Ion Trap Mass Spectrometry

Philip S.H. Wong
Bioanalytical Systems
West Lafayette, IN
47906-1382

*R. Graham Cooks**
Department of Chemistry
Purdue University
West Lafayette, IN
47907

**Corresponding author*
E-mail:
cooks@purdue.edu

The operating principles of linear quadrupoles and quadrupole ion traps are described, and the performance characteristics of triple quadrupoles and ion trap instruments are compared. The theoretical basis for mass analysis using quadrupole fields is also described. The high performance of quadrupole ion traps is illustrated by introducing some new developments, including mass range extension, high resolution experiments, MS^n experiments, selective ion manipulation techniques, and non-destructive ion detection.

Mass spectrometry, the science and technology of gaseous ions (1), has as its basis the measurement of mass-to-charge ratios (m/z) of ions. All atomic and molecular ions are, in principle, accessible by mass spectrometry, making it a universal method for chemical analysis. Its implementation requires suitable methods of ion generation, ion analysis, and ion detection. We treat each of these processes in turn and show below that there are multiple methods of accomplishing each.

The first step in recording a mass spectrum is to convert analyte molecules (or atoms) into gas phase ions. In biological applications, the most common ionization techniques are electrospray ionization (ES) (2), atmospheric pressure chemical ionization (APCI) (3,4), and matrix-assisted laser desorption ionization (MALDI) (5). These are soft ionization methods in the sense that at least some analyte molecules are converted, intact, into corresponding ions. Solution phase samples are examined with ES and APCI while MALDI is particularly appropriate for solid phase samples. Having successfully generated gas phase ions, they must then be mass analyzed. There are several different types of mass analyzers, all based on the interactions of charged particles with electric and/ or magnetic fields. ***T1*** summarizes the most common mass analyzers and lists some analytical performance characteristics by which they can be compared (6). As with the various ionization methods, there is no single right choice — the nature of the problem and the resources of the laboratory will dictate which mass analyzer is most appropriate.

Most uses of mass spectrometry are made in combination with chromatographic separation, principally in the form of the GC/MS or LC/MS technique. These combinations have been used, for example, in organic analysis in the environmental sciences and in characterization of biological compounds, including molecular weight (MW) determinations, and sequence analyses of biopolymers (7). Increasingly important applications have been found in drug metabolism and protein sequencing due to the high sensitivity and chemical specificity of mass spectrometry. These advantages apply even when the samples are presented to the mass spectrometer as mixtures since the two-stage tandem mass spectrometry (MS/MS) experiment serves as a method of separation as well as characterization of the separated components.

Quadrupoles and Ion Traps

With the above background on ionization and mass analysis, we can now introduce a family of mass analyzers whose operation is based on ion motion in rf electric fields. The quadrupole mass filter (8), or linear quadrupole, consists of a linear array of four symmetrically arranged rods (***F1***) to which rf and dc voltages are supplied. Forces are exerted in a plane normal to the direction (z-direction) in which the ions drift through the array in their journey from the ion source to the detector. The rf potential gives rise to a field which alternatively reinforces and then dominates the dc field, also applied by coupling opposite sets of rods. Ions oscillate in the x,y-plane with frequencies which depend on their m/z values and with excursions which depend on the amplitudes of the applied potentials and their initial positions. If the oscillations of an ion in this plane are stable, the ion will continue to drift down the rod assembly and reach the detector. Stable oscillations are only achieved by ions of given m/z values for a given rod assembly, oscillation frequency, rf voltages, and dc voltage. The range of values of m/z which correspond to stable motion can be made

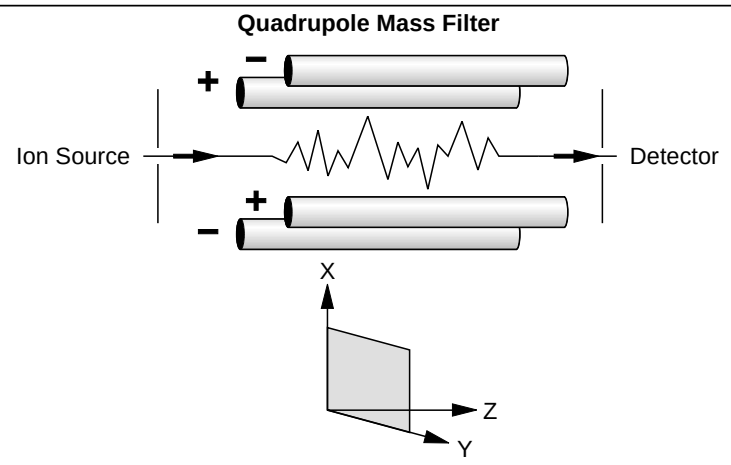
T1

Characteristics of Different Mass Analyzers. (Adapted from reference 6.)

Method	Quantity Measured	Mass/charge (m/z) range	Resolution at m/z = 1,000	Dynamic Range
Sector Magnet	momentum/charge	10^4	10^5	10^7
Time of Flight	flight time	10^6	10^3 - 10^4	10^4
Ion Cyclotron Resonance	cyclotron frequency	10^5	10^6	10^4
Ion Trap	frequency	10^4	10^4	10^4
Quadrupole mass filter	filters for m/z	10^3 - 10^4	10^3 - 10^4	10^5

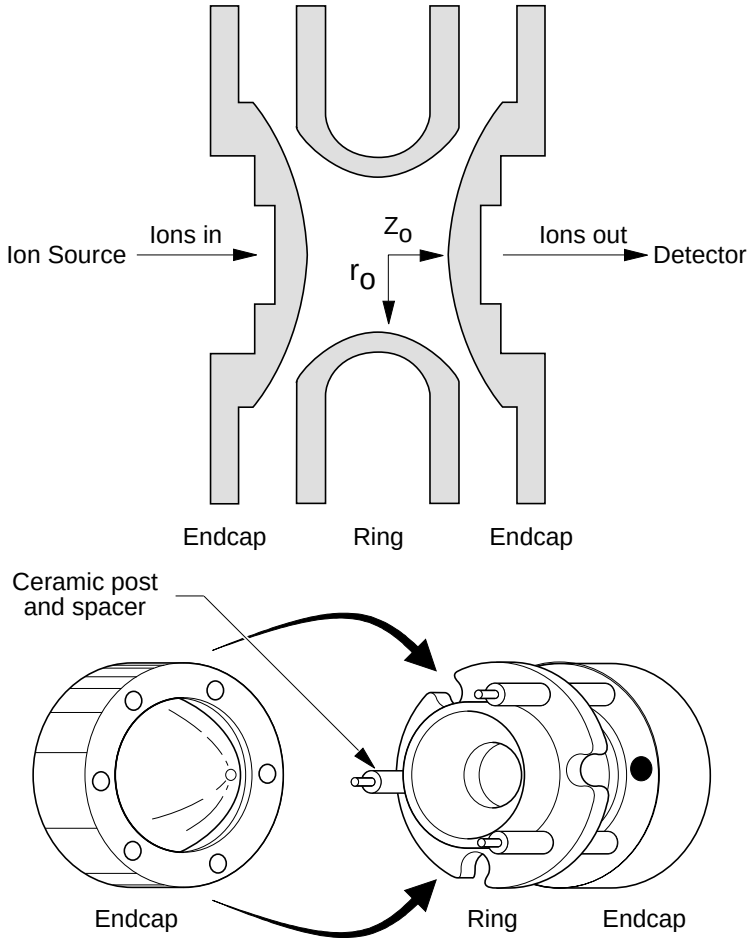
F1

Schematic diagram showing the operation of the quadrupole mass filter. Note that as ions drift through the array of rods they are subjected to forces which cause oscillation in the x,y-plane (shaded).



F2

The ion trap consists of three electrodes with hyperbolic surfaces, the central ring electrode, and two adjacent end-cap electrodes. The schematic of the assembly shows how the electrodes are aligned and isolated using ceramic spacers and posts. The device is radially symmetrical, and r_o and z_o represent its size.



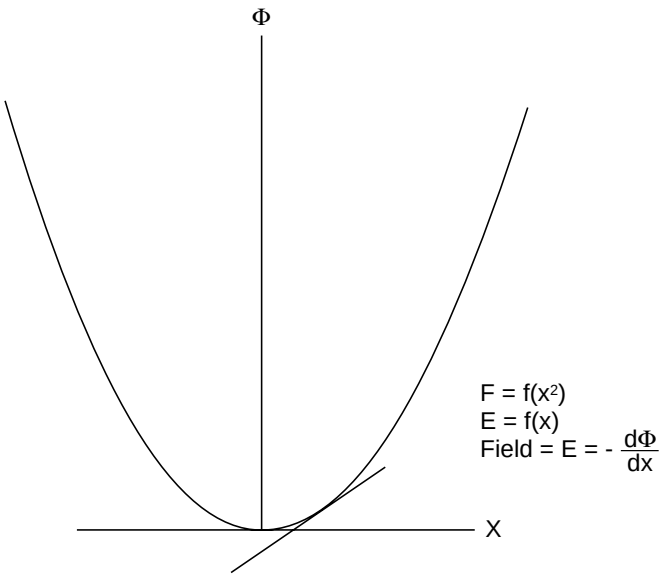
very large (wide band pass) or it can be a single m/z value (narrow band pass). In practice, ions of a particular m/z value are often selected, and mass scanning is usually achieved by sweeping the dc and rf voltages, keeping their ratio and the oscillator frequency constant.

The quadrupole ion trap, (9,10), the subject of this article, is the three dimensional analogue of the linear quadrupole mass filter. In this device too, ions are subjected to forces applied by an rf field but the forces occur in all three, instead of just two, dimensions. Stable motion of ions in the linear quadrupole allowed ions freedom of motion in one dimension (z-direction); in the ion trap, stable motion allows no degrees of freedom. Hence, ions are trapped within the system of three electrodes-a ring electrode and two end-cap electrodes of hyperbolic cross-section (***F2***). The principal advantages of the quadrupole ion trap in chemical analysis can be summarized as follows:

(i) high sensitivity,
(ii) compactness and mechanical simplicity in a device which is nevertheless capable of high performance,
(iii) tandem mass spectrometry experiments are available by performing sequential mass analysis measurements,
(iv) ion/molecule reactions can be studied for mass-selected ions,
(v) high resolution (>10^6 at m/z >1000) is accessible through slow scans, but mass measurement accuracy is relatively poor,

F3

Potential and field strength in a hypothetical one-dimensional quadrupole field. The slope of the plot of potential (Φ) against position (x) yields the field strength E(x).



(vi) ions of high mass/charge are accessible using resonance experiments, and

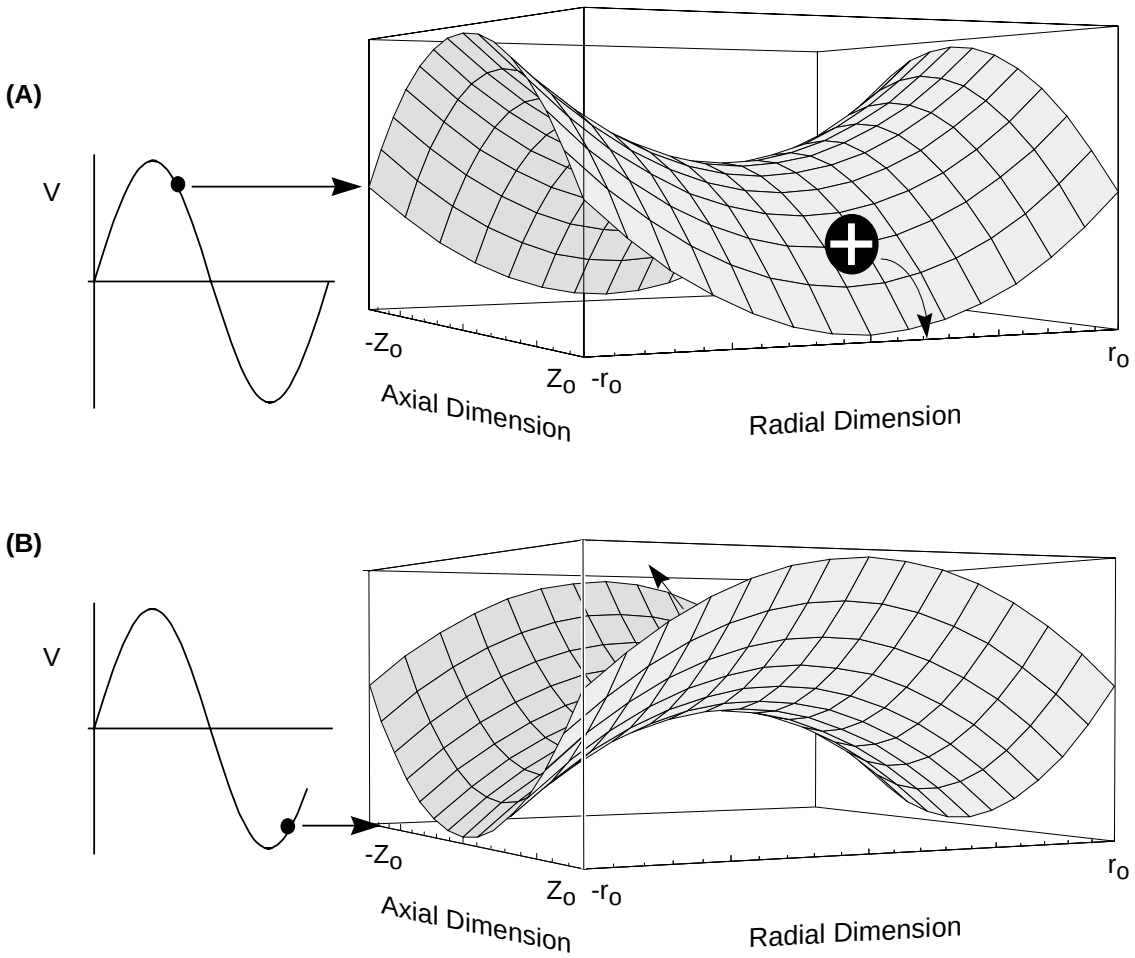
(vii) non-destructive detection is available using Fourier transform techniques.

Comparisons of the Ion Trap with the Triple Quadrupole

The differences in operating principles of the linear quadrupole and the ion trap have just been described. In comparing their performance characteristics, one immediately notes that a unique feature of an ion trap is that MS/MS experiments are possible. Even when compared with a triple quadrupole MS/MS instrument, the ion trap can perform multiple stage mass spectrometry (MS^n) simply by the use of additional operations which are performed sequentially in time. The triple quadrupole has the advantage of access to parent ion and neutral loss scans, and analytically useful versions of the MS/MS experiment; however, MS^n experiments can only be performed in multi-quadrupole instruments. Although ion/molecule reactions can be studied in both instruments, the reaction time can only be varied in the ion trap. This allows the kinetics and equilibrium of ion-molecule reactions to be studied. On the other hand, the triple-quadrupole instrument provides good control over the kinetic energies of the ions

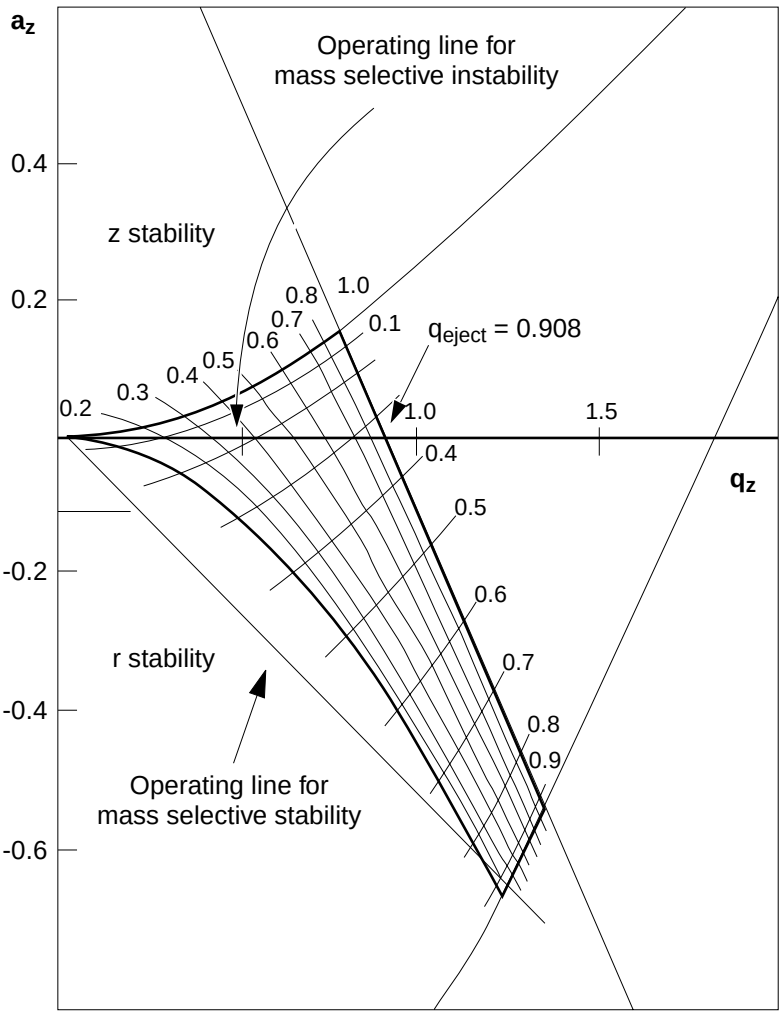
F4

Potential used for trapping ions (A) in the radial direction and (B) in the axial direction. An ion in the position shown is accelerated away from the trap center in the axial direction at the rf phase shown in (A) and towards it in (B) (Adapted from reference 13).



F5

The Mathieu stability diagram for the quadrupole ion trap. Ions are stable in both the r- and the z-direction if their Mathieu parameters a_z and q_z fall within the shaded area in the diagram. The common mode of mass analysis is the mass-selective instability scan in which the rf potential is raised to increase the value of q_z to the instability point q_z = 0.908, while a_z = 0.



which are important for thermochemical studies.

A recent, instructive comparison of the Finnigan LCQ ion trap with the Finnigan TSQ 700 triple quadrupole mass spectrometer was made using an LC/APCI/MS assay for several spinosyns (11). The overall sensitivity of the LCQ in the full-scan mode was found to be 5-10 times greater than the TSQ. In contrast, in the selected ion monitoring mode, in which a single ion is monitored, the TSQ was found to be 3-5 times more sensitive than the LCQ. Similar results were obtained in a comparative study of the LCQ ion trap and the PE/Sciex API 300 triple quadrupole instrument using LC/MS/MS quantitation of orlistat in human plasma (12). Clearly, both instruments have unique strengths. Given the small size, relatively low cost, modest pressure requirements, and experimental flexibility of the quadrupole ion trap, an increasing number of analyses will be performed with ion traps coupled with ion sources (ES or APCI) which allow solution analysis.

Operating Principle of Quadrupole Ion Traps

Quadrupole Fields

A quadrupole field is one in which the field strength E varies linearly with displacement x,

$$E = E_O x \qquad (1)$$

The applied potential Φ which establishes the electric field must vary quadratically in order that the field strength vary linearly with x. Hence

$$\Phi = f(x^2) \qquad (2)$$

and

$$E = -\frac{d\Phi}{dx} = f(x) \qquad (3)$$

If it were possible to employ a system of electrodes and construct a one-dimensional quadrupole field, then the potential distribution and the field strength would be as shown in ***F3***. Ions located an increasing distance from the center would be subjected to a force which would increase linearly with displacement and which would tend to return the ions to the center of the device. Ions could be trapped in such a hypothetical field. If the field direction were reversed, a potential maximum would occur and ions would be accelerated away from the center.

In the three-dimensional quadrupole field present in an actual ion trap, ions are alternatively subjected to stabilizing and destabilizing forces and oscillate in both the r- and z-directions. When the phase of the rf signal is positive, the quadrupole potential surface is saddle-shaped as shown in ***F4A***. An ion located as shown is on a potential downhill in the z-direction and it will be accelerated from the center of the device. As the rf field changes sign, the field inverts and the same ion is accelerated towards the center of the trap (***F4B***). Similar considerations apply with respect to an ion displaced in the radial (r) direction. If the field inverts at an appropriate rate, the ions will be trapped in both the r- and z-directions, in the volume defined by the ring and the end-cap electrodes (13).

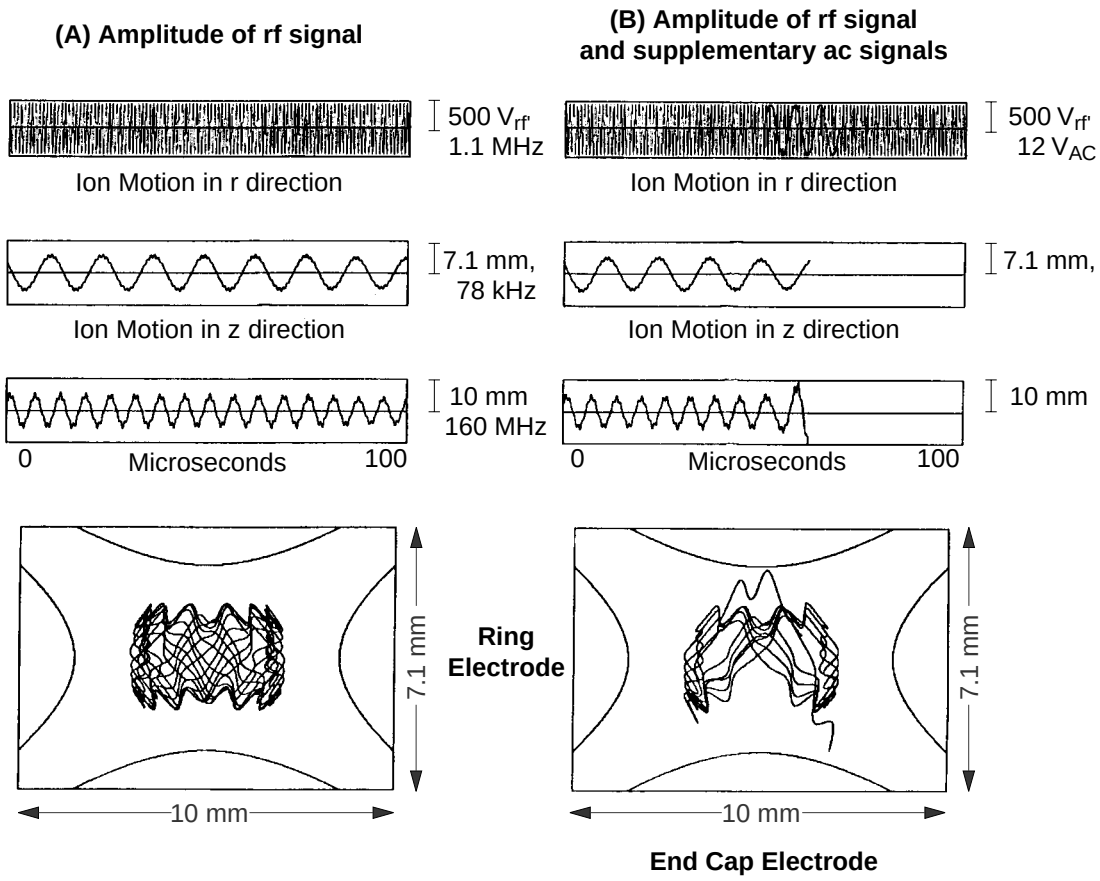
Mass Analysis Using Quadrupole Fields

Physically, ion traps are made up of a rotationally symmetrical ring electrode of hyperbolic shape and two endcap electrodes of the same cross-section. An rf voltage is applied to generate an electric quadrupole field. Because the electric field is rotationally symmetric, it is convenient to consider only radial $r = \sqrt{x^2 + y^2}$ and axial (z) displacements. The potential ($\Phi_{r,z}$) at any point in this field is given by

$$\Phi_{r,z} = (U + V\cos\omega t)\left(\frac{r^2 - 2z^2 + 2z_0^2}{r_0^2 + 2z_0^2}\right) \qquad (4)$$

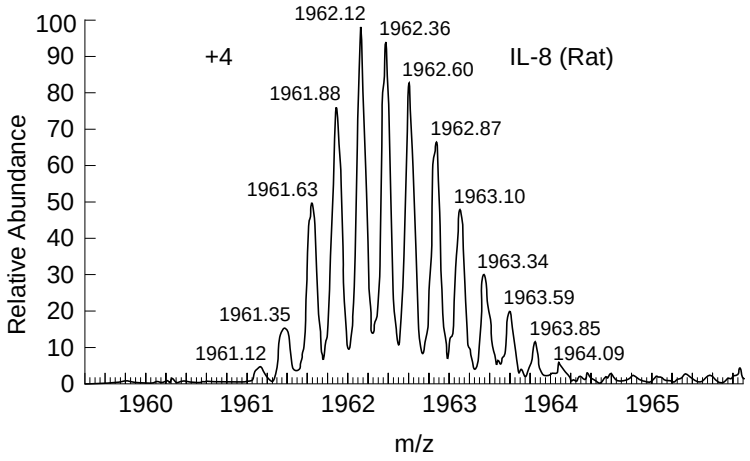
F6

(A) A simulation of the trajectory of an ion of m/z 100 in a r_0 = 1 cm ion trap operated at a rf voltage of 500 V and a frequency of 1.1 MHz. The first three boxes are time plots of the instantaneous rf amplitude, the excursion of the ion from the center in the r-direction, and the z-excursion, respectively. The last box is a plot of r, z-motion. (B) The same simulation in which a supplementary ac voltage is applied at the time indicated to resonantly excite ion motion. (Adapted from reference 9.)



F7

Zoomscan showing part of the ESI mass spectrum of rat interleukin-8, including the isotope envelope around around the $[M+4H]^{4+}$ ion at m/z 1,962. (Adapted from Finnigan LCQ Operator's Manual, Revision B, July 1996.)



where the first term describes its temporal variation and the second its spatial dependence (9). Note again that r_o is the internal radius of the ring electrode and z_o is the closest distance from the center to the end-cap, while U is the dc potential and V is the rf potential (zero-to-peak) applied between the ring and end-cap electrodes, ω is its angular frequency, and t is time. Ions of a given m/z value may undergo stable motion in the trap for the reasons already given qualitatively. The quantitative solution to the stability condition is described by a second order differential equation of the Mathieu form. The solutions to this equation (actually two independent equations which describe the uncoupled motion of an ion in the r- and z-directions) represent stability conditions which are readily summarized in the form of a stability diagram (***F5***) expressed in terms of the Mathieu coordinates a_z and q_z (***EQ5-6***).

$$a_z = -2a_r = \frac{-16zU}{m(r_0^2 + 2z_0^2)\,\omega^2} \quad (5)$$

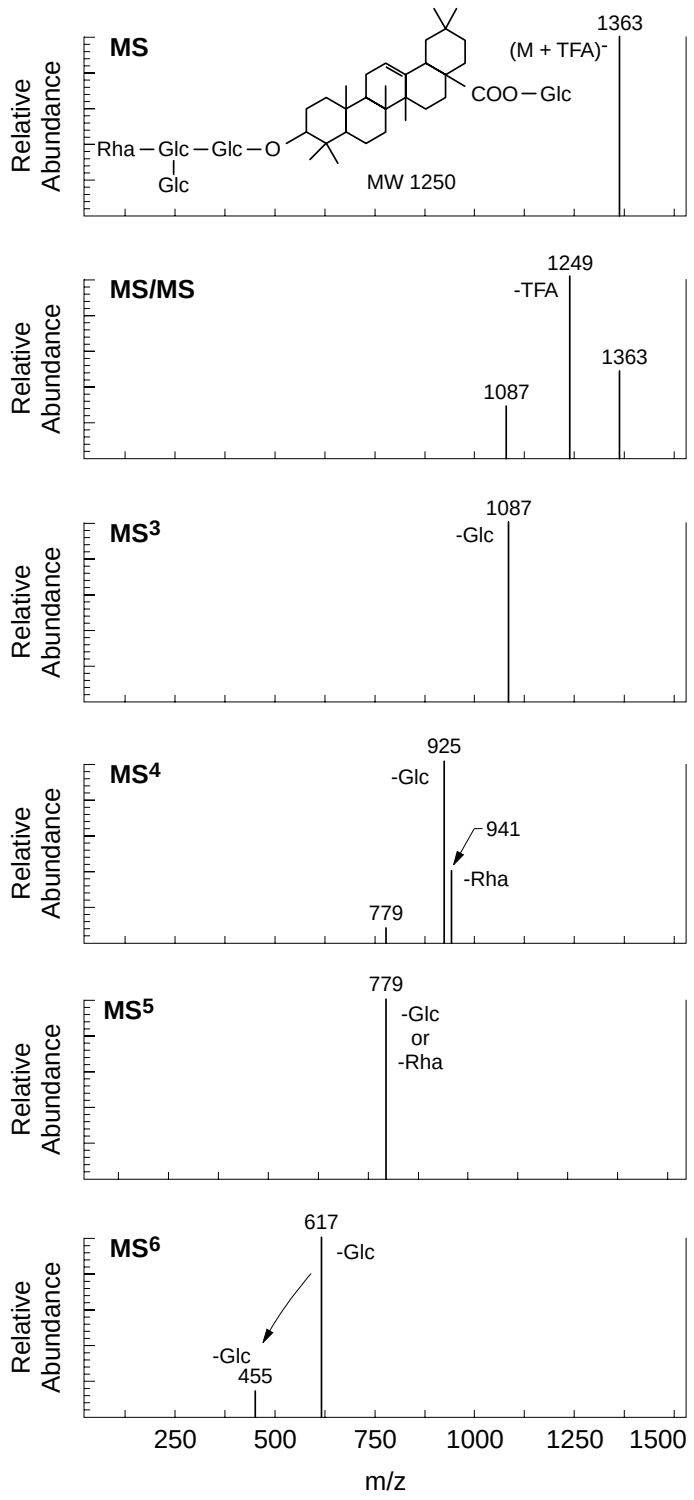
$$q_z = -2q_r = \frac{8zV}{m(r_0^2 + 2z_0^2)\,\omega^2} \quad (6)$$

Radial stability, expressed in terms of a_r and q_r, must also be maintained simultaneously with stability in the z-direction. Note that ions with identical Mathieu parameters but different m/z values behave identically. Optimum operation requires the ions have favorable initial conditions, which is achieved by using a helium buffer gas (~1 mTorr) to remove kinetic energy from the ions and cause them to occupy the central region of the trap. Typically, the ion trap can hold up to about 10^5 - 10^6 ions before coulombic repulsions significantly affect their trajectories and greatly reduce the mass resolution.

Mass spectra are normally recorded by operating the quadrupole ion trap in the mass selective instability scan mode (9). In this experiment, the amplitude V of the applied rf is increased so as to "move" ions along the q_z axis (***F5***) until they become unstable at the boundary, where q_z = 0.908. As they ap-

F8

Sequential MS^6 analysis of an oleanolic acid glycoconjugate performed using a Finnigan LCQ ion trap instrument showing control over loss of the sugar monomers, to allow simple, rapid elucidation of a complex structure. (Adapted from Finnigan LCQ Catalog 1996.)



proach the region of instability, their kinetic energies and z-direction excursions increase and they exit the trap through a hole in the end-cap electrode and reach an external detector. Ions of increasing m/z are ejected and detected as the rf voltage V is raised, so yielding a mass (actually m/z) spectrum. The mass analysis equation for a quadrupole ion trap operated in the mass-selective instability mode is obtained simply by rearranging the expression for the Mathieu parameter q_z (***EQ6***)

$$m/z = \frac{8V}{q_z(r_0^2 + 2z_0^2)\,\omega^2} \qquad (7)$$

This emphasizes the fact that in this mode of operation, ion motion is constrained to the $a_z = 0$ axis, i.e., no dc voltages are applied to the end-cap electrodes. For traps built with the so-called ideal geometry, , ***EQ7*** $r_o = \sqrt{2}\,z_o$ can be simplified to ***EQ8***

$$m/z = \frac{4V}{q_z r_0^2 \omega^2} \qquad (8)$$

Trapped ions have characteristic frequencies of oscillation, known as secular frequencies, again separately in both the r- and z-directions. The principal component of these secular frequencies is $(\omega/2)\beta$ radian per second, where β is a parameter that varies with the coordinates a and q of which it is a continuing fraction. (At low values of a_z and q_z, βz is approximately given by $\sqrt{a_z + q_z^2/2}$. Motion is uncoupled in the r- and z-directions and the r-frequency is half that in the z-direction. Because ions have the characteristic frequencies just noted, a supplementary ac potential of frequency equal to the secular frequency of motion of the ions will cause ions to pick up increasing amounts of kinetic energy. If the signal is applied between the end-cap electrodes, ions will be activated in the z-direction. If the resonant signal is strong enough, these translationally activated ions can be ejected from the trap in the z-direction.

This resonance experiment is extremely valuable in causing particular ions to be excited so that they can be made to dissociate or eject so that the population of ions in the trap can be controlled. ***F6A*** shows a simulation of the trajectory of an ion of m/z = 100 in an ion trap operated at an rf voltage of 500 V and a frequency of 1.1 MHz. Because of the particular initial conditions chosen, the center of the trap is not visited; instead, a "donut" of space is accessed. ***F6B*** shows the simulated ion trajectory when a supplementary ac potential, in resonance with the frequency of ion motion in the z-direction, is applied across the endcap electrodes. It can be seen that there is no effect on ion motion in the r-direction. However, the excursion in the z-direction in-

creases, and the ion is energized and ejected through the apertures in the end-cap electrodes after a few cycles of application of the ac potential. Other ions of different m/z values are not affected, so the experiment can be used for selective ejection or activation (see section on Ion Population Control).

High Performance and Biological Applications

Mass Range Extension By Resonant Ejection

The mass range of an ion trap can be calculated by substituting appropriate values into ***EQ7***. Note that $q_z = 0.908$ is the q_z value at which instability occurs in the normal mass-selective instability mode of operation. However, under resonance conditions, q_z becomes a variable provided the supplementary resonance frequency can be varied. Since it appears in the denominator of ***EQ7***, it can be decreased to increase m/z. Typical operating conditions for the Finnigan LCQ are $V_{0\text{-}p}$ = 0 - 8500 V, r_o = 0.707 cm, z_o = 0.783 cm, ω = 0.76 MHz and $(q_z)_{eject} = 0.83$. The maximum m/z range that can be achieved under these conditions is about 2000 dalton/charge.

Decreasing the size of the trap or lowering the frequency has been used to extend the mass range of the ion trap. However, the most straightforward method is to lower $(q_z)_{eject}$ by modulating the ion motion at a chosen frequency using the dipolar electric field applied across the end caps. Ions of a particular m/z value in resonance with the applied frequency then pick up translational energy and are ejected from the trap. Conceptually, the resonant ejection experiment creates a "hole" in the stability region (***F5***) at that value of q_z which corresponds to the frequency applied to the end-cap electrodes. By scanning the amplitude of the main rf voltage in the normal way, ions of different mass sequentially acquire q_z values that give them the frequency which corresponds to this hole and causes resonant ejection. They exit the ion trap in sequence of m/z values but at a lower rf amplitude than would ordinarily be required for ion ejection.

Slow Scans and High Resolution

In the usual mode of operation (mass selective instability scan) of an ion trap mass spectrometer, ions of different m/z values arrive at the detector separated in time. Ions of increasing mass are ejected in turn as increasing rf voltages are applied to the ring electrode. If the rate at which the amplitude V of the main rf is changed is too fast, ions will fail to respond to the instability condition completely before ions of next value begin to be ejected. Loss of resolution will result. By slowing the rate at which V is increased, an improvement in resolution is expected (14, 15). In fact, this type of experiment has been shown to produce extremely high resolution: in excess of 10^6 at m/z 3000 (15). It is most appropriately applied in a zoom-scan mode in which ions of interest of a narrow mass window (<10 dalton/charge) are examined. The zoom-scan mode is able to resolve the isotopic forms of multiply-charged ions observed in electrospray ionization mass spectra. ***F7*** illustrates a zoomscan of the +4 charged state of rat interleukin-8, i.e. $[M+4H]^{+4}$. The resolved isotopic cluster reveals a one-fourth m/z unit difference between carbon isotopes, which are separated in mass by one dalton due to the $^{12}C/^{13}C$ difference. Therefore, the charge on the ion must be +4.

MS/MS and MS^n

Mass spectrometry/mass spectrometry (MS/MS), or tandem mass spectrometry (16), is a procedure for examining individual ions in a mixture of ions. The ions of interest are isolated by their characteristic m/z values, activated by collision, and allowed to dissociate. The resulting product ions are examined in a second mass measurement step.

In an ion trap mass spectrometer, MS/MS is achieved by the use of an additional sequence of operations in the scan function. The scan function begins with ionization and is followed by selection of a parent ion in a step that involves ejecting all other ions from the trap. The parent ion is then translationally excited, typically by applying a supplementary rf voltage to the end caps. The product ions resulting from collision-induced dissociation of these excited ions with the helium buffer gas are recorded by scanning the rf voltage to perform a second mass-analysis scan. The main advantage of the MS/MS experiment is its enhanced specificity. This is useful in isomer distinction, sequencing of biopolymers, and most particularly in the analysis of complex mixtures. Tandem mass spectrometry experiments eliminate or greatly reduce signals due to other matrix components or instrumental background (chemical noise).

A unique feature of the ion trap is the MS^n capability which has unprecedented power in structural elucidation. The selectivity of MS^n means that a compound can be fragmented, and the resulting fragments further isolated and analyzed to yield structural information about complex molecules in the presence of mixtures. ***F8*** shows a sequential MS^6 experiment performed on an oleanolic acid glyconjugate demonstrating dramatic control over the loss of the sugar monomers. The experiment allows simple, rapid elucidation of a complex molecular structure.

Ion Population Control By Selective Ion Manipulation Techniques

A significant weakness of ion traps is the poor dynamic range due to space charge effects, defined as changes in ion motion which result from the mutual coulombic interactions of ions. Space charge effects can be alleviated by removing matrix ions. Similar reasons for developing a capability for exciting ions of specified m/z values exist in ion

cyclotron resonance instruments. The basis for selective excitation is the resonance experiment described above. It can be used to extend the m/z range, as already noted, or to allow only specified ions to fragment by collision induced dissociation. Resonance excitation experiments are most effectively implemented by applying a mixture of frequencies so as to manipulate ions of different m/z values simultaneously. This can be done using a time domain signal in a technique known as SWIFT (stored waveform inverse Fourier transform) (17). This was the first procedure applied to quadrupole ion traps for the general purpose of ion population control. In trace level analysis, it is desirable to selectively fill the trap with the analyte ions while the matrix ions are ejected (18). The ability to selectively store ions is expected to provide a substantial improvement in limits of detection. This and related selective ion storage techniques have been used in ultra-trace-level analysis of volatile organic compounds at levels as low as parts-per-quadrillion (pg/L) (19).

Non-Destructive Ion Detection

A new and simple method of ion detection in the quadrupole ion trap is that in which ions approach an electrode and polarize it so that a current flows toward and away from the electrode through an external conductor in response to the oscillating ion motion. The induced current flow has a frequency equal to that of the coherently moving ions, which in turn depends on their m/z value. Since the ions are not destroyed, they can be remeasured. A non-destructive method of ion detection (20) is achieved in ion traps by impulsive excitation of a collection of trapped ions, typically of different m/z values. The ion image currents are induced on a small detector electrode embedded in, but isolated from, the end-cap electrode. The image currents are directly measured using a differential preamplifier, filter, and amplifier combination and then Fourier analyzed to obtain the broad-band frequency domain spectra characteristic of the sample ions. An advantage of non-destructive ion detection is the ability to measure a single-ion population multiple times.

Conclusions

Ion trap mass spectrometry has recently undergone very rapid development and is emerging as a high performance technique which show signs of becoming one of the leading tools in the discipline. These instruments allow tandem mass spectrometry experiments which are possible only using combinations of multiple quadrupoles such as the highly successful triple quadrupole instrument. Extension to high mass/charge measurements, the development of high resolution capabilities and the very recent demonstration of non-destructive, broad-band Fourier transform capabilities, all suggest an increased role in the future. Limitations occur in dynamic range, accurate mass measurement, and quantitative precision.

Acknowledgement

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