# Collision and reaction cells in atomic mass spectrometry: development, status, and applications†

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The development and utilization of collision and reaction cells in atomic mass spectrometry is reviewed. These devices have been used for decades in fundamental studies of ion–molecule chemistry and have only recently been applied in the GD-MS and ICP-MS fields. Such cells are used to promote reactive and non-reactive collisions, with resultant benefits in interference reduction, isobar separation, and thermalization/focusing of ions in ICP-MS. Novel ion–molecule chemistry schemes, using a variety of reaction gas reagents selected on the basis of thermodynamic and kinetic principles and data, are now designed and empirically evaluated with relative ease. These chemical resolution techniques can avert interferences requiring mass spectral resolutions of $>600\,000$ ($m/\Delta m$). Purely physical ion beam processes, including collisional dampening and collisional dissociation, are also employed to provide improved sensitivity, resolution and spectral simplicity. Collision and reaction cell techniques are now firmly entrenched in current-day ICP-MS technology, enabling unprecedented flexibility and freedom from many spectral interferences. A significant body of applications has now been reported in the literature. Collision/reaction cell techniques are found to be most useful for specialized or difficult analytical needs and situations, and are employed in both single- and multi-element determination modes.

## Introduction

Inductively coupled plasma mass spectrometry (ICP-MS) was first demonstrated about 25 years ago and has been commercially available for just over 20 years. During that time it has proven to be a remarkably successful and robust technique. The ICP-MS technique is now indispensable in environmental, geological, clinical, nuclear, and semiconductor analysis laboratories. Its rise to prominence has coincided with the demise of spark-source mass spectrometry and the gradual obsolescence of atomic absorption spectroscopy. The past 25 years of development has been a fast-paced and exciting period. It is interesting to view the history of ICP-MS in terms of development periods, or ages (see Table 1 for our proposed ages). These ages are categorized according to periods of active (but not necessarily seminal) development in the community. It is seen that ICP-MS has revitalized itself with some form of innovation about every 5 years. During the formative years of 1978–1983, ICP-MS was first demonstrated and refined.[1–3] From 1983–1988, conventional quadrupole ICP-MS became commercially available and instrument manufacturers introduced first- and second-generation instruments in response to avid analytical community interest. Sector-field, high-resolution ICP-MS instruments came on the scene in the 1988–1993 period, providing new-found relief from certain spectral interferences, while also enabling markedly increased sensitivity.[4–7] In the mid–late 1990s ICP-MS practitioners became instrumentally creative, resulting in a number of alternative mass analyzers being adapted. During this period, ion trap,[8,9] time-of-flight,[10,11] ion cyclotron resonance,[12] exotic quadrupoles,[13–15] and multi-collector sectors[16–18] were all investigated and demonstrated. Most recently (1998–present), ion–molecule chemistry techniques, using collision and/or reaction cells of various types, have dominated development

activity. Each of these periods has been given a relevant, tongue-in-cheek name in Table 1 (the Massocene, Quadrucene, Sectorcene, Analyzocene, and Cellocene, respectively).

One realization from such a retrospective view is that much of the development activity in ICP-MS has been directed at the elimination of interferences. Despite all its advantages, ICP-MS is not (yet) a panacea for elemental analysis for exactly this reason. The principal nemesis of the technique has been, and remains, the occurrence of various (spectral and non-spectral) interferences. While various means to accommodate or ameliorate such interferences have been devised, they remain a persistent analytical hindrance. In ICP-MS, polyatomic ion interferences derive from plasma gas (typically Ar, but occasionally He or other mixed gases), solution (water, organic), matrix (acids, buffers, salts, *etc.*) and plasma entrained atmospheric gas ($O_2$, $N_2$, *etc.*) sources. Many papers describing the nature, manifestation, and minimization of such interferences are available in the ICP-MS literature.[19–22]

Another prevalent plasma source MS technique, glow-discharge mass spectrometry (GD-MS), also suffers significantly from spectral interference problems. In this case, the source of such interferences again derives from the discharge gas (typically Ar or He) but also emanate, to a comparatively greater extent, from the sample itself and include analyte or

**Table 1** Proposed ages, or development periods, of ICP-MS

| Period | Age[a] | Development(s) |
|---|---|---|
| 1978–1983 | Massocene | Initial ICP-MS evolution, demonstration, adoption |
| 1983–1988 | Quadrucene | Quadrupole ICP-MS reigns |
| 1988–1993 | Sectorcene | Sector-field, high-resolution ICP-MS arrives |
| 1993–1998 | Analyzocene | Miscellaneous analyzers in vogue (ion trap, TOF, ICR, MC) |
| 1998–present | Cellocene | Collision/reaction cells rage |

[a] *–cene*: a variation of *–ceno*, Greek, meaning "new".

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matrix dimer ions, oxide ions, and other complex polyatomic ions.[23,24]

Of the various options available for the removal or elimination of polyatomic ion interferences in atomic mass spectrometry, recently developed collision/reaction cell techniques have become increasingly popular. These techniques offer simplicity, efficacy, and cost-effectiveness while providing freedom from many difficult interference problems, including those requiring very high resolution ($R(m/\Delta m) > 10\,000$; as yet unattainable by conventional sector-field HR-ICP-MS instruments).[9,25,26] Most commercial ICP-MS instruments now offer collision/reaction cell options, and routine use and exotic applications are increasingly being reported. A very thorough and excellent review of collision/reaction cell techniques in ICP-MS, by Tanner and colleagues, is available.[27] In the two years since its publication, however, considerable new activity has occurred. It is therefore appropriate to provide a selective review, perspective and outlook for this important, and recent, development in atomic mass spectrometry.

## Development history and perspective

### Collision cells and collisional processes

The first use of collision/reaction cell techniques in atomic mass spectroscopy occurred during the late 1980s with nearly concurrent reports in GD-MS and ICP-MS. These developments, in turn, took a page from the organic mass spectrometry and ion physics/chemistry fields, where collisionally induced dissociation (CID) had been investigated for many years. The early plasma source MS investigations were motivated by hopes of easy and effective removal of interferent ions using simple, collision processes.

Harrison and co-workers first reported (1988) the use of triple quadrupole MS techniques in GD-MS,[28] using an intermediate collision cell to dissociate $Fe_2^+$ and $FeAr^+$. This approach was later extended to the dissociation of $TaO^+$, an extremely refractory oxide ion (bond dissociation energy $\sim 8.9$ eV).[29] Effective dissociation was demonstrated in both cases. A somewhat simpler double-quadrupole MS was later employed by Duckworth and Marcus, this time coupled to a radiofrequency (rf) GD ion source.[30] Sputtering of more difficult glass and ceramic materials was shown, resulting in higher levels of certain polyatomic and $MO^+$ interferences, which were nonetheless effectively mitigated using (predominantly) collisional techniques. Investigators at Oak Ridge National Laboratory later coupled a rf GD ion source to a quadrupole ion trap, surmising (and demonstrating) that better dissociation efficiencies could be obtained with this type of cell.[31] The experience in GD-MS, based on these early reports, was that effective collisional dissociation of polyatomic ion interferences could be achieved and could be analytically beneficial.

Just after the initial GD-MS report surfaced, two reports on the CID approach for interferent ion reduction in ICP-MS were also published (1989). These reports, by Douglas[32] and Rowan and Houk,[33] were quite intriguing. Douglas' paper was a wide-ranging report describing various experimental forays in ICP-MS. It included a brief mention of some triple quadrupole ICP-MS experiments. The initial aim of this work was to assess the efficacy of CID for polyatomic ion destruction. The evaluation examined measured total loss (dissociation + charge transfer + scattering) cross sections, using Ar as the target or collision gas. Comparable loss cross sections for both atomic and polyatomic ions were observed and the conclusion was made that large gains in reducing polyatomic interferences were not possible, since atomic ion loss due to scattering and charge transfer would counteract any gains achieved in reducing interferent ion intensity *via* dissociation. This result was at least partly corroborated by the work of Rowan and

Houk,[33] who also found approximately equivalent loss rates of analyte ions ($As^+$) and polyatomic ions ($Ar_2^+$), using Xe as the target gas at typical CID energy conditions (10–30 eV). Based on these reports, by two highly respected co-founders of the ICP-MS technique, the CID approach was dismissed by the ICP-MS community. This was despite the apparent success and positive results reported in the GD-MS applications. The fact that analyte losses of some 30–50% were reported in the Rowan and Houk work solidified the negative view—at the time the community was seemingly preoccupied with achieving better and better sensitivity and detection limits. In addition, the arrival of high resolution, sector-field instruments—offering purely instrumental and nearly unequivocal separation and identification of many interferent ions—captured much attention.[5,34] This was especially so when it was also realized that the inherently higher transmission efficiencies of the sector based instruments also translated to better sensitivity and detection limits. Thus, the collisional dissociation approach was discounted or forgotten while ICP-MS development activity turned elsewhere.

In other MS areas, rapid developments were occurring, however. The technique of ion trap mass spectrometry (ITMS) was particularly topical in the early 1990s. The aforementioned GD-ITMS work by the Oak Ridge group, using ion traps to effect CID of polyatomic ions, was reported during this period. About this time, the present authors also became interested in the elemental and isotopic analysis benefits that ion trap MS might afford in ICP-MS. Chief among these was the realization that an ion trap, by virtue of its trapping operation and long residence times, would serve as a more efficient collision (and reaction) cell. The ability to selectively retain only ions of interest while rejecting other matrix ions was feasible with the technology and appeared attractive for elemental applications. A first, prototype ICP-ITMS instrument was built and tested to investigate and evaluate these possibilities. The very first results were pleasantly surprising: almost none of the classical ICP-MS polyatomic ions were observed (see Fig. 1 for demonstrated freedom from 45–85 *m/z* interferences).[8,9] It was presumed that CID was responsible for reduction of many such ions; this
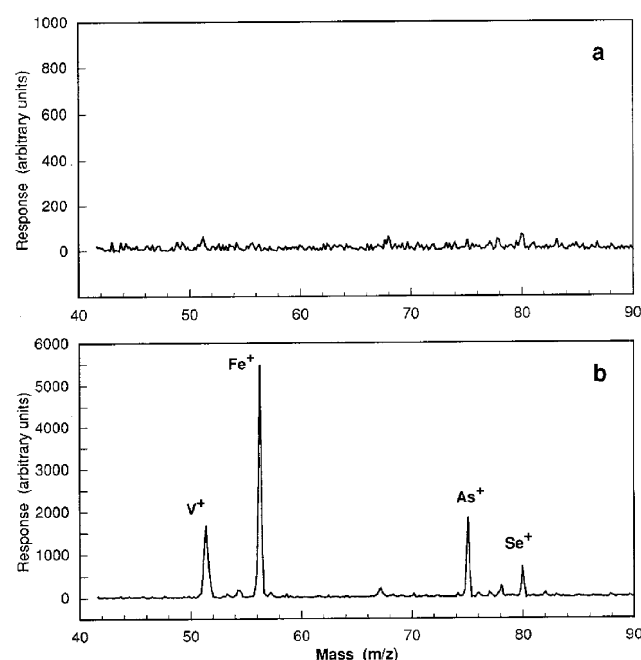


**Fig. 1** ICP-ITMS mass spectra of the *m/z* 45–85 region which in typical ICP-MS spectra is cluttered with various polyatomic matrix ions. a, 2% HCl blank and b, V, Fe, and As, 1 μg mL$^{-1}$ 2% HCl. Note response scale differences. Ion trap ion injection time 1 ms; linear quad rf only, cut off approximately *m/z* 10; ITMS trapping rf level *m/z* 10 (from ref. 9).

conclusion appeared to fit given that under the conditions used few collisions would be required for dissociation of the weakly bound polyatomic ion species. However, additional work here indicated that other mechanisms were also operative, and our studies led us to consider reactive collisions.

## Reaction cells and ion–molecule reactions

In reviewing developments in reaction cells and ion–molecule chemistry, we return to the 1989 tandem quadrupole ICP-MS work of both Douglas[32] and Rowan and Houk.[33] While the results of these investigations were perhaps disappointing in terms of CID interference removal efficacy, both works indicated potential promise for chemical mitigation of interferences, using simple ion–molecule reactions. The former work showed an atom addition reaction of Ce with $O_2$ to generate CeO (but without additional oxidation to $CeO_2$ or other oxy-species). On this basis a cautious statement was made that ion–molecule chemistry might provide interference relief. The work of Rowan and Houk provided somewhat stronger evidence and assertion to this effect. These workers used Xe and $CH_4$ to significantly reduce or remove $ArO^+$ and $Ar_2^+$, respectively. Affected analyte ion intensities ($Fe^+$ and $Se^+$) with reaction gas present were 60–70% of that obtained without gas. The workers recognized that useful ion–molecule reactions were occurring, and attributed interferent ion reduction, in part, to such reactions. They also observed various side reaction products at other masses. In addition, the authors deduced that the energies of reaction product ions would be lower than ions from the extracted plasma beam, and showed that they could be discriminated against by biasing the mass filter positive relative to the collision cell. They thus established the basis for what would later be termed kinetic energy discrimination techniques. Both works demonstrated that gas-phase chemistry might be usefully applied to the problem of ICP-MS interferences. Curiously, however, these results again did not ignite immediate attention or action in the ICP-MS field at the time. Even the research groups of Douglas and Houk moved on to other research topics and pursuits.

Similar observations were also made in the GD-MS field. McLuckey and co-workers,[35] in investigating the use of ion traps with glow discharge sources, noted that both charge exchange and hydrolysis reactions could be utilized, in concert with CID reactions, to reduce polyatomic ion interferences. A clever example included the conversion of the refractory $BaO^+$ to $BaOH^+$ through reaction with adventitious water vapor in a GD-ITMS system, and subsequent facile CID of that species to elemental $Ba^+$.

The PNNL group also came to realize the efficacy of the ion trap to promote and utilize ion–molecule reactions. They also noted that adventitious water vapor, with significant vapor pressure at the 1–3 mtorr level of He bath gas used in ion trap operations, was both a blessing and a curse. It was eventually realized that much of the $Ar^+$ intensity reduction was effected through reaction with water (and to a lesser extent other background gases), following the same reaction scheme that the Oak Ridge group had noted.[9,26] Thus the original charge on $Ar^+$ is transferred first to $H_2O^+$. This then reacts with additional water to form $H_3O^+$. Argon ion intensity is thus removed (good), but the reaction product $H_3O^+$ is an especially strong protonation reagent and consequently protonates/ionizes many background gas species (bad). In addition, reaction of many atomic ions with water results in the formation of oxide, hydroxide, and various complex oxy-hydroxy ions. It was quickly decided that the disadvantages of this reagent far outweighed the advantages, and that other means to selectively reduce $Ar^+$ and associated species had to be found. The primary factors considered included reaction efficiency (high efficiency for Ar, low efficiency for other atomic ions), simplicity (minimal side/chain reactions), and low reagent mass

(to minimize new interferences). It was quickly realized that $H_2$ ideally met these requirements. The reaction chemistry of $Ar^+ + H_2$ had been extensively studied by the physical chemistry community, reaction rate data with both Ar and other metals were available, and a review of the thermodynamics and kinetics was favorable to the interference reduction application. A quick experiment with $H_2$ reagent gas was conducted and the results splendidly confirmed that complete reduction ($>10^7$ fold) in $Ar^+$ intensity could be achieved. The PNNL group first reported their $Ar^+/H_2$ results to the community in early 1996 (Winter Plasma Conference), with the first publication[36] following shortly thereafter. A patent application preceded these disclosures and allowance was subsequently made.[37] Other groups subsequently adopted this approach and these reports served to validate its utility.[38,39] This work was then extended by applying a series of other reagent gases to other generic and specific analytical problems (see Table 1) during the 1996–1998 period.[26,40–42] Others in the MS field also realized the value of ion–molecule reactions to effect isobar separations. Beauchamp and co-workers, using LA-FT-ICRMS, demonstrated the use of $CH_4$ and $CO_2$ as reaction gases to separate $^{187}Re/^{187}Os$ (Re reacts, Os does not) and $^{186}W/^{186}Os$ (W reacts, Os does not), respectively. They termed this approach 'post ionization chemical separation' (PICS);[43] this term preceded the currently vogue term 'chemical resolution.' At this time (1998), enough evidence of the usefulness of ion–molecule reactions had accumulated and the analytical atomic MS community took serious notice. Developments since have been steady and revealing. Micromass Inc. (now GV Instruments) and PerkinElmer SCIEX announced the first commercial implementations of instruments, based on either multipole ion guides or quadrupole bandpass collision/reaction cells, respectively. These instruments were soon joined by other offerings from Thermo Instruments (1999) and Agilent Corporation (2001). Hitachi also introduced (in Japan) a commercial ion trap ICP-MS instrument (P-5000 ICP ITMS, later called the ICP 3DQ MS) about this time.[44] The new era of collision/reaction cells in ICP-MS was thus underway.

## Status

### Instrumentation, operation and techniques

The main features of collision/reaction cells as used in ICP-MS instruments are reviewed next. The physical features of collision/reaction cells include the number, length, diameter and spacing of the rf multipole rods, the length and the location of the rods relative to the gas containment vessel, the position and orientation of the cell within the instrument (distance from differential pumping apertures, beam stop or cell offset/angle to block directed neutral species from the ICP), the use of additional rf/dc fields (*e.g.*, an axial dc field) to supplement the functions of the main multipole ion guiding field, and the design of the ion injection/extraction optics. Instruments have appeared that use quadrupoles, hexapoles and octopoles to provide the confining field for the cell. The length of the rods used have ranged from ~2 inches in our early ion trap ICP-MS work to 6 inches in our later "PSQ" instrument and in certain commercial instruments, *e.g.*, GV Instruments Platform™. All commercial instruments use some means to prevent the neutral species from the ICP (Ar metastable atoms, UV photons) from entering the cell or reaching the detector, where they might otherwise create new, potentially interfering ions, non-mass-resolved background signal, or detector noise. The commercial instruments use a cell angled relative to the axis of the ion beam (GV Instruments Platform and Agilent 7500c and 7500cs), an on-axis beam stop (PE-Sciex DRC+), or a "chicane" lens downstream of the cell (ThermoElemental X-Series). When high pressures of relatively heavy gases are used, scattering losses can be significant. These losses can be somewhat offset

by use of an axial accelerating field. PE-Sciex has reported the use of such axial fields in collision cell work and have incorporated such fields in their latest CRC-ICP-MS. Most details of the design of these instruments are kept confidential by the instrument manufacturers so that only limited comparisons can be made with other instruments. Nevertheless, we will provide a few comments on the general features of these instruments and the design principles around which they were built.

## Design features of ion guides and cells

Gerlich has described in detail the physical principles underlying operation of rf multipole ion guides.[45] His treatise also provides useful engineering formulae and guidance in design of these devices. Collision/reaction cell ICP-MS practitioners who desire a thorough and detailed understanding of these devices are encouraged to refer to the Gerlich treatise. Among the design principles pointed out by Gerlich is the effectiveness with which different multipole orders (quadrupole, hexapole, octopole, *etc.*) can guide a range of ion masses simultaneously. Gerlich observes that an octopole provides good ion transmission efficiency for a maximum to minimum ion mass ratio of about 100. This is about the range encountered in elemental/isotopic MS. Quadrupoles are unique in that narrow bandwidth operation is possible, along with other modes that are highly selective with respect to mass-to-charge ratio. Another important aspect of rf multipole ion guides is the shape and depth of the confining potential well. The quadrupole has the steepest confining potential (potential rises quickly from the center of the device to the rods), while hexapoles, octopoles, and higher order multipoles have progressively flatter potential well minima. These higher order multipoles thus provide higher ion transmittance (higher acceptance) as well as reduced scattering losses. The wider potential well in an octopole means the ions occupy a larger volume and the ions travel farther in passing through the cell. A higher order multipole ion guide thus provides a greater gas thickness (at comparable pressures) compared with a lower order multipole. Since the extent of reaction depends exponentially on the number of collisions, this increased thickness has an enormous effect on the extent of reaction and thus on the efficiency of the cell. As mentioned above, scattering losses are reduced in higher order multipoles, especially when comparing hexapoles or octopoles operated far from the stability boundaries (ion guiding mode) *versus* a quadrupole operated in a narrow bandwidth mode, near a stability boundary.

In summary, the main advantage of quadrupoles is that they enable mass-selective ejection of precursor and/or product ions with a narrow bandwidth (high degree of mass-to-charge ratio specificity). The downsides of quadrupoles are that acceptance/transmission is lower, scattering losses are greater, especially with heavy reagent gases or when rejecting precursor ions by operating at high $q$. The advantages of hexapoles and octopoles are that a wide range of ion masses can be simultaneously transmitted and with higher efficiency than with quadrupoles. However, since mass-selective operation is not possible with higher order multipoles, at least not with narrow bandwidth, the ion chemistry employed must be more selective with respect to the analyte/interfering ions of interest. Good analytical performance has been realized with all of these devices. Issues that have not been addressed or resolved with respect to multipole order in these instruments include rf heating, different "thickness" for a given gas pressure, and cell/rod length, the effect of an axial dc field on the higher order multipoles (axial field effect has been addressed by Tanner *et al.* and earlier workers for quadrupoles only,[27] but the method is well known in earlier multipole devices—see treatise by Gerlich[45]).

The available commercial instrumentation can thus be rather simply classified on the basis of cell designs—primarily either quadrupole cells or multipole cells. As a general rule, the former device uses more reactive reagent gases and the latter use more selective gases. The former device requires bandpass rejection of unwanted reaction products formed as a consequence of the less selective chemistry. The latter devices do not provide for such rejection, but their use with more selective reagents does not demand this characteristic. Ion trap instruments may provide for either mode of operation as selective filtering/rejection of unwanted ions, using applied filtered noise or designed waveforms, has been demonstrated many times in the organic ion trap and FT-ICRMS literature as well as in the early ion trap ICP-MS work of Eiden and co-workers.[46,47]

## Entrance/exit ion optics

Various cell entrance/exit ion optics are used, but little detail (design, characterization or modeling) is available in the literature. Sciex uses an on-axis beam stop and a single cylinder lens. ThermoElectron uses a high voltage extraction lens followed by a two-element lens ahead of the collision cell and a two-element lens after the cell. Neutrals are selected against by steering the ions through a "jogged" path lens ("chicane" lens). Agilent and GV Instruments use cells whose main axis is angled with respect to the ICP ion beam axis such that the ion detector no longer has a direct line-of-sight view of the ICP. In every case it appears that manufacturers have established empirical operational success but little additional information on design features or critical parameters is available for these devices. Informed discussion or comparison of the ion optics designs is therefore difficult.

## Vacuum conditions and considerations

With respect to vacuum quality, there have been no significant changes in collision/reaction cell ICP-MS instruments over earlier ICP-MS instrumentation. All instruments use oil-sealed pumps to evacuate the first vacuum region, the so-called expansion region, and turbo pumps farther downstream in the higher vacuum regions (typically backed by oil-sealed rotary vane pumps). This results in a vacuum quality that would not be acceptable for careful studies of ion–molecule chemistry in a conventional beam instrument and would be even more problematic in an ion trapping instrument. Future instrument generations will likely provide improvements in this area. Such improvements could include bakeable cells, the elimination of "high" vapor pressure materials (plastic coated wires), and better plumbing of the reagent gases into the cell, including bakeable, stainless steel, all metal gasketed gas lines.

## Ion–molecule reaction chemistry—general aspects

Although many different types of gas-phase, ion–molecule reactions exist, to date only a relative few have been shown to play important roles in interferent reduction in ICP-MS or GD-MS. Thermodynamic and kinetic considerations must, of course, be taken into account in developing reaction chemistry
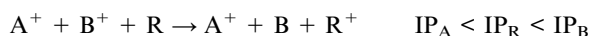
**Table 2** Reagent gases used to address isobaric interferences in PNNL ion trap ICP-MS investigations, 1996–1998

| Reagent gas | Interferent ion | Analyte ion |
| --- | --- | --- |
| $H_2$ | $Ar^+$ | $^{40}Ca$, $^{40}K$ |
| | $ArH^+$ | $^{39}K$ |
| | $ArN^+$, $ArO^+$ | Fe |
| | $Ar_2^+$ | Se |
| $O_2$ | $^{129}Xe$ | $^{129}I$ |
| | $^{90}Y$, $^{90}Zr$ | $^{90}Sr$ |
| $CH_3OH$ | $^{135,137}Ba$ | $^{135,137}Cs$ |
| $NH_3$ | $^{79}Br$ | $^{79}Se$ |
| | $^{87}Sr$ | $^{87}Rb$ |
| $H_2O$ | $Ar^+$, $ArN^+$, $ArO^+$ | Various |

strategies. The reader is referred to the excellent work by Tanner and colleagues for a complete discussion of reaction thermodynamics and kinetics considerations in ICP-MS.[27,48] More fundamental aspects of ion thermochemistry can be found in Lias *et al.*[49] In brief, reactions must be thermodynamically allowed under the reaction conditions used (*i.e.*, they must be experimentally exothermic), and the rates of reaction must be such that they are analytically useful. Compilations of thermodynamic data and reaction rates are available[50] and can/should be consulted to guide experiments, but empirical testing and verification under actual instrumental conditions is nonetheless advised.

The important, beneficial reactions in elemental mass spectrometry are those that (1) neutralize the more intense chemical ionization species in the beam, and (2) shift either the interferent ion or the analyte ion from each other in mass/charge. These transformations are accomplished using a variety of reaction types: charge exchange, atom transfer, adduct formation or condensation reactions. Charge-transfer reactions require a reagent gas with an ionization potential intermediate between the interferent ion and the analyte ion (in the following reactions, A denotes analyte, B denotes isobaric interferent, and R denotes reagent).
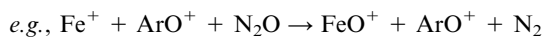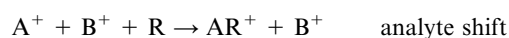
Charge-exchange reaction

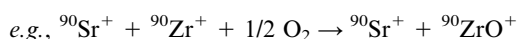$$A^+ + B^+ + R \rightarrow A^+ + B + R^+ \qquad IP_A < IP_R < IP_B$$

*e.g.*,
$$Ca^+ + Ar^+ + H_2 \rightarrow Ca^+ + Ar + H_2^+ \quad IP_{Ca} < IP_{H_2} < IP_{Ar}$$
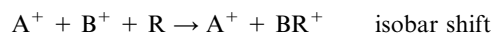
Condensation, adduction, or atom-addition reaction reactions have no such restriction on ionization potential of the reagent gas, but may have thermodynamic and kinetic constraints:

Atom-addition reaction

$$A^+ + B^+ + R \rightarrow AR^+ + B^+ \qquad \text{analyte shift}$$

*e.g.*, $Fe^+ + ArO^+ + N_2O \rightarrow FeO^+ + ArO^+ + N_2$
or

$$A^+ + B^+ + R \rightarrow A^+ + BR^+ \qquad \text{isobar shift}$$

*e.g.*, $^{90}Sr^+ + {}^{90}Zr^+ + 1/2\ O_2 \rightarrow {}^{90}Sr^+ + {}^{90}ZrO^+$

Each of the above reactions resolves an analyte/interferent pair. It must be recognized, however, that both types of reactions have potential to create other interferent ions. For example, in the reactions above new ions are formed at *m/z* = 2 ($H_2^+$) or *m/z* = 106 ($^{90}Zr^{16}O$). If other analyte isotopes are present at these mass/charge values (*e.g.*, Pd, Cd), new interferences are possibly created. This consideration has to be taken into account in the design of reaction chemistry strategies and applications.

Other types of gas-phase reactions occur, but have, to date, had only limited utility in ICP-MS applications. These reactions include clustering reactions with more reactive, less selective reagents like $H_2O$ and $NH_3$. Typically, these reactions are more deleterious than useful in many ICP-MS applications. An exception exists with the PerkinElmer SCIEX DRC instrument[27,43,48] (see following for discussion), which has been specifically designed to avert undesired clustering and secondary reactions, at least to some extent.

The list of useful reagent gases in ICP-MS is not onerously long or complicated. The list is, in fact, relatively short, consisting of only a few charge-exchange reagent gases, a handful of oxidation gas reagents, and relatively few adduction and other reagent gases (Table 3). Approximately 6 reagent gases are in routine use with collision and reaction cells in ICP-MS today. Good reagent gases are generally those with high reaction efficacy, *i.e.*, they react at fast rates, are highly selective, and achieve significant ($> 10^6 \times$) resolution efficiency from interfering species. Primary product ions are thus

**Table 3** Reagent gases employed in collision/reaction cell ICPMS (routinely used reagent gases in bold)

Collision gases

**He**, Ar, Ne, Xe

Charge exchange gases

**H$_2$**, **NH$_3$**, Xe, CH$_4$, N$_2$

Oxidation reagent gases

**O$_2$**, **N$_2$O**, NO, CO$_2$

Reduction reagent gases

H$_2$, CO

Other reaction (adduction) gases

**CH$_4$**, C$_2$H$_6$, C$_2$H$_4$, CH$_3$F, SF$_6$, CH$_3$OH

produced quickly and (preferably) exclusively. Secondary products are removed easily or re-react minimally, and result in minimal spectral complexities. Low mass gas ions have the advantage of being converted to low *m/z* products and being easily swept or ejected from the reaction cell. Heavier gases, in general, are both more reactive with everything (owing to higher cross sections and better damping characteristics) and less specific.

### Ion–molecule chemistry—analytical considerations

The main performance features on which most researchers have focused in "chemical resolution" MS studies are the magnitude of interfering ion signal reduction and the improvement in the signal-to-background ratio. What is typically ignored is the loss of analyte signal. While an improved signal-to-background is of obvious interest, in many applications severe reductions in analyte signal are not tolerable. Ideally, one should consider all of the following in providing a complete assessment of "chemical resolution" MS performance:
(1) interferent signal reduction;
(2) analyte signal reduction;
(3) analyte signal noise;
(4) background noise.

Additional performance features that are of interest include the creation of new interferences by the cell, how general or specific a given interference reduction scheme is (single element/isotope application or multi-element/isotope), mass bias effects of the cell, and collisional dampening and focusing effects.

### Analyte ion loss

In our own early collision/reaction cell work, we felt that significant losses of analyte ion signal would not be accepted by the community and so chose conditions which resulted in very small, typically unmeasurable, losses in analyte ion signal. More recent collision/reaction cell (CRC) work has tolerated as much as an order of magnitude loss in analyte signal, as long as the signal-to-background ratio improves. However, it is often of interest to measure an analyte at ultratrace levels in a limited sample, or chemical processing of the sample may be sufficiently difficult that it is desirable to use all analyte extracted with the highest possible efficiency (high chemical recoveries, high analytical efficiencies). In such cases, lower analyte signal loss is a primary goal. However, the large range of analyte loss in various literature reports makes comparison of the interferent reduction achieved more difficult to assess. These data need to be normalized for the analyte loss, that is, the efficacy of the "chemical resolution" process needs to be quantified.

In addition, methods need to be developed to help establish

what fraction of analyte losses are due to non-reactive scattering *versus* reactive processes. Thermometer reactions have been suggested as a means for more quantitative comparison of different instrument designs or of different instruments of the same or similar design that are operated differently.[51] Another potentially useful set of thermometer reactions is that between selected transition metal cations and various low molecular weight hydrocarbons, *e.g.*, $Zr^+$ reaction with $CH_4$ or $C_2H_6$. Armentrout has reported detailed cross section data for the various product channels in these systems as a function of kinetic energy.[52,53] These thresholds and energy dependencies might provide a useful benchmark for CRC-ICP-MS instruments. $CH_4$ is one of the gases commonly used in CRC-ICP-MS and $Zr^+$ can be readily produced with an ICP. Such thermometer data could provide a useful QA/QC check on instrument operating conditions in CRC-ICP-MS. This technique might prove useful and be analogous to the Mg ion/atom 'robustness' ratio criterion suggested by Mermet[54] for evaluation and comparison of ICP-OES operating conditions.

### New interference production

It must be kept in mind that the collision/reaction cell does not remove ions from the beam, it only alters the chemical nature of the ions present. That is, interfering ions are only "relocated" by virtue of chemical reaction. In addition to the interfering ion being converted to some other ion, other ions in the beam can react with the reagent gas or background gases to form other new ions. These may interfere with some analyte ion of interest. This is obviously an issue for the more complex reagent gases since they undergo more varied reaction with the atomic and polyatomic cations encountered in ICP-MS. There are several potential sources for the creation in the cell of new, interfering ions: reaction of incoming ions with background gases, "side" reactions of the reagent gas with incoming ions, and secondary reaction of in-cell produced ions with reagent gas and/or background gas.

### Kinetic energy discrimination: mass selected ion chemistry

Methods that have been reported that mitigate the formation of new interfering ions include kinetic energy discrimination and mass-selected ion chemistry. Kinetic energy discrimination (KED) refers to the use of a potential barrier between the cell and mass analyzer, typically by operating the cell at a dc offset potential somewhat lower than that of the analyzing quadrupole. Beam ions from the ICP retain a significant portion of their original kinetic energy and trajectory whereas ions formed inside the cell are typically formed at lower kinetic energy and/or off-axis trajectory. The lower energy ions formed in the cell are unable to surmount the potential barrier and are thus prevented from passing into the analyzing quadrupole and on to the ion detector. Mass selected ion chemistry methods have been known for decades in the ion trap mass spectrometry field and these methods are now available in ICP-MS in the form of the "DRC" instruments from PerkinElmer Sciex. In this approach, the low mass cut-off of the quadrupole is raised while the high mass stability edge is lowered. This creates a narrow window of masses that are stable in the quadrupole field. Application of supplemental rf frequencies (either singly, in a range, or a series of frequencies/ranges) can also be applied to mass filter devices. The frequencies are selected to be resonant with components of ion motion so that undesired ions can be excited and ejected. Such bandpass or 'notch' methods are well known in quadrupole ion trap mass spectrometry;[46,47,55] they are less commonly applied in linear quadrupole mass filters. The bandpass of the cell is set to a fairly narrow width such that the ion of interest is stable in the trap, but very few others are. The transmission function of the DRC in its bandpass mode has not been reported, but based on earlier work with pressurized quadrupoles, the bandwidth is probably greater than a single amu. As the bandpass is narrowed, the transmission of the quadrupole decreases sharply so that sensitivity is traded off for suppression of new interferences. This is analogous to high resolution mass spectrometry where high resolution comes at the expense of sensitivity. Reported DRC efficiencies are lower by a factor of 3–5 than typical efficiencies reported by our laboratory and other researchers using other collision/reaction cell ICP-MS instruments. It is difficult to say whether this is due to the quadrupole used in the DRC cell (*versus* higher transmittance hexapole or octopole) or to other ion optical or transport inefficiencies.

Another aspect of bandpass collision cells that has not been addressed to date is the rate at which undesired precursor ions (ions that can react and lead to interfering product ions) are ejected and thereby prevented from reacting with the cell gases. Different mass precursor ions are ejected at different rates under a given set of operating conditions and this could possibly affect how well reactions of the precursor ions are suppressed. The issue is one of how rapidly an ion near the edge of or outside the stability region is ejected from the trapping/guiding field. The number of rf cycles an ion must experience before it is destabilized is not known but can probably be modelled. Whether the rejection rates currently used are optimal is also unknown; studies to investigate this are recommended.

Our group originally recognized the unique capabilities of hydrogen as a reagent gas for CRC-ICP-MS. Mass selective chemistry is less necessary for hydrogen as it is unreactive with most metal cations of interest. Hydrogen is unique with respect to this chemical selectivity for at least two reasons. First, the H–H bond in $H_2$ is quite strong (4.5 eV dissociation energy), at least 2 eV stronger than most $MH^+$ bonds.[56,57] H atom transfer reactions with metal cations are thus usually endothermic. While 2–3 eV does not seem like a very large energy to provide to overcome this endothermicity, compared with the $\sim 5$–10 eV energy of ions extracted from an ICP, the former energy is in the center-of-mass frame of the reaction while the latter refers to laboratory frame kinetic energy. Because of the very low mass of $H_2$, the center-of-mass energy of a metal cation collision with $H_2$ is typically an order of magnitude smaller than the laboratory frame kinetic energy. Thus, laboratory frame energies of at least 20–30 eV are typically needed to drive H atom abstraction reactions. Charge exchange reactions are also energetically forbidden as the ionization potential of $H_2$ is 15.4 eV, 6–9 eV greater than that of a typical metal atom.

While the low mass of hydrogen is an advantage for the reasons given above, it has been claimed that hydrogen gas by itself is not efficient in thermalizing the incoming ion beam in the cell. However, contrary to this assertion, neat $H_2$ and mixtures of $H_2$ in He have been shown to suppress various argide interferences by 5–9 orders of magnitude.[41,58,59] Hattendorf and Gunther report that thermalization of the ion beam can be improved by mixing $H_2$ with a heavier, inert gas.[60] They report increased efficiencies of interfering ion suppression using a mixture of $H_2$ and Ne (results for He and Xe were also reported). Others have reported similar results for $H_2$ mixed with Ar.[61]

## Applications of collision/reaction cell techniques

Collision/reaction cell techniques are being applied to an ever-growing variety of sample types, particularly those of biological and environmental origin. Just as electrospray ionization (ESI) and matrix assisted laser desorption ionization TOFMS (MALDI-TOF) techniques have been increasingly useful in biological investigations, collision/reaction cell ICP-MS techniques may be enabling new insights in bioinorganic studies. This is perhaps demonstrated by the increasing appearance of ICP-CRC-MS elemental analyses in other

than traditional elemental and atomic spectroscopy publications. Many of the analyses are for the heteroatoms of biological molecules, *i.e.*, phosphorus, sulfur and selenium, and the toxic species of arsenic, selenium and chromium. Another observation is that collision/reaction cell techniques are more fully opening the ICP-MS window to the elements of periods 2, 3 and 4 of the periodic table. The role of transition metals in biology (especially Fe, Cu and Zn) is also being more clearly defined, with growing interests in their interaction and functions in biological systems. Both CRC and high-resolution ICP-MS techniques seem to be fueling such interests. Indeed, investigators are now speaking of the "metallome" in terms that parallel the genome and proteome concepts.[62]

The applications cited here cover the 2000–2003 period (some early 2004 work is also referenced). Applications are defined as analyses of real samples, including SRM-type samples, but not including neat solution sample surrogates as used in method development efforts. This applications survey is just that—an illustrative review and not an exhaustive compilation. A listing of applications is given in Table 4 and discussed briefly below. For earlier applications the reader is again referred to the review by Tanner and colleagues.[27] In many cases the ICP-MS analyses of analytes and sample types reported are similar to those prior to the advent of collision/reaction cell techniques; however, now with significantly better detection limits afforded by collision/reaction cell techniques, the results are much more

meaningful. Although several reported applications are multi-elemental, many are directed at and optimized for single elements, usually driven by sample or experiment. Since there are no 'perfect' techniques or methods, many authors (ourselves included) caution the analyst to always be wary of matrix affects and polyatomic spectral interferences created by sample matrix, preparation, and/or reagent gases.

The biological category includes foodstuffs, serum, urine, tissue, plant material, nucleic acids, lipids, amino acids, and proteins. In the study of foodstuffs, interests are typically in nutritional elements,[63–66] toxic species,[63,67] nutritional/toxic selenium species,[68] and heavy metals.[63] Classically interfered elements (V, Cr, Fe, As, Se) in sera or urine are sought directly,[69–72] while their various oxidation or derivative species are separated first by various separation techniques, *e.g.*, on-line liquid chromatography (LC)[73,74] and off-line LC.[75] The presence and degree of phosphorylation on nucleic acids, lipids, and proteins are very important for their function and activity, and are of intense interest. The collision/reaction cell removal of interferences for the sensitive determination of phosphorus has been applied to on-line capillary electrophoresis (CE) and LC separated nucleic acid monophosphates,[76] to on-line LC separated phospholipids,[77] to proteins directly,[78] and to proteins separated by 1-D electrophoresis gel and sampled by laser ablation (LA) directly from the gel.[79] Transition metals and sulfur associated with various amino acids and proteins are

**Table 4** ICP-CRC-ICP-MS Applications Survey, 2000–2003

| Application | Sample | Analyte | CRC gas | Comments | Ref. |
|---|---|---|---|---|---|
| Biological | Incubation media | Cr species | $H_2$ | Chelation IC for Cr(III), -(VI) | 67 |
| | Milk powder | Ca, Fe, Zn | $CH_4$ | | 65 |
| | Milk powder, cereal | Ca, P | $CH_4$, $O_2$ | | 64 |
| | Milk powder | Cr, Zn, Cd, Pb | $NH_3$ | Ultrasonic slurry sampling ETV | 66,107 |
| | Nucleic acid phosphates | P | He | On-line CE, HPLC | 76 |
| | Phospolipids | P | He | On-line LC | 77 |
| | Amino acids | S | $O_2$ | On-line CE | 82 |
| | Proteins | S, Fe, Mn | $O_2$ | Size exclusion LC | 80 |
| | Protein, cancer | P, S | $O_2$ | LA of 1-D gels, phosphorylation | 79 |
| | Protein | P, S | $O_2$ | Phosphorylation | 78 |
| | Proteins, fish, liver | S, Cu, Zn, Cd | Xe | On-line CE | 81 |
| | Protein, biofluids | Se | $CH_4$ | Enriched Se-77 | 83 |
| | Protein, yeast | Se | $CH_4$ | HPLC, enriched Se-77 | 84 |
| | Protein, yeast | Se | CO | LA of 2-D gels | 87 |
| | Protein, yeast | Se | CO | LA of 2-D gels | 86 |
| | Protein, yeast | Se | $H_2$/He | 2-D-LC | 85 |
| | Rice flour | Cr, Cu, Cd, Hg, Pb | $NH_3$ | ETV | 63 |
| | Serum | Se species | $H_2$ | LC, post col. IDA | 75 |
| | Serum | V species | $NH_3$ *et al.* | Size exclusion LC | 73 |
| | Serum, urine, tissue | Se isotopes | $H_2$ | IDA | 69 |
| | Urine, serum | Cr, V | $NH_3$ | 10 × dilution | 71 |
| | Urine, serum | Se | $CH_4$ | 20 × dilution | 70 |
| | Urine | Se species | $H_2$/He | HPLC | 74 |
| | Yeast, flour | Se species | $H_2$ | IDA | 68 |
| | Water, urine | Cr | $NH_3$ *et al.* | 2 ×, 10 × dilution | 72 |
| Environmental | Air | Cr species | $NH_3$ | KOH, separation, precon. for Cr(IV) | 88 |
| | Coal, fly ash | Hg | He | Isotope ratio, transient signals | 96 |
| | Sea-water | 13 elements | $H_2$/He | 10 × dilution | 97 |
| | Sea-water | As species | He | LC, hydride generation | 94 |
| | Sea-water | Cu, Cr, Ni, Mn, V | $NH_3$ | 10 × dilution | 90 |
| | Soil | Cr, Cu, Zn, Cd, Pb | $NH_3$ | LA of pressed pellets | 91 |
| | Water | V species | $NH_3$ | On-line LC | 95 |
| | Water | Cr species | $NH_3$ | On-line LC | 89 |
| | Waters | As species | $H_2$/He | On-line IC | 93 |
| | Waters | As species | $H_2$/He | On-line IC | 92 |
| | Waters | P pesticides | He | On-line GC | 98 |
| Geological | Precambrian rock | Os isotopes | He | ICP-SFMS, -CRC-MS, -MC-MS | 99 |
| | Pb button | Pt, Pd, Rh | $NH_3$ | LA of fire assay Pb buttons | 100 |
| Nuclear | Soil | Rn-226 | He | Resin extraction/separation | 104,105 |
| | Soils | U isotopes | He | ICP-CRC-MS, -HRMS -MC-MS | 101 |
| | Soils | U-236 | He | ICP-CRC-MS, -HRMS | 102 |
| | Soils | I-129/I-127 | $O_2$ | Thermal desorption of soil | 103 |
| High purity reagents | Perovskite, thin film | Ba, Sr, Ti | $H_2$/He | ICP-CRC-QMS, -QMS, -HRMS | 106 |
| | $H_2O_2$ | 21 elements | $NH_3$ | High purity reagent | 108 |
| | $AgNO_3$ | Fe | $NH_3$ | AgBr ppt., ultra-trace Fe, ID | 109 |

detected after on-line size exclusion LC[80] and on-line CE.[81,82] The relationship and function of selenium in certain proteins continues to have significant interest.[83] Separation of these proteins is achieved by on-line LC[84,85] and 2-D gel electrophoresis sampled directly by LA.[86,87]

Environmental samples included air, coal, fly ash, sea-water, water, and soils. Again, this area is dominated by elements and species whose limits of detection were unusable until collision/reaction cell techniques removed the various spectral interferences. Chromium species were collected from air,[88] water,[89] sea-water,[90] and soil.[91] Arsenic, likewise, was sampled from water[92,93] and sea-water[94] and separated on-line by LC or ion chromatography. Vanadium, like selenium, is both trace-nutritive and toxic, and interest in it is growing. Vanadium was determined in water after on-line LC.[95] The isotope ratio differences of mercury in coal and coal fly ash were determined by preconcentration onto gold traps followed by thermal desorption into the plasma.[96] The study favorably compared the results from six ICP-MS instruments (CRC-QMS, four MC-MS's, and TOFMS). Multi-element analyses were reported for $10 \times$ diluted sea-water[90,97] and for the LA of pressed soil pellets.[91] Organophosphorus pesticides in water were determined by sensitive ICP-MS detection following on-line gas chromatographic separation.[98]

There are fewer, but no less important, collision/reaction cell applications in geological, nuclear, and high purity materials. The osmium isotope ratios of Precambrian rock were determined and compared by three different MS techniques.[99] A new collision/reaction cell twist to the time-honored fire assay for precious metals was also reported.[100] Analytes were preconcentrated from the ore matrix by the classical, elegant lead fire assay, which results in the precious metals being dissolved in a small lead 'button'. Instead of dissolving the button for solution analysis, it was sampled by LA with ICP-CRC-MS analysis for platinum, palladium, and rhodium.

Uranium isotopes were determined from Chernobyl contaminated soils by several different MS techniques.[101,102] The removal of the Xe-129 interference, allowing the determination of I-129 from contaminated soils, was reported.[103] A resin based extraction and separation procedure for radium-226 from uranium ores and plants was developed followed by ICP-MS detection.[104,105]

High purity materials are critically important in various industries, e.g., semiconductor, film photography, etc. Many of the critical impurities in these materials are precisely the ones that evaded the high sensitivity powers of ICP-MS due to low m/z interferences that are addressed by collision/reaction cell techniques. Dissolution of perovskite thin films and multi-element analysis by multiple instruments was reported.[106]

A 21-element suite of ultra-trace determinations was reported for high purity hydrogen peroxide.[108] Similarly, iron impurities at ultra-trace levels were determined for high purity silver nitrate.[109]

Whether collision/reaction cell techniques are utilized for single element, specialized analysis or for multi-element analysis (the ICP-MS forte), it is clear by the above examples that ICP-CRC-MS is being effectively employed for improved and unequivocal detection of nearly every element in a wide range of matrices. This is especially true for biological applications and we expect this area to continue to be significantly impacted by ICP-CRC-MS. It is apparent that biological speciation techniques in particular will benefit by development and application of ICP-CRC-MS techniques.

## Perspectives and conclusions

In just a few short years, collision/reaction cell techniques have been developed to the point where they offer unique interference reduction potential to the ICP-MS practitioner.

Complex spectral interferences can be minimized or avoided completely using low-cost instrumentation and readily available gaseous reagents. Collision/reaction cell techniques offer considerable experimental flexibility for the analyst, as a wide range of reactions and reagents can be effectively employed. The ion–molecule chemistry knowledge that is required is largely available through years of fundamental studies, and promises to lead to new advances and improvements in the application of these techniques. The Perspective by Armentrout (in this issue, following) gives the reader an appreciation of gas-phase chemistry fundamentals and provides some thoughts and directions for future efforts.

Most collision/reaction ICP-MS instruments in use today employ linear multipoles as reaction cells. Conventional 3-dimensional ion traps, used in early work to demonstrate the efficacy of the approach, were limited by fundamental ion capacity and dynamic range limitations. New linear ion trap technology, based on electrostatically confined multipole assemblies, are now in use in organic mass spectrometry and offer significant relief from the limitations of the Paul-type traps.[110] Their use in ICP-MS is certain to be explored soon too. The use of such ion guides to thermalize and efficiently transport ions to sector based ICP-MS instruments is already realized and such cells in reaction modes could also be used in concert with high resolution mass spectrometry. It is thus apparent that multipole devices in various forms will continue to be utilized in ICP-MS instruments. Accordingly, a greater appreciation of the strengths and limitations of such devices is needed. Gerlich provides such a view in his accompanying Perspective.

This review has focused on the use of reactive chemistry techniques to reduce interferences. Purely collisional techniques, although leading to the reactive techniques discussed, have been largely downplayed or ignored. Conventional wisdom dictates that collisional techniques cannot yield the many orders of magnitude of interference reduction that is required for ICP-MS. But it is time to revisit, explore, and perhaps debunk this view. The Perspective provided by Marcus in this issue questions why collisional techniques have been overlooked and provides a challenge for the revisiting of this approach. Based on apparent simplicity, it is a compelling challenge. Collisional techniques may provide a universal, albeit limited, approach to interferent ion reduction. They may provide a useful role in avoiding the easy interferences and being used in more effective combination with reactive techniques. Careful studies are needed to clearly define and distinguish between purely collisional processes and reactive processes that accompany them. Improvements in beam focusing and thermalization, with resultant sensitivity and resolution payoffs, can also result from new insights here.

The development of collision/reaction cell techniques has led to an increased number of applications studies in the last few years. Use of the technique is most notable for application to those elements with traditional interference problems, e.g., P, S, Ca, Fe, Cr, As, and Se. This group includes many elements of biological importance and thus a preponderance of biological sample applications have recently been observed. But atypical analytes/samples requiring a higher level of interference reduction or improved S/N are also being addressed by these techniques (including analytes I, Cd, Pb, Hg, and U). In any case, it is apparent that the technique is sufficiently useful and robust that it is now in the hands of not only instrument developers but also pragmatic analytical chemists.

What does the future of collision/reaction cell techniques hold? Certainly one of the criticisms that have been levelled at the technique is that it reduces an inherently multi-element technique to a single element method. There are both general and specific interference problems that can be addressed using these techniques, and such a criticism is perhaps unfair. It is rare in the authors' laboratory that an entire elemental mass

spectral scan is done in anything other than a semi-quantitative mode. Typically, multiple analyte acquisitions are performed based on constraints associated with sample preparation, concentration levels, interference potential, calibration issues, standards availability, or other factors. It is frequent that instrument conditions are optimized for ultimate detection or quantitation of a select group of analytes or even single isotopes/elements. Given this actual state of operation for ICP-MS, the use of a few or several reagent gases to avoid nearly all interferences is not overly burdensome or limiting. As the technique matures, both general and specific reagent applications for different analytical problems will be proposed, tested, and accepted. More efficient and universal schemes will become apparent. The use of collision/cell techniques will thus extend, not limit, the power and application of the ICP-MS method.

Finally, a review of the development history in this area reveals that investigators were tantalizingly close to realization of this capability some years ago, but that the then current trends and efforts delayed such realization by almost 10 years. This is of historical note and is curious in that the scientific community has seen missed opportunities of this kind many times before. It is perhaps simply a reflection that new ideas and new technology take time to germinate before active development and use begins. In any case the development of collision/reaction cell techniques seems to have dominated the ICP-MS field for the last ~5 years. Whether and how this development effort influences (prompts or impedes) the next development '–cene' in ICP-MS remains to unfold.

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## References

1   R. S. Houk, V. A. Fassel, G. D. Flesch, H. J. Svec, A. L. Gray and C. E. Taylor, *Anal. Chem.*, 1980, **52**, 2283–2289.
2   D. J. Douglas, E. S. K. Quan and R. G. Smith, *Spectrochim. Acta, Part B*, 1983, **38**, 39–48.
3   A. R. Date and A. L. Gray, *Analyst*, 1981, **106**, 1255–1267.
4   I. Feldmann, W. Tittes, N. Jakubowski, D. Stuewer and U. Griessmann, *J. Anal. At. Spectrom.*, 1994, **9**, 1075–1078.
5   N. Bradshaw, E. F. H. Hall and N. E. Sanderson, *J. Anal. At. Spectrom.*, 1989, **4**, 801–803.
6   L. J. Moens, F. F. Vanhaecke, D. R. Bandura, V. I. Baranov and S. D. Tanner, *J. Anal. At. Spectrom.*, 2001, **16**, 991–994.
7   N. M. Reed, R. O. Cairns, R. C. Hutton and T. Takaku, *J. Anal. At. Spectrom.*, 1994, **9**, 881–896.
8   C. J. Barinaga and D. W. Koppenaal, *Rapid Commun. Mass Spectrom.*, 1994, **8**, 71–76.
9   D. W. Koppenaal, C. J. Barinaga and M. R. Smith, *J. Anal. At. Spectrom.*, 1994, **9**, 1053–1058.
10  D. P. Meyers, G. Li, P. Yang and G. M. Hieftje, *J. Am. Soc. Mass Spectrom.*, 1994, **5**, 1008–1016.
11  D. P. Meyers, G. Li, P. Yang and G. M. Hieftje, *J. Am. Soc. Mass Spectrom.*, 1994, **6**, 400–410.
12  K. E. Milgram, F. M. White, K. L. Goodner, C. H. Watson, D. W. Koppenaal, C. J. Barinaga, B. H. Smith, J. D. Winefordner, A. G. Marshall, R. S. Houk and J. R. Eyler, *Anal. Chem.*, 1997, **69**, 3714–3721.
13  L. Allen, H. Pang, A. Warren and R. S. Houk, *J. Anal. At. Spectrom.*, 1994, **10**, 267–271.
14  Z. H. Du, D. J. Douglas and N. Konenkov, *J. Anal. At. Spectrom.*, 1999, **14**, 1111–1119.
15  Z. H. Du, T. N. Olney and D. J. Douglas, *J. Am. Soc. Mass Spectrom.*, 1997, **8**, 1230–1236.
16  A. J. Walder, I. Platzner and P. A. Freedman, *J. Anal. At. Spectrom.*, 1993, **8**, 19–23.
17  A. J. Walder and P. A. Freedman, *J. Anal. At. Spectrom.*, 1992, **7**, 571–575.
18  A. J. Walder, I. D. Abell, I. Platzner and P. A. Freedman, *Spectrochim. Acta, Part B*, 1993, **48**, 397–402.
19  G. Horlick and A. Montaser, in *Inductively Coupled Plasma Mass Spectrometry*, ed. A. Montaser, Wiley-VCH, New York, 1998, pp. 503–613.
20  N. S. Nonose, N. Matsuda, N. Fudagawa and M. Kubota, *Spectrochim. Acta, Part B*, 1994, **49**, 955–974.
21  S. H. Tan and G. Horlick, *Appl. Spectrosc.*, 1986, **40**, 445–460.
22  S. H. Tan and G. Horlick, *J. Anal. At. Spectrom.*, 1987, **2**, 745–763.
23  W. W. Harrison, K. R. Hess, R. K. Marcus and F. L. King, *Anal. Chem.*, 1986, **58**, A341–7.
24  J. W. Coburn and W. W. Harrison, *Appl. Spectrosc. Rev.*, 1981, **17**, 95–164.
25  S. D. Tanner and V. I. Baranov, *J. Am. Soc. Mass Spectrom.*, 1999, **10**, 1083–1094.
26  C. J. Barinaga, G. C. Eiden, M. L. Alexander and D. W. Koppenaal, *Fresenius' J. Anal. Chem.*, 1996, **355**, 487–493.
27  S. D. Tanner, V. I. Baranov and D. R. Bandura, *Spectrochim. Acta, Part B*, 2002, **57**, 1361–1452.
28  F. L. King, A. L. McCormack and W. W. Harrison, *J. Anal. At. Spectrom.*, 1988, **3**, 883–886.
29  F. L. King and W. W. Harrison, *Int. J. Mass Spectrom. Ion Process.*, 1989, **89**, 171–185.
30  D. C. Duckworth and R. K. Marcus, *Anal. Chem.*, 1989, **61**, 1879–1886.
31  S. A. McLuckey, G. L. Glish, D. C. Duckworth and R. K. Marcus, *Anal. Chem.*, 1992, **64**, 1606–1609.
32  D. J. Douglas, *Can. J. Spectrosc.*, 1989, **34**, 38–49.
33  J. T. Rowan and R. S. Houk, *Appl. Spectrosc.*, 1989, **43**, 976–980.
34  M. Morita, H. Ito, T. Uehiro and K. Otsuka, *Anal. Sci.*, 1989, **5**, 609–610.
35  S. A. McLuckey, G. J. Van Berkel, D. E. Goeringer and G. L. Glish, *Anal. Chem.*, 1994, **66**, 689A–696A.
36  G. C. Eiden, C. J. Barinaga and D. W. Koppenaal, *J. Anal. At. Spectrom.*, 1996, **11**, 317–322.
37  G. C. Eiden, C. J. Barinaga and D. W. Koppenaal, *A Method for Reduction of Selected Ion Intensities in Confined Ion Beams*, US PTO P/N 5,767,512, US Patent Office, June 16, 1998.
38  I. Feldmann, N. Jakubowski and D. Stuewer, *Fresenius' J. Anal. Chem.*, 1999, **365**, 415–421.
39  I. Feldmann, N. Jakubowski, C. Thomas and D. Stuewer, *Fresenius' J. Anal. Chem.*, 1999, **365**, 422–428.
40  D. C. Duckworth, D. H. Smith and S. A. McLuckey, Abstracts, 1998 Winter Conference on Plasma Spectrochemistry, Scottsdale, AZ, January 5–10, 1998, p. 298.
41  G. C. Eiden, C. J. Barinaga and D. W. Koppenaal, *Rapid Commun. Mass Spectrom.*, 1997, **11**, 37–42.
42  G. C. Eiden, C. J. Barinaga and D. W. Koppenaal, *J. Anal. At. Spectrom.*, 1999, **14**, 1129–1132.
43  K. K. Irikura, E. H. Fowles and J. L. Beauchamp, *Anal. Chem.*, 1994, **66**, 3447–3448.
44  N. Furuta and J. Takeda, in *Plasma Source Mass Spectrometry: The New Millenium* eds. G. Holland and S. Tanner, Royal Society of Chemistry, Cambridge, 2001, pp. 90–96.
45  D. Gerlich, in *State-selected and state-to-state ion-molecule reaction dynamics*, eds. C.-Y. Ng and M. Baer, John Wiley & Sons, Inc.: New York, 1992, vol. 82, p. 176.
46  G. C. Eiden, C. J. Barinaga and D. W. Koppenaal, *Proceedings of the 43rd ASMS Conference on Mass Spectrometry and Allied Topics*, Atlanta, GA, May 21–26, 1995, p. 938, 1104.
47  G. C. Eiden, C. J. Barinaga and D. W. Koppenaal, *J. Am. Soc. Mass Spectrom.*, 1996, **7**, 1161–1171.
48  D. R. Bandura, V. I. Baranov and S. D. Tanner, *Fresenius' J. Anal. Chem.*, 2001, **370**, 454–470.
49  S. G. Lias, J. E. Bartmess, J. F. Liebman, J. L. Holmes, R. D. Levin and W. G. Mallard, *J. Phys. Chem. Ref. Data*, 1988, **17**, 1–861.
50  V. G. Anicich, *Astrophys. J. Suppl. Ser.*, 1993, **84**, 215–315 (also available from http://techreports.jpl.nasa.gov/2003/03-2964.pdf).
51  S. D. Tanner, V. I. Baranov and U. Vollkopf, *J. Anal. At. Spectrom.*, 2000, **15**, 1261–1269.
52  P. Armentrout and M. Sievers, *J. Phys. Chem. A*, 2003, **107**, 4396–4406.
53  M. Sievers and P. Armentrout, *Organometallics*, 2003, **22**, 2599–2611.
54  J. M. Mermet, *Anal. Chim. Acta*, 1991, **250**, 85–94.
55  R. E. Reinsfelder and M. B. Denton, *Int. J. Mass Spectrom. Ion Processes*, 1981, **37**, 241–250.

56 M. Sievers, Y. Chen, J. Elkind and P. Armentrout, *J. Phys. Chem.*, 1996, **100**, 54–62.
57 J. Elkind and P. Armentrout, *J. Phys. Chem.*, 1987, **91**, 2037–2045.
58 C. P. Ingle, P. K. Appelblad, M. A. Dexter, E. J. Reid and B. L. Sharp, *J. Anal. At. Spectrom.*, 2001, **16**, 1076–1084.
59 N. Yamada, J. Takahashi and K. Sakata, *J. Anal. At. Spectrom.*, 2002, **17**, 1213–1222.
60 B. Hattendorf and D. Gunther, *J. Anal. At. Spectrom.*, 2000, **15**, 1125–1131.
61 K. Neubauer and U. Vollkopf, *At. Spectrosc.*, 1999, **20**, 64–68.
62 H. Haraguchi, *J. Anal. At. Spectrom.*, 2004, **19**, 5–14.
63 P. C. Li and S. J. Jiang, *Anal. Chim. Acta*, 2003, **495**, 143–150.
64 M. C. Wu, S. J. Jiang and T. S. Hsi, *Anal. Bioanal. Chem.*, 2003, **377**, 154–158.
65 K. L. Chen and S. J. Jiang, *Anal. Chim. Acta*, 2002, **470**, 223–228.
66 C. Y. Ho and S. J. Jiang, *Spectrochim. Acta, Part B*, 2003, **58**, 63–70.
67 A. P. Vonderheide, J. Meija, K. Tepperman, A. Puga, A. R. Pinhas, J. C. States and J. A. Caruso, *J. Chromatog. A*, 2004, **1024**, 129–137.
68 V. D. Huerta, L. H. Reyes, J. M. Marchante-Gayon, M. L. F. Sanchez and A. Sanz-Medel, *J. Anal. At. Spectrom.*, 2003, **18**, 1243–1247.
69 L. H. Reyes, J. M. M. Gayon, J. I. G. Alonso and A. Sanz-Medel, *J. Anal. At. Spectrom.*, 2003, **18**, 11–16.
70 D. E. Nixon, K. R. Neubauer, S. J. Eckdahl, J. A. Butz and M. F. Burritt, *Spectrochim. Acta, Part B*, 2003, **58**, 97–110.
71 D. E. Nixon, K. R. Neubauer, S. J. Eckdahl, J. A. Butz and M. F. Burritt, *Spectrochim. Acta, Part B*, 2002, **57**, 951–966.
72 Y. L. Chang and S. J. Jiang, *J. Anal. At. Spectrom.*, 2001, **16**, 1434–1438.
73 C. C. Chery, K. De Cremer, R. Cornelis, F. Vanhaecke and L. Moens, *J. Anal. At. Spectrom.*, 2003, **18**, 1113–1118.
74 J. M. Marchante-Gayon, I. Feldmann, C. Thomas and N. Jakubowski, *J. Anal. At. Spectrom.*, 2001, **16**, 457–463.
75 L. H. Reyes, J. M. Marchante-Gayon, J. I. G. Alonso and A. Sanz-Medel, *J. Anal. At. Spectrom.*, 2003, **18**, 1210–1216.
76 D. Profrock, P. Leonhard and A. Prange, *J. Anal. At. Spectrom.*, 2003, **18**, 708–713.
77 M. Kovacevic, R. Leber, S. D. Kohlwein and W. Goessler, *J. Anal. At. Spectrom.*, 2004, **19**, 80–84.
78 D. R. Bandura, V. I. Baranov and S. D. Tanner, *Anal. Chem.*, 2002, **74**, 1497–1502.
79 D. R. Bandura, O. I. Ornatsky and L. Liao, *J. Anal. At. Spectrom.*, 2004, **19**, 96–100.
80 S. Hann, G. Koellensperger, C. Obinger, P. G. Furtmüller and G. Stingeder, *J. Anal. At. Spectrom.*, 2004, **19**, 74–79.
81 D. Profrock, P. Leonhard and A. Prange, *Anal. Bioanal. Chem.*, 2003, **377**, 132–139.
82 C. F. Yeh, S. J. Jiang and T. S. Hsi, *Anal. Chim. Acta*, 2004, **502**, 57–63.
83 J. J. Sloth, E. H. Larsen, S. H. Bugel and S. Moesgaard, *J. Anal. At. Spectrom.*, 2003, **18**, 317–322.
84 E. H. Larsen, J. Sloth, M. Hansen and S. Moesgaard, *J. Anal. At. Spectrom.*, 2003, **18**, 310–316.
85 T. Lindemann and H. Hintelmann, *Anal. Chem.*, 2002, **74**, 4602–4610.
86 C. C. Chery, D. Gunther, R. Cornelis, F. Vanhaecke and L. Moens, *Electrophoresis*, 2003, **24**, 3305–3313.
87 H. Chassaigne, C. C. Chéry, G. Bordin, F. Vanhaecke and A. R. Rodriguez, *J. Anal. At. Spectrom.*, 2004, **19**, 85–95.
88 Y. R. Li, N. K. Pradhan, R. Foley and G. K. C. Low, *Talanta*, 2002, **57**, 1143–1153.
89 Y. L. Chang and S. J. Jiang, *J. Anal. At. Spectrom.*, 2001, **16**, 858–862.
90 H. Louie, M. Wu, P. Di, P. Snitch and G. Chapple, *J. Anal. At. Spectrom.*, 2002, **17**, 587–591.
91 Y. L. Lee, C. C. Chang and S. J. Jiang, *Spectrochim. Acta, Part B*, 2003, **58**, 523–530.
92 D. A. Polya, P. R. Lythgoe, F. Abou-Shakra, A. G. Gault, J. R. Brydie, J. G. Webster, K. L. Brown, M. K. Nimfopoulos and K. M. Michailidis, *Mineral. Mag.*, 2003, **67**, 247–261.
93 Q. L. Xie, R. Kerrich, E. Irving, K. Liber and F. Abou-Shakra, *J. Anal. At. Spectrom.*, 2002, **17**, 1037–1041.
94 T. Nakazato, H. Tao, T. Taniguchi and K. Isshiki, *Talanta*, 2002, **58**, 121–132.
95 H. T. Liu and S. J. Jiang, *J. Anal. At. Spectrom.*, 2002, **17**, 556–559.
96 R. D. Evans, H. Hintelmann and P. J. Dillon, *J. Anal. At. Spectrom.*, 2001, **16**, 1064–1069.
97 P. Leonhard, R. Pepelnik, A. Prange, N. Yamada and T. Yamada, *J. Anal. At. Spectrom.*, 2002, **17**, 189–196.
98 A. P. Vonderheide, J. Meija, M. Montes-Bayon and J. A. Caruso, *J. Anal. At. Spectrom.*, 2003, **18**, 1097–1102.
99 S. F. Boulyga, I. Segal, T. I. Platzner, L. Halicz and J. S. Becker, *Int. J. Mass Spectrom.*, 2002, **218**, 245–253.
100 F. Vanhaecke, M. Resano, E. Garcia-Ruiz, L. Balcaen, K. R. Koch and K. McIntosh, *J. Anal. At. Spectrom.*, 2004, **19**; DOI: 10.1039/b311318c.
101 S. F. Boulyga, J. L. Matusevich, V. P. Mironov, V. P. Kudrjashov, L. Halicz, I. Segal, J. A. McLean, A. Montaser and J. S. Becker, *J. Anal. At. Spectrom.*, 2002, **17**, 958–964.
102 S. F. Boulyga, J. S. Becker, J. L. Matusevitch and H. J. Dietze, *Int. J. Mass Spectrom.*, 2000, **203**, 143–154.
103 A. V. Izmer, S. F. Boulyga and J. S. Becker, *J. Anal. At. Spectrom.*, 2003, **18**, 1339–1345.
104 D. Lariviere, V. N. Epov, R. D. Evans and R. J. Cornett, *Can. J. Anal. Sci. Spectrosc.*, 2002, **47**, 119–124.
105 D. Lariviere, V. N. Epov, R. D. Evans and R. J. Cornett, *J. Anal. At. Spectrom.*, 2003, **18**, 338–343.
106 S. F. Boulyga, H. J. Dietze and J. S. Becker, *J. Anal. At. Spectrom.*, 2001, **16**, 598–602.
107 C. Y. Ho and S. J. Jiang, *J. Anal. At. Spectrom.*, 2002, **17**, 688–692.
108 J. M. Collard, K. Kawabata, Y. Kishi and R. Thomas, *Micro*, 2002, **20**, 39–46.
109 L. Balcaen, I. Geuens, L. Moens and F. Vanhaecke, *Anal. Bioanal. Chem.*, 2003, **377**, 1020–1025.
110 J. C. Schwartz, M. W. Senko and J. E. P. Syka, *J. Am. Soc. Mass Spectrom.*, 2002, **13**, 659–669.