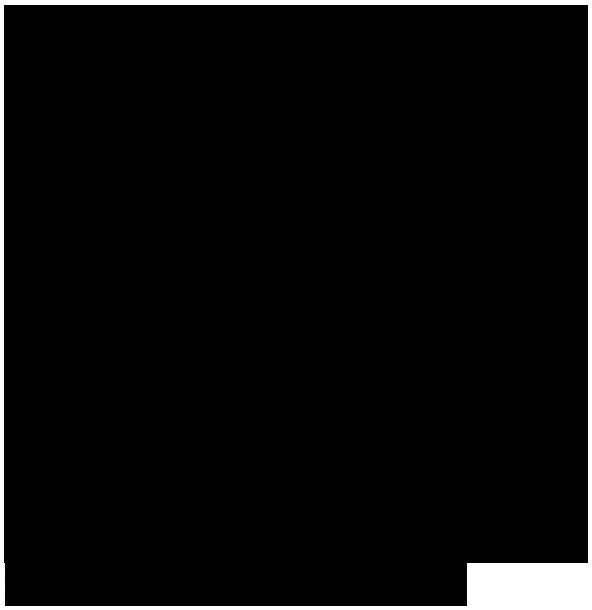
Very frequently, these types of samples are aqueous in nature, such as blood, urine, and other body fluids, water, and wastewater. 5 h 53	Thông thường, những loại mẫu này là các chất lỏng trong tự nhiên, chẳng hạn như máu, nước tiểu, và các chất lỏng trong cơ thể, nước và nước thải.
The sensitivity at the lower molecular weight range (1500 Da) is increased	Trong khoảng trọng lượng phân tử thấp (1500 Da), độ nhạy tăng hai bậc

by two orders of magnitude over conventional FAB. Further, the background is reduced because of the reduced amount of glycerol present. In addition, when the solvent alone is injected, a background signal can be recorded. This can be subtracted from the signal due to sample plus solvent, and the net signal of the sample is obtained. This is especially valuable for trace analysis; concentrations as low as 10_12 g have been detected using CFFAB.

độ lớn so với phương pháp FAB truyền thống. Hơn nữa, nhiễu nền cũng giảm do lượng glyxerin giảm. Ngoài ra, chúng ta cũng có thể ghi nhận tín hiệu nền khi chỉ tiêm dung môi. Sau đó, chúng ta sẽ trừ tín hiệu mẫu-dung môi với tín hiệu này và thu được tín hiệu của riêng mẫu. Phương pháp này cực kỳ hữu dụng khi phân tích các mẫu có hàm lượng cực kỳ thấp; người ta đã phân tích được các mẫu có nồng độ thấp vào cỡ ….bằng CFFAB.

The CFFAB system can be incorporated into LC-MS systems. The mobile phase is the solvent used. The effluent from the LC is transported directly into the mass spec- trometer and the MS obtained by CFFAB. This provides a mass spectrum of each separ- ated peak in mixtures. (See Chapter 13 for a detailed discussion of LC/MS.)

In summary, FAB and CFFAB have greatly increased the potential of mass spectrometry by increasing the molecular weight range of molecules whose molecular ion can be determined. The system can be directly attached to LC, permitting identification of the components of a solution. Also, trace analysis is possible. The method can be applied to the important research areas of the health sciences, biology, and environmental science, as well as to chemistry.



9.2.2.5. Ionization Sources for Inorganic MS

The following ionization sources are used mainly in inorganic (atomic)

MS, where the elemental composition of the sample is desired. The glow discharge (GD) and spark sources are used for solid samples, while the inductively coupled plasma (ICP) is used for solutions. All three sources are also used as atomic emission spectroscopy sources; they are described in more detail with diagrams in Chapter 7.

GD Sources and Spark Sources. The GD source and spark source are both used for sputtering and ionizing species from the surface of solid samples and have been dis- cussed in Chapter 7 for use as atomic emission sources. As MS ionization sources, they are used primarily for atomic MS to determine the elements present in metals and other solid samples. The DC GD source has a cathode and anode in 0.1-10 torr of argon gas. The sample serves as the cathode. When a potential of several hundred volts is imposed across the electrodes, the argon gas ionizes forming a plasma. Electrons and positive argon ions are accelerated toward the oppositely charged electrodes. The argon ions impact the cathode surface, sputtering off atoms of the cathode material. The sample atoms are then ionized in the plasma by electrons or by collision with excited argon (Penning ionization). The sample ions are extracted from the plasma into the mass analy- zer by a negatively charged electrode with a small aperture. The DC GD source is used for the analysis of conductive samples including metals, alloys, and semiconductors. The sample must be conductive to serve as the cathode.

RF GD sources have been developed that enable the sputtering of electrically nonconductive samples such as ceramics and other insulators. Spark sources also can be used for sputtering of solids, but the GD source produces a more stable ion beam with better signal-to-noise ratio. The GD source sputters more material from a sample and gives more representative and more quantitative results of the elemental bulk composition than the spark source.

ICP Source. The argon ICP source has also been described in Chapter 7 for use with atomic emission spectrometers. The source produces ions from the elements intro- duced into the plasma as well as radiation; these ions can be extracted into a mass analyzer. The ICP torch is usually mounted horizontally with the tip of the plasma at the entrance to the mass analyzer as shown in Fig. 9.14. Most of the plasma gas is deflected by a metal

Figure 9.14 Argon ICP torch used as an ionization source for ICPMS. (From Ewing, used with permission.)

cone with a small orifice in its center, called the sampling cone. The gas that enters through the orifice expands into an evacuated region. The central portion passes through another metal cone, the skimmer cone, into the evacuated mass analyzer. Singly charged positive ions are formed from most elements, metallic and nonmetallic. The ICP has a high ioniz- ation efficiency, which approaches 100% for most of

the elements in the periodic table. The mass spectra are very simple and elements are easily identified from the m/z values and the isotope ratios observed. Background ions from the solvent and from the argon gas used to form the plasma are usually observed. Such ions include Ar+, ArH+, ArO+, and polyatomic ions from water and the mineral acids used to dissolve most samples.

9.2.3. Mass Analyzers

The mass analyzer is at the core of the mass spectrometer. Its function is to differentiate among ions according to their mass-to-charge ratio. There are a variety of mass analyzer designs. Magnetic sector mass analyzers and quadrupole mass analyzers are scanning instruments; only ions of a given mass-to-charge ratio pass through the analyzer at a given time. The m/z range is scanned over time. Other mass analyzers allow simultaneous transmission of all ions; these include time-of-flight (TOF), ion trap, and ion cyclotron resonance mass analyzers as well as dispersive magnetic mass analyzers. Tandem (cấu trúc nối tầng, cách bố trí trước sau) mass spectrometers are instruments with several mass analyzers in sequence; these allow the selection of one ion in the first analyzer (the precursor ion) and the analysis of fragmenta- tion or decomposition of that ion into product ions in the second analyzer.

9.2.3.1. Magnetic and Electric Sector Instruments

The principle of operation of a simple single-focusing magnetic sector mass analyzer was described briefly in Section 9.1. An ion moving through a

magnetic field B will follow a circular path with radius r [Eq. (9.6)]. Changing B as a function of time allows ions of different m/z values to pass through the fixed radius flight tube sequentially. This scanning magnetic sector sorts ions according to their masses, assuming that all ions have a +1 charge and the same kinetic energy. A schematic of a 90° sector instrument is shown in Fig. 9.15. A variety of other magnetic mass spectrometers are shown in Fig. 9.16; some of these will be discussed later. The sector can have any apex angle, but 60° and 90° are common. It can be demonstrated that a divergent beam of ions of a given m/z will be brought to a focus by passing through a sector shaped magnetic field, as shown by the three ion paths in Fig. 9.15.

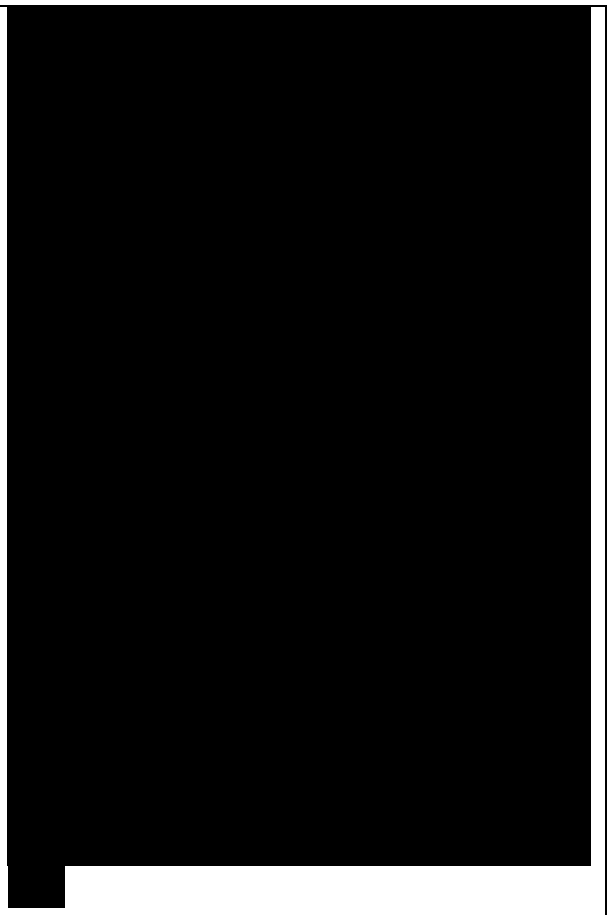


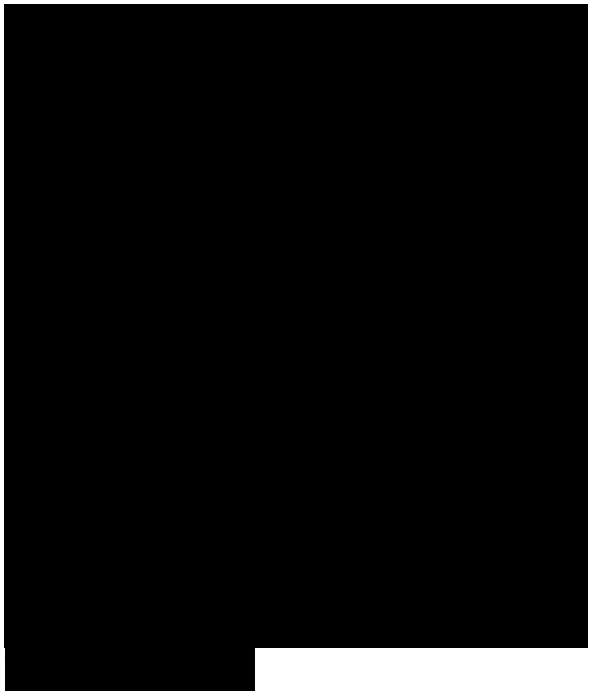
Figure 9.15 A 90° magnetic sector mass spectrometer. (From Ewing, used with permission.)

A dispersive magnetic sector mass analyzer does not use a flight tube with a fixed radius. Since all ions with the same kinetic energy but different values of m/z will follow paths with different radii, advantage can be taken of this. The ions will emerge from the magnetic field at different positions and can be detected with a position-sensitive detector such as a photoplate or an array detector. Examples of dispersive magnetic sector systems are shown in Fig. 9.16(c) and (d).

Figure 9.16 Early mass spectrometer designs. (a) Aston, 1919; (b) Dempster, 1918; (c) Mattauch-Herzog, 1935; (d) Bainbridge, 1933. In each case, B signifies the magnetic

field. Spectrometers (c) and (d) are dispersive mass spectrometers; (c) the Mattauch-Herzog design is also a double sector instrument, using an electric sector before the magnetic field.

A single-focusing instrument such as the system shown in Fig. 9.16(b) has the disadvantage that ions emerging from the ion source do not all have exactly the same velocity. This is due to several factors. The ions are formed from molecules that have a Boltzmann distribution of energies to begin with. The ion source has small variations in its electric field gradient, causing ions formed in different regions of the source to experi- ence different acceleration. Also, when fragmentation occurs, kinetic energy is released. This results in a distribution of velocities and adversely affects the resolution of the instru- ment by broadening the signal at the detector.



However, ions in a radial electrostatic field also follow a circular trajectory. The electrostatic field is an electric sector and separates ions by kinetic energy, not by mass (Fig. 9.17). The ion beam from the source can be made much more homogeneous with respect to velocities of the ions if the beam is passed through an electric sector before being sent to the mass analyzer. The electric sector acts as an energy filter; only ions with a very narrow kinetic energy distribution will pass through.

Most magnetic sector instruments today combine both an electric sector and a magnetic sector. Such instruments are called double-focusing mass spectrometers. One

common commercial double-focusing design is the Nier-Johnson design (Fig. 9.18), introduced in 1953; a second common design using two sectors is the Mattauch- Herzog dispersive design, shown in Fig. 9.16(c).

Mass ranges for magnetic sector instruments are in the m/z 1-1400 range for single-focusing instruments and m/z 5000-10,000 for double-focusing instruments. Very high mass resolution, up to 100,000, is possible using double-focusing instruments.

9.2.3.2. Time of Flight (TOF) Analyzer

A TOF analyzer does not use an external force to separate ions of different m/z values. Instead, pulses of ions are accelerated into an evacuated field free region called a drift tube. If all ions have the same kinetic energy, then the velocity of an ion depends on its mass-to-charge ratio, or on its mass, if all ions have the same charge. Lighter ions will travel faster along the drift tube than heavier ions and are detected first. The process is shown schematically in Fig. 9.19.

A schematic TOF mass spectrometer is shown in Fig. 9.20. The drift tube in a TOF system is approximately 1-2 m in length. Pulses of ions are produced from the sample using pulses of electrons, secondary ions, or laser pulses (e.g., MALDI). Ion pulses are produced with frequencies of 10-50 kHz. The ions are accelerated into the drift tube by a pulsed electric field, called the ion-extraction field, because it extracts (or draws out) ions into the field-free

region. Accelerating voltages up to 30 kV and extraction pulse frequencies of 5-20 kHz are used.

Figure 9.18 A Nier-Johnson double focus mass spectrometer. (From Ewing, used with permission.)

Ions are separated in the drift tube according to their velocities. The velocity of an ion, v, can be expressed as:

v = J— (9.10)

where V is the accelerating voltage. If L is the length of the field-free drift tube and t is the time from acceleration to detection of the ion (i.e., the flight time of the ion in the tube),

v = L (9.11)

Figure 9.19 A pulse of ions of two different m/z values enters the field free drift tube of a TOF mass spectrometer at time 1. The large white circles have m/z > than the small dark circles. As they travel down the tube, the lighter ions move faster, and by time 3, have been separated from the heavier ions.

and the equation that describes ion separation is:

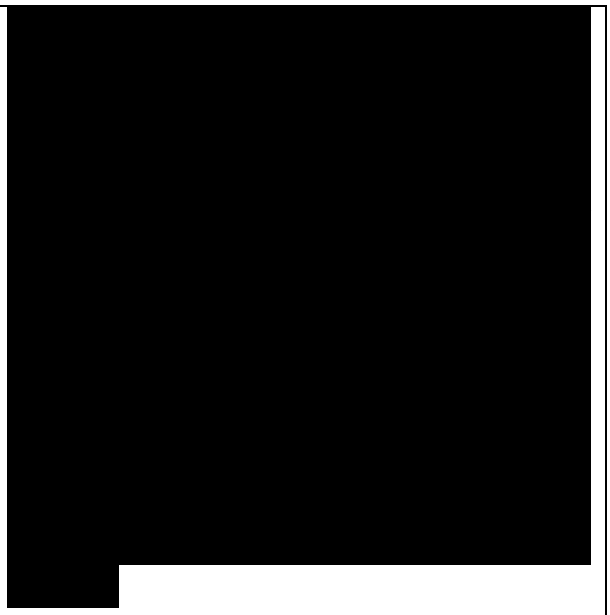
The flight time, t, of an ion is:

(9.13)

Eq. (9.13) can be used to calculate the difference in flight time between ions of two different masses. Actual time separations of adjacent masses can be as short as a few nanoseconds, with typical flight times in microseconds.

TOF instruments were first developed in the 1950s, but fell out of use because of the inherent low resolution of the straight drift tube design (as in Fig. 9.20). The drift tube length and

flight time are fixed, so resolution depends on the accelerating pulse. Ion pulses must be kept short to avoid overlap of one pulse with the next, which would cause mass overlap and decrease resolution. Interest in TOF instruments resurfaced in the 1990s with the introduction of MALDI and rapid data acquisition methods. The sim- ultaneous transmission of all ions and the rapid flight time means that the detector can capture the entire mass spectral range almost instantaneously.



The resolution of a TOF analyzer can be enhanced by the use of an ion mirror, called a reflectron. The reflectron is used to reverse the direction in which the ions are traveling and to energy-focus the ions to improve resolution. The reflectron's electrostatic field allows faster ions to penetrate more deeply than slower ions of the same m/z value. The faster ions follow a longer path before they are turned around, so that ions with the same m/z value but differing velocities end up traveling exactly the same distance and arrive at the detector together. The use of a curved field reflectron permits the focusing of ions over a broad mass range to collect an entire mass spectrum from a single laser shot. In a reflectron TOF, the ion source and the detector are at the same end of the spec- trometer; the reflectron is at the opposite end from the ion source. The ions traverse the drift tube twice, moving from the ion source to the reflectron and then back to the detector. A schematic of a commercial reflectron TOF mass

analyzer is shown in Fig. 9.21.

The mass range of commercial TOF instruments is up to 10,000 Da. Resolution depends on the type of TOF and ranges from 1000 for instruments designed as dedicated detectors for GC (GC-TOFMS) to 20,000 for reflectron instruments. One limitation to the use of a conventional reflectron instrument is a loss in sensitivity; about 10% of the ions are lost with a conventional wire grid reflectron.

Figure 9.21 A commercial reflectron TOF mass analyzer, the Pegasus III from LECO. The ana- lyzer is shown with sample introduction from a GC. [Diagram courtesy of LECO Corporation (www.leco.com).]

The rapid collection of the entire mass spectrum made possible by the TOF makes it ideal for interfacing with a chromatograph. It is especially useful when combined with fast GC, which requires the rapid collection of hundreds of mass spectra. For example, the LECO Pegasus 4D GC-TOFMS collects the entire mass range from 1 to 1000 Da in 170 ms and collects up to 500 mass spectra/s. (A detailed description of this instrument can be found at www.leco.com.)

9.2.3.3. Quadrupole Mass Analyzer

The quadrupole mass analyzer does not use a magnetic field to separate ions. The quadrupole separates ions in an electric field (the quadrupole field) that is varied with time. This field is created using an oscillating radio frequency (RF) voltage and a constant direct current (DC) voltage

applied to a set of four precisely machined parallel metal rods (Fig. 9.22). This results in an AC potential superimposed on the DC potential. The ion beam is directed axially between the four rods.

The opposite pairs of rods A and B, and C and D, are each connected to the opposite ends of a DC source, such that when C and D are positive, A and B are negative. The pairs of electrodes are then connected to an electrical source oscillating at RFs. They are con- nected in such a way that the potentials of the pairs are continuously 180° out of phase with each other. The magnitude of the oscillating voltage is greater than that of the DC source, resulting in a rapidly oscillating field. The RF voltage can be up to 1200 V while the DC voltage is up to 200 V. The rods would ideally be hyperbolic instead of circular in cross- section to provide a more uniform field. Under these conditions, the potential at any point between the four poles is a function of the DC voltage and the amplitude and frequency of the RF voltage. The shape of the rods varies with different manufacturers; cheaper circular cylindrical rods are often used instead of hyperbolic rods.

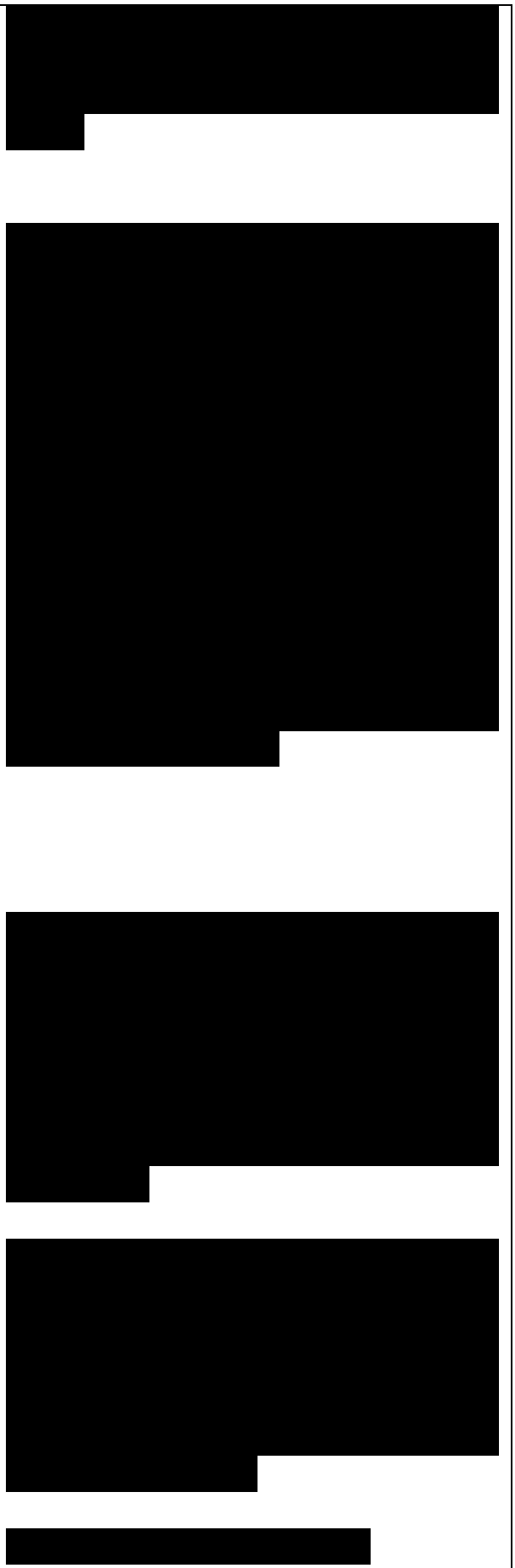
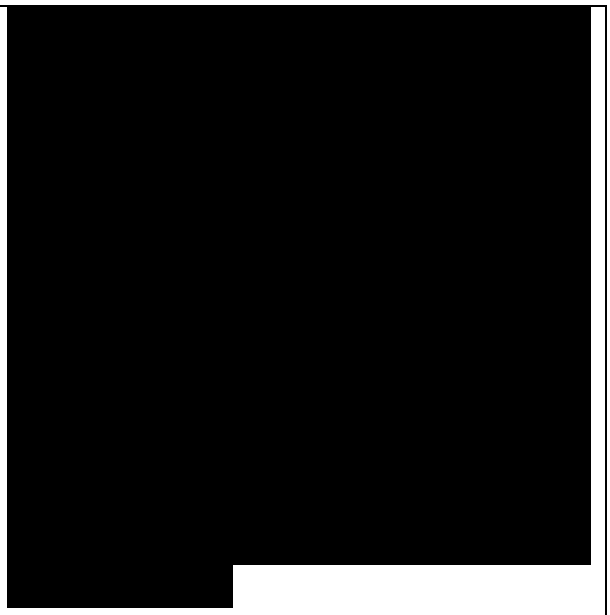


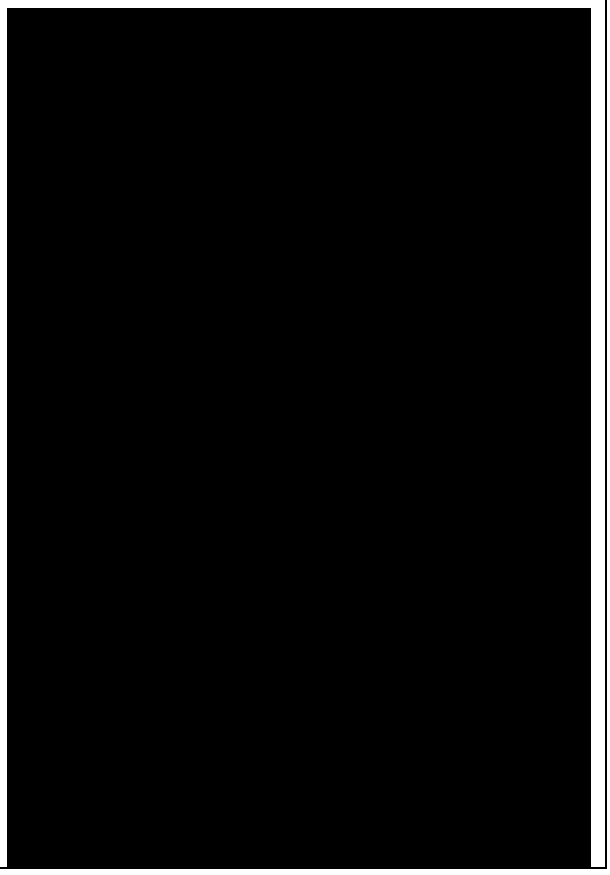
Figure 9.22 (a) Transmission quadrupole mass spectrometer. Rods A and B are tied together elec- trically, as are Rods C and D. The two pairs of rods, AB and CD, are connected both to a source of direct potential and a variable RF excitation such that the RF voltages are 180° out of phase. (b) The geometry of the rods.

An ion introduced into the space between the rods is subjected to a complicated lateral motion due to the DC and RF fields. Assume that the x direction is the line through the midpoint of the cross-sections of rods A and B; the y direction is the line through the midpoint of the cross-sections of rods C and D, as shown in Fig. 9.22(b). The forward motion of the ion in the z direction (along the axis between the rods) is not affected by the field. The following equations describe the lateral motion of the ion:



where VDC is the voltage of the DC signal; VRF , the amplitude of the voltage of the RF field; f, the frequency of oscillation of the RF field (rad/s); r, the half the distance between the inner edges of opposing poles such as A and B as shown in Fig. 9.22(b); and t, the time.

The motion is complex because the velocity in the x direction is a function of the position along y and vice versa. In order for an ion to pass through the space between the four rods, every time a positive ion is attracted to a negatively charged rod, the AC electric field must be present to push it away; otherwise, it will collide with the rod and be lost. The coordination between the oscillating (AC) field and the time of the ion's arrival at a rod surface over the fixed distance between the rods is critical to an ion's move- ment through the quadrupole. As a result of being alternately attracted and repelled by the rods, the ions follow an oscillating or "corkscrew" path through the quadrupole to the



detector. For a given amplitude of a fixed ratio of DC to RF at a fixed frequency, only ions of a given m/z value will pass through the quadrupole. If the mass-to-charge ratio of the ion and the frequency of oscillation fit Eqs. (9.14) and (9.15), the ion will oscillate toward the detector and eventually reach it. If the m/z value and the frequency do not meet the conditions required by Eqs. (9.14) and (9.15), these ions will oscillate with an increas- ingly wide path until they collide with the rods or are pulled out by the vacuum system. In any case, the ions will not progress to the detector. Only a single m/z value can pass through the quadrupole at a given set of conditions. In this respect, the quadrupole acts like a filter, and is often called a mass filter.

The separation of ions of different m/z can be achieved by several methods. The frequency of oscillation of the RF field can be held constant while varying the potentials of the DC and RF fields in such a manner that their ratio is kept constant. It can be shown mathematically that the best resolution is obtained when the ratio VDC/VRF is equal to 0.168. If the ratio is greater than this number, a stable path cannot be achieved for any mass number; if the ratio is lower than this number, resolution is progressively lost.

The resolution of the system is dependent on the number of oscillations an ion undergoes in the drift chamber. Increasing the rod lengths, therefore, increases resolution and extends the use of the system to higher molecular weight

compounds. Increasing the frequency of the RF field can bring about this same improvement. The rod diameter is also important. If the diameter is increased, the sensitivity is greatly increased, but then the mass range of the system is decreased. The manufacturer must come to a compromise with these factors when designing an instrument for analytical use. The resolution achiev- able with the quadrupole mass spectrometer is approximately 1000; the m/z range for a quadrupole mass analyzer is 1-1000 Da. As with other mass spectrometers, the sample must be available in the gas phase and must be ionized.

Quadrupole mass analyzers are found in most commercial ICP-MS instruments, in most GC-MS instruments (Chapter 12) and in many LC-MS instruments (Chapter 13). Quadrupoles are also used in MS-MS systems as mass analyzers and ion lenses. This use will be described in Section 9.2.3.4.

Although the quadrupole mass analyzer does not have the range or resolution of magnetic sector instruments, it is very fast. It can provide a complete mass spectrum in less than 100 ms. This property and its wide angle of acceptance make it suitable for coupling to transient signal sources such as those from chromatography or laser ablation. In addition the quadrupole mass analyzer is inexpensive, compact, and rugged. Most GC-MS and LC-MS instruments with quadrupoles are small enough to fit on a benchtop.

Quadrupoles are the most common mass analyzer in commercial use. The term trans- mission quadrupole mass spectrometer is sometimes used for this mass analyzer to avoid confusion with the quadrupole ion trap mass spectrometer discussed in Section 9.2.3.5.

9.2.3.4. MS-MS and MSn Instruments

Many analytical questions require the mass spectrometrist to obtain more information about the structure of fragment ions or about ion-molecule reactions than can be obtained from the initial ionization of an analyte. In such cases, the technique of MS-MS, also called tandem MS may be useful. MS-MS is a mass spectral technique that uses two (or more) stages of mass analysis combined with a process that causes a change in mass of the ion of interest, such as dissociation into lighter fragment ions by collision with an inert gas or conversion into a heavier ion by reaction with a neutral molecule.

The stages of mass analysis may be performed by two physically separate mass ana- lyzers, such as two quadrupoles coupled in series; this type of arrangement for MS-MS is called “tandem in space”. Figure 9.23 shows a quadrupole MS-MS instrument with three quadrupoles for “tandem in space” analysis. Alternatively, ion traps, discussed in Sections 9.2.3.5 and 9.2.3.6, may be used to perform MS-MS experiments within the same mass analyzer; this type of MS-MS experiment is called “tandem in time”.

Using Fig. 9.23, we will look at a

simple MS-MS experiment. For example, an analyte may be ionized as usual by the ion source. One ion of a particular m/z value is

Figure 9.23 A commercial quadrupole tandem MS-MS instrument. [Courtesy of Thermo Electron Corporation (www.thermo.com).]

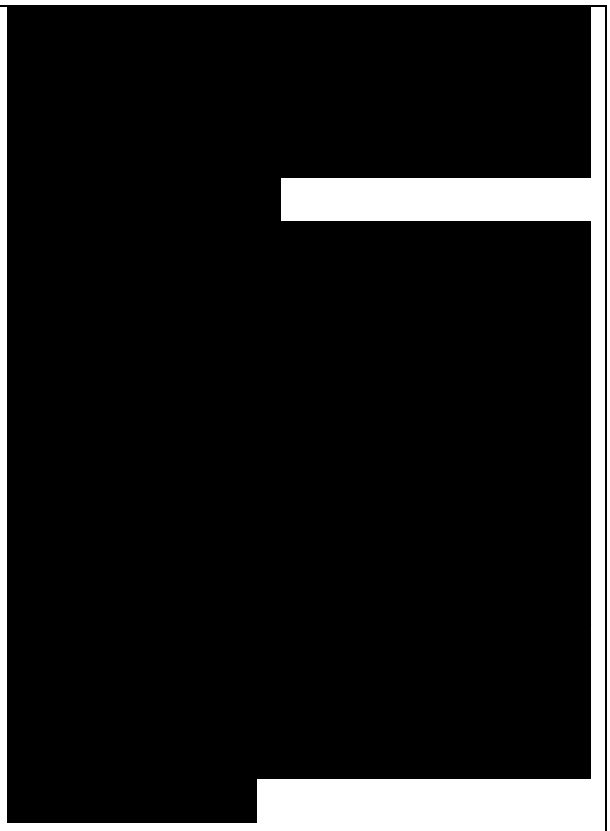
of interest. This ion is called the precursor ion. The precursor ion is selected by the first quadrupole, which is operating as a mass analyzer. The precursor ion enters the second quadrupole. This second quadrupole is the reaction region and acts as a collision cell and ion lens, not as a mass analyzer. An inert gas may be added in this region to cause collision-induced fragmentation of the precursor ion into lighter product ions or a reactive reagent gas may be introduced to form heavier product ions through ion-molecule reac- tions. The second quadrupole also serves to focus the product ions; that is:

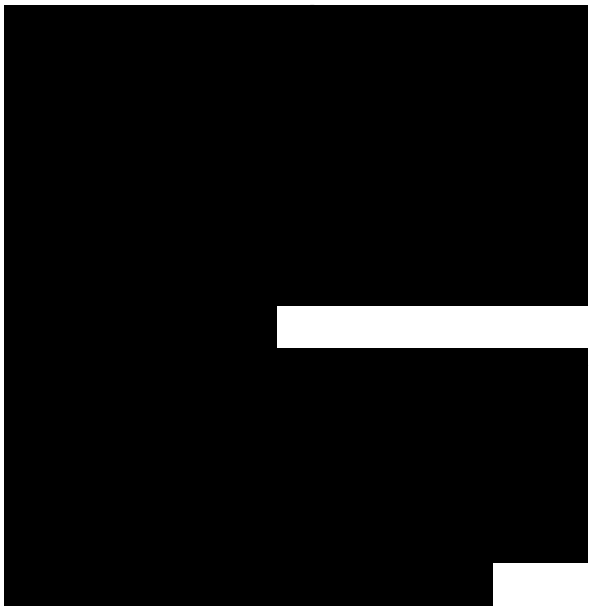
where the precursor and product ions have different m/z values. The product ions then undergo mass analysis as usual in the third quadrupole. This type of design, where the first and third quadrupoles are used for mass analysis and the center quadrupole is used for collision and focusing, is often abbreviated as a QqQ design, to indicate that there are only two stages of mass analysis symbolized by the capital Q.

If we had an instrument with three mass analyzers, the fragmentation process could be repeated before final

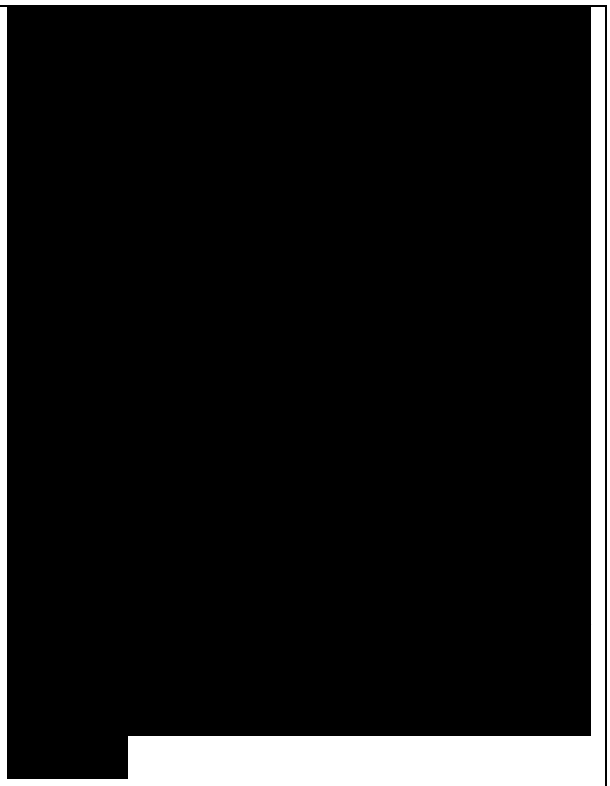
analysis. A precursor ion is selected, fragmented, a given product ion is selected and fragmented again before mass analysis of its product ions; that is:
where all three ions have different m/z values. This is an example of MS-MS-MS or MS3; the number of steps can be increased to give an MSn experiment. It is not practical to build "tandem in space" instruments with large numbers of mass analyzers; three or four is the upper limit. Commercial MS-MS instruments are limited to two mass analysis stages. Ion trap instruments are used for higher order experiments. In general, n = 7 or 8 is a practical upper limit in ion trap instruments.

Tandem mass spectrometers have been built with three quadrupoles as shown in Fig. 9.23, and with other combinations of sector and TOF mass analyzers. Electric and magnetic sector analyzers have been combined with quadrupoles and with TOF analyzers.
An ion trap is a device where gaseous ions can be formed and/or stored for periods of time, confined by electric and/or magnetic fields. There are two commercial types of ion traps in use in MS, the quadrupole ion trap (QIT) and the ion cyclotron resonance trap (ICR).
The QIT mass spectrometer is also called a Paul ion trap or more commonly, just an ion trap. This analyzer uses a quadrupole field to separate ions, so "quadrupole" is used in the name to distinguish this system from the ICR trap discussed in the next section. The QIT is shown



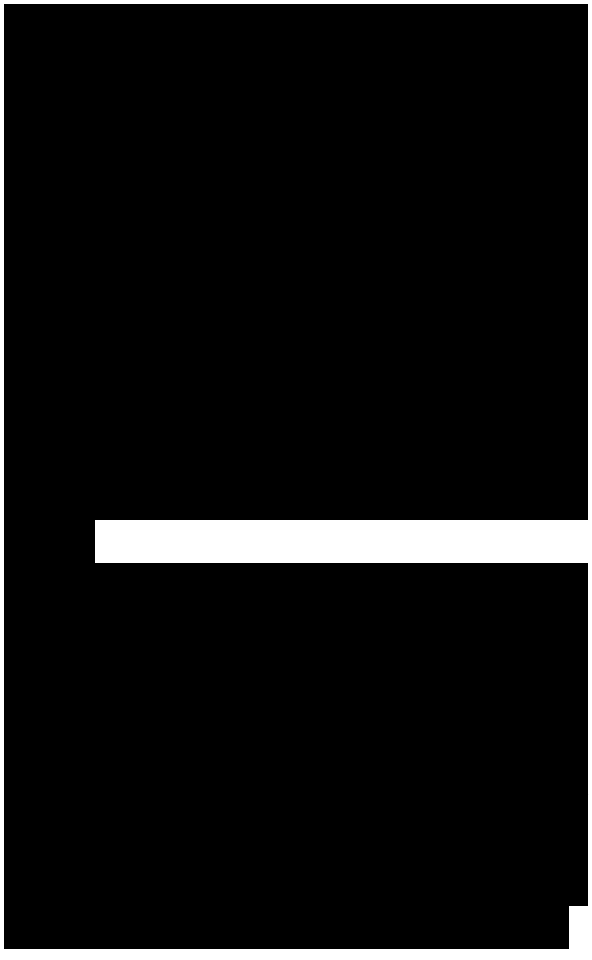


schematically in Fig. 9.24. A ring-shaped electrode and two end cap elec- trodes, one above and one below the ring-shaped electrode, are used to form a 3D field. A fixed frequency RF voltage is applied to the ring electrode while the end caps are either grounded or under RF or DC voltages. Ions are stored in the trap by causing them to move in stable trajectories between the electrodes under the application of the field. This is done by varying the potentials, so that just before an ion collides with an elec- trode the potential changes sign and repels the ion. Ions with a very broad range of m/z values can be stored simultaneously in the ion trap.



Ionization of the sample can take place outside of the ion storage area of the ion trap; such external ionization is required for LC-MS using an ion trap and may be used for GC- MS. Alternatively, ionization can take place inside the ion storage area; this internal ion- ization approach can be used for GC-MS. Inert gas may be introduced into the trap after initial ionization for MS-MS experiments using collision-induced dissociation.

Ions are extracted from the trap by changing the amplitude of the ring electrode RF. As the amplitude increases, the trajectory of ions of increasing m/z becomes unstable. These ions move toward the end caps, one of which has openings leading to the detector. Ions of a given m/z value pass through the end cap sequentially and are detected.



The use of various RF and DC waveforms on the end caps allows the ion trap to selectively store precursor ions for MS-MS experiments or to selectively store analyte ions while eliminating ions from the matrix. This can result in improved detection limits in analysis. The ion trap has limitations. Because the stored ions can interact with each other (a space-charge effect), thereby upsetting stability of trajectories, the concentration of ions that can be stored is low. This results in a low dynamic range for ion trap mass spectrometers. Trace level signals from a target analyte ion at one mass can be destabilized by the presence of great excesses of contaminant ions, even if these are of sufficiently different mass to be well resolved from the ion of interest. Ion trap MS instruments are less forgiving of "dirty samples" than are quadrupoles, which "throw away" such unwanted ions as they are measuring the target ion. The stored ion interaction also limits the accuracy of the mass-to-charge ratio measurement. Resolution of commercial QIT mass spectrometers is on the order of 0.1-1, with an m/z range of 10-1000.

9.2.3. Fourier Transform Ion-Cyclotron Resonance (FTICR)

The ICR instrument, also called a Penning ion trap, uses a magnetic field to trap and store ions. As shown in Fig. 9.25, six conducting plates arranged as a cube serve as the ion trap. The cubic cell is about 100 mm on a side, is under high vacuum (<10_8 torr) and is located inside a strong magnetic field produced by a

superconducting magnet. Sample is introduced into the cell and ionized by an external ion source such as an electron beam passing through the trap. Ions in the presence of a magnetic field move in circular orbits perpendicular to the applied field, at a frequency called the cyclotron frequency:

(9.16)

where vc is the frequency of rotation of ions (radians/s); e, the charge on electron (coulombs); B, the magnetic field (tesla); z, the charge on the ion; m, the mass of the ion; v, the velocity of the ion; and r, the radius of orbit.

The frequency of motion of an ion depends on the inverse of its m/z in a fixed magnetic field. Mass analysis is performed by applying an RF pulse of a few milliseconds duration to the transmitter plates. The RF pulse provides energy to the ions, causing them to move in larger circular orbits at the same frequency. For a given m/z value, a pulse at a frequency of vc causes all ions of that m/z value to absorb energy and increase their orbit of rotation. When the RF pulse is off, the motion of the ions is detected by current induction in the receiver plates. As a group of positive ions approaches the receiver

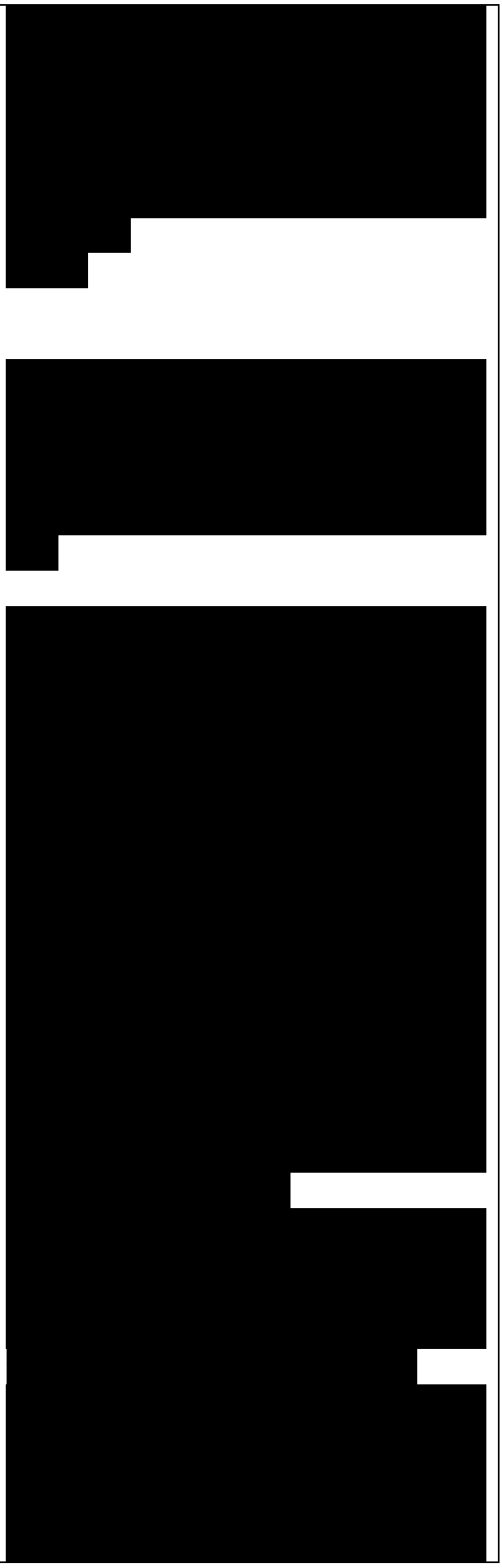


Figure 9.25 “Exploded” view of an ICR ion trap. The ICR has been the primary mass analyzer used in FTMS, both alone and in newer “hybrid” FTMS instruments.

plate, its charge attracts electrons to the inside surface of the plate. As the group recedes, the electrons are released. This induced current, called an “image current” is a sinusoidal

signal with frequency vc. The larger the orbit, the larger is the induced current. The fre- quency provides the m/z information about the ion and the current amplitude depends on the number of ions of that m/z value, providing information about the concentration of ions.

It would be possible to scan the RF and measure the magnitude of the image current at each m/z value to obtain the mass spectral information but the process would be very slow. Instead, an RF pulse is used that contains a range of frequencies. The range of fre- quencies is chosen to excite the desired m/z range.

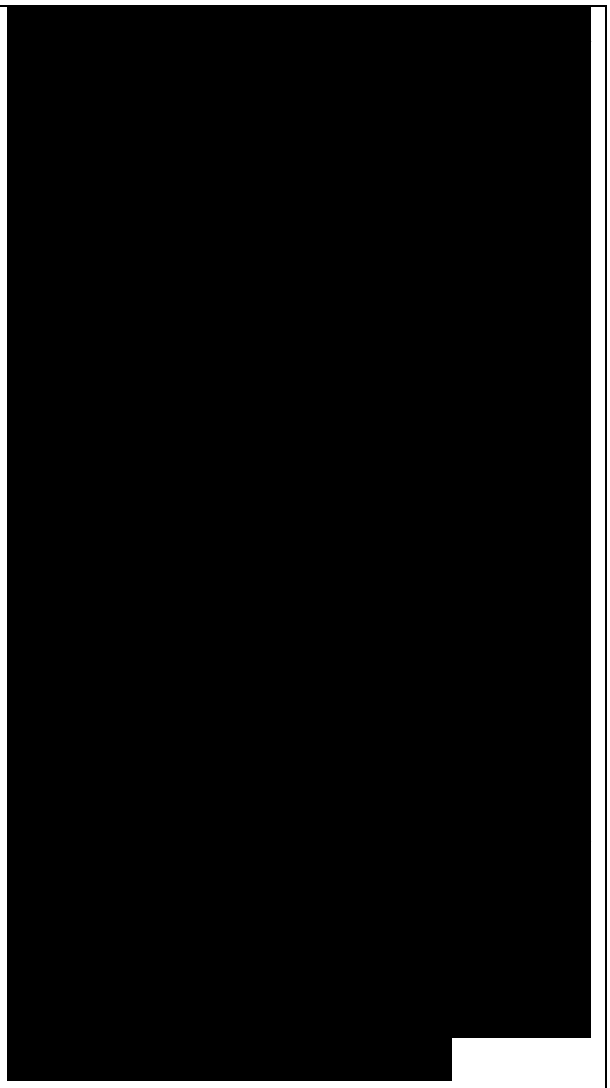
When the pulse is off, all of the exited ions induce image currents in the receiver plates as they rotate. The output current, which contains all of the frequency and magnitude information from all of the ions present can be converted mathematically to a mass spectrum by application of the Fourier transform (FT). The use of an ICR ion trap and Fourier transformation is called Fourier transform ion-cyclotron resonance mass spectrometry (FTICRMS) or just FTMS. As of early 2003, this was the only type of FTMS instrument commercially available.

There are several advantages to the ICR. One is that the ion detection is non- destructive. Therefore, signals can be accumulated by averaging many cycles, resulting in greatly improved S/N and signal-to-background as well as very low detection limits. Detection of

attomoles of analyte is possible. Frequency can be measured very accurately, so the mass accuracy of these FTMS systems can be very high, on the order of 1 ppb for a mass of 100 Da. In order to acquire sufficient information to achieve such high resolutions by the FT process, the data must be acquired over a longer period. In order that collisions with residual gas atoms in the ICR trap not remove the ions during this period, it must be operated at very high vacuum (e.g., < 10_8 torr), if such high resolution is to be attained. The ICR can also be used for MS-MS and MSn experiments, by storing precursor ions and fragmenting them in the trap using a collision gas, lasers, or ion beams. An advantage of the FTMS system is that it is nondestructive, so ions at all stages of an MSn experiment can be measured. A QIT instrument expels ions to be analyzed, so only ions in the final step can be measured.

The major disadvantages of the ICR are a limited dynamic range due to the same space-charge effect described for the quadrupole ion trap, a more complex design, and high instrument cost.

Despite the high cost of the FTICR instrument, new "hybrid" FTMS instruments costing significantly more than 1 million US dollars were introduced commercially in 2003 because of their ability to determine the structure of proteins. Protein structure deter- mination is critical to fundamental biology, genomics, proteomics, and the understanding of drug-biomolecule interactions for development of pharmaceuticals.



"Hybrid" FTMS instruments combining either an ion trap or quadrupole(s) on the front end with the FTICR on the back end exhibit both high sensitivity and high resolution.

9.2.4. Detectors

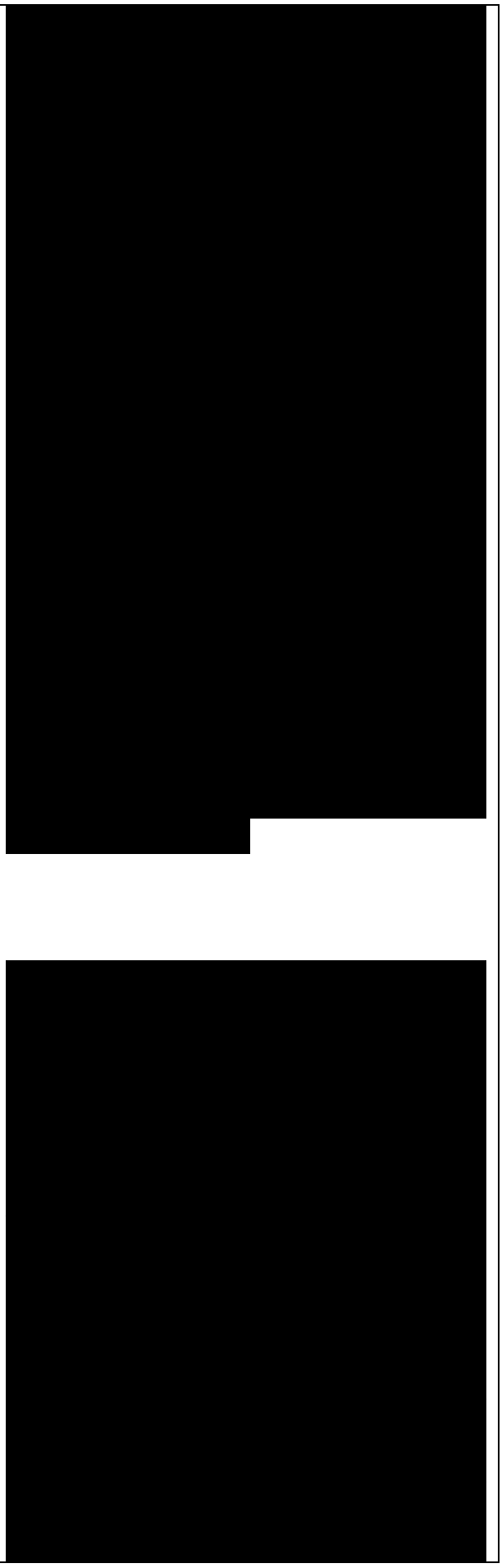
Most mass spectrometers measure one m/z value at a time. A single channel ion detector is used for these instruments, either an electron multiplier or a Faraday cup. TOF, ion trap, and FTICR mass spectrometers have the ability to extract ions with many m/z values sim- ultaneously, so simultaneous detection of these ions is desirable. One approach to multiple ion detection has been to use multiple detectors. Multiple detectors are also used for high-resolution magnetic sector MS instruments designed for very precise isotope ratio determination and for quantitative analysis using isotope dilution. Instruments with multiple detectors are called "multicollectors". New detector developments in array detec- tors hold the promise of simultaneous m/z measurement over a wide mass range.

9.2.4.1. Electron Multiplier (EM)

The most common detector used for ions in mass spectrometers is the electron multiplier (EM). The EM is very similar in concept to the photomultiplier tube for optical detection. It is very sensitive and has fast response. The EM is based on the dynode, which has a surface that emits electrons when struck by fast-moving electrons, positive ions, negative ions, or neutrals. A discrete-dynode EM uses a series of 12-24

dynodes, each biased more positively than the preceding dynode. A collision releases several electrons from the dynode surface. These electrons are then accelerated to a second such surface, which, in turn, generates several electrons for each electron that bombards it. This process is con- tinued until a cascade of electrons (an amplified current) arrives at the collector. The process is shown schematically in Fig. 9.26. Typically, one ion can produce 105 electrons or more; this ratio of electrons measured per ion is referred to as the gain. The gain of the detector can be adjusted, with operating gains of 104-108 used, depending on the application. Figure 9.26(b) shows a commercial discrete-dynode electron multiplier. A continuous-dynode EM, also called a channel electron multiplier (CEM) uses a continuous glass tube, either lead-doped or coated on the inside with a conductive surface of high electrical resistance, such as those shown in Fig. 9.27. A potential difference is applied across the tube ends so that the potential varies in a linear manner along the tube. Each incident ion releases electrons that are accelerated and strike the tube again, resulting in the same cascade effect seen in the discrete-dynode EM. The curved or coiled form is designed to reduce electrical noise by preventing positive ions from returning upstream.

A disadvantage to dynode-based detectors is that the number of secondary electrons released depends on the type of incident primary particle, its angle and energy. The



depen- dence of the number of secondary electrons emitted on incident energy is shown for electron impact in Fig. 9.26(c); the same plot for ion impact would be similar. Therefore, they can exhibit mass discrimination due to differences in ion velocity. Heavy ions from quadrupole mass analyzers and from QIT mass analyzers impact the dynode surface at lower velocities than light ions. EM detectors for these instruments must be designed to overcome the difference in velocities, often by accelerating the ions prior to them striking the first electron-emitting dynode. An excellent source of information on how discrete dynode electron multipliers work is the SGE website at www.sge.com, which describes their ETP electron multipliers. Similarly, the Burle Technologies website at www.burle.com provides technical information on their Channeltron® continuous-dynode electron multiplier.

www.sge.com

9.2.4.2. Faraday Cup

The least-expensive ion detector is the Faraday cup, a metal or carbon cup that serves to capture ions and store the charge. The resulting current of a few microamperes is measured and amplified. The cup shape decreases the loss of electrons from the metal due to ion impact. The Faraday cup is an absolute detector and can be used to calibrate other detec- tors. The current is directly proportional to the number of ions and to the number of charges per ion collected by the detector. Unlike dynode-based detectors, the Faraday cup does not exhibit mass

discrimination. The detector does have a long response time, which limits its utility. The Faraday cup detector is used for making very accurate measurements in isotope-ratio MS, where the ion currents do not change rapidly. The

Figure 9.26 (a) A schematic discrete-dynode electron multiplier, showing the electron gain at each successive dynode after impact of an ion on the first dynode surface. The electron cascading process results in gains of up to 108 being achieved with approximately 21 dynodes. (b) An ETP electron multiplier schematic showing the position of the dynodes in the detector. (c) Dependence of the number of secondary electrons emitted on impact energy. [Images courtesy of SGE, Inc. (Austin, TX) and ETP Electron Multipliers Pty Ltd, a division of SGE (Sydney, Australia). (www.etpsci.com and www.sge.com).]

Faraday cup detector has no gain associated with it, unlike dynode-based detectors. This limits the sensitivity of the measurement.

High-precision isotope ratio mass spectrometers are designed with combinations of multiple Faraday cup detectors and multiple miniature electron multipliers (used as ion counters) for simultaneous isotope measurement. For example, the TRITON and NEPTUNE multicollector mass spectrometers from Thermo Electron Corporation can be configured with up to nine Faraday cups and eight ion counters to detect 17 ion beams simultaneously. Details of these instruments can be found at

www.thermo.com. The use of multicollector instruments improves precision by two to three orders of

www.thermo.com

[redacted]

Figure 9.27 (a) A schematic channel electron multiplier (CEM), consisting of a glass or interior- coated ceramic tube that emits secondary electrons upon ion impact. (b) A schematic curved CEM. The curved shape minimizes ion feedback noise. (c) Photo of the Channeltron® electron multiplier, showing the curved glass tube without the associated electronics. [Courtesy of BURLE Electro- Optics (www.burle.com).]

[redacted]

magnitude over a single collector magnetic sector instrument, and this high precision is needed for isotope ratio measurements.

[redacted]

9.2.4.3. Array Detectors

The microchannel plate is a spatially resolved array detector formed of 105-107 continuous-dynode electron multipliers, each only 10-100 mm in diameter. This detector is used in focal plane mass spectrometers as a replacement for photograph plate detectors and is used in some TOFMS instruments.

[redacted]

The focal plane camera (FPC), still in initial development, consists of an array of 31 Faraday cups, each 145 mm wide. Up to 15 m/z values can be measured simultaneously. This detector shows improved precision compared with single channel detectors and has the ability to measure fast transient signals such as those from laser ablation. The detector design is described in the references by Barnes et al. and Knight

[redacted]

et al. cited in the bibliography.

PROBLEMS

9.1 What is meant by "molecular ion"? What is the importance of identifying it to a chemist?

9.2 How are resolving power and resolution defined for a mass spectrometer?

9.3 What is the difference between hard ionization and soft ionization?

9.4 Describe how an EI source forms ions from analyte molecules. Is this a hard or soft ionization source? What are the advantages and disadvantages of this source?

9.5 Describe how a CI source forms ions from analyte molecules. Is this a hard or soft ionization source? What are the advantages and disadvantages of this source?