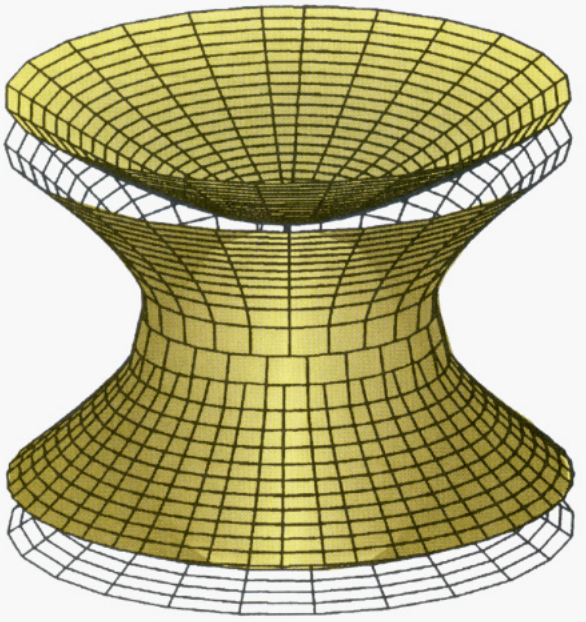
Ion Trap Mass Spectrometry of Externally Generated Ions

Ion traps provide a significant improvement in efficiency compared with beam-type mass spectrometers



For years the physics community has used the quadrupole ion trap or Paul trap, named after its inventor Wolfgang Paul (*1*), in a variety of fundamental studies (*2*). With a few notable exceptions (*3, 4*), however, the chemistry community had largely ignored the ion trap until George Stafford and co-workers at Finnigan Corp. developed novel means for using it as a mass spectrometer (*5, 6*) in the early 1980s. This development attracted the attention of the analytical MS community to the quadrupole ion trap for the first time. Since then, researchers have made many significant improvements in the ion trap analytical figures of merit; several recent reviews describe the evolution of the ion trap as a mass spectrometer (*7, 8*). Today, ion trap techniques that use either the quadrupole ion trap or its relative, the ion cyclotron resonance (ICR) instrument, collectively represent one of the most intense areas of research in analytical MS.

The two most common approaches to ion storage are strikingly similar in many ways, but they have evolved along decidedly different avenues. One may argue that the watershed event in the development of the ICR instrument as an analytical mass spectrometer was the application of FT techniques in ion detection, which led to unparalleled mass resolution (*9–11*). The inverse relationship between pressure and mass resolution dictated high vacuum conditions.

In contrast, the ion trap was developed initially as a detector for GC. Using helium carrier gas under high pressure (~1 mtorr) in the ion trap vacuum system improved both sensitivity and mass resolution compared with the use of much lower background pressures (< 10^{-4} torr). Most quadrupole ion trap applications have therefore used ~10^{-3} torr of helium in the vacuum system in contrast to most applications of FT-ICR, which typically use pressures of 10^{-7} torr or lower in the analyzer region.

All MS experiments include ionization, m/z analysis, and detection. The m/z analysis and detection methods involved in FTICR contrasts sharply with the methods most commonly used with the quadrupole ion trap. However, both approaches routinely use in situ ionization methods, which convert neutral analyte species to ions, preferably at or near the center of the ion trap volume. This is desirable because optimum trapping efficiencies are obtained when ions with low kinetic energy are formed in the center of the trapping volume. Electron ionization, chemical ionization, and photoionizaton are commonly used to produce ions in an ion trap experiment. Currently, all commercially available quadrupole ion traps offer either electron or chemical ionization or both.

In situ ionization methods can be used to address a wide variety of analytical problems, but their use is limited to relatively volatile analyte species. Many important ionization approaches, however, do not

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readily allow for ion formation within the trapping volume. All of the so-called desorption ionization methods fall into this category, as do high-pressure ionization techniques (arbitrarily defined here as ~1 torr and higher). In recent years, much of the R&D effort in ion trapping has therefore been devoted to coupling quadrupole ion traps and FTICR spectrometers with means of forming ions external to the ion-trapping region. Examples of desorption ionization methods coupled with the quadrupole ion trap include Cs^+ bombardment (*12*), laser desorption (*13–15*), and matrix-assisted laser desorption (*16–20*). Examples of high-pressure ionization methods coupled with the quadrupole ion trap include electrospray (*21–25*), thermospray (*26*), inductively coupled plasma (*27*), glow discharge for organic (*28, 29*) and inorganic (*30, 31*) ion formation, and chemical ionization (*32, 33*).

Given the small size, relative low cost, modest pressure requirements, and experimental flexibility of the quadrupole ion trap, it seems likely that an increasing number of analyses (both organic and inorganic) will be performed with ion traps coupled with high-pressure ion sources. In this Report, the first of a two-part series, we will provide a conceptual framework for the use of ion injection/quadrupole ion trap MS as opposed to conventional beam-type MS. In part 2, to be published in the July 15 issue, we will review the work that combines high-pressure ionization methods with the quadrupole ion trap.

Quadrupole ion trap MS and ion injection

The choice of mass analyzer for a particular application depends on several mass analyzer characteristics, including mass range, resolution, and accuracy; analysis time; and practical considerations such as size, weight, and cost. The relative importance of these characteristics depends on the application, but attaining lower limits of detection is usually a primary consideration.

The mass analyzer affects limits of detection via its efficiency. To compare ion injection/ion trap MS with conventional scanning beam-type MS, the efficiency of the mass analyzer is defined as the fraction of analyte ions issuing from an ion source that is eventually detected. The efficiency of the mass analyzer is the product of transmission and duty cycle, two analyzer characteristics discussed below. The typical quadrupole ion trap experiment can be divided into two steps—ion accumulation and mass analysis/detection—because they are separated in time. We discuss each step below, with particular emphasis on transmission and duty cycle and how they compare with those in other forms of MS.

Mass analysis/detection

As mentioned above, the mass analysis/detection approach used with an ion trap instrument can play a major role in determining the analyzer pressure requirements. Collisions cause dephasing of ion packets and limit transient lifetimes in ion image current measurements. Therefore, they limit mass resolution in FT experiments that use image current detection. However, high background pressures can be tolerated with the ion ejection/external detection methods commonly used with the quadrupole ion trap. (We use the term "tolerate" here because the bath gas affects mass analysis/detection in several ways. The role of the bath gas could be the subject of lengthy discussion and, indeed, some detailed effects of the bath gas are only now coming under scrutiny. However, most of the bath gas effects are usually quite subtle under common operating conditions and therefore are not emphasized in this discussion.) The so-called mass-selective instability method of Stafford and coworkers (*5, 6*) and its subsequent variations are key to the potential sensitivity advantages of the ion trap over beam-type instruments and to the tolerance of high background gas pressures.

A typical quadrupole ion trap experiment can be considered as two steps—ion accumulation and mass analysis/detection.

Beam-type scanning MS. Beam-type scanning mass spectrometers (e.g., quadrupole mass filter and magnetic sector instruments) operate on the principle of mass-selective stability. That is, ions that have a small range of m/z values maintain "stable" trajectories throughout the analyzer and can pass to an ion detector. The mass resolution of the instrument relates to the magnitude of the range of m/z values that can pass through the analyzer without striking a wall, slit, or electrode. The mass spectrum is collected by "scanning" the analyzer field so that the window of stable m/z values is sequentially swept across the entire m/z range of interest. The ratio of the width of the transmitted m/z window to the total width of the m/z range of interest determines the fraction of time during a scan that any given ion can be transmitted.

In a scanning beam-type instrument this ratio can be considered the "duty cycle." The duty cycle in a scanning beam-type mass spectrometer is therefore determined by the mass resolution and by the scan range. In most scanning experiments the duty cycle is a fraction of 1%. For a continuous ionization method, therefore, > 99% of the ions are lost simply because of the small magnitude of the duty cycle. A duty cycle of 100% is possible with a beam-type spectrometer but only in a nonscanning situation, as in single-ion monitoring or array detection.

The duty cycle is an important factor in determining the efficiency of the mass analyzer. Transmission is the other important factor, which for a beam-type experiment is the fraction of ions that issue from the ion source and is transmitted to the detector when the ions fall within the nominal m/z window of stable trajectories. For the quadrupole mass filter, for example, the angle, velocity, and position at which an ion enters the analyzer, along with the phase of the radio frequency (rf) field, are important factors in determining the likelihood for transmission even when the static and dynamic voltages applied to the quadrupole rods are nominally appropriate. As mass resolution in-

creases, the ranges of angles, velocities, and positions that lead to ion transmission decrease. All ionization methods yield ion populations with distributions in energy, angle, and position. Thus, mass resolution is inversely related to transmission and, in beam-type MS, mass resolution can affect the lower limit of detection in two ways: via duty cycle and transmission.

Mass-selective instability. To understand how mass-selective instability works, it is important to appreciate a few simple concepts regarding the behavior of ions in dynamic quadrupole electric fields. Figure 1 shows the shape of the electric potential in a quadrupole ion trap (comprising two end-cap electrodes and a ring electrode) at three points along a sine-wave signal applied to the ring electrode. The vertical axis represents electric potential, and the horizontal axes represent the radial plane defined by the ring electrode (frequently called the *r*-dimension) and the inter-end cap dimension (commonly called the *z*-dimension). When a potential exists between the ring electrode and the end caps, a quadrupole electric field is created within the electrodes because of their hyperbolic shape.

Real ion traps do not create "perfect" quadrupole fields because of the finite dimensions of the electrodes; holes in the electrodes that allow ions, electrons, or photons to pass; and imperfections in machining. Commercial ion traps are also modified to intentionally create higher order fields within the trapping volume (*34–37*). However, for our purposes we will not specifically address the important but subtle effects of higher order fields on analytical ion trap MS but mention them at relevant points in the discussion.

At point A, a large positive voltage is applied to the ring electrode, creating a potential valley in the *r*-dimension for a positive ion at the center of the ion trap. Simultaneously, this ion finds itself on a potential hill in the *z*-dimension. If this situation continued for a sufficiently long period, any motion away from the center of the ion trap would result in acceleration of the ion to one of the end-cap electrodes. At point C, the opposite situation prevails and the positive ion is attracted to the ring electrode. However, if the potential is alternated at a sufficiently high frequency, an ion present at the center of the ion trap with a low initial kinetic energy cannot reach an electrode before it is repelled.

Under any given set of conditions (i.e., amplitude and frequency of the trapping signal and electrode dimensions), ions of a wide m/z range can be stored simultaneously. The lower m/z limit is sharply defined and is reached when the electric field gradient is sufficiently steep to allow an ion to accelerate and strike an electrode before the phase of the field changes to repel the ion. The velocity of an ion is inversely related to the square root of its mass; therefore, low-mass ions reach this condition at lower trapping field strengths than do higher mass ions. The low m/z limit is given by

$$m/z_{min} = 4.44V/(r_o^2\Omega^2) \qquad (1)$$

where V is the amplitude of the trapping signal applied to the ring electrode, Ω is the angular frequency of the trapping signal, and r_o is the inscribed radius of the ring electrode.

The upper m/z limit is not as well defined as the lower m/z limit. It is useful to consider this point in terms of the "pseudopotential well" model of the ion trap introduced by Hans Dehmelt, who shared the 1989 Nobel Prize in Physics with Paul, and Fuad Major (*38*). This approximation relates the depth of a trapping well in each of the *z*- and *r*-dimensions, in terms of potential energy, for an ion of a given m/z to the frequency and amplitude of the trapping signal and the ion trap dimensions as shown below

$$eD_z = eV^2/(4mZ^2\Omega^2) \qquad (2)$$

and

$$eD_r = eD_z/2 \qquad (3)$$

where eD is the well depth in electron volts for the respective trapping dimensions and Z is the distance from the center of the trapping volume to an end-cap electrode. Note that the well depth is inversely related to the m/z of the ion. There is not a particularly sharp high m/z cut-off; the trapping efficiency decreases with mass-to-charge because the potential well in which ions are trapped at a fixed V becomes increasingly shallow, which increases the likelihood for ion loss.

It is apparent from Equation 2 that under a fixed set of conditions ions of different m/z values have different trapping well

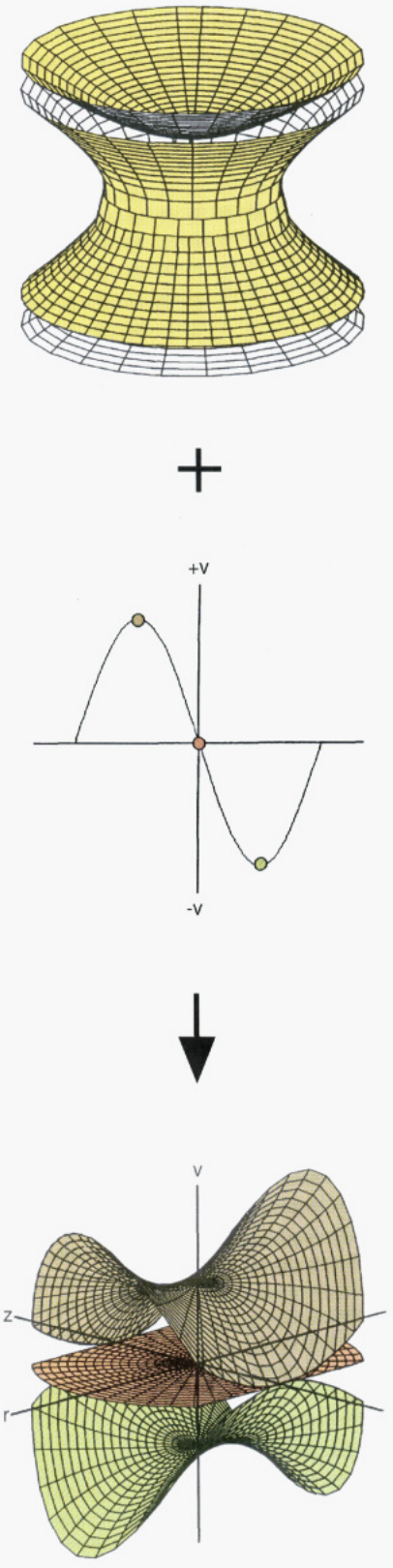

Figure 1. Inverting (floppy) saddle analogy for trapping ions in an oscillating quadrupole electric field.

Plot of electric potential as a function of the radial (*r*) and axial (*z*) dimensions at three points of a sine wave applied to the ring electrode.

depths. They also undergo motion with a unique set of frequencies (*39*). This characteristic allows the quadrupole ion trap to be used as a mass spectrometer rather than simply as an ion storage device. Although a variety of frequencies characterize the motion of a particular m/z ion in a quadrupole ion trap, only two are significant to mass analysis by mass-selective instability: One is the so-called fundamental z-dimension secular frequency, symbolized as $\omega_{0,z}$, and the other is $\Omega/2$. Without a dc potential between the ring electrode and the end caps, $\omega_{0,z}$ is given by the approximate relationship

$$\omega_{0,z} = \sqrt{2}eV/(2\pi m r_o^2 \Omega) \qquad (4)$$

The fundamental z-dimension secular frequency is important because it is the motion that couples most strongly with a dipolar electric field applied to the end caps. The $\Omega/2$ is important because the $\omega_{0,z}$ value of an ion at the low m/z limit of the ion trap is equal to this frequency and therefore the ion can absorb power directly from the trapping signal in the z-dimension. By far, most quadrupole ion trap experiments performed in the past decade have used ion ejection through holes in an end cap to an external ion detector by bringing the z-dimension ion motion into resonance with either the rf trapping potential or with a supplementary alternating potential applied to the end caps.

Stafford called the former approach mass-selective instability, and the latter has been called either axial modulation or resonance ejection. The latter term is most frequently used when the m/z range extends significantly beyond that of the ion trap that uses mass-selective instability. Ion frequencies can be altered either by scanning the amplitude of the rf trapping potential or by scanning its frequency (Equation 4).

Duty cycle, transmission, and mass-selective instability. In the mass-selective instability approach to mass analysis, ions of a wide m/z range are collected during an ion accumulation period and are stored until ejected sequentially to an external detector. Usually ions are ejected in an m/z-dependent fashion from low m/z to high m/z. This is mandatory for mass-selective instability and desirable for resonance ejection with current commercial ion traps (*40*). The duty cycle of an ion trap experiment that uses a continuous analyte consumption scenario is determined by the ratio of the ion accumulation time to that of the entire ion trap experiment, including mass analysis and any other ion manipulation steps. Ionization and mass analysis must occur simultaneously in scanning beam-type experiments, whereas ion accumulation and mass analysis typically occur consecutively in ion trap experiments. A consequence is that mass resolution and scan range are important in a beam-type experiment and scan rate is irrelevant, whereas scan time relative to the time for ion accumulation is important in an ion trap experiment in determining duty cycle.

Scan range affects scan time, and scan rate affects mass resolution and scan time. Therefore, the option to make tradeoffs among mass resolution, scan range, and duty cycle by varying the scan rate is available in the ion trap experiment but not in the scanning beam-type experiment. (In a pulsed ionization scenario in which analyte is consumed only during ionization, the ion accumulation can be made to encompass the entire ionization event, providing a duty cycle of 100%. The parallel nature of ionization and mass analysis/detection precludes a high duty cycle in a beam-type scanning experiment.)

The major advantage in duty cycle can be obtained with weak ion beams.

The serial nature of ion trap experiments (both quadrupole ion trap and ICR) allows for variable duty cycle experiments without compromising mass range. That is, the ion accumulation time can be varied independently of the mass analysis/detection time, with the upper limit determined by the ion storage capacity. Commercial ion traps have ion storage capacities of $\sim 10^6$ ions. (Degradation of mass resolution as a result of ion–ion interaction can be observed with even lower numbers of ions.) When the potential associated with repulsion of like charges equals the z-dimension well depth, no more ions of like charge can be accumulated. Therefore, the time required to "fill" the ion trap places an upper limit on ion accumulation time and hence can limit duty cycle.

Consequently, the major advantage in duty cycle over beam-type scanning mass spectrometers can be obtained with weak ion beams. If the ion trap can be filled in 1 ms and the mass analysis time is ~ 50 ms, the duty cycle is but a few percent. However, if the ion accumulation rate for an analyte ion of interest is sufficiently low to require an ion accumulation time of up to 1 s, a duty cycle as high as 95% is obtained. Such a situation is encountered with "dim" ion sources, such as electrospray. In these cases, the ion trap serves to convert a low ion current to a higher ion current. This amplification is determined by the ratio of the ion accumulation time (milliseconds to seconds) to the ejection time of the ion of interest (usually a few hundred microseconds).

The ion trap can also be used to amplify weak ion currents present in intense ion beams, provided the intense components of the ion beam are not permitted to accumulate and quickly fill the ion trap, precluding concentration of the ions of interest (*41*). This problem, already encountered in FTICR, has been addressed by using the stored waveform inverse FT (SWIFT) technique (*42*). Recently, SWIFT (*43*) and filtered-noise field experiments (*44*) with ion traps have demonstrated highly flexible means for mass-selective accumulation of ions injected from external ion sources. Such techniques allow the full dynamic range of the ion trap to be available for any ion of interest and will be highly useful for the simultaneous monitoring of targeted species at widely different m/z values.

Just as there is a tradeoff between mass resolution and efficiency in scanning beam-type experiments, efficiency and mass resolution are inversely related in the ion trap that uses resonance ejection, but for different reasons. Whereas mass resolution is related to the width of the transmitted m/z window in a beam-type experiment, mass resolution obtained by using resonance ejection with the ion trap is a function of the scan rate (*22, 45–48*).

Insofar as the scan rate affects the total scan time, mass resolution affects duty cycle. For an experiment using continuous analyte consumption, improving mass resolution without reducing duty cycle can be accomplished only at the expense of scan range. Thus, high mass resolution ion trap experiments are typically performed over a narrow mass range.

A unique aspect of quadrupole ion trap MS operated with ~1 mtorr of helium bath gas is that mass analysis by mass-selective ejection/external detection is essentially independent of the characteristics of ionization. That is, mass resolution and accuracy, and any discrimination effects arising from mass analysis and detection, are not influenced by the kinetic energy and angular distributions of the ions as they issue from the ion source. This is due to the role that the bath gas plays in thermalizing the trapped ion population before mass-selective ion ejection. For all practical purposes, the ions are cooled to the center of the ion trap by collisions with helium, provided ion–ion interactions do not preclude this, and it is from this starting point that ions are subjected to resonance ejection. The ions retain a narrow spatial distribution in the *r*-dimension and exit through a hole in the center of the end caps. Essentially 100% of the ions can be ejected from the ion trap, but because they do so in equal numbers from each end cap and only ions ejected from one end cap are detected, "transmission" is reduced by a factor of 2 as part of the mass analysis step. Unidirectional mass-selective ion ejection techniques have been demonstrated (*35, 49*) but have not yet been used with external ionization.

Ion injection/accumulation

The ions most likely to be trapped in a quadrupole ion trap are those formed at the center of the ion trap, with very low kinetic energy. As a result, they remain in the center of the saddles of Figure 1. The pseudopotential well model shows the ion at the bottom of both the *z*- and *r*-dimension wells, with only a minor amount of kinetic energy available to allow movement up the sides of the wells (Figure 2). An ion formed away from the center of the ion trap is on a potential gradient and therefore executes larger amplitude oscillations. As a rule, the likelihood for ion loss increases the farther the ions are from the center of the trap. Imperfections in electrode geometries that lead to field distortions are most influential away from the center of the ion trap, and ion–neutral or ion–ion collisions can lead to dephasing of ion motion that is sufficient to cause it to roll out of the saddle when it otherwise would not. The major goal in maximizing transmission in the ion injection/ion trap experiment is to convert as many ions in the injected ion beam as possible to low-kinetic-energy ions in the center of the ion trap.

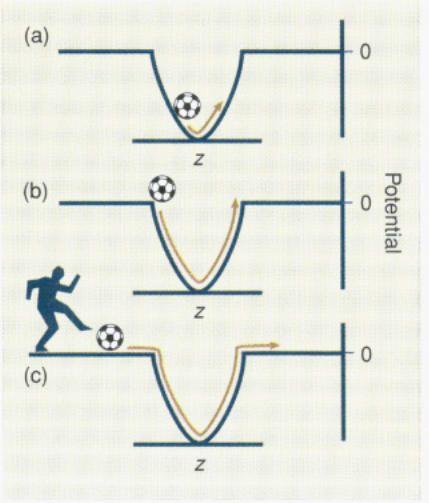

Figure 2. The pseudopotential well picture.

Representations of (a) ion formation within the ion trap, (b) ion formation at an end-cap electrode, and (c) ion injection into the ion trap. In a and b the ball is assumed to be placed in the ion trap with zero kinetic energy; therefore, it rolls back and forth with an amplitude determined by the potential at its initial placement. In c it is assumed that the ion enters the trapping well with an initial kinetic energy provided by the kicker.

In situ ionization. In situ electron ionization in the ion trap is usually effected by injecting electrons into the interior of the electrode structure through a hole in the center of one of the end caps. Ions are initially formed, therefore, at various locations primarily along the *z*-axis, with thermal kinetic energy. The ions formed in the center are, of course, in the optimum location for ion storage; those formed away from the center are accelerated because they are formed on a potential gradient. Depending on the phase of the trapping field at the instant of ion formation, an ion formed away from the center of the ion trap might be accelerated to an electrode within one or a few cycles of the alternating trapping field or it might execute oscillatory motion within the three electrode structures for a somewhat longer period.

As discussed above, collisional focusing of the ions by helium has beneficial effects on the efficiency of ion ejection, but the major role of the bath gas is to increase the fraction of ions—formed initially by the electron beam—that are eventually stored. That is, helium improves trapping efficiency even with in situ electron ionization. The presence of helium enhances ion trap sensitivity because ions collide with the helium, which removes kinetic energy from the ions, forcing them toward the bottom of the potential wells. The helium can be thought of as providing friction on the surface of the pseudopotential wells. Helium therefore focuses the ions to the center, with the only major countervailing force arising from ions of like charge (i.e., space charge).

It is important to use a light atom or molecule as a bath gas for kinematic reasons. In a binary collision, the laboratory scattering angle of the heavier collision partner is always smaller than that of the lighter partner. The large disparity in mass between most ions of analytical interest and helium causes very little change in ion direction as a result of collision. The major effect is a small loss of kinetic energy. A significant change in direction resulting from scattering upon collision enhances the likelihood for ion loss. One can understand this conceptually by imagining an ion formed a little away from the middle of the saddle of Figure 1a but at a phase of the alternating quadrupole field that is conducive to the assumption of a stable trajectory as the saddle inverts itself repeatedly. Therefore, any abrupt change in direction of an ion undergoing stable oscillatory motion can sufficiently dephase the ion motion to cause it to accelerate to an electrode. This is a major reason why heavier bath gases are highly deleterious to the ion trap MS of small molecules; they are much less so for large molecules such as biopolymers (*17, 50*).

Ion injection and transmission. The previous description of in situ electron ionization provides the basis for consideration of ion injection. Essentially all of the ion injection experiments reported to date that

involve high-pressure ionization sources have admitted the ions through a hole in the center of one of the end caps, which is the same method used with most electron injection work. Perhaps the major difference is that injected ions have some initial kinetic energy that is greater than thermal energy, and these ions enter the ion trap from a boundary, namely, through an end cap. Both conditions disfavor ion storage compared with in situ ionization. From the point of view of the pseudopotential well model, this situation looks like that shown in Figure 2c in which an ion enters the well with some kinetic energy and, lacking "friction," simply rolls back out with the same kinetic energy. (We have already shown—by using the floppy saddle analogy—that a kinetic energy less than the potential energy associated with the trapping well is not a sufficient condition for trapping. An inappropriate phase relationship, the major source of ion loss from an ion population formed by in situ electron ionization, can also lead to ion loss.) Therefore, although some ions would be trapped using in situ ionization even without some mechanism for removing kinetic energy, because they are formed within the trapping well with very little kinetic energy, no ions injected from an external ion source can be stored indefinitely without some means for cooling them. Hence, the role of the bath gas is even more important in an ion injection scenario than it is with conventional ion trap MS.

Given this unfavorable situation for storing ions injected from an external ion source, it is not surprising that most ion losses associated with an ion injection experiment occur during the ion accumulation part of the experiment and that efforts to improve ion trap transmission are most profitably directed there. It is beyond our scope to discuss all of the parameters that are important for optimizing trapping efficiency for injected ions. However, it has been widely observed that, besides the use of a light bath gas, trapping efficiency is optimized with relatively low injected-ion kinetic energies (e.g., < 10 eV), comparable to those often used with quadrupole mass filters.

Another important parameter is the amplitude of the rf trapping potential. There tends to be a broad optimum well depth, experimentally controlled via the amplitude of the rf trapping potential during ion accumulation, that depends on the m/z of the injected ion and its kinetic stability to fragmentation. High m/z ions tend to show optimum trapping efficiencies at lower well depths than low m/z ions. Because only one trapping amplitude is applied during ion accumulation, the well depth decreases with m/z (see Equations 2 and 3), which minimizes m/z discrimination. This is a fortunate situation because it allows for the simultaneous accumulation of ions spanning a wide m/z range. (For example, we have observed simultaneous accumulation of ions that differ in m/z by several thousand.)

Nevertheless, severe discrimination effects can be observed, particularly if an injected ion happens to assume a frequency of motion that matches a frequency induced by a higher order field (*51*). Quantitation based on relative ion abundances in an ion injection experiment must include calibration with the trapping field amplitude to be used in the analysis.

It was noted in early ion injection studies that some ions fragmented upon injection into the ion trap as the well depths were increased during ion accumulation (*28, 52*). Figure 3 shows a comparison of electrospray mass spectra of hematin acquired using various z-dimension well depths. A similar effect can be observed by varying the kinetic energy of the ions as they are injected (*53, 54*).

Recent modeling studies in our laboratory that incorporate inelastic collisions suggest that this phenomenon is a result of internal heating of the injected ion as it is kinetically cooled in the center of the ion trap (*55*). This internal heating persists until the ions are kinetically cooled, when they also cool internally via collisions with helium. This effect is expected to be sensitive to well depth because injected ions gain kinetic energy, due to the trapping field, in proportion to well depth (see Figure 2). For relatively fragile ions, this brief heating process can be sufficient to induce fragmentation.

Fragmentation upon injection sometimes may be desirable (*52*), but it is usually desirable to be able to measure the mass spectrum of the ions that issue from the ion source without contributions from processes that occur in the ion trap, such as fragmentation or ion/molecule reactions. Ions are therefore usually injected at the lowest well depth possible without compromising trapping efficiency.

Virtually all of the analytical applications of ion injection/ion trap MS inject the ions into the ion trap volume in which one to several millitorr of helium serves as the bath gas. This is the simplest approach for removing energy from the ions once they are in the trapping volume. Under optimum conditions, injection efficiency, which is the ion injection component of transmission, has been noted as being as high as 10% (*56*).

More sophisticated methods may al-

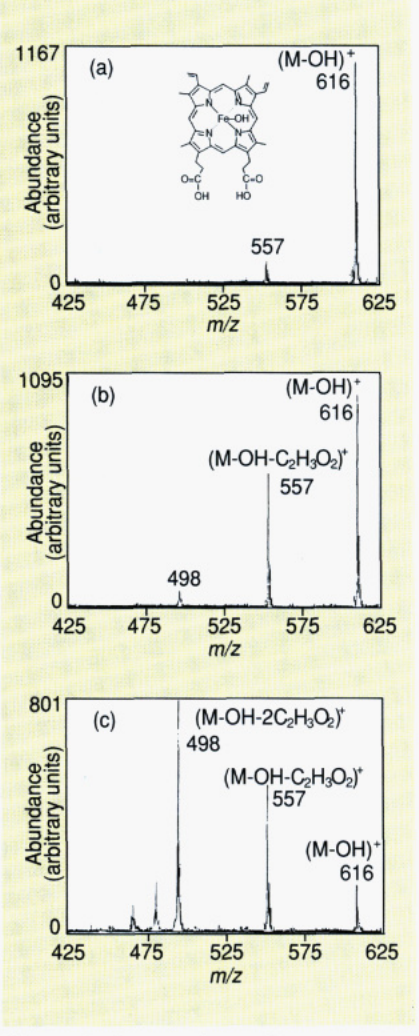

Figure 3. Comparison of electrospray mass spectra of hematin.

Spectra are acquired using z-dimension well depths of (a) 5 eV, (b) 22 eV, and (c) 49 eV.

low for improved ion injection efficiency. For example, an injection efficiency of 50% for a specific m/z ion was achieved by actively removing ion kinetic energy by use of a properly phased signal applied to the end caps (*57*). Most analytical applications, however, require the simultaneous accumulation of ions over a broad range of m/z to capitalize on the duty cycle advantage of the ion trap. Therefore, significant opportunity for improvement remains in the area of transmission for ion injection/ion trap experiments.

The preceding discussion provides background for consideration of the merits of ion trap MS in conjunction with an external ion source relative to a scanning beam-type form of mass analysis. Emphasis has been placed primarily on efficiency. However, a variety of other factors can be major considerations, depending upon the application. For example, the ion trap has clear advantages over most other forms of MS in terms of size, weight, and pumping requirements. These advantages make the ion trap attractive for field applications, particularly because the performance characteristics of the ion trap need not be compromised in a compact system. One of the most significant advantages is the high efficiency obtainable with tandem MS experiments (*58*) by using collisional activation via resonance excitation (*59*).

Under favorable conditions, the conversion of 100% of the parent ions to product ions can be achieved, although 10–50% conversions are more typical. The analogous conversion in most beam-type tandem MS experiments is typically 1–3 orders of magnitude lower; thus, significant reductions in detection limits by use of the ion trap can be anticipated in analyses requiring two or more stages of MS.

Perhaps the major drawbacks of the ion trap as a mass analyzer relative to beam-type analyzers arise from the much greater ion densities that can be encountered in an ion trap instrument relative to those encountered in ion beams in most analytical mass spectrometers. High number densities of ions of like charge can adversely affect the ion trap experiment in several ways, such as imposing a limit on the number of ions that can be stored, thereby limiting the dynamic range.

Several tactics have been devised to improve the dynamic range of the ion trap. One approach is to vary the ionization time, which alters the duty cycle, to keep the number of ions in the ion trap within an optimal range. Some commercial systems can perform this procedure in an automated fashion—called "automatic gain control" for electron ionization and "automatic reaction control" for chemical ionization (*60*). The former technique varies the electron ionization time, and the latter varies the ion/molecule reaction time. Mass-selective ion accumulation methods are also important tools for extending the dynamic range for ions of relatively low abundance (*43, 44*).

The presence of nearby ions of like charge affects the electric field seen by an ion, altering the ion's frequencies of motion. High ion number densities both broaden and shift the distribution of frequencies (*39*). Because resonance ejection and mass-selective instability eject ions on the basis of their frequencies, both mass resolution and mass accuracy can be affected by space charge. The ion trap can provide remarkably high mass resolution (*22, 45–48*) and has been shown to provide mass accuracies of 0.005% using internal standards (*61*). However, much more care must be taken to control the number of ions involved to achieve the high performance that is necessary in most other forms of MS. Part 2 of this series will review the work that combines high-pressure ionization methods with the quadrupole ion trap.

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