were shown to be in the range of 1–5%. Performance therefore rivals that of far more costly and complex multicollector sector-field ICP-MS instruments. The system was also much freer from mass bias than more conventional detectors.

Recently, the authors have shown that this system is also valuable for the interrogation of transient signals, such as peaks eluting from a chromatographic separation [68]. One example is illustrated in Fig. 6, where the separation of six brominated hydrocarbons was accomplished by GC-ICP-MS, here representing the injection of 140 pg of each compound. In Fig. 6A, the spectrum is presented as the total ion current (TIC) as a function of retention time, while the accompanying Fig. 6B represents the output of the FPC during the same separation. From Fig. 6B, it is clear that isotope information is easily accessible when the FPC is employed, and the observation of the entire mass range of interest allows

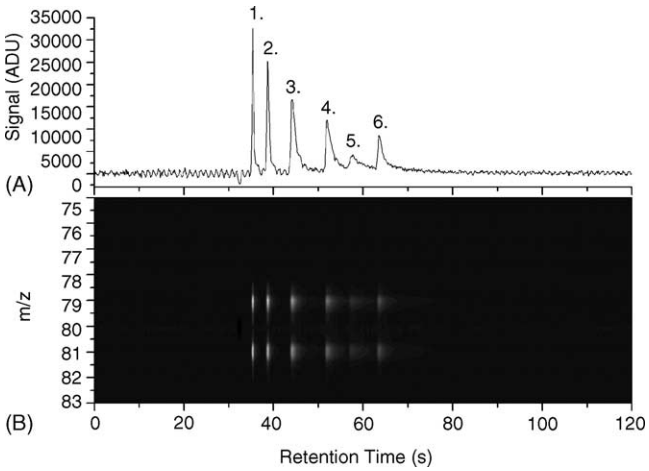

Fig. 6. Background-corrected chromatograms for the injection of 1.4 ng of six brominated hydrocarbons with: (A) total ion-current response; and (B) *m*/*z*-dependent response. Peaks: (1) 1-bromopropane; (2) 1-bromobutane; (3) 1,2-dibromoethane; (4) bromoform; (5) bromobenzene; (6) bromocyclohexane [reproduced from reference [68] with permission].

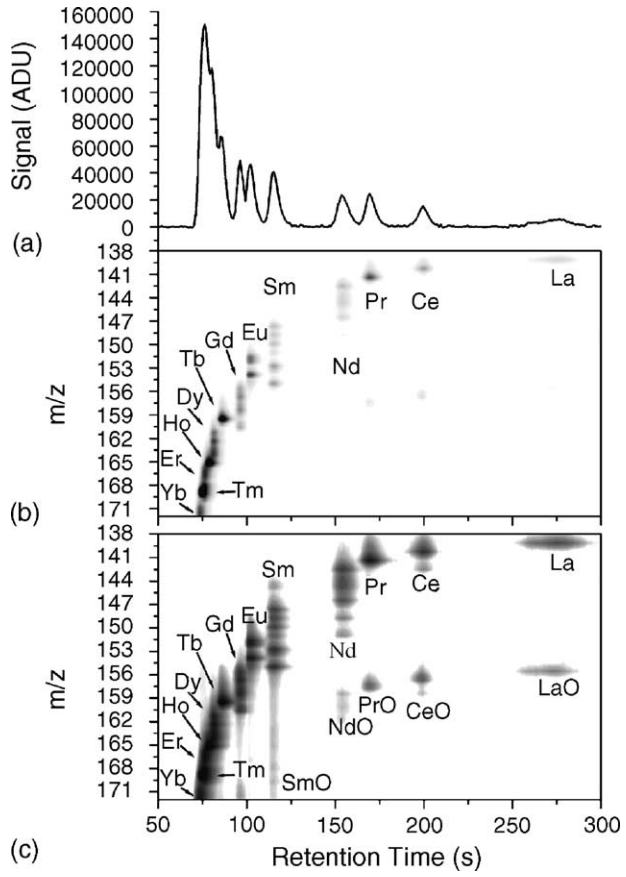

Fig. 7. Conventional (a) and mass-resolved (b) chromatograms for the separation of a multielement lanthanide solution. To more clearly show the presence of oxides, the mass-specific chromatogram has been plotted also on a logarithmic intensity scale (c). The use of a separation step enables the removal of polyatomic interferences [reproduced from reference [69] with permission].

the detection of unexpected species that might otherwise be missed. Absolute limits of detection for a variety of volatile organometallics spanned the range from 1 pg to 34 fg. The temporal resolution is a function of the read-time of each pixel of interest; here camera frames were integrated and recorded every 100 ms.

The authors have also achieved the speciation of several organometallic compounds by coupling the FPC system with HPLC [69]. In Fig. 7, results are shown for a 10 μL injection of a 1 ppm multielement lanthanide solution separated on a C_{18} column using a mobile phase consisting of 180 mM 2-hydroxyisobutyric acid (HIBA) and 5 mM 1-octanesulfonic acid monohydrate (SOS). Fig. 7a again illustrates the total ion current observed as a function of retention time, revealing incomplete separation of many components. Of course, element-selective detection requires only that species containing the same element be separated by chromatographic means. Thus, the mass spectra in Fig. 7b and c illustrate separation of co-eluting components by mass spectrometry. Absolute limits of detection for a variety of analytes ranged from 0.3 to 98 pg for a variety of metals and organometallics, and are comparable to or better than earlier values in the literature.

The authors note that the FPC detection system is still in its early developmental stages and still suffers some limitations. The current pixel array covers only a small portion of the focal plane with 32 Faraday cups, so the magnetic field strength or accelerating potential must be varied in order to move the desired *m*/*z* range onto the array. Also, the minimum data-acquisition time for multiple images is currently 1 ms/image with a dead time of 3.2 ms between images, which limits the ability of the current unit to monitor extremely short transient signals. All these shortcomings are technical in nature, and it is expected that the next generation of FPC will improve these values.

5. Mitigating spectroscopic interferences in ICP-MS

Spectral interferences represent one of the greatest limitations hampering ICP-MS determinations in elemental speciation. Many elements of interest in bioinorganic speciation analysis such as Ca, K, As, and Fe suffer from a serious spectroscopic overlap with some interferent ion. These interferences can arise from the plasma gas (ca. $^{40}Ar^{+}$ with $^{40}Ca^{+}$), adducts that are formed through condensation (ca. $^{80}Ar_2{}^{+}$ with $^{80}Se^{+}$), or polyatomic ions formed from solvent or matrix products (ca. $^{40}Ar^{35}Cl^{+}$ with $^{75}As^{+}$). To be sure, many of these isobaric interferences can be overcome simply by application of greater resolving power, on the order of $R_{10\%} = 3000$. Commercial double-focusing ICP-MS instruments can attain resolution values of $R_{10\%} = 10{,}000$, sufficient for overcoming interferences such as $^{56}Fe/^{40}Ar^{16}O^{+}$ ($R_{10\%} = 2500$), $^{52}Cr/^{40}Ar^{12}C^{+}$ ($R_{10\%} = 2375$), and $^{45}Sc/^{29}Si^{16}O$ ($R_{10\%} = 2900$) [70,71]. Consequently, sector-field ICP-MS instruments have been successfully applied to the determination of transition metals in geological, environmental and biological materials [70,72–74].

From a spectroscopic standpoint, the separation of two ions based upon their dissimilar *m*/*z* values is dependent not only on resolution but also on the abundance sensitivity of the mass spectrometer. Abundance sensitivity is a measure of the contribution of a peak at a given *m*/*z* value to a peak 1 amu distant, and is a reflection of peak shape and other factors. Unfortunately, many instances of isobaric interference in plasma source mass spectrometry require the separation of an interfering ion present at very high abundance from an analyte ion present at ultra-trace concentrations. Thus, even though the instrumental resolving power might predict adequate separation of the two peaks, in reality the contribution of the highly abundant interfering ion to the neighboring *m*/*z* value where the analyte ion resides can be unacceptably high. Further, double-focusing instruments tend to be expensive, and the resolving power of other ICP-MS instrument platforms cannot be easily modified. It is therefore important that several methods exist that mitigate isobaric overlaps by changes in the plasma spectrochemistry.

As illustrated principally by Sakata and Kawabata [75] and Tanner [76], the operating parameters of an ICP can be adjusted to lessen the severity of several spectral interferences. The formation of many of the interfering plasma-ion species, and particularly of the polyatomic ions, is highly dependent on the plasma operating conditions, which are in turn governed largely by the rf power and the nebulizer gas flow rate. An ICP under conventional analytical conditions might operate with 1000–1400 W rf forward power and a nebulizer gas flow rate of 0.8–1.0 L/min. These authors found that by reducing the forward power and raising the nebulizer gas flow rates, the plasma became much "cooler", and many of the Ar-based background species were drastically reduced. Typical "cool" plasma conditions were an rf power of 500–800 W and nebulizer gas flow rates from 1.5 to 1.8 L/min. Sakata and Kawabata [75] also reported the use of a torch-shielding system intended to capacitively decouple the plasma from the coil, and found further reductions in the background signal. These authors reported detection limits of 1.1, 1.7, and 20 ng/L for Fe, K and Ca, respectively, when operating under such conditions. Thus, while a typical high-resolution instrument is unable to resolve ^{40}Ca and ^{40}K from the highly abundant $^{40}Ar^{+}$, the dramatic reduction in background species under cold-plasma conditions permits the determination of K, Ca and Fe at trace levels.

While this approach possesses the great advantage that it requires almost no modification of ICP-MS instrumentation, the cold-plasma strategy has been shown to be sensitive to polyatomic species originating from the sample matrix, to suffer from more severe matrix effects, and generally to offer less robust operation. As the detection limits for many elements are degraded under cold-plasma conditions, two different sets of operating conditions are often selected for complete determination of a range of elements. Of course, this approach is somewhat unattractive when the method must be coupled to a separation step to perform elemental speciation.

Conveniently, matrix interferences can themselves be overcome by separating the analyte and matrix species. Also, such interferences can be held in check in well-known matrices. Park and Suh [77] determined Fe and Cr in reference materials (rice flour) using cold-plasma ICP-MS. In order to eliminate interferences produced by the high levels of Ca, an on-line separation procedure using immobilized 8-hydroxyquinoline was adopted. Murphy et al. [78] recently reported the determination of Ca and K in oyster tissue reference material. Cation exchange chromatography was used in order to eliminate interferences caused by the matrix components. In order to determine Ca isotopes in different biological materials, Patterson et al. [79] used cold-plasma conditions after the separation of the analyte by precipitation. Cold-plasma conditions are also used for some determinations in the electronics industry, where extremely low detection limits are required and matrix composition is well known [80].

A drawback of employing a cool plasma is the necessity of changing instrument conditions for different analytes; the response of many elements under cold-plasma conditions is severely degraded. Recently, McClenathan and Hieftje [81] investigated the possibility of switching between hot and cold plasma conditions on a chromatographic timescale. They showed that rapid modulation of a supplemental gas flow added between the nebulizer and ICP torch permits hot and cold plasma conditions to be generated sequentially at rates above 10 Hz. One example is included as Fig. 8, where the signal at m/z = 56 amu (representing the contribution of both $^{56}Fe^{+}$ and the interferent ion $^{40}Ar^{16}O^{+}$) is monitored as "hot" and "cold" cycles are alternately accessed at 1 Hz. The signal resulting from the nebulization of a 50 ppb Fe solution, and a 1% HNO_3 blank, are compared as plasma conditions are modulated. During the "hot plasma" portion of the cycle, lack of any additional gas flow results in an $^{40}Ar^{16}O^{+}$ background equivalent to approximately 0.5 mg/L of iron, making trace analysis of iron difficult. Upon addition of 0.45 L/min Ar as a supplemental flow (cold cycle) the contribution of ArO^{+} drops by approximately four orders of magnitude. In Fig. 8, the addition of 50 ppb Fe to a nitric acid solution results in an observable difference from blank during both hot and cold plasma conditions; however, the lack of a large ArO^{+} background under cold-plasma conditions yields detection limits for Fe in the single ng/L range. While the lower sensitivity of Fe under cold-plasma conditions hampers this application somewhat, reported detection limits represent an improvement of more than an order of magnitude over typical ICP-MS conditions. The authors note that these detection limits are

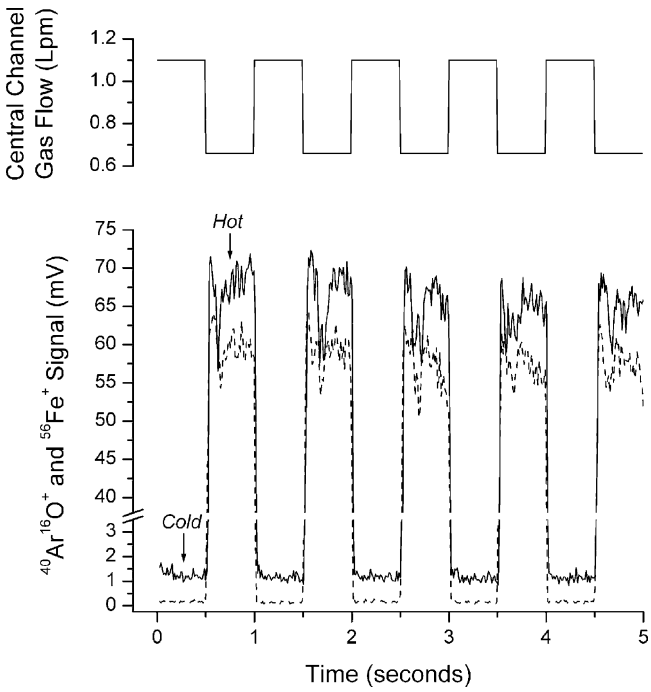

Fig. 8. Sequential switching between hot and cold ICP-MS conditions by modulation of central-channel gas flow at 1 Hz. Signal traces at m/z = 56 amu represent $^{56}Fe^{+}$ and interfering ArO^{+}. Broken line indicates response under hot and cold conditions upon introduction of a 1% HNO_3 blank solution. Solid line represents 50 ppb Fe solution under identical conditions.

comparable to those obtained under steady-state cold-plasma conditions. With this plasma-switching approach, the advantages of each mode of operation might be able to be exploited during the course of a chromatographic separation.

6. Controlling spectral interferences through reaction cells

Rather than changing the chemical environment within the plasma and thus the ion population ahead of the mass analyzer, several investigators have pursued strategies aimed at altering the state of particular ions in the primary ion beam. The use of advantageous ion chemistries to alleviate spectral interferences in PS-MS has been pioneered by a number of investigators employing a variety of experimental conditions [82–86]. Conceptually, a reaction cell for ion chemistry is operated under conditions that permit a controlled reaction or conversion of some target ion, to change its *m*/*z* and thereby alleviate the spectral interference. Conversion of the interferent might involve different types of reactions, such as collisionally induced dissociation (CID), the formation of an oxide, or a specific charge-exchange reaction.

Instrumentally, the reaction volume usually consists of some form of ion-trapping device [87,88]. Many experiments employ a linear rf multipole ion guide filled with a selected gas to a pressure of 1–30 m Torr. In some such systems, the rf ac voltage is augmented with a slight dc offset voltage. The transmission efficiency of a given ion through the cell will depend on the chemical and physical processes that occur in it, and the addition of the voltage offset allows the multipole to act as a low- or high-mass cutoff filter.

Alternately, a three-dimensional (3D) quadrupole ion trap can be employed for the selective accumulation of ions, their selective reaction, and ejection [89]. The accumulation of ions of a particular *m*/*z* is both an advantage and potentially a necessity when one operates with plasma ionization sources, as QIT have an ion-storage capacity limited to 10^4–10^5 ions imposed by space-charge effects. Tanner [90] has noted that a linear quadrupole ion guide cell operated as a two-dimensional ion trap should offer a higher trapping efficiency and ion capacity than the QIT, although this assertion has yet to be experimentally demonstrated with plasma sources. Collision- and reaction-cell devices form the basis of several commercial offerings, and a number of reviews cover the topic in more detail [82,89–94].

Over the period of several rf cycles, numerous collisions between incoming ions and a light bath gas (He or H_2) serve to thermalize analyte ion energies and collisionally focus the incoming ion beam into the center of an ion trap. Energy transfer by elastic collision becomes more efficient as the mass of bath gas approaches the mass of the incoming ion. However, the propensity for ion scattering and thereby loss of analyte ions from the trap also increases as the masses become nearer. A low-mass bath gas such as He is therefore often employed along with higher bath-gas pressures or extended collision lengths. Douglas and French [86] demonstrated that the transmission efficiency of the ion beam increased with use of a collision cell, and that the improvement was proportional to the mass of the incoming ion. Boulyga and Becker [95] found as much as an order of magnitude improvement in sensitivity for heavier elements, and that transmission was a strong function of the analyte mass. Linear multipole devices have been shown to enhance the performance of ICP-MS by collisional dampening of the ion beam, and thereby averaging fluctuations of the ion beam on the millisecond timescale caused by the plasma source. Bandura et al. [96,97] report improvement of isotope-ratio precision to values limited by counting statistics (0.02–0.03% R.S.D. for Pb and Ag present at 40 ng/L) when employing a quadrupole mass filter; a similar advantage has been shown to exist for double-focusing ICP-MS instruments.

Collisional energy dampening of the ion beam offers two additional advantages when a TOFMS is employed. Because the mass resolution of TOFMS depends in part on the energy distribution of the sampled ions, collisional thermalization of ion energies serves to improve mass resolving power [98]. Further, slowing the ion beam increases the instrument duty cycle, and thus should lead to lower limits of detection. Leach and Hieftje [98] have coupled an octopole ion-guide collision cell to an ICP-TOFMS and reported a significant reduction of the noise level (up to seven times); however, in this example the sensitivity for most elements was found to decline so that detection limits were similar to those obtained with conventional instrumental optics.

Having evolved from a tool for tandem MS, the collision-induced dissociation of polyatomic species would seem a natural application of such systems. Rowan and Houk [83] used a quadrupole in rf-only mode with 10^{-5} Torr Xe in a collision cell, and reported that Ar^+, ArO^+ and ArN^+ could be removed while only slightly diminishing the analyte signal. QIT are very efficient in this regard, and several authors have demonstrated that Ar-based interferents (Ar^+, ArO^+, $ArCl^+$, etc.), metal argides, and many metal oxide polyatomics could be almost completely dissociated [34,92,99]. Collisionally activated dissociation by inelastic collision; that is, by the transfer of energy to the internal degrees of freedom of a molecule in sufficient quantity to break a chemical bond, is a somewhat inefficient process. The energy required to break the bonds of polyatomic interferents in ICP-MS is significant and rarely occurs from a single collision. Thus, a sort of "energy pumping" is required in order to accumulate energy through multiple collisions until the bond is broken, a process better achieved by means of a QIT. Bandura et al. [94] calculated that the fragmentation of Ar_2^+ (B.E. = 1.2 eV) would require at least four sequential collisions with He, and that the rate of ion loss due to scattering is often comparable to the rates of CID. Of course, heavier neutral gases can be used, but at the expense of increased losses by ion scattering.

Undoubtedly of greater utility than CID is the use of selective ion chemistries to overcome spectral interferences.

Most famously, the use of preferential charge exchange between Ar^+ and various gases (especially H_2) reduces the argon background by as much as nine orders of magnitude, permitting the isobaric overlap with $^{40}Ca^+$ to be overcome [93]. Similarly, many background ions attributable to or derived from argon can be removed by two to five orders of magnitude [95]. Charge-exchange reactions have the advantage that they can be extremely selective and highly efficient; the reaction rate of Ar^+ with H_2 is 10^6 times faster than for other typical ions [93]. The removal of Ar^+ is also important in the reduction of space-charge effects [91].

The ideal attributes of a CID cell and a reactor for collisional ion chemistry are somewhat different. Collisionally activated dissociation relies on the kinetic energy of the colliding partners for reactions to occur, so high-energy collisions are sought. In contrast, ion-molecule reactions rely on both kinetic energy and the potential energy of the chemical reaction [88]. In other words, while CID is always an endothermic process, the reactants in an ion-molecule reaction can be selected in order to produce an exothermic or nearly exothermic process. The change in enthalpy of the reaction involved can then play an essential role for defining which reactions take place. With this in mind, an environment approaching thermalized conditions is often selected in the ion-reaction cell. The collisional cross-sections (and thus the rate) for the ion-molecule reactions increase exponentially as the system tends toward thermalized energies, permitting reactions to be predicted at least in the first order based on equilibrium conditions [94]. In this way, specific species can be separated based upon their disparate thermochemistry or rates of reaction with a reagent gas.

A potential limitation of reaction cells can arise from the by-products formed in the reaction. In the QIT this is not a major inconvenience, since the product species can be resonantly ejected from the cell. In the multipole ion guides, however, any by-product can potentially reach the mass analyzer and itself create a new spectral interference or increase the background level. Two main discrimination strategies to avoid this problem have been employed. When the analyte and reaction products are considerably different in kinetic energy, Rowan and Houk [83] propose the use of a slightly positive offset potential on the ion guide. The resulting kinetic-energy discrimination does not allow the reaction products to pass through the multipole. However, to preserve the initial difference in kinetic energy the ions must not be thermalized after the reaction. Thus, this strategy can be employed with light bath gases, such as H_2 or He, at low pressures. Alternatively, under more thermalized conditions the cell can be tuned to act as a coarse mass filter. This type of strategy is more appropriate for scanning mass spectrometers [90]. For systems with simultaneous (or pseudo-simultaneous) multielemental detection capabilities, such as TOFMS, the global analytical performance may be seriously affected.

Not surprisingly, a great number of publications have been dedicated to alleviating specific isobaric interferences, and have employed many different reagent gases, and in a number of matrices. A comprehensive treatment falls beyond the scope of this review, and the interested reader is referred to the excellent review of Tanner et al. [90], and to the many other reviews that treat aspects of its application in more detail [80,100,101]. Here, several examples selected from the literature will illustrate the utility of the technique as a means of overcoming interferences in atomic spectrometry.

The reaction rate of Os^+ with CH_4 to form $OsCH_2^+$ and H_2 is five orders of magnitude faster than the analogous reaction of methane with Re^+. Irlkura et al. [102] used this reaction to alleviate the isobaric interference of $^{187}Re^+$ upon $^{187}Os^+$ formed by laser ionization in an FTICR cell. The ratio of these two isotopes, which is relevant in decay-rate geochronological dating applications, would require a resolving power of 6.2×10^7 if attempted by mass spectrometry alone [103]. Eiden et al. [91] have used an ICP-QIT-MS for selective reaction of Zr and Y with oxygen to alleviate an isobaric overlap on the radioisotope ^{90}Sr. The preferential reaction of Zr^+ and Y^+ with a 10^{-5} Torr background pressure of O_2 to form ZrO^+ and YO^+, thereby shifting both by 16 amu, permits determination of $^{90}Sr^+$, whereas the mass-spectral resolution of $^{90}Sr^+$ from $^{90}Y^+$ would require a resolving power of at least 150,000. A charge-exchange reaction between Xe^+ and O_2 was employed by the same authors to alleviate the overlap of $^{129}Xe^+$ with $^{129}I^+$, the latter of which is a nuclear waste by-product. Barinaga and Koppenaal [34] found that O_2 undergoes charge exchange with Xe^+ at a rate 10^4 times faster than with I^+, so Xe is preferentially neutralized leaving iodine ions untouched. A resolving power of 600,000 would have been required in this case. Boulyga and Becker [95] have employed charge exchange of various argides with H_2 to determine isotope ratios of Ca, Fe, and Se with a precision of 0.8–0.16% R.S.D. and good accuracy at a concentration of 10 μg/L.

The use of charge-exchange reactions has also been used extensively in elemental speciation analyses. Hann et al. [104] used reaction cells in ICP-MS coupled to size exclusion chromatography for the determination of metal-sulfur ratios in metalloproteins. Here, the polyatomic overlap at m/z = 32 amu was alleviated by the exothermic reaction of O_2 with S^+ and subsequent formation of SO^+, with Fe and Mn observed under the same instrument conditions. The authors reported limits of detection of 4 μg/L for sulfur as SO^+, and the sulfur-to-metal ratios of several protein standards were determined to be in good agreement with what would be predicted from known protein structure. The ratio precision was 1–3% R.S.D. A similar method has been used with capillary electrophoresis coupled to ICP-MS for the determination of sulfur-containing amino acids [105]. Additionally, a collision cell was recently applied to the speciation of Cr by HPLC-ICP-MS. Here, H_2 was employed to alleviate overlap of Cr^+ with ArC^+ stemming from the organic mobile phase, yielding detection limits of 7.5 pg and 20 pg for Cr^{III} and Cr^{VI}, respectively.

7. Laser ablation ICP-MS for speciation studies

Certainly, hybrid speciation strategies composed of a chemical or physical separation followed by element-selective detection by PS-MS are tremendously powerful, and have been successfully applied to bioinorganic speciation [5,8,10–13]. For the most part, however, the separation methods employed in these investigations are based upon sequential elution, so coupling to PS-MS is relatively straightforward and efficient. Less simple is to couple with ICP-MS a separation technique that uses solid media, such as 1D or 2D slab gel electrophoresis. Such methods are ubiquitously used in many areas of biological research as they are capable of distinguishing tens of thousands of biopolymers with kDa masses, each of which is present at the picomolar level. Typically, the output of such separations is a spatial array of mixture components (based on molecular weight, isoelectric point, size, or affinity); thus the task of elemental speciation analysis lies in mapping the spatial distribution of elements within the gel (or other matrix) after a separation [106]. A number of strategies have been described, involving band excising, spot picking, or extraction of particular mixture components followed by more conventional approaches, such as ETV-ICP-MS [107]. Recently, many researchers have turned to the direct analysis of gel electrophoresis separations by laser-ablation ICP-MS (LA-ICP-MS).

In this solid-sampling technique, a short laser pulse is focused onto the agarose or polyacylamide gel to ablate a 50–300 μm diameter spot. The resulting aerosol is transported to the ICP-MS, and by rastering the laser focal spot across the sample surface, direct multielemental analysis of the gel separation can be accomplished. Neilsen et al. [108] first used this method for the speciation of metal-binding serum proteins in 1D and 2D inmunoelectrophoretic separations. The laser ablation of gels doped with various concentrations of cobalt (0.7–700 mg/L) yielded good linearity and reproducibility (∼6% R.S.D.), and a detection limit of 8.2 mg/L (or 0.075 μg/cm^2). The uniform distribution of Co in the enriched gels also suggested that elements might successfully be used as calibration or internal standards. The authors also reported the resolution of serum samples doped with Co.

Evans and Villeneuve [109] applied LA-ICP-MS to the characterization of humic and fulvic acids separated by SDS–PAGE, in which the gel was doped with ^{206}Pb as an internal standard. The great variety of molecular weights and structures of humic and fulvic acids translated into a virtually continuous distribution of compounds across the gel, emphasizing the importance of high and continuous spatial resolution. The difficulty in establishing absolute concentrations in solids by LA-ICP-MS and in ablating optically transparent samples are problems familiar to the technique. Here, the authors employed NIST glass standards for calibration, and noted that the efficiency of the ablation depended on the relative opacity and concentration of the analyte bands. Thus, an internal standard (^{13}C in this case) was employed; in this way, the relationship between Pb affinity and molecular size could be established.

More complex systems have also been investigated using this approach. For example, Binet et al. [110] investigated metal binding to various proteins in *Escherichia coli* bacteria. The cytoplasmic fraction of bacteria incubated in the presence of controlled concentrations of Zn and Cd was separated by gel electrophoresis and analyzed by LA-ICP-MS. Calibration was performed by doping the gels with standard metal solutions, resulting in a linear range of 10–100 mg/L; no detection limits were reported. In this case, sulfur (^{34}S) was used to monitor protein profiles, and specific protein fractions showing metal accumulation due to metal stress were identified. A similar approach was reported by Allardyce et al. [111] who used LA-ICP-MS to identify cis-platin or Pt-binding proteins in *E. coli* after separation in 2D gels. Fan et al. [112] reported the use of this technique for the speciation of selenoproteins in Se-contaminated wildlife, and described a semiquantitative method able to estimate selenium concentrations to low ng levels.

A more systematic approach was developed by Chery et al. [113], who evaluated the detection of many metals (Li, V, Cr, Mn, Ni, Cu, Zn, As, Se, Mo, Pd, Ag, Cd, Pt, Tl, Pb) in polyacrylamide gels using LA-ICP-MS, and then applied the strategy to the determination of Se. A 193 nm ArF laser was used and the authors reported limits of detection (LODs) from 0.4 ng/g (for ^{205}Tl) to 1 μg/g (for ^{66}Zn) for elements within the gel, and calculated absolute limits of detection from 0.05 (Mo) to 90 fmol (Se), based on the quantity of material ablated. With ^{13}C used as an internal standard, precision between 14 and 19% R.S.D. was obtained. The authors note that care must be taken in the choice of an internal standard element as preferential biological affinity for a particular metal might skew results. Linearity between 0.5 and 10 μg analyte/g gel was found in most of the cases. Chassaigne et al. [114] determined Se by LA-ICP-MS, employing a reaction cell and CH_4 for eliminating the Ar_2^+ interference. The authors reported the determination of as little as 6.75 pg of Se in a 1D protein separation, and used subsequent analysis by electrospray ionization mass spectrometry (ESI-MS) to gain complementary information about protein mass and potential identity. Multidimensional strategies such as this are capable of determining element identity and concentration, as well as the identity of the associated biomolecule.

The determination of phosphorus in biological samples is an area of intense interest, as this element plays an essential role in numerous metabolic pathways and their regulation. Marshall et al. [115] have studied protein phosphorylation by means of LA-ICP-MS of gels. Of course $^{31}P^+$ suffers from isobaric interference with several species ($^{15}N^{16}O^+$, $^{14}N^{17}O^+$, $^{14}N^{16}O^1H^+$), so such analyses must be conducted at higher resolving powers or, as here, by employing a collision cell. The authors also noted extremely high background levels of phosphorous within the gel itself, a common difficulty with this technique, which unavoidably compromises

limits of detection. The authors report a signal-to-noise ratio of 10 during determination of 16 pmol of β-casein.

Wind et al. [116] improved on this method for the detection of phosphorylated proteins by transferring the originally separated gel spots to another phosphorous-depleted membrane for analysis by LA-ICP-MS. This scheme greatly reduced nonspecific phosphorous binding and its background. A mixture of phosphorylated and non-phosphorylated proteins was analyzed and a high degree of specificity demonstrated. Separations using different amounts of proteins (from 3 to 25 pmol per individual protein) were performed, and a linear relationship with ^{31}P concentration obtained. A limit of detection of 5 pmol ^{31}P was estimated.

Becker et al. [117] have studied ^{31}P, ^{28}Si, ^{32}S, ^{27}Al, ^{63}Cu and ^{64}Zn in brain samples taken from Alzheimer patients. After a 2D gel separation, LA-ICP-MS employing a sector-field instrument with resolution of $R_{10\%}$ = 4000 yielded limits of detection of 0.6 μg/g for phosphorous in a single protein spot (assuming a single phosphorylation site per protein molecule). The authors also recorded high background levels of phosphorous, as well as many other elements, within the gel. Because the sulfur content in a protein is often known from other methods, these investigators proposed the use of S as an internal standard to overcome sampling irreproducibility, contamination, or as an additional means of selectivity. Initially employing P/S ratios [118], the authors extended the method to include many elements ratioed to sulfur, observing that metal/protein ratios changed over two orders of magnitude for the proteins studied [117].

One of the benefits of using a spatially selective microsampling technique such as LA-ICP-MS is that analysis is conducted with minimal sample preparation or pretreatment. Otherwise, digestion, dissolution, chemical modification, or filtration greatly increase the potential for contamination, reduce sensitivity due to dilution or poor extraction yields, and increase the likelihood of speciation modifications during or after a separation. Of course, LA-ICP-MS is used exclusively for elemental analysis, as molecules are necessarily decomposed into their constituent atoms in the plasma. Not surprisingly, direct gel analysis for molecular information based on matrix-assisted laser desorption ionization (MALDI) has been developed, based predominately on soaking gels in matrix-containing solutions before analysis, or by transferring gel separations to an auxiliary surface [119–121]. Recently, however, Harrison et al. [122–125] have used laser desorption coupled with a corona-discharge plasma for the direct analysis of gel separations for molecular mass spectrometry.

Their laser desorption/atmospheric pressure chemical ionization (LD-APCI) source is illustrated in Fig. 9 [122]. Shots from a pulsed CO_2 laser (10.6 μm) focused to ~0.5 mm diameter spot were used to desorb neutral molecules from a target into a flowing corona discharge, where they were ionized (typically forming MH^+) and sampled into an ion trap mass spectrometer. While both desorption and ionization occur simultaneously in techniques such as MALDI, several

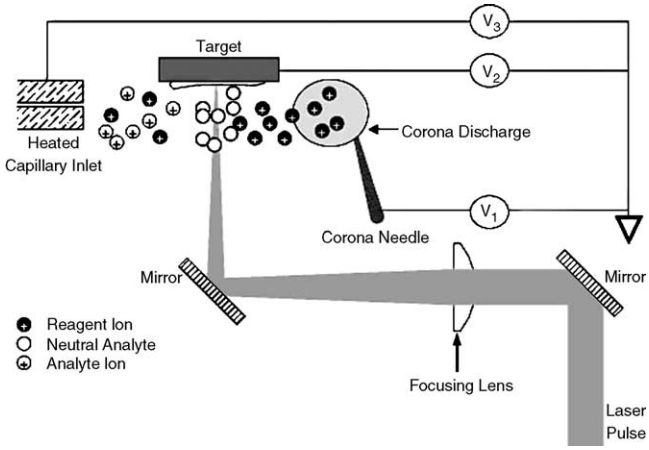

Fig. 9. Schematic diagram of the laser desorption-atmospheric pressure chemical ionization (LD-APCI) setup [reproduced from reference [122] with permission].

authors have shown that decoupling these two processes permits independent optimization of each and thus improved analytical utility. Large numbers of intact gas-phase neutral molecules, together with a smaller portion of gas-phase ions, can be generated by IR laser desorption. These neutral molecules are then ionized by corona discharge via proton transfer, and efficiently thermalized by collisional cooling at atmospheric pressure. Electron-impact ionization (EI) [126], chemical ionization (CI) [127], ^{63}Ni β particle ionization [128], and resonant multiphoton ionization [129] have also been coupled to laser desorption.

Recently, LD-APCI has been employed for the analysis of gel separations [124]. Gel bands corresponding to protein standards were applied directly to the target and yielded predominantly intact parent ions (MH^+). The authors observed much lower continuum background levels than in MALDI, especially at lower masses, which can be valuable in the analysis of smaller peptides and fragments. After an in-gel tryptic digest of horse myoglobin, 13 of 16 possible tryptic fragments within the mass range of the instrument were identified, resulting in 43% coverage of the total protein sequence [123]. The authors also noted preferential ionization of gas-phase neutrals with increasing proton affinity, and reported limits of detection of ~100 pmol of protein for several analytes.

The LD-APCI technique has also been employed to investigate single amino acid polymorphic mutations within the human protein carbonic anhydrase II (HCA II) [123]. The mutant HCA II has three known single-point mutations, only one of which fell within the mass range of the mass analyzer used this study. The results of the analysis of tryptic digests of HCA II and HCA II mutant by LD-APCI, representing the average of 100 laser shots, are illustrated in Fig. 10A and B, respectively. Among the identified tryptic fragments, the authors theorized that the peptide fragment at m/z = 690.4 amu in Fig. 10A had been mutated to the fragment m/z = 722.3 amu in the mutated HCA II by the substitution of an alanine residue with cysteine. This hypothesis was confirmed by treating the

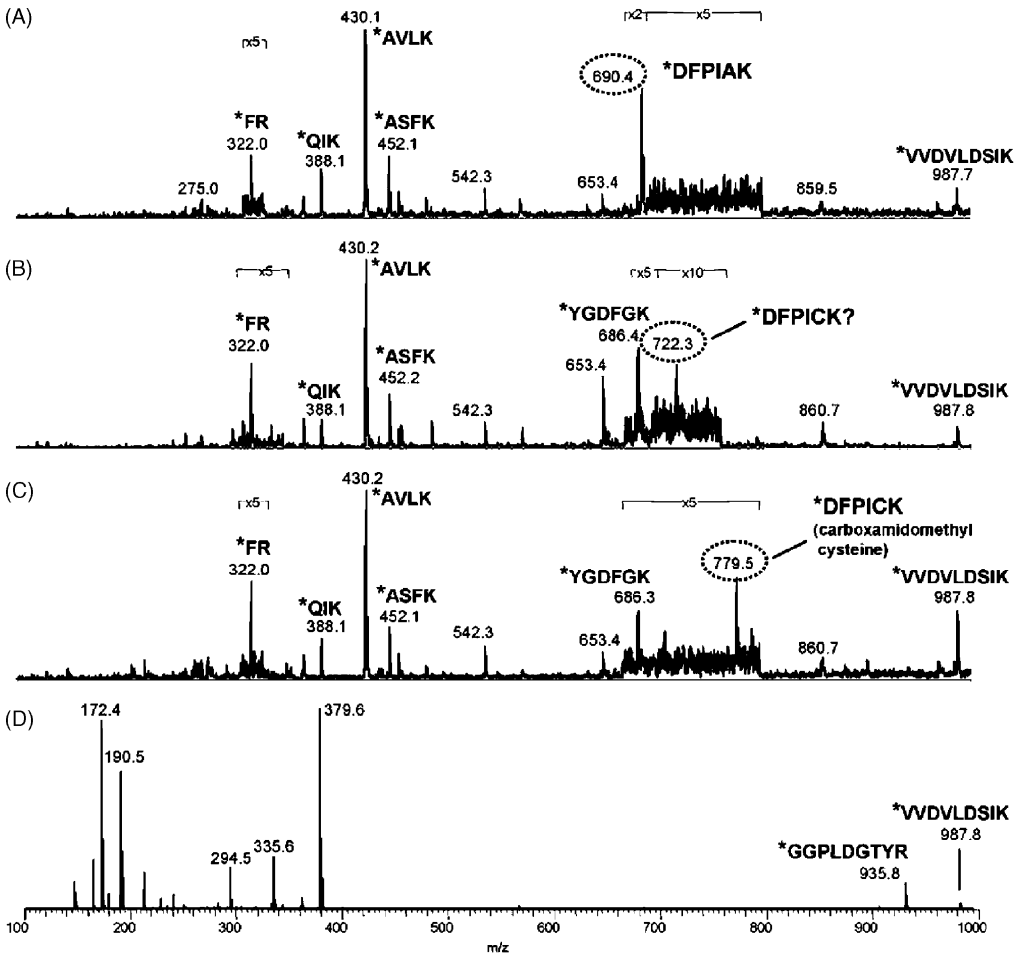

Fig. 10. LD-APCI-MS and MALDI-TOF mass spectra of in-gel protein digests. (A) Direct in-gel LD-APCI sampling of human carbonic anhydrase II (HCA II) wild-type protein digest, (B) HCA II mutant, (C) HCA II mutant treated with iodoacetamide prior to digestion, and (D) MALDI-TOF analysis of HCA II mutant (iodoacetamide treated) in-gel digest extract. The LD-APCI-MS data represents the average of ~100 single-shot mass spectra, while the MALDI-TOF-MS mass spectrum results from the accumulation of 100 single-shot mass spectra [reproduced from reference [123] with permission].

HCAII mutant protein with iodoacetamide prior to digestion, resulting in the chemical modification of this cystein residue and a mass shift of an additional 57 mass units. The disappearance of the peptide at m/z = 722.3 amu and the subsequent appearance of a peptide at m/z = 779.5 amu in Fig. 10C confirmed this single-point mutation. For comparative purposes, Fig. 10D illustrates analysis of the mutant HCA II tryptic digest by MALDI-MS (also 100 laser shots), and thus should be compared with Fig. 10B. MALDI did not produce an ion from the mutated peptide fragment, and in general fewer fragments were observed with a much larger abundance of matrix peaks at low m/z values.

8. Microwave-induced plasma sources

Despite the deserved popularity of ICP-MS for chromatography-based speciation, it suffers several limitations that hinder its application. Most ICPs are sustained in argon and, because the first ionization potential of argon lies at 15.8 eV, elements whose ionization energies lie near or above this value are not efficiently ionized in the ICP [16]. This fact has obvious implications in the determination of halogens, whose first ionization potentials lie between 10.5 and 17.4 eV, but it can also lead to unacceptable sensitivity in the determination of some non-metals and metalloids. Calculations based on the assumption of local thermodynamic equilibrium within a typical ICP predict that 52% of the arsenic atoms (IP = 9.8 eV), 33% of the selenium atoms (9.8 eV), 14% of sulfur atoms (10.4 eV), and only 0.9% of the chlorine atoms (IP = 13.0 eV) will be ionized [16]. Unfortunately, it is often these non-metal, metalloid, and halogen elements that are of interest in environmental and biological elemental speciation applications.

The use of argon in ICP-MS can often lead to additional complications from spectral overlaps, as was detailed earlier. The determination of calcium, for example, is hindered by a direct overlap of its major isotope with that of argon at m/z = 40 amu. Additionally, spectral interferences often complicate the determination of important heteroatoms, such as $^{31}P^{+}$ and $^{32}S^{+}$, which can be obscured in the presence of nitrogen oxide or oxygen dimer species, respectively. Although modifica-

tions in plasma conditions (i.e. operating with a cold plasma), the use of collision-cell technology or high-resolution mass spectrometry can mitigate many of these interferences, figures of merit obtained in such situations often suffer. It is also certainly true that the ICP is a relatively costly ionization source to operate, as substantial power (>1 kW) is required and large quantities of plasma gas (∼20 L/min argon) are consumed.

Even though ionization of non-metal and halogen species is limited in the ICP, using atomic emission spectrometry (AES) with this ionization source has permitted quantification of such species. By utilizing emission lines in the ultraviolet range, atomic detection limits for bromine, chlorine, iodine, phosphorus and sulfur have been reported to be between 0.9 and 19 μg/L [130,131]. Additionally, such nonmetals have also been detected by ICP-AES in waste oil with only slightly higher (poorer) limits of detection, between 0.04 and 1.6 mg/kg [132]. Interestingly, many halogens can be detected with ICP-MS as negative ions. Vickers et al. [133] have reported LOD between 10 and 400 μg/L for halogens by such a method. The authors hypothesized that these ions are created by electron attachment, potentially within the first stage of the mass spectrometer. Although halogen determination is possible through these strategies, such methods provide relatively poor sensitivity. For these reasons, alternatives to the ICP have been examined.

Since their initial development in the late 1940's and early 1950's, microwave-induced plasmas (MIPs) have enjoyed success as an ionization source for both atomic emission and mass spectrometry. In contrast to the ICP, which is sustained by induced magnetic fields oscillating in the MHz regime, MIPs are typically sustained on resonant wave structures tuned to GHz frequencies. Direct comparison of the ICP and MIP, however, is somewhat difficult. It must be appreciated that analytical plasma sources do not typically exist in thermodynamic equilibrium, nor are they spatially homogeneous. Thus, it is important to consider both the kinetic gas temperature (T_g) and the temperature of the electron population (T_e) when the overall conditions within the plasma are discussed. Additionally, such temperatures are location-specific, as plasmas exhibit very strong temperature gradients throughout their volume. As shown in Table 1, experimental measurements reveal that MIPs typically have similar electron number densities but higher electron temperatures than those observed in the ICP. Further, MIPs can be operated with many alternative support gases: nitrogen, helium, argon, hydrogen, and air have all been demonstrated. When helium is employed as the discharge gas, for example, its high ionization potential permits the determination of most non-metals, including halogens, with good sensitivity. As Table 1 indicates, the gas temperatures in MIPs are typically lower than those observed in the ICP. Thus, microwave plasmas typically suffer from more severe matrix effects than the ICP, and are less tolerant of liquid samples, organic material, or particles. The operation, characteristics, and capabilities of many MIPs have been outlined in a review by Broekaert [134].

Microwave-induced plasmas at both reduced and atmospheric pressure have been successfully coupled with both atomic emission spectrometry and mass spectrometry [135]. Detection limits for the determination of various metals by MIP-AES and MIP-MS have been shown to be between 0.1 and 100 ppb and 0.02–39 ppb, respectively [136]. Additionally, the linear range in MIP-MS has been reported to cover approximately three to four orders of magnitude [136]. Microwave plasmas operate easily with comparatively low flows rates of various carrier gases (0.05–2 L min^{-1}), which reduces dilution of analyte species within the plasma and improves the fidelity of the overall analysis. Coupled with the ability to directly determine halogens and a moderate tolerance of molecular species, MIPs are a natural choice as an element-selective detector for gas chromatography. Indeed, the first GC-MIP studies performed in 1965 [137] were followed by the introduction of a commercial GC-MIP-AES system [138], which has enjoyed extensive use for the analysis of a wide range of environmental samples. Analysis of pesticides by this method is particularly attractive because the microwave plasma is capable of generating simultaneous quantitative information for carbon-, chorine-, sulfur- and phosphorous-containing molecules or can provide molecular ions to help identify the parent pesticide species [139]. In addition, a vast number of studies have focused on speciation of volatile compounds by coupling the microwave plasma with gas chromatography for the determination of arsenic [140], mercury [141–143], tin [141,142], and selenium [144], to name a few. A number of reviews have been prepared to cover speciation of a wide range of elements by MIPs and their use in both emission and mass spectrometry [134,145,146].

A relatively new type of MIP, the microwave plasma torch (MPT), was described by Jin et al. [135,146,147] for use in AES and MS, and has subsequently been improved upon by Pack and Hieftje [148] and Bilgic et al. [149]. The MPT

Table 1
Comparison of temperatures and number densities between the MIP and ICP

	Ar ICP	Ar MIP	He MIP
T_e (K)[a]	7000–8500	12,300–13,700	15,900–21,000
T_g (K)[b]	5000–7000	1000–6000	1400–2200
n_e ($\times 10^{15}$ cm^{-3})[c]	1.9–7.0	000.06–1.01	0.06–0.12

[a] Electron temperature (T_e).
[b] Gas kinetic temperature (T_g).
[c] Electron number density (n_e).

offers several advantages over the conventional Beenakker (TEM_{010}) cavity. First, the MPT can be operated at atmospheric pressure with various discharge gases, including nitrogen, argon, helium, and air. Second, the flame-like structure of the MPT is much like that of the ICP, and thus does not suffer from problems associated with the deposition of sample or analytes (particularly carbon) on the walls of a discharge tube, as do TEM_{010} resonators. Finally, and perhaps most importantly, the MPT plasma produces higher gas temperatures (1000–6000 K) but similar electron number densities (10^{14}–10^{15} cm^{-3}) and temperatures (16,000–17,000 K) as typical MIPs (see Table 1), and is therefore more tolerant to the direct introduction of both aerosols and molecular species [146,150]. The tolerance of the MPT to molecular species permits direct analysis of materials containing high concentrations of organic compounds [151]. Also, coupling an ultrasonic nebulizer (USN) to the microwave plasma can help improve limits of detection and facilitate the analysis of aqueous sample solutions [140,152,153].

The MPT is particularly well suited for the analysis of solutions of various non-metal containing species. In one example, an MPT was interfaced with a TOFMS for the measurement of halogenated aliphatic and aromatic hydrocarbons separated by GC [154]. As with the ICP, utilization of a TOFMS permitted complete mass spectra to be generated at a rapid rate (~20,000 mass spectra per second) during the separation, and to be collected without error from spectral skew. Because all ions were simultaneously extracted from the incoming beam, ratioing techniques could be employed to overcome multiplicative noise, to obtain isotope-ratio information, and to provide accurate elemental ratios for identification of analytes in the original solution.

The authors found that the GC-MPT-TOFMS system offered equal sensitivity for Cl, Br and I, and reported absolute detection limits from 160 to 330 fg for compounds detected as halogens, an improvement of a factor of 5–35 over previous results [154]. Interestingly, the ability to monitor all isotopes and elements of interest simultaneously permitted informa-

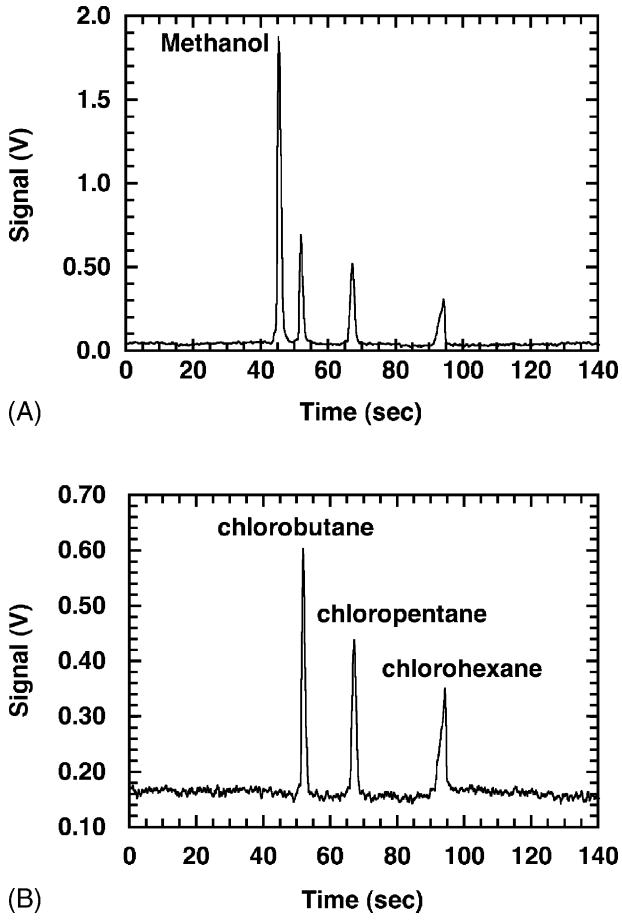

Fig. 11. Isotope-selective chromatograms of halogenated hydrocarbons (chlorobutane to chlorohexane) in methanol. Twin boxcar averagers used for data collection. (A) Signal from ^{12}C. (B) Signal from ^{35}Cl [reproduced from reference [154] with permission].

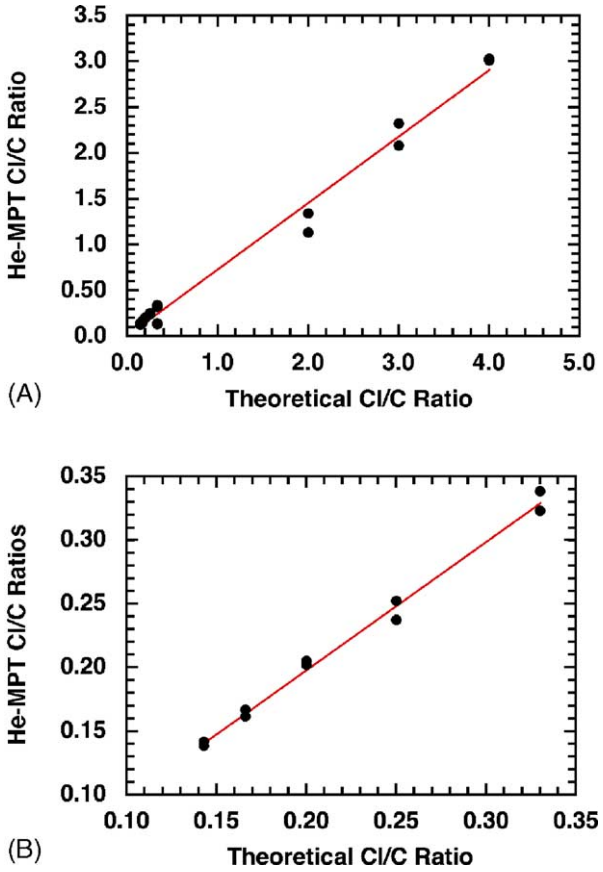

Fig. 12. Comparison of Cl/C ratios obtained from flow cell MPT-TOFMS measurements to values derived from empirical formulas. (A) Ratios obtained from both aromatic and aliphatic species. Compounds used and corresponding Cl/C ratios: chlorotoluene (Cl:C 0.143), chlorobenzene (Cl:C 0.167), dichlorobenzene (Cl:C 0.333), chloroheptane (Cl:C 0.143), chlorohexane (Cl:C 0.167), chloropentane (Cl:C 0.200), chlorobutane (Cl:C 0.250), chloropropane (Cl:C 0.333), methylene chloride (Cl:C 2.0), chloroform (Cl:C 3.0), and carbon tetrachloride (Cl:C 4.0). Correlation coefficient, r = 0.994. (B) Expanded view of the low Cl:C ratio region in (A) which consists of a homologous series of aliphatic halogenated hydrocarbons (chloropropane to chloroheptane) [reproduced from reference [154] with permission].

tion beyond simple elemental ion abundances to be exploited. As illustrated in Fig. 11, both carbon and halogen isotopes (here chlorine) could be monitored throughout the separation, allowing the detection of molecules that did not contain any halogen atoms. Further, eluting peaks could be differentiated based not only on retention time, but also on their different elemental distributions. In Fig. 12, for example, a solution containing eleven chlorinated species were differentiated from one another based upon their individual carbon-to-chlorine ratios. Here, the $^{12}C/^{35}Cl$ ratios determined experimentally are plotted as a function of the ratio expected from the empirical formula. Clearly, experimental and theoretical ratios for the aromatic, aliphatic, and substituted chlorinated hydrocarbons were all in good agreement with the expected values, and a correlation coefficient >0.99 was observed between the experimental data and calculated values when using either peak heights or peak areas. The analysis of eluting peaks in this manner provides an additional, orthogonal dimension of chemical analysis. Compounds can then be identified on the basis of both retention time and elemental composition, permitting unambiguous classification of eluting peaks and potentially improving accuracy; a change in elemental ratio across an eluting peak, for example, would indicate the presence of unresolved components or co-eluting species. Recent work on MIPs has focused on overcoming interferences found in the MPT by means of "off-cone" sampling with time-of-flight mass spectrometry, and by development and characterization of a compact microwave plasma. Duan et al. [155,156] have found that sampling in an "off-cone" geometry yields a reduction in the background species present in the mass spectrum. Such a reduction permits determination of analytes ordinarily obscured by isobaric interferences.

9. Miniaturization of plasma sources for elemental speciation

Recently, significant interest has arisen in miniaturizing plasma ionization sources as components in micro-total analytical systems (μ-TAS), for field portable instrumentation, and in response to the similarly shrinking dimensions of separations used in lab-on-a-chip technologies. Some benefits of miniaturization are obvious: smaller sources demand less power, lessen dilution of analyte within the plasma, require smaller quantities of reagents, gases, and sample, and can be manufactured at lower cost. Less obvious are benefits derived from the scaling laws followed to ensure the plasmas remain physically equivalent with decreasing dimensions [157–159]. Because power density scales with the volume of the discharge, micrometer scale 'microplasmas' can attain power density similar to, or greater than their conventional counterparts while requiring much lower absolute power levels. Further, shrinking plasma chamber dimensions alleviates the reduced-pressure requirements of many microplasmas. For example, direct-current glow discharges require that the product of gas pressure and the linear chamber dimension remain relatively constant in order to maintain similar plasma conditions. Miniaturized GDs can therefore operate at higher gas pressures; Eijkel et al. [160] have constructed a 9 W micrometer-sized dc glow discharge on a microchip that possesses a total volume of 180 nL and is operated at atmospheric pressure. The design and performance of microplasmas for analytical spectroscopy have recently been reviewed elsewhere [161,162], therefore only select examples will be included here.

In a series of papers, Brede et al. [163,164] have described a novel low-power rf microplasma ionization source designed specifically for use with GC-MS. The 1–5 W plasma possesses a volume of 3–4 μL and operates within the high vacuum environment of the mass analyzer on a carrier He gas flow of 1–2 mL/min. Both positive and negative ions have been employed for the element-selective detection of F, Cl, Br, I, and C following GC separations, with LODs of 6–53 [165], and 0.13–12 pg/s [166], respectively. The authors have reported the speciation of tin compounds within cod liver samples, and the determination of halogenated species in sludge, wine, and complex crude oil samples at pg-μg levels [163,165,167].

Because many intended applications of microplasmas revolve around portability, numerous investigators have turned to optical detection strategies. Bessoth et al. [168] have recently coupled a 0.8 W atmospheric-pressure dc GD microplasma contained within a borosilicate microchip to a conventional GC separation. The authors accomplished the detection of several halogenated hydrocarbons by atomic emission spectroscopy, reporting a LOD of 0.8 ng/s for chlorine (detected as methylene chloride). Schepers and Broekaert have described a millimeter-dimension hollow-cathode GD operated at 7–50 W, capable of LODs from 0.1 to 17 pg/s for several chlorine and bromine-containing compounds [169]. Blades et al. [170,171] have developed a 2 mm × 4 mm rectangular capacitively-coupled plasma (CCP) operated at 50 W for use as a detector for GC. The authors reported a LOD of 82 fg/s for iodine as diiodopropane detected by atomic emission [170], as well as the speciation of several organotin compounds by GC with detection limits from 0.079 to 0.190 ng/s [171]. Guchardi and Hauser [172] have recently developed a smaller 20 kHz CCP contained entirely within a 250 μm i.d. fused silica capillary. With hydride generation sample introduction, As, Sb, Hg, were detected by atomic emission through the wall of the capillary with LODs from 500 to 240 ng/mL.

10. Plasma sources for molecular mass spectrometry

Overwhelmingly, present elemental speciation methods employ hybrid techniques wherein a chemical or physical separation is followed by element- or isotope-specific detection. The popularity of this approach is evidence of its many advantages. Atomic spectrometry offers the greatest sensitivity of detection in most cases and provides the same response

for a particular element independent of the molecule containing it. This strategy allows direct intercomparison of the concentrations of species within a mixture. Chromatographic detection by plasma sources also directly yields elemental and isotopic information in a simple spectrum, and with comparatively mild matrix effects. However, plasma sources necessarily destroy all molecular information in the act of atomization and ionization. The identity of the molecule that is associated with an eluting peak must therefore be determined indirectly based on its retention time, so the identity of a particular component in a mixture is established with an accuracy limited by the chromatographic resolution.

Unfortunately, retention-time matching becomes impractical when a sample contains a large number of unknown analytes [173]. Moreover, even in situations for which some previous knowledge of the mixture components is at hand, many of the constituents might not be immediately available, are difficult to synthesize, costly, labile, or have limited storage lifetimes, making chemical identity difficult to establish [174,175]. Further, overlapping peaks that contain the same element can be mistakenly quantified together, and any chemical conversion of species that might occur during the separation often go undetected [176]. This final situation is further exacerbated by the fact that most detection methods for mass and emission spectrometry focus on one or a handful of elements to the exclusion of all others, thereby ignoring the total elemental composition of a molecule.

It has been known for some time that plasma sources operated under appropriate conditions can produce molecular information. Of course, molecular mass spectra alone (parent ion peak, ion fragments, or decomposition products) are not proof-positive of the identity of an eluting species. However, such information does contribute a level of selectivity beyond what is offered by element-selective detection, as it is able to differentiate between compounds containing the same element. Further, molecular mass spectral information can greatly aid in identifying unknown species based on structural information contained in the spectra, by MS/MS analysis, by accurate mass determinations, or by consulting spectral libraries developed for that purpose. Without question, electron-impact ionization (EI) and chemical ionization (CI) represent the standard techniques in this regard.

It is useful to question why a plasma source should be considered when such powerful methods as EI and CI exist. In a typical EI source an electron trap current of 1 mA represents a flux of 10^{15} e^-/s, so a trap volume of 1 mL will contain an electron density of 10^7 e^-/cm^3. Also, EI creates odd-electron molecular ions almost exclusively as a result of electron impact by the ballistic, mono-energetic electrons with translational energies of 70 eV. Such a source is typically operated at pressures below 10^{-4} Torr, and the appreciable mean free path (0.5 m) and low collision frequency (10^{17}/s) under such conditions dictates that most of the ion chemistry occurs by unimolecular ion reactions [177].

By contrast, a reduced-pressure plasma source might contain 10^{10}–10^{12} e^-/cm^3 and a comparable concentration of positive ions in a macroscopically neutral plasma volume. Such systems are best characterized by temperatures, that in turn, describe a distribution of particle energies within the plasma. Although operating parameters such as power and pressure have a dramatic impact upon the plasma environment, one can assign rough temperatures of 10^4 K for the electrons and 10^3 K for gas molecules within reduced-pressure discharges (∼1 Torr) for purposes of this comparison. Thus, EI sources possess energies a factor of 30–70 greater than that available for the ionization of analytes via collisions in plasma sources. Yet, plasma sources exceed the density of charged species (and therefore of potential ionizing reaction partners) of EI sources by three to five orders of magnitude. The collision frequency in reduced-pressure plasmas is also 10^4 times greater than that in EI sources, and coupled with the greater gas temperatures of plasmas one might expect multiple paths of bimolecular ion reactions to occur under conditions more closely related to equilibrium. In this sense, then, reduced-pressure plasmas are more closely related to CI ionization sources, as CI conditions often call for local reagent gas pressures of 0.5 Torr, albeit with much lower densities of charged species.

In spite of such differences, the mass spectra produced by 70 eV EI ionization and reduced-pressure plasma sources are often very similar [178]. A number of investigators have reported that microwave and glow-discharge plasmas have the ability to produce mass spectra similar enough to EI spectra that EI libraries could be searched for identification [179–183]. Although the processes responsible for ionization in these plasmas remains an area of some conjecture, several potential mechanisms might contribute. Ionization might occur simply by electron impact, which would directly explain the similarity of observed mass spectra. Reduced-pressure discharges, and in particular glow discharges, are know to possess high densities of electrons at appreciable energies. While the bulk of the population of electrons are of relatively low energies, the population extends as high as the potential applied to the cathode, often more than a thousand volts.

Alternatively, or more likely acting in concert, molecular ions can be the result of Penning ionization. Penning ionization occurs by a collisional potential-energy transfer between long-lived metastable atoms and an analyte molecule. The energy available for ionization can be appreciable: argon possesses metastable states at 11.72 and 11.55 eV, and helium possesses states at 19.8 and 20.7 eV. Further, the number densities (concentrations) of such metastables can be substantial. For example, Bogaerts et al. have estimated metastable argon densities above $10^9/cm^3$ in a pulsed GD, and Steiner et al. [184] have estimated that 40–80% of ions are created by this mechanism in static GD plasmas.

Thus, plasma sources produce environments rich in the variety of potential excitation and ionization pathways that might be exploited. Moreover, the ionization environment can be readily tailored by selection of the discharge gas, pressure, or power, and thus can be tuned to provide a specific ionization environment and type of chemical information. A review

on tunable plasma sources has been published [185], so we will focus below mainly on recent progress in the field and on associated speciation developments.

11. Reduced-pressure plasmas as tunable ion sources

The ICP is the predominant example of a high-powered plasma in analytical spectrometry. When operated under typical conditions at atmospheric pressure, its high electron and gas-kinetic temperatures provide very efficient atomization and ionization of most analyte species, albeit at the cost of molecular information. In order to retain the analytes' molecular information, ICP operating conditions such as the applied rf power, discharge pressure, central-channel gas flow rate, and identity of the plasma gas or reagent gas have been modified. For example, molecular protonated ions of glycine, glycose, and tartaric acid were observed with detection limits of 100, 2000, and 160 mg/L, respectively, when the ICP was operated at a reduced power and increased central-channel flow rates [186]. Perhaps the most successful modification of the ICP involves operating the plasma at a reduced pressure, typically of 10–200 m Torr [179]. In this arrangement, the plasma is contained in an enclosure so undesired molecular species, such as those arising from air entrainment, do not interfere with ionization mechanisms or produce isobaric overlaps with the molecular analytes. More importantly, reducing the pressure of the discharge serves to lower the gas temperature of the plasma while raising the electron temperature, both of which aid in generating molecular mass spectra.

Evans et al. [187,188] have reported the use of a low-pressure (LP) ICP to obtain both elemental and structural information from gas chromatography separations. In this study, plasma parameters such as rf power and plasma gas flow were varied to tailor the system for either element-selective detection or to produce molecular fragmentation mass spectra. Atomic ions were observed at higher forward power (200 W) and upon concurrent addition of an argon plasma-gas flow of 1.0 L/min, whereas molecular fragmentation was obtained at low forward power (15–50 W) and with no argon plasma gas flow. Mass spectra similar to those from 70 eV EI ionization were obtained when the plasma was sustained on only the chromatograph's helium carrier gas. In this manner, EI libraries could be used to identify unknown analytes. This ability is illustrated in Fig. 13, where mass spectra resulting from the injection of 500 ng of chlorobenzene, bromobenzene, and iodobenzene into the LP-ICP are shown [179]. The mass spectra shown in Fig. 13 are reminiscent of those produced by EI ionization, although the ratios of fragment ions are often skewed to the greater production of $(MH)^+$ ions by the LP-ICP. When the LP-ICP was operated in the element-selective mode the authors reported limits of detection in the range of 13–500 pg for organolead, organotin, organoiron, and several organohalide compounds.

O'Connor and Evans [189,190] found that the addition of different reagent gases to a LP-ICP could be used to promote

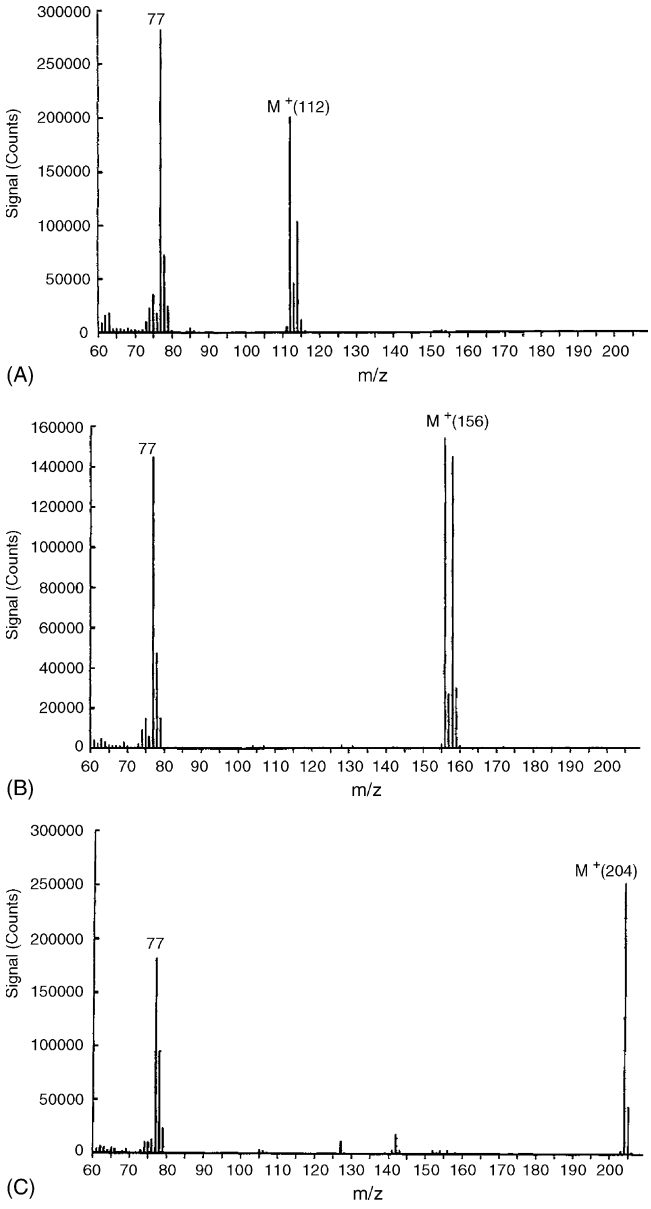

Fig. 13. Mass spectra for (A) chlorobenzene, (B) bromobenzene, and (C) iodobenzene; 500 ng of each [reproduced from reference [179] with permission].

fragmentation of organohalides after GC separation. For example, only the atomic isotopes of bromine were observed for a dibromobenzene analyte when no reagent gas was present. In contrast, phenyl fragment ions and molecular parent ions were observed when 0.07 ml/min of isobutane reagent gas was added. Further additions of isobutane promoted formation of the molecular parent ion almost exclusively. Thus, by titrating a reagent gas into the discharge the formation of parent ion, ion fragments, or atomic ions could be favored. Methane and ammonia were also investigated as potential reagent gases for organomercury speciation in tissue and sediment with GC-LP-ICPMS, where it was found that ammonia gave the best stability and sensitivity [191]. Limits of detection of 8 pg for Me_2Hg were obtained in the 'atomic' mode

and detection limits of tens of pg for MeHgEt, MeHgCl and Me_2Hg in the 'molecular' mode.

Caruso et al. [192,193] have also used GC-LP-ICPMS to obtain elemental and structural information from chromatographic eluents. Limits of detection at the pg level were obtained for organobromine compounds when helium was used as the plasma gas [193]. In addition, the authors demonstrated the capability of the system to produce tunable fragmentation of organotin compounds by varying the helium/argon plasma-gas ratio [192]. The ratio of elemental tin ions to molecular fragment ions was shown to increase for tetraethyltin as the Ar/He ratio was raised from 0 to 35% Ar. Operation of the LP-ICP with a small ratio of Ar/He, or no Ar at all, yielded the preferential formation of molecular species whereas elevating the Ar/He ratio to 35% Ar/He-induced fragmentation that yielded more elemental information.

In a similar way, both MIPs and GDs have been used to produce molecular mass spectra [181,194]. For example, Poussel et al. [180] employed a low-power atmospheric-pressure surfatron cavity as a molecular ionization source. They found that the parent-ion peak observed with a surfatron comprised a larger fraction of the total mass spectrum than that produced by a typical EI source. These 'soft' ionization conditions were obtained for limonene while operating at tens of watts forward power and Ar as the plasma gas. A number of reduced-pressure microwave plasmas have been investigated for the same purpose [195]. Recently, a low-pressure MIP was coupled to GC for the purpose of screening volatile organic compounds in food, and its performance was compared to that of a GC-LP-ICP [196]. The surfatron MIP was operated with He as the support gas, whereas the LP-ICP was operated in He or Ar. The best performance was obtained from the LP-ICP in Ar, where limits of detection from 92 to 7800 pg for ^{13}C detection, and between 7 and 206 pg for ^{35}Cl detection were reported for a collection of compounds including trichlorobenzene and tetrachloroethylene. Very good correlations were found between the observed Cl/C ratios and those expected from empirical formulae for a number of chlorinated organic compounds.

McCluckey et al. [197,198] developed an atmospheric-sampling glow discharge (ASGD) to monitor air for volatile components of explosives. In this device, the ambient atmosphere was sampled into a discharge cell held at approximately 1 Torr, where a dc glow discharge was sustained. The plasma was then sampled by an ion-trap mass spectrometer, and positive or negative ions detected. The authors obtained mass spectra dominated by the molecular parent ion, and reported impressive limits of detection from 1 to 2 ng/L for 2,4,6-trinitrotoluene and a linear dynamic range spanning more than six orders of magnitude [197]. Guzowski et al. [199] coupled a similar device, a direct current gas sampling glow discharge (GSGD), to a TOFMS; Fig. 14 shows the GSGD-MS interface used in the work. Detection limits for several halogenated hydrocarbons, including bromobenzene and carbon tetrachloride, ranged from 20 to 90 pg/s.

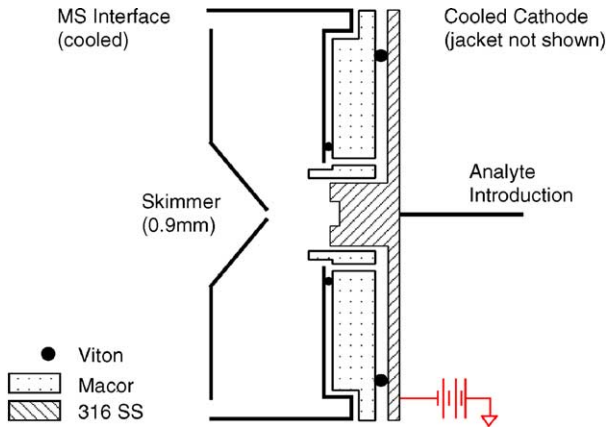

Fig. 14. Diagram of the gas sampling glow discharge (GSGD) ionization source. The cathode is constructed from 316 stainless steel (SS). The Macor sleeve restricts the discharge to the region between the cathode and the grounded skimmer. The discharge is contained within the first vacuum stage of the mass spectrometric interface [reproduced from [199] with permission].

Recently, Manson et al. [200] combined GC with a fast-flow glow discharge (FFGD) for mass spectrometric detection. The dc-FFGD consists of a pin-type GD cathode positioned coaxially with the sampling orifice of the mass spectrometer. When the plasma gas flow is supplied from the back of the cathode, a vacuum pumping exit near the MS sampling orifice creates a flowing plasma region after the active discharge. Compounds introduced into this flowing plasma, such as in a gas chromatography effluent, were found to produce chiefly molecular ions. Adjusting operating parameters such as pressure, voltage and current, and plasma gas flow rate allowed the ionization conditions to be tuned to produce atomic or molecular mass spectra. The GC-FFGD has been used for the determination of several halogenated hydrocarbons; limits of detection between 0.3 and 4.3 pg were reported for the analysis of several compounds based on detection of the halogen ion.

A potential drawback of reduced-pressure plasma sources operated at low input power (1–60 W) is the relatively low gas-kinetic temperatures they attain (800–1000 K). These plasmas cannot tolerate significant amounts of solvent or solvent vapor, so almost all studies thus far have been performed in combination with GC. One way to reduce the solvent load is by employing highly efficient desolvation, such as is possible with a particle beam (PB) interface [201]. In this way, Marcus et al. [185,195,202] have shown that liquid chromatographic separations can be coupled with GDMS quite simply and at a wide range of flow rates and solvent polarities.

Fig. 15 shows a schematic diagram of the PB-GDMS. In this arrangement, an LC eluent is converted into an aerosol by means of a thermo-concentric nebulizer, and the aerosol subsequently dried to form particles sent to the glow discharge, where atomization and ionization occur. Gibeau and Marcus [185] have shown that LC/PB-GD-MS could be used for analysis of inorganic and organic compounds, with limits of detection of 5.8–6.1 μg/L for Fe, Ag, and Cs, and 13 μg/L for

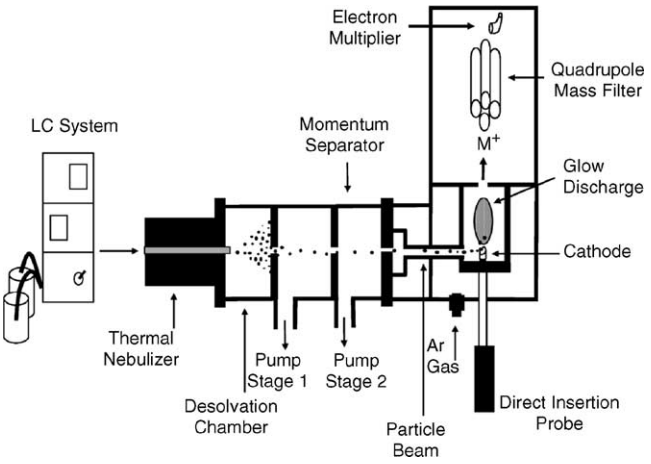

Fig. 15. Diagrammatic representation of the basic components of the particle beam-glow discharge mass spectrometry (PB-GDMS) apparatus [reproduced from reference [185] with permission].

caffeine as the molecular ion. This system has been employed for the analysis of several polycyclic aromatic hydrocarbons, steroids, selenoamino acids, and alkyllead compounds [202], for arsenic speciation [195], and recently for the investigation of individual nucleobases in single-stranded DNA and RNA fragments. In this last application, mass spectra of the four bases were found to be very similar to those observed in EI spectra (radical cation), and individual bases in 22mer oligomer strands were detected at the nanomolar level.

Similarly, Dalton and Glish [203] recently described a tandem source comprised of ESI followed by an atmospheric sampling glow discharge. The authors' main aim was to investigate the suitability of ESI as a means to introduce species into the ASGD, where ionization would occur through electron impact and ion-molecule reactions with reagent ions originating from ionization of air molecules. It was found that the ES-ASGDI could generate EI-like spectra for some small organic compounds, such as *n*-butylbenzene, but not for all of the studied compounds, such as for 2,3-butanedione. Nevertheless, molecular information could be obtained for the latter compounds. Limits of detection between 26 and 130 μg/L were obtained for several organic compounds, such as *n*-butylbenzene, in aqueous solution.

Tunability of the ionization conditions within plasma sources is perhaps of most value when considered in the context of chromatographic separations, where both atomic and molecular information might be obtained for each eluting compound. The concept of such a "modulated source" as applied to elemental speciation is illustrated in Fig. 16 [204]. During one period of the ionization cycle, termed the "atomic" mode, the ionization source is operated so as to produce only atomic ions. In this way, the elemental and isotopic distribution of a compound is recorded in a manner that potentially provides highest sensitivity, because each molecule is decomposed into its multiple constituent atoms before being detected by the mass spectrometer. During another period of the ionization cycle, termed the "molecular" mode

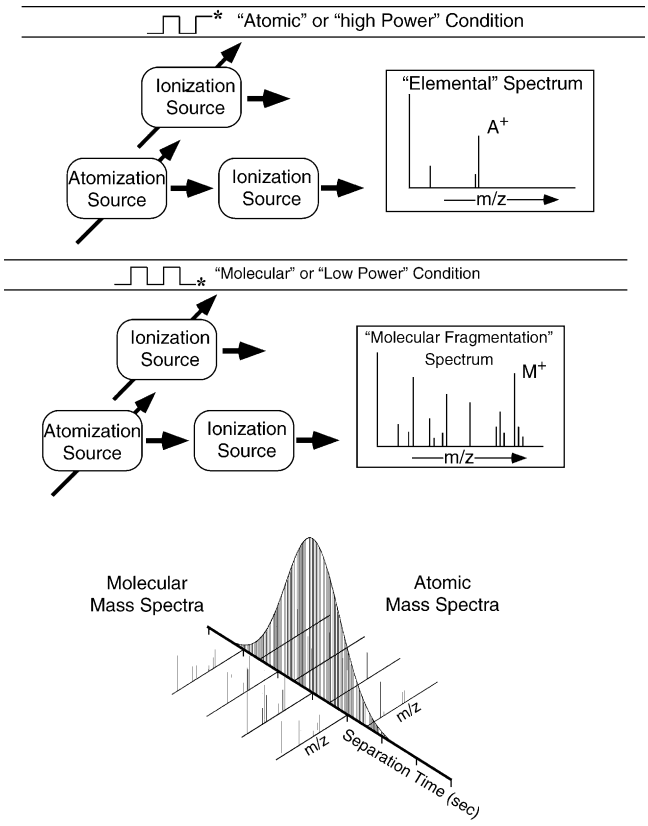

Fig. 16. Concept of modulated or switched source for elemental analysis. A^+ denotes an atomic ion; M^+ denotes the molecular ion. See text for discussion [reproduced from reference [183] with permission].

of operation, the plasma conditions are then modified so the production of molecular mass spectra is favored. When this sequence is repeated in a rapid manner, both the elemental and molecular chemical information, and therefore the element's speciation, can be collected across an eluting peak.

It can readily be appreciated that this concept can be extended to include multiple conditions selected to produce various types of orthogonal chemical information. An intermediate step might be included, for example, to produce more severe fragmentation conditions in order to aid in determination of molecular structure, or conditions chosen to facilitate the formation of negative ions. Generally, this strategy rests on the realization that multiple, orthogonal dimensions of chemical information can be employed to improve the specificity of analytical methods without sacrificing their applicability to a wide range of compounds.

Guzowski and Hieftje [205] have designed and evaluated such a modulated source based upon a direct current GSGD coupled to a TOFMS. The interface employed in these studies is the same employed for the DC GSGD, illustrated in Fig. 14. The authors found that by varying the polarity and magnitude of the voltage applied to the sample-introduction electrode, it was possible to toggle the ionization conditions to produce molecular fragmentation ("molecular" mode) or elemental ions ("atomic" mode). When operated convention-

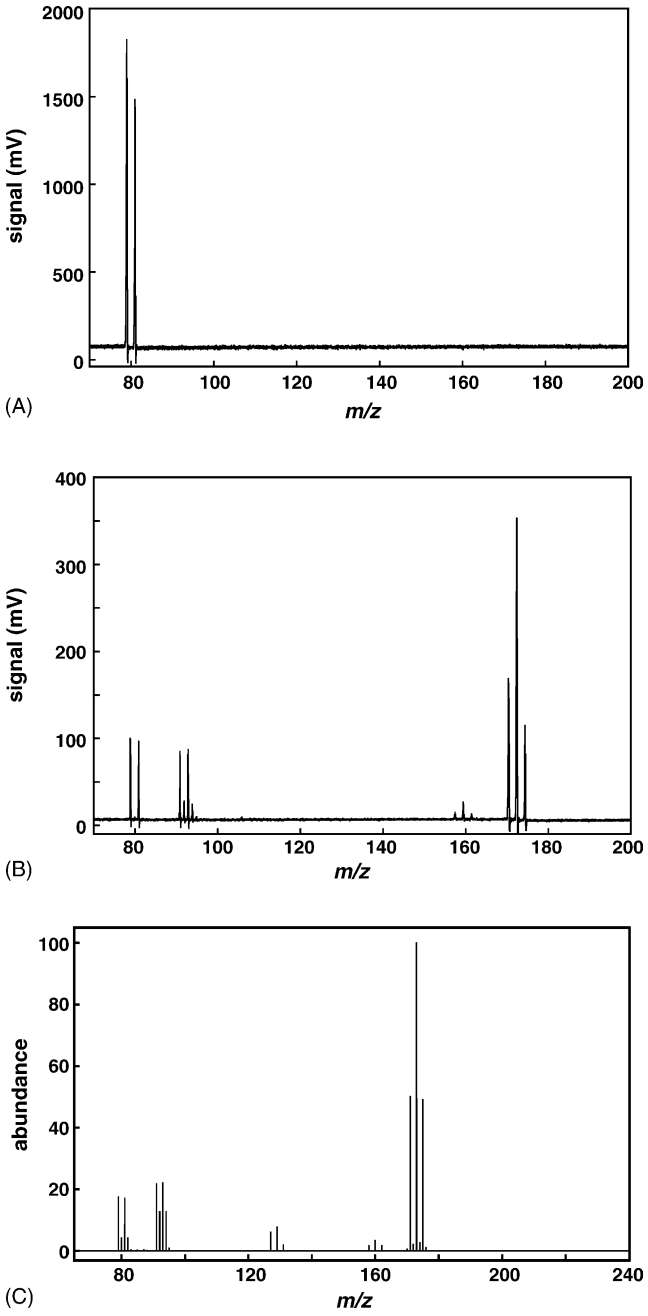

Fig. 17. Atomic and molecular mass spectra from bromoform vapor swept into the GSGD-TOFMS while the plasma was modulated at 10 Hz. Data were collected on a digital oscilloscope (1000 transients averaged). (A) Atomic ionization mode; discharge conditions: 5.50 Torr helium, 30 mA, 350 V. (B) Molecular fragmentation mass spectrum; discharge conditions: 5.50 Torr helium, 20 mA, 250 V. (C) Reconstructed 70 eV EI mass spectrum for bromoform provided as a comparison. Other halogenated compounds analyzed by the GSGD-TOFMS technique also produce spectra that compare favorably to those from an EI source [reproduced from [205] with permission].

ally as an abnormal GD, elemental information was obtained. The application of −350 V, 30 mA under a 5.5 Torr He atmosphere yielded atomic ions from bromoform, as illustrated in Fig. 17A. However, when the polarity of the potential applied to the GD was reversed and a positive voltage was applied (+225 V/20 mA), the discharge structure changed and a 'normal' discharge was produced. Under these conditions, molecular spectra where obtained which resembled those of a 70 eV EI source, as can be appreciated by comparing Fig. 17B and C. This system has the advantage that the different modes of operation are accessed by simple electronic adjustments as opposed to modification of discharge pressure or gas mixture. Thus, cycling between modes can be accomplished quickly; the authors reported that the plasma could be modulated at a frequency up to 130 Hz, an instrumental limit imposed by the electronic components used to switch the plasma potentials.

Interrogating the ions produced by such a source requires that the mass analyzer be capable of accessing different mass ranges quickly and without experimental artifact. Ions produced by an atomic ion source fall in the mass range from 1 to 238 amu and accurate quantification is required over a wide dynamic range. In contrast, the parent molecular ion and various fragment ions cover an indeterminate mass range, and the molecular mass spectra are employed in this framework in a qualitative or semi-quantitative manner. Clearly, a simultaneous mass analyzer is best suited to such a situation, and here the modulated source was coupled to a TOFMS. The use of a TOFMS permits sequential mass spectra to be generated at rates of 10–30 kHz without spectral skew, and the comprehensive elemental and molecular composition of an eluting transient could thereby be obtained. Further, because the TOFMS is based upon simple linear electric fields, the mass range observed and ion-optic conditions can be swiftly adjusted in step with the modulating source, to provide optimum conditions for each set of source conditions.

The switched dc GSGD-TOFMS system was coupled to a gas chromatograph to analyze halogenated hydrocarbons [205]. For 10 halogenated hydrocarbons, the detection limits were reported to extend from 3 to 34 pg/s for 'atomic' measurements and 7–135 pg/s for 'molecular' measurements. In addition, elemental ratios such as Cl/C were successfully obtained, which could be used to distinguish between different chemical compounds. However, when the source was operated in static mode (not switched) the limits of detection improved by approximately an order of magnitude for the same observation time. This situation illustrates potential limitations of modulated or switched sources. Acquiring different types of chemical information in several sequential steps requires that the duty cycle of each step be limited, here by 50%, compared to what might be expected if a source were operated continuously. Since transients are of a limited lifetime, sensitivity cannot be regained by increasing observation time, and higher limits of detection potentially result. In this regard, sensitivity is sacrificed in order to gain supplementary chemical information.

In a similar fashion, it has been shown that a pulsed GD can be exploited as a modulated source for speciation analysis. The microsecond-pulsed glow discharge has many advantages over more the conventional static GD for the analyses of solid samples [206]. By pulsing the potential applied to the cathode of the GD, much higher instantaneous power levels

can be reached, and sputtered atom yields, ionization and excitation efficiency, and sensitivity all are observed to increase as a consequence. Yet, because of the modest pulse repetition rate, cathode heating is reduced. Further, Harrison, et al. [207,208] found that the detrimental effects of many interfering ions related to the plasma gas could be mitigated by appropriate choice of a sampling delay between the initiation of the GD pulse and the time the ions were sampled into a TOFMS. As might be expected, ions sampled immediately upon initiation of the discharge consisted largely of those from the plasma and their adducts, species that can prove troublesome during the determination of some analytes. By delaying the sampling of the ions (10–100 μs) with respect to the initiation of discharge, and at a point after the discharge itself had extinguished, the authors found that mass spectra consisted almost entirely of analyte ions. The explanation lies in the temporally-varying ionization mechanisms that dominate at different points during the discharge lifetime. At discharge initiation, and throughout the duration of the discharge, ionization occurs mainly by electron impact and atomic sputtering, resulting in high abundances of plasma-gas ions. After the discharge has been terminated, however, this pathway to ion formation is removed. Experimental evidence suggests that long-lived metastable species still residing in the discharge are then responsible for the ionization of sputtered atoms by Penning ionization.

Majidi et al. [184,209] were the first to recognize the utility of this time-dependent ionization phenomenon as a means to elemental speciation. Employing pulsed discharges milliseconds in duration, they found that species introduced into the plasma produced molecular fragment ions and atomic ions when sampled during the pre-peak time frame (during the first 0.5 ms of the plasma onset). During this time, the authors surmised, electron ionization is the dominant means of ion formation, and high gas temperatures aid in the decomposition of molecular species. When ions are sampled during the afterglow of the discharge (0.5–2.0 ms after pulse termination) molecular parent ions are observed, presumably formed by Penning ionization [184]. Thus, with each microsecond discharge, elemental information, EI-fragmentation, and molecular parent ions can be collected [209]. What is more, pulses can be repeated at a rate of hundreds of cycles per second.

Lewis et al. [275] have coupled a millisecond-pulsed GD to a gas chromatograph for speciation of aromatic and halogenated hydrocarbon mixtures. Fig. 18 illustrates the three time segments that are sampled during each GD pulse, something accomplished by employing three independent channels of data collection corresponding to three distinct sampling delay times investigated by the TOFMS. These sampling times are labeled pre-peak, plateau, and afterpeak in Fig. 18. By integrating the shaded areas within the plateau mass spectrum, as shown in Fig. 18, the workers obtained an 'indexing' chromatogram in a manner similar to the total ion current chromatogram often employed.

In the separation of toluene, *o*-xylene, and dichlorobenzene in Fig. 19, the different types of chemical information

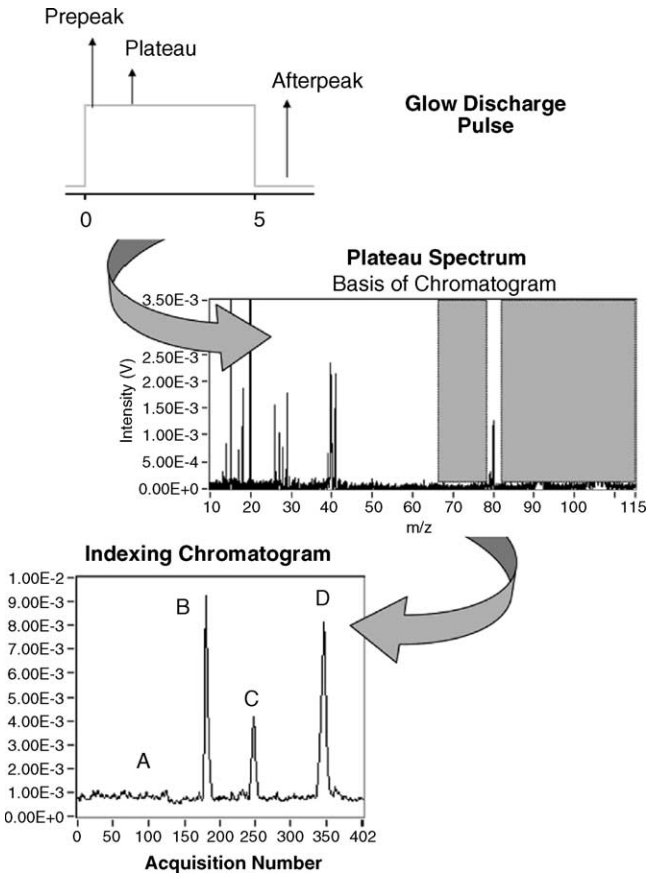

Fig. 18. Glow-discharge pulse profile illustrating temporal regions where mass spectra are collected and how the indexing chromatogram is created. The chromatogram was collected using a 1 μL sample consisting of 100 μL each of toluene, *o*-xylene, and dichlorobenzene diluted to 1 mL with methanol. The cathode was positioned at 3 mm from the ion exit plate, and the spectra represent the background and three analytes during the pre-peak, 0.015 ms; plateau, 0.100 ms; and afterpeak, 5.15 ms [adapted from reference [275] with permission].

were obtained simply by referring to the appropriate delay time. For example, in case D in Fig. 19, corresponding to the eluent dichlorobenzene, mass spectra are observed to change from an initial elemental and molecular fragmentation spectrum during the pre-peak and plateau portions of the millisecond discharge to a spectrum containing almost entirely the molecular parent ion in the afterglow period of the discharge.

Lewis et al. [276] have also reported coupling a millisecond-pulsed GD to a gas chromatograph to study the effect of the discharge parameters on the speciation of several aromatic hydrocarbons. The authors obtained best elemental sensitivity when sampling closer to the cathode, while mass spectra possessing a greater deal of structural information were collected by sampling farther from the cathode. In addition, during the afterglow portion of the discharge the authors found that odd-electron ions (M^+) tended to be favored when sampling occurred at a point near the cathode surface whereas even-electron ions (MH^+) were dominant when sampling occurred farther from the cathode. These results illustrate the potential value of the spatial heterogeneity

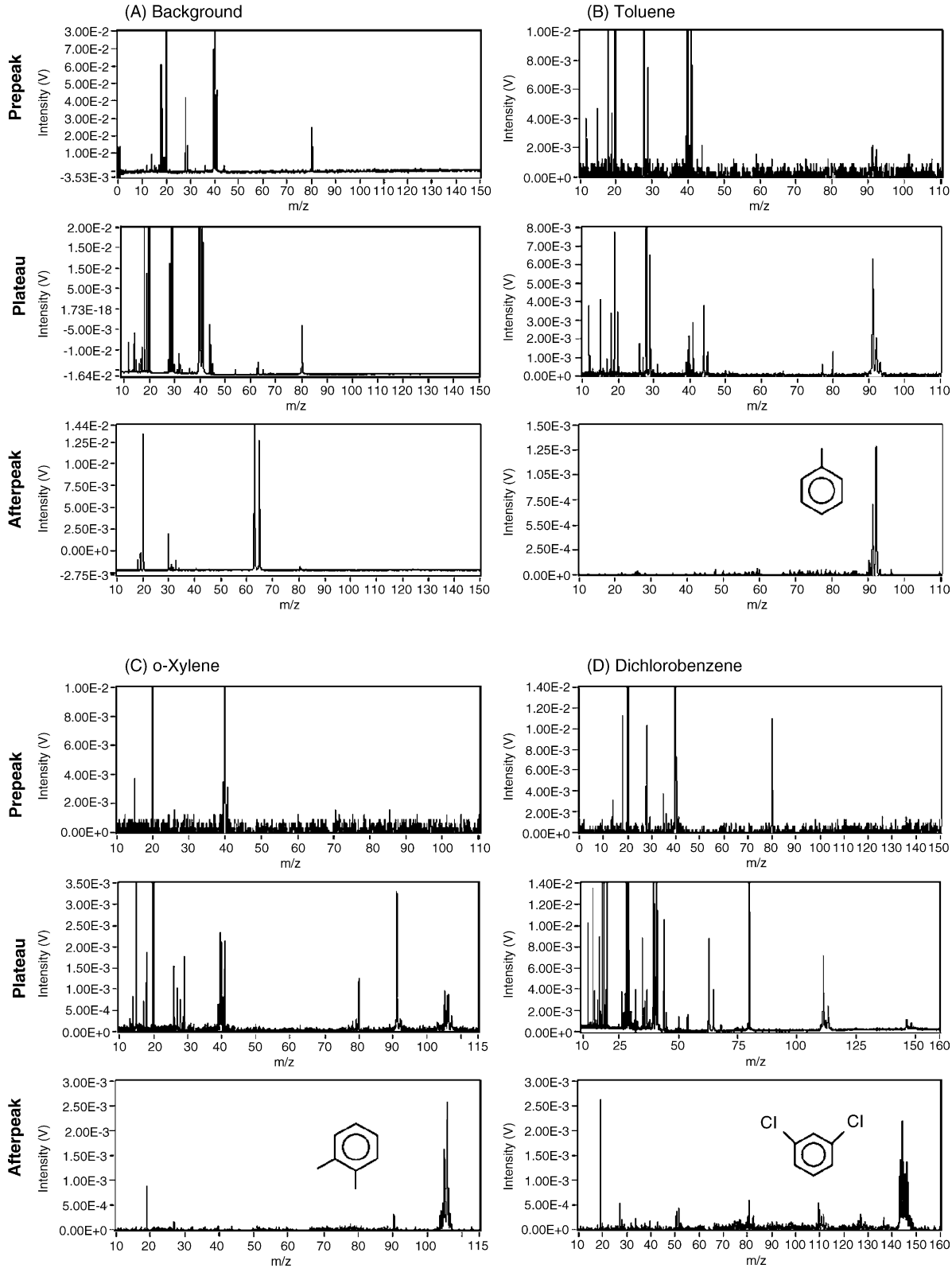

Fig. 19. Glow-discharge pulse profile illustrating regions where data is collected and the mass spectrum collected during the plateau region depicting the *m*/*z* ratios in the construction of the indexing chromatogram. The chromatogram was collected using a 1 μL sample consisting of 100 μL each of toluene, *o*-xylene, and dichlorobenzene diluted to 1 mL with methanol. The cathode was positioned at 3 mm from the ion exit plate, and the following spectra represent the background and three analytes during the pre-peak, 0.015 ms; plateau, 0.100 ms; and afterpeak, 5.15 ms [adapted from reference [275] with permission].

of the plasma, which might be exploited to provide several different types of chemical information simply by sampling an ionization source at different positions.

In contrast to strategies employing a single source that is modulated to provide 'atomic' and 'molecular' operation, two different ionization sources can be combined in series to accomplish the same end. A tandem pair of sources linked in series and composed of one 'atomic' source and one 'molecular' ionization source can be employed to provide both types of information simply by modulating or extinguishing the atomic source. Ray and Hieftje [183] have reported one such source combination based on a MPT-ASGD modulated tandem pair. The MPT is an atmospheric-pressure MIP that has been shown to provide excellent sensitivity as an atomic ionization source, whereas the ASGD has been shown to be a good means of producing molecular mass spectra. In the 'atomic' mode of operation, the tail flame of the MPT is sampled by the ASGD and from there by the mass spectrometer, yielding an atomic mass spectrum. The 'molecular' mode of operation is accessed when the MPT is extinguished, and the ASGD allowed to sample the analyte stream unchanged. Employing two sources in this manner holds the potential advantage that each can be optimized independently. Of course, any number of sources might potentially be configured in a tandem manner.

12. Electrospray ionization for elemental speciation

Electrospray ionization has been widely employed as a means of direct elemental speciation of organometallics [210,211], synthetic inorganic compounds [212], metal-containing biological systems [213], as well as free metal ions in solution. Many researchers have successfully employed ESI to produce positive or negative gas-phase ions directly from solution, and have demonstrated that the appropriate operating conditions can provide an accurate portrait of the chemical form of metals in solution [214–217]. Limits of detection at μg/L concentration levels are often reported, and linear dynamic ranges extending to four orders of magnitude can be achieved by use of an appropriate internal standard [218–220]. ESI represents one of a limited number of techniques capable of observing labile species directly from solution and thus is of great utility for elemental speciation analysis, a fact illustrated by the formidable body of work completed in this area that has been reviewed elsewhere [213,221–224].

It is worth emphasizing, however, that care must always be taken in the interpretation of ESI mass spectra to establish elemental speciation, even for samples seemingly as simple as free metal ions in solution. As Van Berkel and Zhou have shown, the ESI system forms an effective two-electrode controlled-current electrolysis cell wherein redox reactions can alter the oxidation states of many elements from those present in the original sample solution [225]. Changes in pH induced by the ESI process can modify metal-binding proteins and their mass spectra, and some metals (e.g. Ag, Hg, or Cu) can be deposited directly on the ESI emitter tip by electrolytic reduction [226–230]. Indeed, VanBerkel et al. [231] have shown that this electrochemical action can be employed as a means to create solution-phase ions from non-polar species (e.g. polycyclic aromatic compounds) that are ordinarily neutral in solution and otherwise difficult to ionize by ESI. Because a goal of elemental speciation is to determine the oxidation state of an element, however, these electrochemical modifications add a degree of complexity to spectral interpretation that depends upon solution composition, ESI emitter current, and which can change with the ratio of electrolytically active species in solution.

Spectral interpretation can be further complicated by charge-reduction reactions that occur during the desolvation processes involved in electrospray ionization, for example:

$$M(H_2O)_n{}^{3+} \rightarrow M(OH)(H_2O)_{n-1}{}^{2+} + H_3O^+ \quad (1)$$

where M represents some metal species in an aqueous solution. Because the ability of the solvation sphere to stabilize charge lessens as desolvation progresses, at some point during desolvation it may become energetically favorable to form a covalent bond at the expense of a formal charge on the ion according to Eq. (1) [232]. While oxidation-state information is not lost during this reaction, the degree of charge reduction is necessarily dependent upon the relative ionization potentials of the metal (M) and that of the ligand or solvent molecule. Thus, the distribution of ions observed in the mass spectrum depends upon the solvent system, ligand identity, and desolvation conditions, which can make interpretation ambiguous in some cases. Moreover, charge reduction is just one example of the many ion chemistries that can occur (e.g. decarboxylation) during ESI, often with the aid of collisional activation in the gas phase [211].

To date, most ESI used for the purpose of elemental speciation has been aimed at obtaining qualitative rather than quantitative information, for the simple reason that quantification by ESI-MS can be challenging. It is well established that the ESI response of various analytes varies greatly and in a complicated manner according to relative solvophobicity, surface activity [233,234], and gas-phase proton affinity [235], as well as the composition of the solvent system, solution conductivity and pH [236], and generally with changes in ESI conditions or in the presence of concomitant species [229,237]. Indeed, the distribution of a given analyte amongst ions of various adducts and charge states, many of which themselves do not accurately represent solution-phase distributions, can change with matrix composition and the concentration of the analyte [229]. It has been shown that the ESI process can behave as either a mass-sensitive or concentration-sensitive detector, based upon the emitter dimensions and concentration range at issue [238]. Further, ESI is known to suffer from appreciable matrix effects, leading to the suppression of analyte signals in the presence of concomitant species [239], or in the presence of a solvent of higher proton

affinity [240]. Despite these limitations, however, ESI is routinely used for quantitative analysis; although none of these complicating factors precludes the use of ESI on a quantitative basis, they do necessitate a sufficiently sophisticated understanding of the chemical system at hand.

Because ESI represents such a potentially important tool for elemental speciation, considerable effort has been focused on overcoming these limitations. For example, ESI is often used in conjunction with separation techniques, with the benefit that the number of ionizable species present at any given time is limited, reducing the likelihood of suppression effects. The stability of ESI and the linearity of response has been addressed by Agnes and Horlick [214], who added supporting electrolytes as internal standards. Further, the voltage between the skimmer and sample orifice plates has been manipulated to produce clusters, fragmentation, or bare metal ions, thereby generating additional structural information [241,242]. Further, the isotopic distribution of a metal can serve to indicate its presence among fragment ions. As a result, one can begin to elucidate the metal moieties within a chromatographic peak.

Recently, dramatic results have been obtained when ESI is coupled with high-field asymmetric waveform ion mobility spectrometry (FAIMS). The FAIMS technique has been employed as a means of increasing signal-to-background (S/B) ratios and providing further selectivity in elemental speciation [243,244], and has been described in detail elsewhere [245–247]. For the purposes of the present discussion, it is sufficient to say that FAIMS exploits molecule-specific differences between the low-field ion mobility (K) of an ion, where ion mobility is independent of field strength, and the mobility of the same ion under high-field conditions (K_h), where the observed ion mobility follows some function of the applied electric field. By application of a temporally varying asymmetric voltage to a cylindrically symmetrical ion mobility cell, ions of a selected high and low-field ion mobility ratio (K/K_h) can be transmitted to the exclusion of all others. Thus, FAIMS permits the partitioning of ions produced by the ESI source at atmospheric pressure without chromatographic separation, and inserts a further degree of orthogonality between the ESI source and the mass analyzer.

Handy et al. [244] have reported increases in S/B ratio of more than four orders of magnitude over conventional ESI-MS when ESI-FAIMS-MS was employed for the determination of perchlorate and sulfate ions directly from aqueous solution. Such dramatic increases in S/B vastly improve detection capabilities; the authors report limits of detection of 0.1 ng/L for perchlorate ion in aqueous solution. A similar degree of enhancement is illustrated by Ells et al. [243] in Fig. 20, where mass spectra of bromodichloroacetic acid present at 100 ng/L in a solution of 9:1 methanol/water (v/v) obtained by ESI-MS and ESI-FAIMS-MS under similar conditions are compared. Each spectrum represents the average of 10 scans by a quadrupole mass filter. As shown in Fig. 20A, under typical ESI-MS conditions, the presence of a significant chemical background makes it difficult to distinguish the

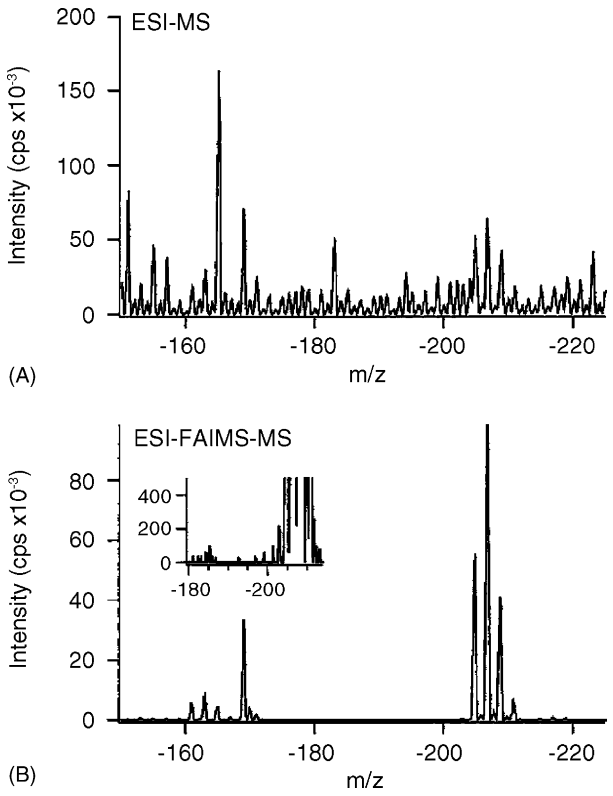

Fig. 20. Comparison of ESI mass spectra with FAIMS mass spectra of a 100 ppb solution of BDCAA in 9/1 methanol/water (v/v) containing 0.2 mM ammonium acetate. (A) ESI-MS, (B) ESI-FAIMS-MS at compensation voltage (CV) = 12.5 V, dispersion voltage (DV) = −3600 V. Inset is an expansion of the baseline [reproduced from reference [243] with permission].

isotopes of $BrCl_2C_2O_2^-$; the authors report S/B = 12 and a detection limit of approximately 100 ng/L based on the isotopes at m/z = 207 amu. When ESI-FAIMS-MS is employed (Fig. 20B), however, identical ESI conditions yield a dramatic reduction in chemical background. Here, the isotopes of the bromodichloroacetic ion are clearly visible, yielding a calculated S/B of approximately 25,000 and a limit of detection of 13 pg/L, an improvement of over four orders of magnitude. The authors reported limits of detection of 5–36 pg/L for the nine haloacetic acids studied in aqueous systems [243].

Limits of detection better by several orders of magnitude than those achievable by ESI-MS or GC-MS, and without any chromatographic separation, have made ESI-FAIMS-MS a popular means of determining trace constituents in aqueous systems [248,249]. McSheehy and Mester [250] have recently reported the use of ESI-FAIMS-MS for the determination of trace arsenic metabolites in biological reference materials.

Because ions of the same nominal m/z can have different ion-mobility characteristics (K/K_h), the isobaric overlap of structural isomers [251] and stereoisomers [252] can be successfully resolved by ESI-FAIMS-MS. A number of studies have detailed the use of ESI-FAIMS-MS in the separation and analysis of microcystins, tryptic digests of proteins

Table 2
Figures of merit for ESI-TOFMS and ICP-TOFMS

	ICP	ESI
Sensitivity	10^7 cps/ppm (^{238}U)	2000 cps/mM (reserpine)
Resolving power ($m/\Delta m$)	2000	3000–6000
Mass range (m/z)	6–240	6–10,000
General information		
Principal information	Elemental	MH^+ fragment ions
Dynamic range	10^6	10^2–10^4
Noise	35 cps/50 ns window	<1 cps/50 ns window
Detection limits	0.1–1 ng/L	Analyte specific

[253–255], organometallic chemotherapeutic drugs [256], different protein conformations [257–260], and trace quantities of drugs in urine samples [252,261,262]. Amazingly, Barnett et al. [263] have demonstrated that even isotopes of the same element have sufficiently different FAIMS response to allow their separation. In particular, they separated $^{35}Cl^-$ from $^{37}Cl^-$ following ESI of an ammonium chloride solution.

However dramatic the improvements provided by ESI-FAIMS-MS, the formation of ions still occurs via the mechanisms of ESI, so the use of ESI alone as a means of elemental speciation continues to reflect limitations of the technique. In order to overcome these shortcomings, several investigators have suggested that ESI and the ICP be used in parallel in elemental speciation analysis for the complementary types of chemical information they provide [221,264–267]. The degree to which the strengths of one source can compensate for the shortcomings of the other is readily apparent from an examination of Table 2, where the analytical merits of ESI and ICP ionization achieved on instruments constructed in the authors' laboratory are contrasted.

The ICP produces simple atomic mass spectra in which isotopic information is readily obtained, with comparatively mild matrix effects and with similar ionization efficiency for all elements. The harsh conditions within the ICP do, however, necessarily destroy all molecular information. In contrast, ESI is capable of producing intact gas-phase ions from fragile clusters, bare ions, or biological species directly from solution. Thus, direct elemental speciation is possible by a "soft" ionization source such as ESI, something the ICP alone cannot do.

When the ESI is used in conjunction with the ICP, those analytical aspects in which the ESI is weakest can be mitigated. While the ionization efficiency of ESI can vary greatly from compound to compound, ICP affords virtually the same

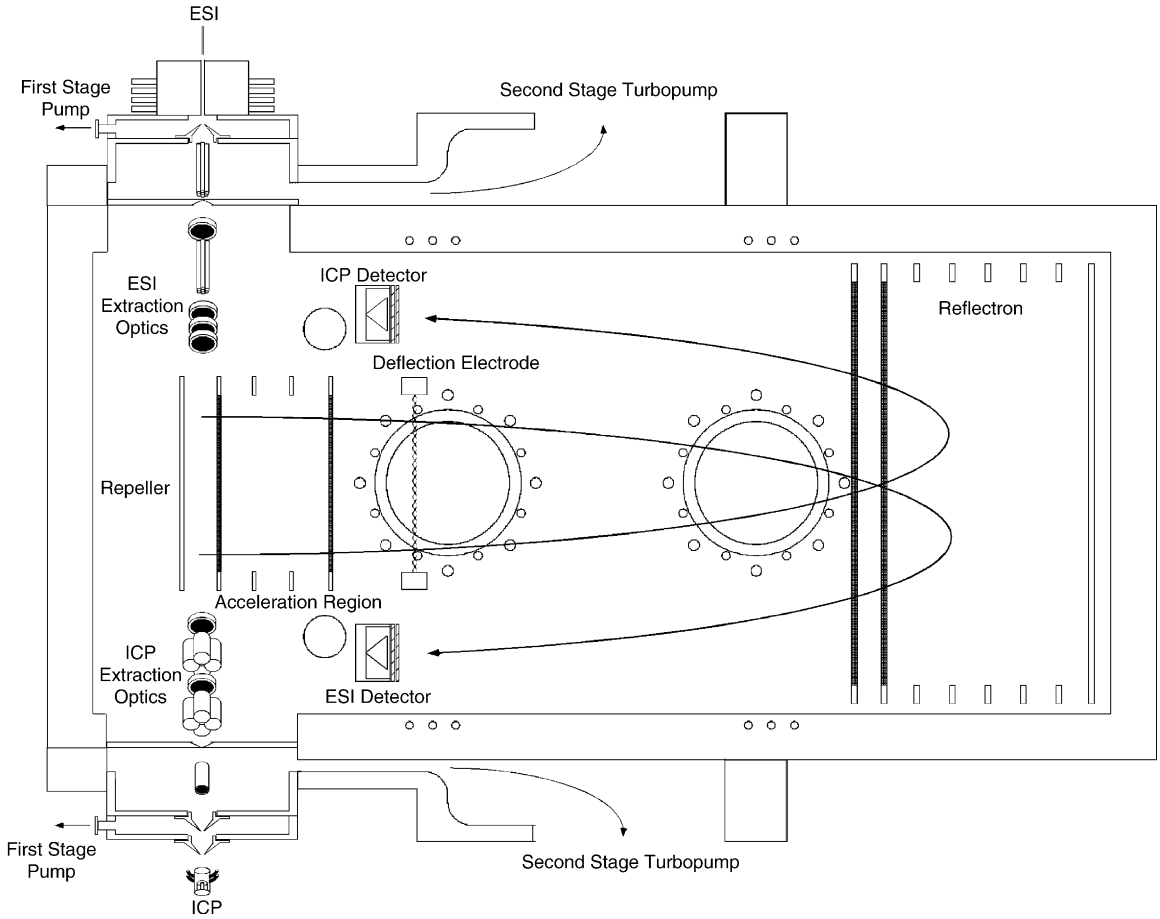

Fig. 21. Dual source ESI/ICP-TOFMS instrument diagram.

response independent of the initial chemical state of an element. The ICP can thereby provide quantitative information, permitting the direct comparison of the various components within a mixture, while the ESI provides mostly qualitative information. The ICP also holds an additional advantage for this quantitation step, as larger molecules are decomposed into their constituent atoms before being detected. Thus, the sensitivity of atomic detection of molecules can exceed that offered by molecular detection by a factor representing the abundance of a particular element within a molecule. Knowledge of the identity and concentration of the elements that are present, obtained from an ICP, also greatly simplifies interpretation of ESI spectra. The identities of adduct ions, molecular fragments, and the contributions of various elements to the overall isotopic distribution of an ion can be unraveled by the information provided by the ICP. Viewed together, these two ionization sources provide a means of directly quantifying elements amongst various forms in a sample by providing two orthogonal dimensions of chemical information.

There has been a recent trend towards elemental speciation by parallel use of ESI-MS and ICP-MS (e.g. references [239,268–273]). Often, both techniques are employed to analyze the eluent from a chromatographic separation in an online or offline manner, and the chromatographic data from ESI-MS and ICP-MS aligned to establish the identity, isotopic distribution, and concentration of elements associated with the molecular ions produced by ESI. Such analyses are perhaps most valuable in bioanalytical applications, where very little is often known concerning the eluting components of complex mixtures, and where multiple compounds might co-elute [266,273,274]. For this reason, tandem mass spectrometry is also often employed to aid in structural characterization. The indirect nature of this methodology, however, inherently leads to the introduction of error and difficulties in peak correlation due in large part to separation inconsistencies.

Recently, we have described a novel dual-source ICP/ESI TOFMS, a diagram of which is shown in Fig. 21. Here, the effluent from a single separation is split between two ionization sources, and a single TOFMS employed to collect both channels of chemical information in tight registry. Both ESI and ICP ion beams are sampled through dedicated ion optic trains that are vertically offset from each other and enter from opposite directions, permitting a common TOFMS to analyze each beam independently. Since each ionization source is operated and sampled independently, both can be optimized for the highest duty cycle and sensitivity without compromising the operation of the other source. In this regard, it possesses a potential advantage over switched ionization sources. Further advantage is gained from an instrumental perspective, where several key instrumental components are common between both sources and cycles of operation (e.g. vacuum system, electronics, and data collection). The TOFMS should also be capable of interdigitized collection of mass spectra very efficiently; calculations suggest that the duty cycles for the ICP-TOFMS and ESI-TOFMS should be, respectively 100% and 84% of the duty cycles achieved if each were operated independently. Most importantly, since both sources operate in parallel, the effluent from a separation system can be analyzed simultaneously for elemental and molecular information. Thus, run-to-run variations, which are encountered by duplicating a separation for analysis on separate instruments, are eliminated. The instrument is currently under construction in the author's laboratory.

13. Conclusion

It is difficult to overestimate the importance of elemental speciation to applications across the field of analytical chemistry. Speciation is almost intrinsically multidisciplinary and therefore holds the potential for broad impact on many areas of chemistry. Certainly, a portion of these efforts fall within the compass of traditional atomic spectrometries, where elemental analysis must be accomplished on samples of ever-lower concentrations and absolute quantities of atoms, in samples of reducing size, and those having complex matrices. Such challenges are being met by investigators researching alternate ionization sources, modifications of operating conditions, novel sample-introduction schemes, and by continuing to refine current PS-MS instrumentation. In some instances, however, current methods are not adequate for determining the full chemical information associated with an element. In such situations, new methods and strategies must be developed to provide direct and comprehensive elemental speciation. Ionization sources capable of switching between different types of chemical information rapidly, or the use of multiple ionization schemes to elucidate the identity, concentration, and molecular associations might soon provide a comprehensive picture of the chemical environment within which an element is found.

Acknowledgments

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