CHAPTER 1

History and General Introduction

Robert C. Dunbar

Introduction

Fourier Transform ion cyclotron resonance (FT-ICR) has taken a place as a serious and useful analytical technique after years of being regarded as promising, but not widely adopted. In the last few years, a book (1) and many reviews (2–23) have appeared centering on the analytical capabilities of the instrument, and quite a few instruments are right now being used to solve real-world analytical problems.

In the domain of analytical mass spectrometry (MS), FT-ICR's place is established as combining particular advantages of extraordinary mass resolution and accuracy, a wide array of sample-ionization techniques, and a uniquely wide range of methods for structure characterization of the primary sample ions. Costs are already attractive compared with other high-performance alternatives, and as both magnets and computers (which comprise much of the expense of FT-ICR hardware) become cheaper and more powerful, the performance/cost ratio for the technique will continue to improve.

This introductory chapter will (1) provide an introduction to those who have little previous knowledge of the technique; (2) provide an overview of the technique's outstanding areas of scientific and analytical application; and (3) provide some historical perspective on how we reached the present state of the art.

Origins

The roots of ion cyclotron MS go back to E. O. Lawrence's cyclotron, which served as a mass selector in many experiments where targets were bombarded with ions of various masses. However, the first use in any analytical sense of the mass selective characteristics of the cyclotron motion of ions was the Omegatron of Sommer, Thomas and Hipple

(24). This device used the frequency-selective cyclotron acceleration of ions by a radio frequency (rf) field, the operation we would now call *selective ion ejection*, into an electrometer collector that detected the charge of the ejected ions. It had some popularity as a low-cost ion analyzer for leak detection and other low-performance applications.

Early on the Omegatron was shown to be capable of operation using resonance detection of the ions (25), but this idea was first seriously developed in the solenoid-geometry cyclotron of Wobschall et al. (26) This was a device of impressive sophistication using a marginal-oscillator resonance detector. This instrument was not applied to serious study of ion-molecule reaction chemistry, first, because its design did not achieve efficient ion trapping, and, second, because double-resonance methods were not used. The chemical opportunities open to the new technique were thus missed, leaving as a historical curiosity an instrument that could otherwise have evolved into the modern superconducting solenoid ICR spectrometer.

The modern spectrometer traces its direct ancestry back to the ICR spectrometer invented in the mid-1960s in a collaboration between John D. Baldeschwieler (at Harvard and then at Stanford) and a group led by Peter Llewellyn at Varian Associates (see the Llewellyn patents, 1968–1970, in Table 1.1). The instrument was marketed by Varian until the early 1970s. The ICR technique quickly became widely recognized as a preferred tool in the newly blossoming field of gas-phase ion chemistry, and approximately 20 machines were installed and actively used in a basic research orientation.

During most of the 1970s no commercial instrument was available, but the existing stock of Varian instruments, along with a handful of homebuilt machines, supported a flood of scientific progress in areas of ion-molecule chemistry, ion thermochemistry, ion spectroscopy, and instrument development. Lehman and Bursey's book (27) gives a particularly valuable picture of the state of the art in the mid-1970s and of the instrumental and scientific advances during this period. Among the many people associated with the first few years of this development a number were associated with the Stanford group (for instance, Anders, Beauchamp, Buttrill, Blair, Brauman, Comisarow, Djerassi, Eyler, Huntress, Marshall, McIver, Smyth, Riveros, and this author, among others) and a few independent groups (among them, Bowers and Elleman at Jet Propulsion Lab, Bursey at North Carolina, Futrell at Utah, Henis at Monsanto, and Jennings in England). The remarkable impact of ICR on the recent evolution of chemistry is strikingly suggested by the fact that 4 of the last 20 or so ACS Awards in Pure Chemistry have gone to chemists based primarily on their work in ICR (J. D. Baldeschwieler, J. I. Brauman, J. L. Beauchamp, and B. S. Freiser.)

A new period of evolution of the technique was initiated by Marshall and Comisarow's application beginning in 1974 (28–30) of FT methods to the handling of ICR data. The advantages of speed, high resolution,

Table 1.1 Events in FT-ICR Development

Year	Event	Reference No.
1950	First practical ion cyclotron spectrometer (Omegatron)	24, 25
1963	Wobschall resonance-detection instrument	26
1965	Varian-Stanford ICR instrument (Llewellyn patents)	
1966	ICR double resonance	50
1967	First serious ion-molecule reaction studies	69
1969	ICR photochemical studies	57, 58
1970	Trapped-ion pulsed ICR	70
1971	Ion-molecule equilibrium	55
1974	FT	28, 29
1979	Resolution above 500,000	71
1980	High-field superconducting magnet	72
1980	Combination with analytical GC	73
1981	Nicolet commercial FT-ICR instrument with superconducting magnet	
1982	Laser desorption ionization	74
1982	MS/MS by collision-induced dissociation	51
1983	External source (McIver 1984 patent)	75
1984	Nicolet two-region cell	
1984	SIMS	76
1985	SWIFT excitation	49
1986	Plasma desorption ionization	77
1987	Resolution above 3×10^8	78
1987	FAB	79
1989	Electrospray ionization	80

Abbreviations: FT-ICR, Fourier transform ion cyclotron resonance; GC, gas chromatography; MS, mass spectrometry; SIMS, secondary ion MS; SWIFT, stored waveform inverse FT; FAB, fast atom bombardment ionization.

and effective computer data processing that accompanied the advent of FT techniques made the instrument much more attractive as an analytical MS tool. After an incubation and development period, Nicolet Instruments commercialized the FT-ICR instrument in 1981, and the 1980s saw a rapid rise in the sale of new instruments with a primarily analytical focus. A Bruker Spectrospin instrument (which has chiefly been installed in Europe) and instrumentation offered by the smaller IonSpec enterprise followed later. The present scene sees the Nicolet instrument (now taken over by Extrel) in competition with Bruker Spectrospin and IonSpec in a rapidly evolving commercial analytical marketplace, along with a number of individual instruments such as the instrument described in Chapter 9.

In the era of the Varian drift-cell instruments, the technique was always called *ion cyclotron resonance* (ICR), and with the advent of FT techniques, this was naturally expanded to *Fourier Transform ICR* (FT-ICR). The term *FTMS* (Fourier Transform Mass Spectrometry) (or FT-MS) began appearing in the literature circa 1979. Nicolet adopted this

Table 1.2 U.S. Patents Related to FT-ICR

Year	Authors (Assignee)	Title
1968	Llewellyn (Varian)	Ion Cyclotron Resonance Mass Spectrometer Having Means for Detecting the Energy Absorbed by Resonant Ions (Varian ICR instrument with drift cell)
1969	Baldeschwieler, Beauchamp, and Llewellyn (Varian)	Resonance Mass Spectrometer (double resonance for observing ion-molecule reactions)
1969	Llewellyn (Varian)	Ion Cyclotron Double Resonance Spectrometer Employing a Series Connection of the Irradiating and Observing RF Sources to the Cell (series connection of marginal oscillator, double resonance oscillator)
1969	Littlejohn and Llewellyn (Varian)	Ion Cyclotron Resonance Spectrometer Having the Analyzer Means Pivotally Mounted on the Magnet Yoke (Varian ICR-9 spectrometer)
1969	Gielow and Llewellyn (Varian)	Ion Cyclotron Resonance Spectrometer Employing Means for Recording Ionization Potentials (electron energy sweep)
1970	Baldeschwieler (Varian)	Double Resonance Ion Cyclotron Mass Spectrometer for Studying Ion-Molecule Reactions
1970	Llewellyn (Varian)	Ion Cyclotron Double Resonance Spectrometer Employing Resonance in the Ion Source and Analyzer (modulated source-region double resonance in drift cell)
1970	Llewellyn (Varian)	Ion Cyclotron Resonance Mass Spectrometer with Means for Irradiating the Sample with Optical Radiation (photoionization, photochemistry)
1970	Gielow and Llewellyn (Varian)	Ion Cyclotron Resonance Spectrometer Employing an Optically Transparent Ion Collecting Electrode (ion irradiation, collection of fluorescent light from ions)
1970	Beauchamp	Apparatus for Measuring Ion Relations by Double Resonance Mass Spectrometry (double resonance of reaction pathways)
1972	Baldeschwieler (Varian)	Ion Cyclotron Resonance Stimulated Glow-Discharge Method and Apparatus for Spectral Analysis (scheme to observe flourescence)

Table 1.2 (*Continu*

Year	Aut (Assi
1973	McIver
1975	Beaucha
1976	Fletcher Huntress (NASA)
1976	Comisar Marshall (Nicolet)
1978	McIver a Ledford (Univers Californi
1982	Ledford (Universi Nebraska
1984	Allemani Kellerhal (Spectros
1985	McIver (Finnigar
1985	Allemann Kellerhals (Spectros
1986	Littlejohn Ghaderi (Nicolet)
1986	Kellerhals Allemann (Spectros
1986	Ghaderi, Shohet, a Littlejohn (Nicolet)
1987	Wells (Var

Table 1.2 (*Continued*)

Year	Authors (Assignee)	Title
1973	McIver	Apparatus and Method for Pulsed Ion Cyclotron Resonance Spectroscopy
1975	Beauchamp	Ion Cyclotron Resonance Spectrometer (drift/trapping cell)
1976	Fletcher and Huntress (NASA)	Ion and Electron Detector for Use in an ICR Spectrometer (Q-meter type detection electronics)
1976	Comisarow and Marshall (Nicolet)	Fourier Transform Ion Cyclotron Resonance Spectrometry Method and Apparatus (FT-ICR)
1978	McIver and Ledford (University of California)	Method and Apparatus for Mass Spectrometric Analysis at Ultra-low Pressures (ion-trapping ICR cell)
1982	Ledford (University of Nebraska)	Mass Spectrometer (enclosed cell)
1984	Allemann and Kellerhals (Spectrospin)	Method for Ion Cyclotron Resonance Spectrometry (ion accumulation by multiple ionization pulses, ejection of undesired ions)
1985	McIver (Finnigan)	Apparatus and Method for Injection of Ions into an Ion Cyclotron Resonance Cell (external source with quadrupole guide)
1985	Allemann and Kellerhals (Spectrospin)	Method of Calibrating Ion Cyclotron Resonance Spectrometer (correcting trapping-field shift using upper magnetron sideband)
1986	Littlejohn and Ghaderi (Nicolet)	Mass Spectrometer and Method (Nicolet dual cell)
1986	Kellerhals and Allemann (Spectrospin)	Procedure for Recording Ion Cyclotron Resonance Spectra and Apparatus for Carrying Out the Procedure (ICR SIMS inside a cylindrical ICR cell)
1986	Ghaderi, Shohet, and Littlejohn (Nicolet)	Mass Spectrometer Having Magnetic Trapping (magnetic bottle trapping)
1987	Wells (Varian)	Method and Apparatus for Sample Confirmation in Gas Chromatography

(*continued*)

Table 1.2 (*Continued*)

Year	Authors (Assignee)	Title
		(comparing time-domain transients of the sample and known compounds)
1987	Meek and Stockton (American Cyanamid)	FT-ICR Mass Spectrometer with Spatially Separated Sources and Detectors (American Cyanamid 3-region instrument with automatic gain control)
1987	Ghaderi and Littlejohn (Nicolet)	Mass Spectrometer (off-axis electron beam with filament in magnet fringing field)
1988	Ghaderi, Vosburger, Littlejohn, and Shohet (Nicolet)	Mass Spectrometer with Remote Ion Source (separate source, magnetic bottle trapping)
1988	Marshall, Ricca, and Wang (Ohio State)	Tailored Excitation for Trapped-Ion Mass Spectrometry (SWIFT)
1989	Allemann (Spectrospin)	Method for Eliminating Undesirable Charged Particles from the Measuring Cell of an ICR Spectrometer (ion ejection by exciting the trapping oscillation)
1989	Kellerhals (Spectrospin)	Ion Cyclotron Resonance Spectrometer (dual-cell instrument with source region in magnet fringe field region)
1989	Spencer (Nicolet)	Mass Spectrometer Ion Excitation System (shaped onset of the excitation chirp to give constant excitation amplitude)
1989	Bodenhausen, Pfandler, Rapin, Gaumann, and Houriet (Spectrospin)	Method for Recording ICR Mass Spectrum and ICR Mass Spectrometer Designed for Carrying Out the Said Method (2-dimensional FT-ICR)
1990	Marshall and Wang	Mass Spectrometer with Reduced Static Electric Field (cell with screened trapping plates)
1990	Hunter and McIver (IonSpec)	Method and Apparatus for Acceleration and Detection of Ions in an Ion Cyclotron Resonance Cell (impulse excitation)
1990	Caravatti (Spectrospin)	Method and Apparatus for the Accumulation of Ions in a Trap of an Ion Cyclotron Resonance Spectrometer, by

Table 1.2 (*Continued*)

Year	Authors (Assignee)	Title
		Transferring the Kinetic Energy of the Motion Parallel to the Magnetic Field into Directions Perpendicular to the Magnetic Field
1990	Goodman and Hanna (Extrel)	Method and Apparatus for Producing an Arbitrary Excitation Spectrum for Fourier Transform Mass Spectrometry (a variation of the SWIFT idea)
1990	Cody (Extrel)	Method for External Calibration of Ion Cyclotron Resonance Mass Spectrometers (mass calibration with a reference compound)
1990	Guan and Jones (University of the Pacific)	PC-Based FT/ICR System

Abbreviations: FT/ICR, Fourier transform ion cyclotron resonance; SIMS, secondary ion mass spectrometry; SWIFT, stored waveform inverse FT.

term in promoting their instrument, and this appealing name is now often used.

Table 1.1, which gives a chronology of a few notable advances in the field, and Table 1.2, which tabulates U.S. patents connected with FT-ICR development, may be of interest as we trace the evolution of the field in more detail.

The Basics

An FT-ICR instrument is a mass spectrometer, which is to say an instrument that observes the abundance of ionized molecules, resolved according to their masses. Practically all other mass spectrometers are based on spatially separating ions through a mass-dependent feature of their motion in magnetic or electric fields and collecting ions of different masses separately onto a detector. The FT-ICR approach is distinctive in that the ions are observed without separation or collection, using the absorption and emission of rf energy at their characteristic (mass-dependent) cyclotron frequencies as they undergo cyclotron motion in a strong magnetic field. This resonant absorption and emission of energy at a characteristic frequency as the detection principle, while unique in the mass spectrometer world, sets this technique into the company of other resonance rf spectroscopies like nuclear magnetic resonance (NMR), electron spin resonance, microwave spectroscopy, and nuclear quadrupole resonance.

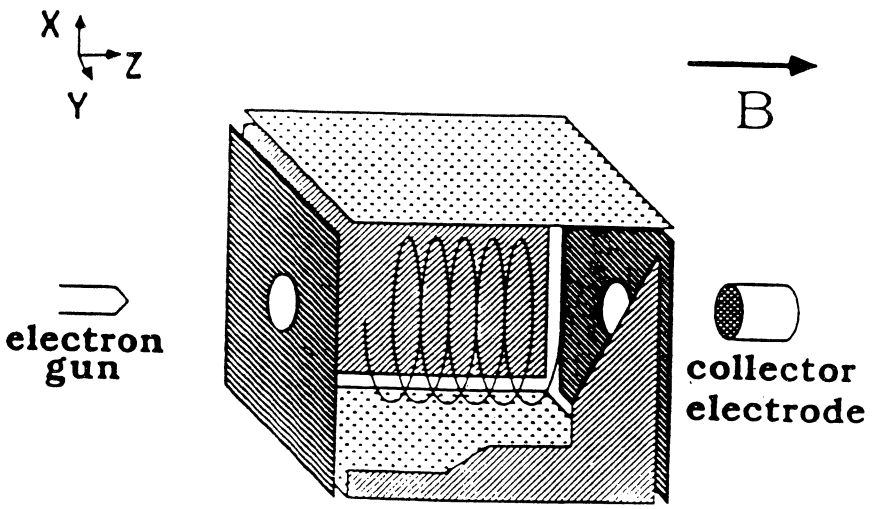

Figure 1.1 Cubical ICR cell set up with an electron beam along the magnetic field direction. The trapping plates are at the left and right; the ion excitation voltage is applied across the front and back plates; and the ion signal is detected across the top and bottom plates. An ion is indicated in the cell undergoing large-amplitude cyclotron motion, and also oscillating along the z axis in the electrostatic potential well. (Reproduced by permission of A. G. Marshall and the publisher from Ref. 18.)

In the FT-ICR instrument, as with other mass spectrometers, the initial phase of the experiment is the production of gas-phase ions from the sample. The ions are either produced in, or introduced into, the ICR analyzer cell (Figure 1.1). In the strong magnetic field ***B***, ion motion in the *x*-*y* plane (the plane perpendicular to the magnetic field) is constrained to circular cyclotron orbits. As it traverses its circular cyclotron orbit, an ion of charge *e*, mass *m*, and velocity ***v*** experiences a force $e\boldsymbol{vB}$ directed toward the center of the cyclotron orbit (i.e., perpendicular to both its velocity and to the magnetic field). This force is counterbalanced by the outward-directed centrifugal force $m\boldsymbol{v}^2/r$, so that a stable orbit exists when $e\boldsymbol{Bv} = m\boldsymbol{v}^2/r$. Since $\boldsymbol{v}/r = \omega_c = 2\,\pi\, f_c$, we can write the cyclotron equation

$$f_c\ (\text{Hz}) = e\boldsymbol{B}/2\,\pi\, m \qquad (1.1)$$

which shows that a group of ions of a given mass-to-charge ratio m/e always cyclotron at the same frequency f_c (for a given value of ***B***). The cyclotron orbit has a small radius for slow-moving ions and an increasingly large radius for larger ion velocities.

After the ions are produced and trapped in the ICR cell, the ions that are to be detected are accelerated into large cyclotron orbits by the application of an external rf pulse (the *excite pulse*). This rf pulse appears to the ion as an alternating electric field between the two trans-

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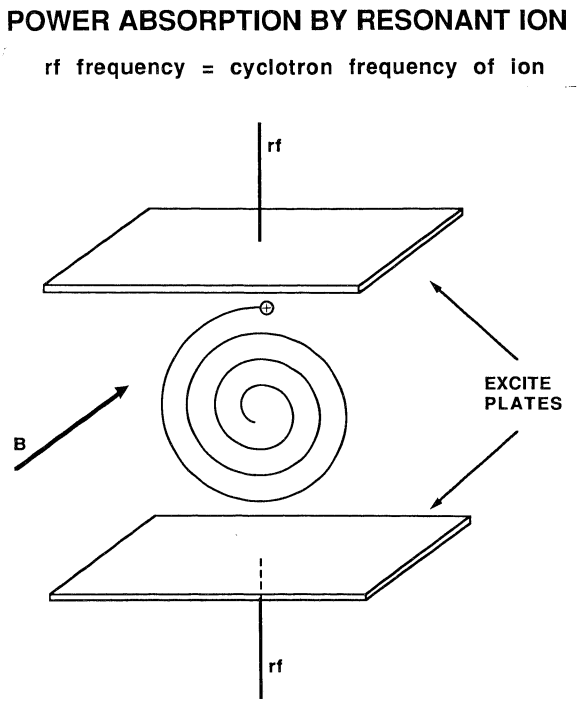


Figure 1.2 An ion undergoing resonant cyclotron excitation by an excite pulse applied to a pair of opposite plates. The outward spiral in the x–y plane continues as long as resonant excitation is applied after which the ion continues to move in a stable cyclotron parking orbit of constant radius. (Reproduced from Nicolet FTMS Technical Report No. 84-1.)

mitter plates, and the ion is accelerated steadily as long as the rf frequency is equal to the ion's cyclotron frequency, as illustrated in Figure 1.2.

Each cyclotroning ionic species emits rf signal intensity to the receiver plates at its characteristic cyclotron frequency. The receiver plates function as an antenna that picks up this signal (the *transient*) emitted by the ions for amplification and processing.

The transient is a sum of sine-wave signals at each of the cyclotron frequencies of the ions that were excited in the cell. In a FT instrument, this complex waveform is decomposed into its individual sine-wave components by the computer, using a fast Fourier transform (FFT) operation (31). The result of this process is a display of the ions in the cell with a peak showing the abundance and cyclotron frequency of each different ion species. Using equation 1.1, this plot of abundance versus frequency is immediately converted into a mass spectrum showing the abundance of ions at each different mass number.

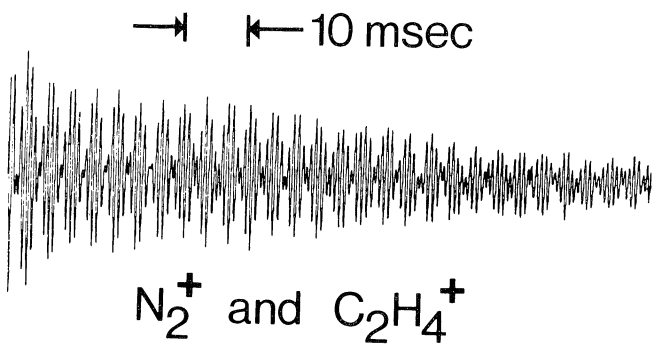


Figure 1.3 The signal transient observed after cyclotron excitation of a mixture of N_2^+ and $C_2H_4^+$. The transient decays (due to collisions and field inhomogeneities) with about a 60-ms time constant, which limits the maximum resolution to less than 58,000. (Reproduced by permission from Ref. 30.)

A simple example of a transient is shown in Figure 1.3; in this case only ions near mass 28 were excited in the cell, and the transient contains frequencies corresponding to the two species of masses 28.006 (N_2^+) and 28.031 ($C_2H_4^+$). The interference pattern of the two frequencies beating against each other is obvious. Fourier transforming the collected transient pulls out the intensities of the individual frequency components, giving the mass spectrum as shown in Figure 1.4. (This early example from 1975 is particularly interesting, because it already showed a mass resolution, $m/\Delta m$ of 26,000 at mass 28, which was extraordinary by previous ICR standards.)

A typical cubical cell is shown schematically in Figure 1.1. In this cell the positive trapping voltage V_t is applied equally to the two trapping plates and may be thought of as preventing loss of ions along the z direction by providing a force always tending to push the ions back to the cell center. (Of course, if we want to trap negative ions instead of positive ions, V_t would instead be a negative voltage.) When the time comes to excite the cyclotron motion of the ions, the rf excite pulse is applied across the opposing pair of transmitter plates. Then the transient is acquired by amplifying the signal voltage induced between the pair of receiver plates by the ions undergoing their cyclotron motion.

The relation between the cyclotron motion of the ions and the signal observed at the detector was clarified in a landmark paper of Comisarow (32). He developed the *rotating monopole* approach to signal modeling, in which the cyclotroning ion is regarded as moving back and forth between the receiver plates, creating a current between the plates by inducing image charges on the plates. (This model is described in more detail in Chapter 2.) Comisarow gave expressions for ICR signal voltages and signal-to-noise values that have been widely used. For calculating signal strengths in real cells of arbitrary shape, the key concept is the *induced-charge*, or *reciprocity* theorem given by

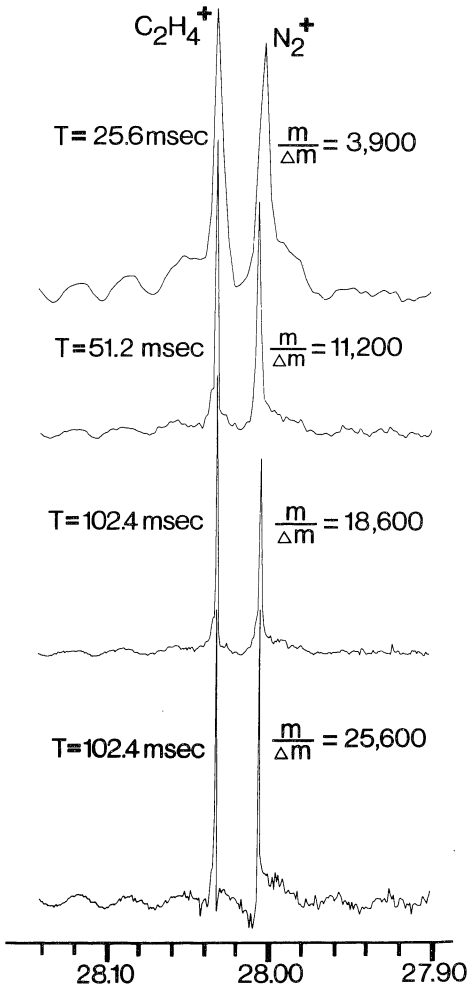


Figure 1.4 High-resolution spectra derived from the transient shown in Figure 1.3. The first three traces are magnitude-mode transforms, whereas the last is absorption mode. T is the length of transient that is transformed. Truncation of the transient clearly decreases the mass resolution, as expected (see Ref. 53).

Dunbar (33), which says that the signal induced on a cell plate by an ion is proportional to the electric potential established at the ion position by putting a standard voltage on the cell plate.

Historical Evolution

We can follow in more detail the evolution of several different aspects of the technique, introducing along the way some additional basic concepts of FT-ICR spectrometry.

Magnets and Instrument Geometry

In the magnetic field ***B,*** ions of mass m move in circular cyclotron orbits in the x–y plane (the plane perpendicular to the magnetic field) at the cyclotron frequency. Any type of magnet giving a field of at least a few tenths of a tesla (T) will give useful FT-ICR performance. The geometry of the magnet is the principal factor governing the basic geometry of the instrument and the ICR cell.

Most instruments before the Nicolet generation were built around a 1.4 (or 2.3)-T iron-core electromagnet. The use of superconducting magnets has no direct connection with FT techniques in ICR spectrometry, but superconducting magnets came into use about the same time as FT in the late 1970s. Nearly all Nicolet and Bruker-Spectrospin instruments have been installed with superconducting solenoids.

The iron-yoke electromagnet geometry has limited space along the z axis, but ample space and access in the x–y plane. This limits the length of the cell between the trapping plates, but lends itself to moving ions around among different cell regions in the x-y plane. Early *drift-cell* designs (34) had separate ion production and ion-detection regions, with the ions being transported from region to region along the x direction by the drift motion. The principle of drift motion is that when an electric field E_d is applied to the ion along the x direction, in conjunction with the magnetic field in the z direction, the ion drifts in the y direction with velocity $v_d = E_d/\boldsymbol{B}$. With a suitable configuration of charged electrodes to establish the requisite electric fields, ions may be transported under complete control from point to point in the x–y plane.

Elaborate multiple-region cell designs, reaching as many as five regions (35), evolved in the era of iron magnet instrument design. In current practice the idea of multiple regions in the x–y plane, communicating through the drift motion, has been continued in some iron-magnet instruments having two or three differentially pumped cell regions connected through slits (36,37).

The solenoidal geometry of superconducting magnets suggests very different design approaches, because length along the z axis is essentially unlimited. Elongation of the cell in the z direction gives a natural benefit by increasing the ion-containing capacity of the cell. Because ions move freely along the lines of magnetic field, ion transport along the z axis is easy. Taking advantage of this, Nicolet adopted a differentially pumped two-region cell design in 1984, with ion transfer from a high-pressure source region to the low-pressure analyzer region along the z axis through a pinhole (38,39). Figure 1.5 shows a laser-desorption spectrum of a polymer from this instrument, with unit mass resolution easily achieved at m/z 3500.

Much current activity involves designing external-source instruments in which the ion source region is entirely outside the magnet (40-42). With the ion production region placed outside a superconducting magnet along the z axis, ions can be generated externally without

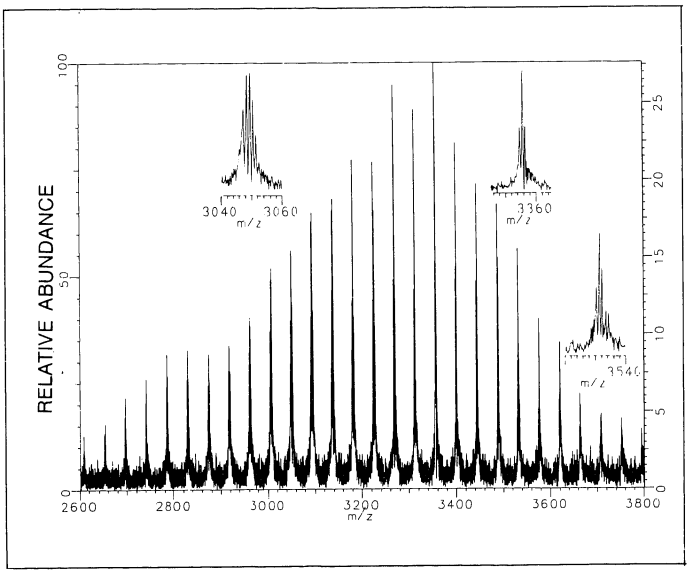


Figure 1.5 Laser-desorption ionization spectrum of poly(ethylene glycol). The overall spectrum shows the molecular weight distribution clearly, whereas the insets show that unit mass resolution was easily achieved above mass 3500. (Spectrum courtesy of Extrel.)

the complications of an ion source located inside the magnetic field and then transported into the high-field region of the ICR analyzer cell. This separation of ion production and ICR detection offers many advantages and seems likely to become the norm in high-performance systems. Figure 1.6 shows a high-resolution spectrum of a nonvolatile biomolecule obtained by fast-atom bombardment ionization in the Bruker-Spectrospin external source.

Transporting ions from an external source into a high-magnetic-field analyzer cell continues to be a challenging task, because the increasing field strength entering the magnet creates a very strong magnetic mirror. The best way to circumvent this is still open to argument. With precise alignment and good ion optics, ions may be introduced efficiently along the magnet center line (42). Alternatively, long quadrupole rods may function as an ion guide into the magnet; the quadrupole guide approach probably gives better collection efficiency with easier alignment and has the potentially useful possibility of mass filtering of the ions transmitted into the analyzer cell by adjusting the direct current (dc) and rf fields applied to the quadrupole rods. Figure 1.7 shows a schematic diagram of the IonSpec version of the quadrupole-guide scheme.

The obvious advantage of superconducting magnets is the high field strength. The trade-off between large magnet volume and high field strength has led to the use in most instruments of lower fields than one might expect, with a field of 3 T being standard on many Nicolet machines. However, some early instruments used fields higher than this,

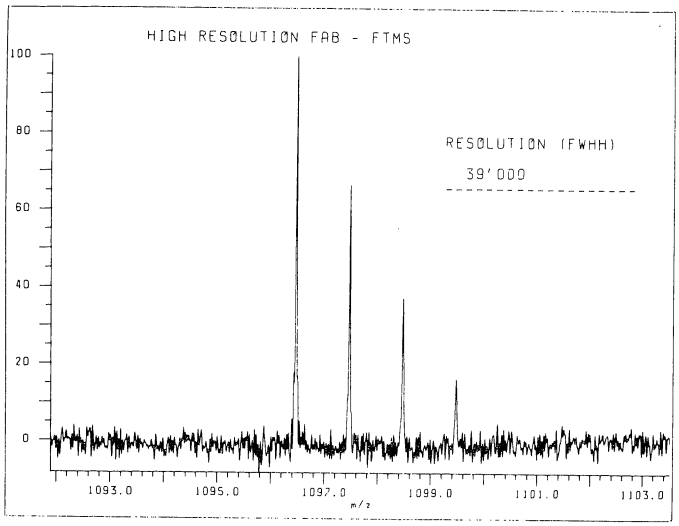


Figure 1.6 FAB ionization spectrum with an external source of an octapeptide (Somatostatin Analog) showing the determination of the molecular ion at mass 1096.4747 (actual mass 1096.4743). The molecule was ionized from a glycerol matrix (1:1) and introduced into the cell at 7 T (400 transients accumulated). (Spectrum courtesy of Bruker-Spectrospin.)

and recent interest in high masses has stimulated manufacturers to offer magnets as high as 8 T.

The advantage of high magnetic field is not as great as in, for instance, NMR, where a factor of 2 increase in field makes a dramatic difference in both sensitivity and chemical information content of the spectra. In FT-ICR, the detection sensitivity increases more or less linearly with field. The mass resolution and the information content of the spectra are not expected to increase with field at low pressure (field-inhomogeneity limited resolution), but under conditions where the mass resolution is collision limited, resolution will increase linearly with field (43).

There is an intrinsic upper limit to the mass of ions that are stably trapped (44) (for given trapping potential), which can become important for masses in the >1000-Da regime. This upper limit goes up linearly with increasing magnetic field strength. For this reason, and also because sensitivity goes down with increasing mass, high-field magnets become essential in high-mass work.

Cell Design

The essential requirements for an ICR cell are two electrodes along the z axis that are positively charged to trap the ions in the z direction and some array of electrodes in the x–y plane to provide the cyclotron excitation and to pick up the ICR signals emitted by the ions. Experi-

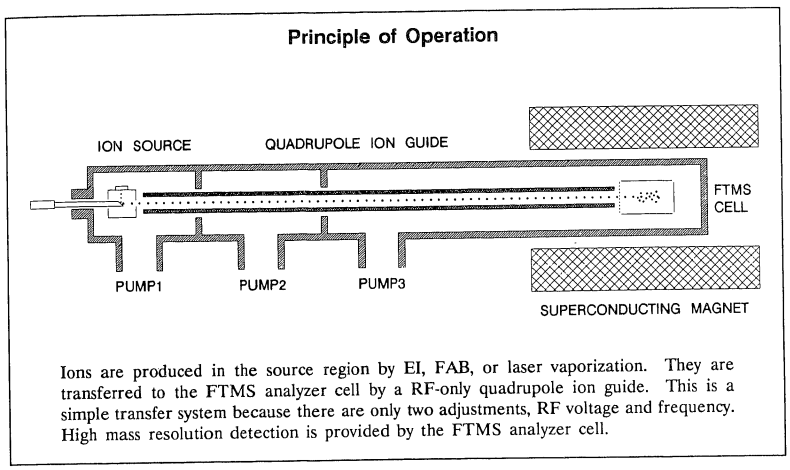


Figure 1.7 Schematic of an external-source design with an rf-only quadrupole ion guide to conduct ions into the magnet. (Courtesy of Ionspec.)

ence with innumerable configurations over the years has shown that almost any geometry meeting these requirements will work reasonably well. Not counting the early drift-cell arrangements mentioned above, the first FT-ICR cells were cubical, as shown in Figure 1.1, and the basic cube remains a popular and effective shape. A formidable variety of cell configurations other than cubical has been described, aimed at optimizing various aspects of instrument performance.

In the early drift-cell configuration, ions were generated and detected continuously. In the early 1970s, it was realized that much better control over the cell chemistry could be achieved using a closed cell in which the ions are trapped for long periods and using pulsed operation with discrete separated ion-production and ion-detection periods (45). Pulsed operation is now universal, with a repeating sequence of ion production, ion trapping, cyclotron excitation, and signal acquisition. During the ion-trapping period there can occur ion-molecule reactions, double resonance ejections, collision-induced dissociation, photodissociation, and other chemical processes. Figure 1.8 illustrates a typical pulse sequence for a laser photodissociation study.

Cells have tended to become larger, because larger cells can trap more ions without space-charge problems, and a larger number of ions gives a larger signal, more sensitivity, and more dynamic range. The limit on the number of ions that can be contained in a trap of given size is governed, first, by the electrostatic capacity of the trap (so that for too many ions, the Coulomb repulsion between ions pushes ions into the trapping plates) and, second, by the observed fact that if the density of ions becomes too large, plasma oscillations and ion–ion interactions (described by the vague term *space-charge effects*) degrade instrument performance. Cubical cells range in size from 2.5 to over 7 cm, and z-axis elongated cells can exceed 10 cm in length.

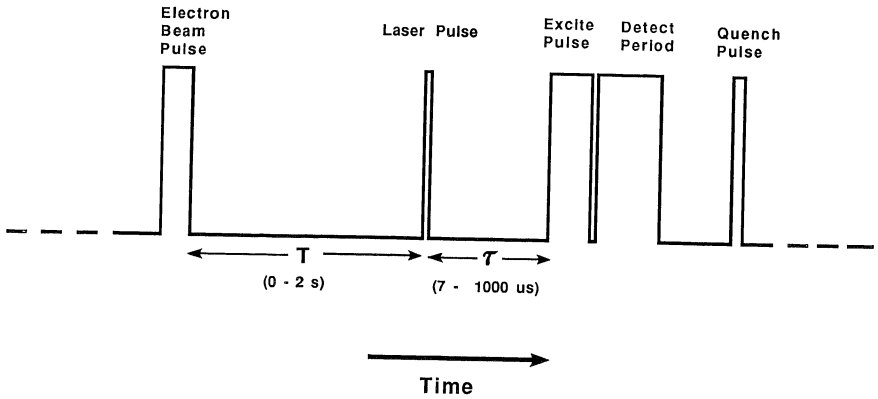


Figure 1.8 Event timing sequence for a time-resolved laser photodissociation experiment, showing ion production by electron impact, ion thermalization during the variable time T, laser pulse, variable delay τ for dissociation to occur, ICR excite pulse, signal transient acquisition, and cell purging by the quench pulse. (Reproduced by permission from Ref. 81.)

Electronics and Pulse Sequences

All ICR experiments involve the excitation of the ion cyclotron motion and observation of the signal induced by the ions on the receiver plates. The first Varian instruments used a marginal oscillator detector (46). This simple, but effective device uses a single oscillator circuit and a single cell plate in an ingenious arrangement that excites the ion cyclotron motion and detects and amplifies the ion signal all in one simultaneous operation. This was, however, largely superseded in the late 1970s by more versatile bridge arrangements in which the ion excitation oscillator is separate from the preamplifier and detector, which observe the ion signal (47). Bridge detectors originally used some type of phase-sensitive detection to process the signal transient. The digital processing used in FT operation is a natural outgrowth and improvement on such analog signal-processing methods.

The shape of the excite-pulse waveform is still the subject of considerable experimentation. In bridge detection instruments before FT, when only a single ion was observed at a time, an rf burst at a single frequency, or a sweep across different ion frequencies, was sufficient. However, the FT method requires nearly simultaneous excitation of many different ion masses.

The first FT scheme, still widely practiced, was the rf "chirp," a waveform that rapidly sweeps over the frequency range of interest (29). This has drawbacks of a somewhat uneven excitation spectrum, complex phase relationships between ions of different masses, and some poorly controlled peak-ratio problems due to space-charge interactions.

There has been recent interest in impulse excitation, which excites all the ions with a single voltage spike, whose Fourier frequency spec-

trum is practically flat and excites all ions simultaneously (48). The most theoretically satisfactory, but most complicated approach to ion excitation is the stored waveform inverse Fourier transform (SWIFT) method, in which a waveform having the desired Fourier excitation components and the desired phase relationships is synthesized by FT techniques. Marshall's group described this approach in 1985 (49), although the considerable complexity of the necessary computer modifications has led to rather slow adoption.

The earliest ICR work recognized the possibilities of ICR *double resonance,* in which rf excitation distinct from the excite pulse is applied to either accelerate an ion species of chosen mass or to eject it entirely from the cell (50). Because cyclotron acceleration only occurs for those ions whose cyclotron frequencies are resonant with the double-resonance frequency, the acceleration or ejection is completely mass specific. This is the feature of ICR spectroscopy that has made it so uniquely well suited to the study of ion-molecule reaction chemistry: It allows the unambiguous identification of each reaction pathway in a complex mixture of reacting ions. In analytical practice, double-resonance sweeps are useful for (1) dynamic range enhancement, by removing abundant, uninteresting ions from the cell before detection, as illustrated in Figure 1.9, and (2) MS/MS through collision-induced dissociation of cyclotron-excited ions (51), as illustrated in Figure 1.10.

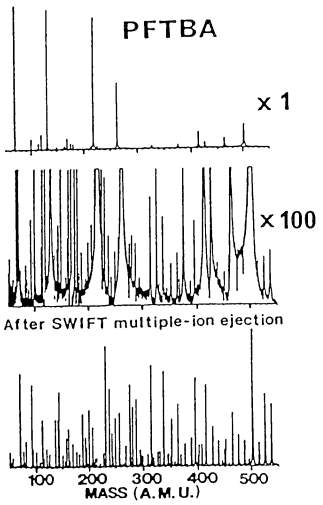


Figure 1.9 Dynamic range enhancement using SWIFT multiple-ion ejection. The top spectrum is the FT-ICR spectrum of perfluorotributylamine, which is shown again in the middle spectrum with the vertical axis expanded. The bottom spectrum corresponds to the middle spectrum, except that before detection, SWIFT ejection was used to remove the 23 largest peaks from the cell. Clearly the spectral information about the small peaks is greatly improved following SWIFT ejection. (Reproduced by permission from Ref. 82.)

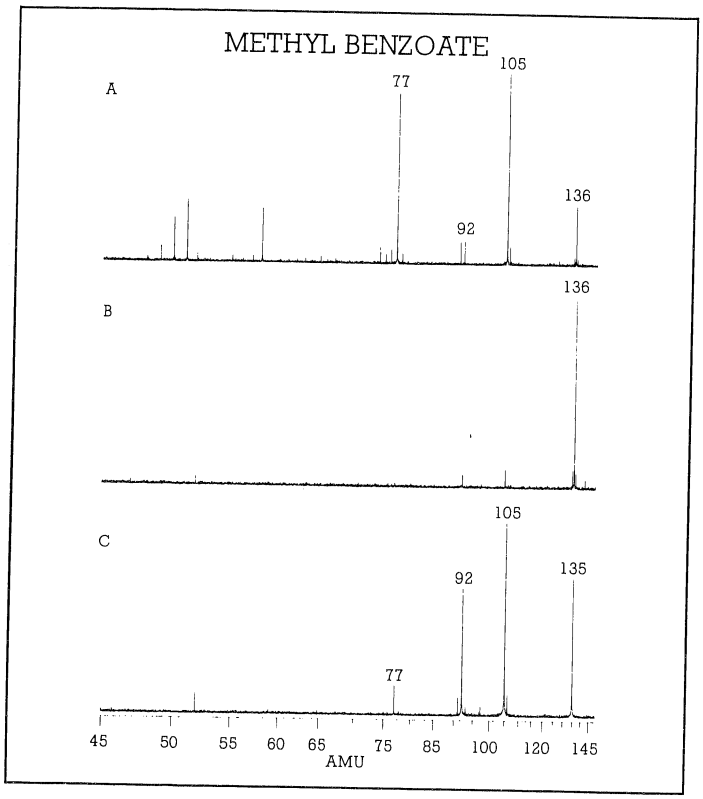


Figure 1.10 Simple MS/MS example. From the electron impact spectrum of methyl benzoate (*a*), the *m*/*z* 136 peak was isolated by an ejection sweep (*b*) and then accelerated and allowed to collide with neutrals to induce fragmentation (*c*). (Spectra courtesy of Bruker.)

Data Acquisition and Processing

Before the advent of FT, spectra were acquired by sweeping the detection across the mass spectrum, with the recorder pen deflecting as each peak was traversed. However, Comisarow and Marshall (28) realized that FT operation decreases the spectrum acquisition time dramatically by eliminating the time spent traversing the empty regions between peaks (Fellgett's advantage), and single-frequency spectrometers have been supplanted almost entirely except in specialized applications where only one or two ion peaks are of interest. A rapid-scan mode of spectral acquisition, in which the spectrum was swept fast enough so that the time between peaks was shorter than the response time of the detector, also achieving some Fellgett's advantage, was used around 1977 (52). As computing cost-effectiveness increased rapidly in this era, however, the large advantages of FT processing in comparison with

all swept data acquisition modes became available at so little extra cost as to make FT an obvious choice.

There is an extensive specialized literature concerning the treatment of FT-ICR data (31). One basic choice is whether to perform the FT in a phased mode with the real (dispersion) and complex (absorption) components of the signals kept separate or to combine them into the magnitude-mode spectrum, which is more convenient, but gives some degradation of resolution and sensitivity. Various choices of apodization (tailoring of the transient envelope) and zero-filling also need to be made in trading off the variables of resolution, side-lobe suppression, and sensitivity.

Mass Resolution

The width of the peaks (which determines the mass resolution) is inversely proportional to the length of the acquired transient (assuming no broadening by collisions or field inhomogeneity), as was clearly seen in Figure 1.4. If we try to increase mass resolution by acquiring signal for a longer time, we run into the limitation of the Nyquist criterion, which says that the data rate must be twice the highest frequency in the spectrum. If the data rate is lower than this (referred to as *undersampling*) the high-frequency signals appear just the same to the computer as if they were at much lower frequency, and the lowest-mass peaks are placed, or *folded back*, at erroneously high masses in the FFT spectrum. This is the phenomenon of *aliasing* (see Chapter 2). If, however, we avoid aliasing by acquiring signal with a high data rate, we can overwhelm the storage and transform-size limitations of the electronics.

This apparent limitation on mass resolution is overcome in the narrowband (mixed or heterodyne) mode, in which the transient is mixed with a reference frequency to heterodyne the ion frequencies near the reference frequency into a low-frequency range. The resulting low frequencies can be acquired for a long time without exceeding the Nyquist limitation. (The transient shown in Figure 1.3 was actually acquired in mixed mode, as is evident from the low frequency of the oscillations displayed.) In effect a limited mass range is accepted in exchange for a lower rate of data acquisition. This trade-off is illustrated and some typical numbers are shown in Table 1.3.

At high pressure, collisions between the ions and neutral molecules interrupt the ion cyclotron orbits, giving an exponential decay to the time-domain waveform. This effectively shortens the length of the transient and broadens the peaks. As suggested in Table 1.3, this pressure broadening can severely reduce the resolution for narrowband observation and leads to the necessity for very low pressures (of the order of 10^{-8} torr) when the very highest mass resolution is sought.

Table 1.3 Illustrative Detection Parameters

Magnetic Field	4 T	
Transient (transform) size	64 K	
Low-pressure, magnitude-mode line shape		
	Broadband	Narrowband
Mass range (Da)	100–2000	100–102.5
Frequency range (kHz)	614–30.7	15.3–0
Nyquist requirement (kHz)	1228	30.6
Acquisition time	55 ms	2.0 s
Resolution at m/z 100	26 000	10^6
Resolution at m/z 100 and 10^{-6} torr	20 000	60 000

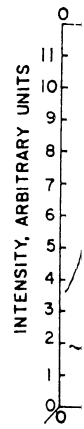
Ion Chemistry

The advent of the modern ICR spectrometer had as its first result a dramatic surge in interest in the chemistry of gas-phase ions, which encompassed both the properties of the ions themselves, and the mechanisms and rates of their reactions with neutral molecules. We can touch on a few leading areas of this development, which still continues on a large scale in many research groups.

The early drift-cell instruments were found well suited with their effective double-resonance capabilities to the mapping out of ion-molecule reaction pathways (29). Some of the main reactivity patterns of important functionalized organics like alcohols, ethers, halides and amines, and inorganics like boranes and metal carbonyls were explored in early work. The proton affinities and other thermochemical properties of a number of molecules were also measured approximately by bracketing reactions, presaging, and leading the way toward the great successes to come later in this area. Some striking and unexpected early results, such as the discovery that toluene is more acidic than water or methanol in the gas phase (54), gave some hints at the revolutionary influence gas-phase results would have on the understanding of solvation effects.

The arrival of the ion-trapping cell and pulsed ICR changed the field greatly. One of the best-known contributions of ICR to chemistry was the new understanding gained by pulsed-ICR equilibrium techniques in the 1970s of acid–base properties of molecules. Figure 1.11 shows an early equilibrium result from one of the first pulsed instruments, as a typical example of such ion-molecule equilibrium studies (55). The observed position of this equilibrium gives a ΔG of -1.8 kcal/mol for the reaction

$$C_3H_6NH_2^+ \text{ (m/z 58)} + C_4H_8NH \rightarrow C_3H_6NH + C_4H_8NH_2^+ \text{ (m/z 72)}$$



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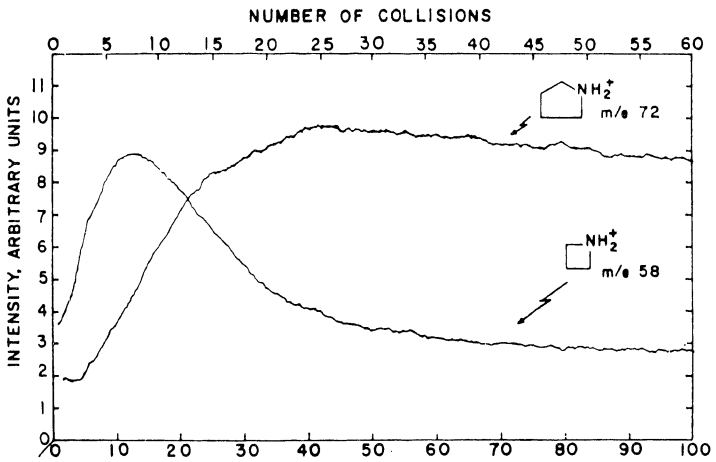

Figure 1.11 A historic ion-equilibrium experiment. In a mixture of the two amines shown, electron impact ionization leads quickly to a mixture of protonated parent ions. After about 50 ms the system has come to equilibrium, following which the ratio of abundances of the two ions remains the same (although they both decay slowly by ion-loss processes). The equilibrium constant is readily calculated from this ratio. (Reproduced by permission from Ref. 55.)

Thermochemical results from such equilibrium studies soon extended to hundreds of molecules (56).

Ion trapping made it possible to irradiate ions with light for almost arbitrarily long times, and the combination of monochromatic light sources with the ion-trapping spectrometer was a success from the start (57,58). The optical irradiation of negative ions (59), giving electron photodetachment, has allowed the accurate determination of the detachment thresholds and electron affinities of a large number of molecules. Irradiation of positive ions (60), in the technique of photodissociation spectroscopy, has made optical spectroscopy of a variety of gas-phase cations practical for the first time. Photodissociation with both visible-UV wavelengths and IR wavelengths (61) is increasingly important for inducing secondary fragmentations in MS/MS applications (62).

Ion chemistry of inorganic systems has been studied steadily since the very beginning, but recent years have seen a great increase in the study of metal-containing systems in particular (63). The most striking developments, pioneered by Freiser's group, have been in chemistry initiated by laser desorption–ionization of metal ions from metal surfaces, followed by ion-molecule reactions of the ions. This chemistry in many ways turns out to be parallel to solution-phase behavior, with such processes as oxidative addition and reductive elimination around transition metals being common.

FT-ICR MS has participated in the recent surge of interest in the

chemistry of gas-phase cluster ions. Building clusters of weakly bound neutral molecules around an ionic core generally requires higher pressures than are available in the ICR cell, and such chemistry has largely been confined to high-pressure mass spectrometers. However, FT-ICR analysis is very well suited to capturing and studying the clusters created by laser desorption–ionization from solid surfaces (64).

Analytical Techniques

The rest of this book serves as a good overview of many of the analytical possibilities and applications of FT-ICR. Although applications in analytical MS were an important motivation for the invention and commercialization of the ICR spectrometer, it did not achieve a position as a credible analytical instrument until FT techniques were offered in an analysis-oriented package in the Nicolet instruments. The mid-1980s saw the first significant number of installations having a sample-analysis focus, as opposed to FT-ICR technique development and basic science studies.

In competition with sector or quadrupole instruments, FT-ICR MS is attractive for its high resolution, which is better than 10^4 under most conditions and better than 10^5 with good, low-pressure conditions. Dynamic range is limited, with the ratio of the strongest to weakest peaks not being much better than 10^4, although special techniques can help circumvent this limitation (as in Figure 1.9, for instance). Ion production has been less versatile than with other techniques, but with the advent of external-source FT-ICR machines there will be available all of the sample-ionization capabilities of the conventional ion source.

From the outset, the strength of the ICR technique has been the ability to observe chemical and photochemical reaction processes of the trapped ions on an arbitrarily long time scale. From the analytical point of view, this gives some interesting possibilities for structural characterization of samples that are inconvenient with other mass spectrometers:

MS^n. By a series of selective ion excitations and ejections, a sequence of collision-induced dissociations is possible, so that the initial parent ion can be characterized by watching its successive breakup into smaller fragments (65). An illustration of this is given in the next chapter.

Ion-molecule reaction probes. The use of characteristic ion-molecule reactions for ion structure analysis (3) was demonstrated early when Jennings' group showed that the methylvinylether ion $CH_2{=}CH{-}O{-}CH_3^+$ cleaves neutral olefins specifically at the double bond to yield ionic products that specify the location of the double bond along the chain (66).

Photodissociation mass spectra. Photon impact gives an often convenient means of depositing energy in an ion, whose subsequent fragmentation can be structurally revealing. A recent illustration of this is Eyler's use of IR multiphoton dissociation as an effective means of distinguishing isomeric oxygen-containing cations (67).

Photodissociation spectroscopy. Dunbar's own interests have long included the use of wavelength-dependent photodissociation as a spectroscopic tool for ion structure determination, as in a recent study of $C_5H_6^+$ (68). The spectra distinguish different isomers easily and can be further analyzed in terms of the different chromophoric groups present in the ions.

It seems clear that the present era of FT-ICR will be dominated by analytical development and applications in contrast to the earlier emphasis on the study of gas-phase ion chemistry. One might guess that progress will be rapid in some areas of exceptional current interest: the analysis of very large molecules, the marriage of sophisticated ion sources to external-source FT-ICR instruments, computer aid in dealing with complex mixtures, and improvement in cell designs and ion detection. It seems assured that the field of FT-ICR will continue to attract and stimulate remarkably capable and diverse researchers who will continue to surprise us with ingenious and unexpected new ideas.

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References

1. M.V. Buchanan, Ed. "Fourier Transform Mass Spectrometry: Evolution, Innovation and Applications", ACS Symposium Series, *359*; American Chemical Society: Washington, D.C., **1987.**
2. H. Hartmann and K.-P. Wanczek, Eds. "Lecture Notes in Chemistry: Ion Cyclotron Resonance Spectrometry II"; Springer Verlag: Berlin, 1982.
3. Dunbar, R.C. In "Physical Methods in Modern Chemical Analysis"; Kuwana, T., Ed.; Academic Press: New York, **1980,** Vol. *2*.
4. Gross, M.L.; Rempel, D.L. "Fourier Transform Mass Spectrometry", *Science* **1984,** *226,* 261–268.
5. Marshall, A.G. "Fourier Transform Ion Cyclotron Resonance Mass Spectrometry", *Acc. Chem. Res.* **1985,** *18,* 316–322.
6. Freiser, B.S. "Investigations of Reactions of Metal Ions and Their Clusters in the Gas Phase by Laser-Ionization Fourier Transform Mass Spectrometry", *Talanta* **1985,** *32,* 697–708.

7. *Anal. Chim. Acta* **1985,** *178,* 1, special issue.
8. Dunbar, R.C. In "Techniques of Chemistry", Vol. VI, "Investigation of Rates and Mechanisms of Reactions"; Bernasconi, C.F., Ed.; Wiley-Interscience: New York, **1986.**
9. Nibbering, N.M.M. " Experiments with Ions in a Fourier Transform Ion Cyclotron Resonance Mass Spectrometer", *Comments At. Mol. Phys.* **1986,** *18,* 223–234.
10. Russell, D.H. "An Evaluation of Fourier Transform Mass Spectrometry for High Mass Applications", *Mass Spectrom. Rev.* **1986,** *5,* 167–189.
11. *Int. J. Mass Spectrom. Ion. Proc.* **1986,** *72,* 1, special issue.
12. Laude, D.A., Jr.; Johlman, C.L.; Brown, R.S.; Weil, D.A.; Wilkins, C.L. "Fourier Transform Mass Spectrometry: Recent Instrumental Developments and Applications", *Mass Spectrom. Rev.* **1986,** *5,* 107–166.
13. Asamoto, B. "Fourier Transform Mass Spectrometry for Industrial Problem Solving", *Spectroscopy* **1988,** *3,* 38–40, 42–46.
14. Cody, R.B. "An Overview of MS/MS and Fourier Transform Mass Spectrometry", *Analysis* **1988,** *16,* 30–36.
15. Freiser B.S., In "Techniques for the Study of Ion Molecule Reactions", *20,* Farrar, J.M.; Saunders, W.H., Jr., Eds.; Wiley: New York, 1988.
16. Hanson, C.D.; Kerley, E.L.; Russell, D.H. In "Treatise on Analytical Chemistry", 2nd ed.; Wiley: New York, 1988; p. 11.
17. Wanczek, K.P. "ICR Spectrometry—A Review of New Developments in Theory, Instrumentation, and Applications. I. 1983–1986", *Int. J. Mass Spectrom. Ion Proc.* **1989,** *95,* 1–38.
18. Marshall, A.G. "Analytical Capabilities and Applications of FT/ICR Mass Spectrometry", *Adv., Mass Spectrom.* **1989,** *11,* 651.
19. Wilkins, C.L.; Chowdhury, A.K.; Nuwaysir, L.M.; Coates, M.L. "Fourier Transform Mass Spectrometry: Current Status.", *Mass Spectrom. Rev.* **1989,** *8,* 67–92.
20. Sharpe, P.; Richardson, D.E. "Applications of Fourier Tranform Ion Cyclotron Resonance Mass Spectrometry in Coordination Chemistry", *Coord. Chem. Rev.* **1989,** *93,* 59–85.
21. Gord, J.R.; Freiser, B.S. "Separation of Experiments in Time and Space Using Dual-Cell Fourier Transform Ion Cyclotron Resonance Mass Spectrometry", *Anal. Chim. Acta,* **1989,** *225,* 11–24.
22. Lubman, D.M., Ed., "Lasers in Mass Spectrometry", Oxford Univ. Press: New York, 1990; Chapter 7, pp 11–15.
23. Nibbering, N.M.M. "Gas-Phase Ion/Molecule Reactions as Studied by Fourier Transform Cyclotron Resonance", *Acc. Chem. Res.* **1990,** *23,* 279.
24. Sommer, H.; Thomas, H.A.; Hipple, J.A. "A Precise Method of Determining the Faraday by Magnetic Resonance", *Phys. Rev.* **1949,** *76,* 1877; "The Measurement of *e/M* by Cyclotron Resonance", *Phys. Rev.* **1951,** *82,* 697–702.
25. Sommer, H.; Thomas, H.A. "Detection of Magnetic Resonance by Ion Resonance Absorption", *Phys. Rev.* **1950,** *78,* 806.
26. Wobscha
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27. Lehman,
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28. Comisar
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29. Comisar
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39. Cody, R.B
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40. McIver, R
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41. Kofel, P.;
ICR Spect
42. Kofel, P.;
Generatio
1985, *65,*

26. Wobschall, D.; Graham, J.R.; Malone, D.P. "Ion Cyclotron Resonance and the Determination of Collision Cross Sections", *Phys. Rev.* **1963,** *131,* 1565; Wobschall, D. "Ion Cyclotron Resonance Spectrometer", *Rev. Sci. Instrum.* **1965,** *36,* 466.
27. Lehman, T.A.; Bursey, M.M. "Ion Cyclotron Resonance Spectrometry"; Wiley-Interscience: New York, **1976.**
28. Comisarow, M.B.; Marshall, A.G. "Fourier Transform Ion Cyclotron Resonance Spectroscopy", *Chem. Phys. Lett.* **1974,** *25,* 282.
29. Comisarow, M.B.; Marshall, A.G. "Frequency-Sweep Fourier Transform Ion Cyclotron Resonance Spectroscopy", *Chem. Phys. Lett.* **1974,** *26,* 489–490.
30. Comisarow, M.B.; Marshall, A.G. "Resolution-Enhanced Fourier Transform Ion Cyclotron Resonance Spectroscopy", *J. Chem. Phys.* **1975,** *62,* 293–295.
31. Marshall, A.G.; Verdun, F.R. "Fourier Transforms in NMR, Optical and Mass Spectrometry", Elsevier: Amsterdam, **1990.**
32. Comisarow, M.B. "Signal Modeling for Ion Cyclotron Resonance", *J. Chem. Phys.* **1978,** *69,* 4097.
33. Dunbar, R.C. "The Effect of Ion Position on ICR Signal Strength", *Int. J. Mass Spectrom. Ion Proc.* **1984,** *56,* 1–9.
34. Beauchamp, J.L.; Anders, L.R.; Baldeschwieler, J.D. "The Study of Ion-Molecule Reactions in Chloroethylene by Ion Cyclotron Resonance Spectroscopy", *J. Am. Chem. Soc.* **1967,** *89,* 4569.
35. Mauclaire, G.; Derai, D.; Fenistein, S.; Marx, R. "Energy Disposal in Thermal-Energy Charge Transfer Reactions Determined by Kinetic Energy Measurements of Product Ions: $Ne^+ + O_2 \rightarrow O^+ + O^+Ne$ and $Ar^+ + O^2 \rightarrow O_2^+ + Ar$", *J. Chem. Phys.* **1979,** *70,* 4017.
36. Mauclaire, G.; Heninger, M.; Fenistein, S.; Wronka, J.; Marx, R. "Radiative Relaxation of Vibrationally Excited Ions", *Int. J. Mass Spectrom. Ion Proc.* **1987** *80,* 99.
37. Wronka, J.; Strobel, F.; Ridge, D.P. "Adaptation of a Drift ICR Cell for Tandem ICR", *Int. J. Mass Spectrom. Ion Proc.* **1986,** *71,* 303.
38. Ghaderi, S.; Littlejohn, D.P. In "Proceedings of the 33rd Annual Conference on Mass Spectrometry and Allied Topics, San Diego, May 26–31, 1985; p. 727.
39. Cody, R.B.; Kinsinger, J.A.; Ghaderi, S.; Amster, I.J.; McLafferty, F.W.; Brown, C.E. "Developments in Analytical Fourier-Transform Mass Spectrometry", *Anal. Chim. Acta* **1985,** *178,* 43–66.
40. McIver, R.T.; Hunter, R.L.; Bowers, W.D. "Coupling a Quadrupole Mass Spectrometer and a Fourier Transform Mass Spectrometer", *Int. J. Mass Spectrom. Ion Proc.* **1985,** *64,* 67.
41. Kofel, P.; Allemann, M.; Kellerhals, H.-P.; Wanczek, K.-P. "Time-of-Flight ICR Spectrometry", *Int. J. Mass Spectrom. Ion Proc.* **1986,** *72, 53–61.*
42. Kofel, P.; Allemann, M.; Kellerhals, H.P.; Wanczek, K.P. "External Generation of Ions in ICR Spectrometry", *Int. J. Mass Spectrom. Ion Proc.* **1985,** *65,* 97–103.

43. Comisarow, M.B.; Marshall, A.G. "Theory of Fourier Transform Ion Cyclotron Resonance Mass Spectroscopy. I. Fundamental Equations and Low-Pressure Line Shape", *J. Chem. Phys.* **1976,** *64,* 110–119.
44. Grosshans, P.B.; Wang, M.; Ricca, T.L.; Ledford, E.B., Jr.; Marshall, A.G. Paper presented at the 36th ASMS Conference on Mass Spectrometry and Allied Topics, June 5–10, 1988, San Francisco, Calif.
45. McIver, R.T.; Dunbar, R.C. "Pulsed Ion Cyclotron Double Resonance for the Study of Ion-Molecule Reactions", *Int. J. Mass Spectrom. Ion Phys.* **1971,** *7,* 471.
46. Robinson, F.N.H. "Nuclear Resonance Absorption Circuit", *J. Sci. Instrum.* **1959,** *36,* 481; Baldeschwieler, J.D. "Ion Cyclotron Resonance Spectroscopy", *Science* **1968,** *159,* 263. See Llewellyn's 1969 patent for details of the Varian circuitry.
47. McIver, R.T., Jr.; Hunter, R.L.; Ledford, E.B. Jr.; Locke, M.J.; Francl, T.J. "A Capacitance Bridge Circuit for Broadband Detection of Ion Cyclotron Resonance Signals", *Int. J. Mass Spectrom. Ion Phys.* **1981,** *39,* 65–84.
48. Baykut, G.; McIver, R.T.; Hunter, R.L. In "Proceedings of the 37th Conference on Mass Spectrometry and Allied Topics, May 21–26, 1989, Miami Beach, Fla."; p. 1220.
49. Marshall, A.G.; Wang, T.C.; Ricca, T.L. "Tailored-excitation for Fourier Transform Ion Cyclotron Resonance Mass Spectrometry", *J. Am. Chem. Soc.* **1985,** *107,* 7893–7897.
50. Anders, L.R.; Beauchamp, J.L.; Dunbar, R.C.; Baldeschwieler, J.D. "Ion Cyclotron Double Resonance", *J. Chem. Phys.* **1966,** *45,* 1062.
51. Cody, R.B.; Freiser, B.S. "Collision-induced Dissociation in a Fourier-Transform Mass Spectrometer", *Int. J. Mass Spectrom. Ion Proc.* **1982,** *41,* 199–204.
52. Hunter, R.L.; McIver, R.T. Jr. "Conceptual and Experimental Basis for Rapid Scan Ion Cyclotron Resonance Spectroscopy", *Chem. Phys. Lett.* **1977,** *49,* 577–582.
53. Equations for mass resolution as a function of pressure and other variables are collected in Comisarow, M.B.; Marshall, A.G. "Theory of Fourier Transform Ion Cyclotron Resonance Mass Spectrosopy. I. Fundamental Equations and Low-Pressure Line Shape", *J. Chem. Phys.* **1976,** *64,* 110–119; Marshall, A.G.; Comisarow, M.B.; Parisod, G. "Relaxation and Spectral Line Shape in Fourier Transform Ion Resonance Spectroscopy", *J. Chem. Phys.* **1979,** *71,* 4434–4444.
54. Brauman, J.I.; Blair, L. "Gas-Phase Acidities of Alcohols", *J. Am. Chem. Soc.* **1970,** *92,* 5986.
55. Bowers, M.T.; Aue, D.H.; Webb, H.M.; McIver, R.T., Jr. "Equilibrium Constants for Gas-Phase Ionic Reactions. Accurate Determination of Relative Proton Affinities", *J. Am. Chem. Soc.* **1971,** *93,* 4354.
56. Lias, S.G.; Bartmess, J.E.; Liebman, J.F.; Holmes, J.L.; Levin, R.D.; Mallard, W.G. "Gas Phase Ion and Neutral Thermochemistry", *J. Phys. Chem. Ref. Data* **1988,** *17* (suppl. 1).
57. Brauman, J.I.; Smythe, K.C. "Photodetachment Energies of Negative Ions by Ion Cyclotron Resonance Spectroscopy. Electron Affinities of Neutral Radicals", *J. Am. Chem. Soc.* **1969,** *91,* 7778.

58. Dunbar, R.C. "Photodissociation of the CH_3Cl^+ and N_2O^+ Cations", *J. Am. Chem. Soc.* **1971,** *93,* 4354.

59. Reviewed by Wetzel, D.M.; Brauman, J.I. "Electron Photodetachment Spectroscopy of Trapped Negative Ions", *Chem. Rev.* **1987,** *87,* 607.

60. Reviewed by Dunbar, R.C. In "Gas-Phase Ion Chemistry," Vol. 3, "Ions and Light"; Bowers, M.T., Ed.; Academic Press: New York, 1984; Chapter 20.

61. Reviewed by Thorne, L.R., Beauchamp, J.L. In "Gas-Phase Ion Chemistry," Vol. 3, "Ions and Light", Bowers, M.T., Ed.; Academic Press: New York, **1984;** Chapter 18.

62. Bowers, W.D.; Delbert, S.; McIver, R.T., Jr. "Consecutive Laser-Induced Photodissociation as a Probe of Ion Structure", *Anal. Chem.* **1986,** *58,* 969–972.

63. Russell, D.H., Ed. "Gas-Phase Inorganic Chemistry"; Plenum: New York, 1989.

64. Alford, J.M.; Williams, P.E.; Trevor, D.J.; Smalley, R.E. "Metal Cluster Ion Cyclotron Resonance, Combining Supersonic Metal Cluster Beam Technology with FT-ICR", *Int. J. Mass Spectrom. Ion Proc.* **1986,** *72,* 33–51.

65. Cody, R.B.; Burnier, R.C.; Cassaday, C.J.; Freiser, B.S. "Consecutive Collision-Induced Dissociations in Fourier Transform Mass Spectrometry" *Anal. Chem.* **1982,** *54,* 2225–2228.

66. Ferrer-Correia, A.J.V.; Jennings, K.R.; Sen Sharma, D.K. "A Mass Spectrometric Method of Locating Double Bonds by the Use of Ion-molecule Reactions", *J. Chem. Soc., Chem. Commun.* **1975,** 973.

67. Baykut, G.; Watson, C.H.; Weller, R.R.; Eyler, J.R. "Infrared Multiphoton of some Oxygen-Containing Hydrocarbon Ions. Differentiation of Isomeric Ion Structures in the Gas Phase", *J. Am. Chem. Soc.* **1985,** *107,* 8036–8042.

68. Asamoto, B.; Dunbar, R.C. "Photodissociation Spectroscopy of Several $C_5H_6^+$ Isomeric Ions", *Int. J. Mass Spectrom. Ion Proc.* **1988,** *86,* 387–400.

69. Beauchamp, J.L.; Anders, L.R.; Baldeschwieler, J.D. "The Study of Ion-Molecule Reactions in Chloroethylene by Ion Cyclotron Resonance Spectroscopy", *J. Am. Chem. Soc.* **1967,** *89,* 4569.

70. McIver, R.T., Jr. "A Trapped Ion Analyzer Cell for Ion Cyclotron Resonance Spectroscopy", *Rev. Sci. Inst.* **1970,** *41,* 555; McIver, R.T., Jr.; Dunbar, R.C. "Pulsed Ion Cyclotron Double Resonance for the Study of Ion-Molecule Reactions", *Int. J. Mass Spectrom. Ion Phys.* **1971,** *7,* 471.

71. Marshall, A.G.; Comisarow, M.B.; Parisod, G. "Relaxation and Spectral Line Shape in Fourier Transform Ion Cyclotron Resonance Spectroscopy", *J. Chem. Phys.* **1979,** *71,* 4434–4444.

72. Allemann, M.; Kellerhals, H.P.; Wanczek, K.P. "A New Fourier Transform Mass Spectrometer with a Superconducting Magnet", *Chem. Phys. Lett.* **1980,** *75,* 328–331.

73. Ledford, E.B., Jr.; White, R.L.; Ghaderi, S.; Wilkins, C.L.; Gross, M.L. "Coupling of Capillary Gas Chromatograph and Fourier Transform Mass Spectrometer", *Anal. Chem.* **1980,** *52,* 2450–2451.

74. McCrery, D.A.; Ledford, E.G.; Gross, M.L. "Laser Desorption Fourier Transform Mass Spectrometry", *Anal. Chem.* **1982,** *54,* 1435–1437.

75. McIver, R.T., Jr.; Hunter, R.L.; Syka, M.S.; Labunsky, M. Paper presented at the 31st Annual Conference on Mass Spectrometry and Allied Topics, Boston, Mass., May 8–13, 1983.

76. Castro, M.E.; Russell, D.H. "Cesium Ion Desorption Ionization with Fourier Transform Mass Spectrometry", *Anal. Chem.* **1984,** *56,* 578–581.

77. Tabet, J.C.; Rapin, J.; Poretti, M.; Gaumann, T. "Californium-252 Plasma Desorption-Ionization with a Fourier Transform Mass Spectrometer: Analysis of Thermolabile and Nonvolatile Biomolecules", *Chimia* **1986,** *40,* 169–171.

78. Bamberg, M.; Allemann, M.; Wanczek, K.-P. In "Proceedings of the 35th ASMS Conference on Mass Spectrometry and Allied Topics", Denver, Color., May 24–29, **1987;** p 1116.

79. Hunt, D.F.; Shabanowitz, J.; Yates, J.R., III; Zhu, N.Z.; Russell, D.H.; Castro, M.E. "Tandem Quadrupole Fourier-Transform Mass Spectrometry of Oligopeptides and Small Proteins", *Proc. Natl. Acad. Sci. USA* **1987,** *84,* 620.

80. Henry, K.D.; Williams, E.R.; Wang, B.H.; McLafferty, F.W.; Shabanowitz, J.; Hunt, D.F. "Fourier-transform Mass Spectrometry of Large Molecules by Electrospray Ionization", *Proc. Natl. Acad. Sci. USA* **1989,** *86,* 9075–9078.

81. So, H.Y.; Dunbar, R.C. "Time-Resolved Slow Dissociation of Benzonitrile Ions by Trapped-Ion ICR Photodissociation", *J. Am. Chem. Soc.* **1988,** *110,* 3080.

82. Marshall, A.G.; Wang, T.L.; Chen, L.; Ricca, T.L. "New Excitation and Detection Techniques in Fourier Transform Ion Cyclotron Resonance Mass Spectrometry", Chapter 2 of Ref. 1.

CHAPTER 2

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