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Fourier Transform Mass Spectrometry

Michael L. Gross and Don L. Rempel

Summary. Fourier transform mass spectrometry will play an important role in the future because of its unique combination of high mass resolution, high upper mass limit, and multichannel advantage. These features have already found application in gas chromatography–mass spectrometry, multiphoton ionization, laser desorption, and secondary ion mass spectrometry. However, its most notable feature is the ability to store ions. This characteristic, when combined with the others, will allow expeditious study of the interaction of gas-phase ions with both photons (photodissociation) and neutral molecules, and the convenient application of this fundamental information for chemical analysis.

Considerable research activity is focused on instrumentation development in mass spectrometry today (*1*). One motivation for this activity is the increasing complexity of problems in application areas. In environmental chemistry and energy research, the mixtures become more complex and the required detection limits decrease. More polar, structurally intricate, and thermally sensitive compounds are now prepared in chemical synthesis and isolated in biochemical and medical research.

Desorption methods of ionization (*2, 3*) have been developed to handle compounds not amenable to traditional methods of vaporization and ionization. These methods include fast atom bombardment, laser desorption, secondary ion methods, ^{252}Cf plasma desorption, and field desorption. The mass analyzer of the future must deal with nonvolatile, highly polar or ionic, thermally sensitive materials with molecular masses approaching or exceeding 10,000 atomic mass units (amu), which will be introduced into the analyzer by using desorption ionization. Thus, the principal motivation for instrument development is the opportunity to solve new problems, an opportunity brought about by desorption ionization methods.

The Fourier transform mass spectrometer is a relatively new type of instrument which has its origins in the omegatron (*4*) and the ion cyclotron resonance (ICR) spectrometer of Wobschall (*5*). Its immediate progenitor is the ICR mass spectrometer of Baldeschwieler and students (*6*). The transition to Fourier transform mass spectrometry (FTMS) required development of a trapped ion cell, first introduced to the ICR community by McIver (*7*), and of methods to excite rapidly and detect simultaneously all the ions. These latter developments were made and the first FT mass spectrometer demonstrated by Comisarow and Marshall in 1974 (*8*).

The technique of FTMS has a number of features that make it a potentially important tool for attacking the difficult problems mentioned above. Some of these features are (i) simple mechanical design, (ii) high mass resolution, (iii) high upper mass limit, (iv) long ion storage, and (v) multichannel advantage.

Mechanical simplicity. The FT mass spectrometer is a relatively simple instrument in terms of mechanical design (*9*). The heart of the spectrometer to date has been a single cell (ion trap), usually a six-electrode 2.5-cm cube introduced by Comisarow in 1980 (*10*). This cell, like the mechanical components of all mass spectrometers, is mounted in a high-vacuum chamber. Its operation also requires a magnetic field, which has been provided by an electro- or a superconducting magnet. The cell serves as the ion source, mass analyzer, and detector, the three essential operating components of any mass spectrometer. Normally, these components are separated spatially; with FTMS the ionization and mass analysis–detection are separated temporally and computer-controlled.

High mass resolution. Improved mass resolution usually leads to better precision and accuracy of mass assignments, which add specificity to quantification and remove ambiguity from the identification of knowns and proof of structure of new substances. The highest resolution attainable with a commercially available sector mass spectrometer is 150,000 (Kratos MS-50), whereas the best resolution demonstrated for FTMS is 100,000,000 at mass-to-charge ratio m/q 18 (*11*). Another noteworthy example is the dramatic mass separation of Cl^+ and Cl^- obtained with FTMS (*11a*) (see Fig. 1).

High mass limit. A focus of mass spectrometry is the determination and

Michael L. Gross is professor of chemistry and director of the Midwest Center for Mass Spectrometry, University of Nebraska, Lincoln 68588. Don L. Rempel is a senior research associate at the Midwest Center for Mass Spectrometry.

quantitative analysis of high molecular weight biomolecules. Recently, biomolecules with masses as high as 10,000 to 12,000 amu have been studied by using sector and time-of-flight (TOF) instruments (*1, 12*). The next generation of magnet sector instruments will have upper mass limits of 10,000 amu under reasonable operating conditions. Quadrupole and TOF mass spectrometers have higher limits but at mass resolving powers of less than 1000. The highest ion masses observed to date with FTMS are about 3000 amu (*13*), but the theoretical limit is in excess of 100,000 amu at a magnetic field strength of 13 tesla.

Ion storage. Ion sources on commercial mass spectrometers are not designed for ion storage. As a result of the short ion residence time (10^{-5} to 10^{-6} second), observation of ion-molecule reactivity (for example, with chemical ionization) requires a high source pressure (0.1 to 1.0 torr). In the future, analysis of complex mixtures and determinations of high-mass molecules will require the development of new channels of information such as chemical reactivity, ion spectroscopy, and photodissociation. The FT mass spectrometer is suitable for these experiments because the cell is an excellent ion trap; trapping times as long as 5×10^4 seconds have been observed (*14*).

Multichannel advantage. The capability of any instrument to obtain simultaneously all information in a large spectral bandwidth is known as the multichannel advantage. In mass spectrometry, magnet sector instruments with photoplate or array detectors and TOF and FT mass spectrometers are examples of instruments that have this advantage. Its utility is in applications that require rapid data acquisition and compatibility with pulsed ionization methods (for instance, with lasers).

Certain types of mass spectrometers may have one or more of these features. However, only the FTMS permits their combination in a single instrument and hence in our view is one of the mass spectrometers of the future. In this article we review the features that contribute to its operational versatility and that provide new channels of information for the analytical chemist. The number of real analytical problems solved by using FTMS remains small as the instrument is still in its formative stage. Nevertheless, a sufficient number of analytical methods have been developed and applications demonstrated that judgments about the future of FTMS can be made with some certainty.

Operation of Fourier Transform Mass Spectrometers

The FTMS experiment involves a temporal sequence of operations performed in an ion trap (cell). These operations may be described in terms of five broad categories: (i) ion formation, (ii) ion storage, (iii) ion manipulation, (iv) ion excitation and detection, and (v) quench and repeat. Because of the temporal nature, many different experiments can be performed by simply modifying the order of the operations.

Ion formation. In the most basic FTMS experiment, neutral molecules are admitted into the ion trap via a suitable sample-handling system. These molecules are ionized by a pulsed electron beam (~500 nA for 5 msec) introduced along the magnetic field lines (see Fig. 2). Other methods of ionization that have been adapted to FTMS include chemical ionization, multiphoton ionization, laser desorption, and secondary ion methods.

Ion storage. Once ions are made, they are confined within the ion trap by the action of the applied electric and magnetic fields. The magnetic field constrains the x,y-component (radial) motions of the ions to circular orbits in planes perpendicular to the magnetic field. The z-component (axial) motion is confined by an electric field produced by applying an electric potential to the two electrodes denoted as trap plates in Fig. 2. In the ion trapping mode, the other four electrodes are at an averaged ground potential.

Although the cubic ion trap is most common in FTMS, other ion traps have been used (*15–19*).

Ion manipulation. The ions oscillate in the trap in three modes: cyclotron, magnetron, and z-mode (*15, 20*). Any or all modes of oscillation can be excited by applying time-varying potentials across electrodes of the ion trap. Because the cyclotron mode gives the best measure of mass, it is the one of most interest in FTMS. Its frequency is given by Eq. 1.

$$\omega_+ = \omega_c/2\{1 + [1 - 4\,(2qV_TG_T/m + \rho q^2G_i/\epsilon_0 m)/\omega_c^2]^{1/2}\} \quad (1)$$

The salient parameters (*21*) are ω_+, the angular frequency of the cyclotron mode; B, the magnetic field strength; V_T, the trap voltage; ρ, the charge density; m and q, the mass and charge of the ion; and ω_c, the classical cyclotron frequency, which is given by

$$\omega_c = qB/m \quad (2)$$

Two of the most useful means of ion manipulation are obtained by exciting the cyclotron mode. The first, called ion ejection or double resonance (*6*), is excitation to the point where the excited ions collide with a cell electrode and are neutralized. Ions are ejected to establish relationships between reactant and products in ion-molecule reaction sequences [called double resonance (*6*)] or to rid the cell of unwanted ions so that an ion of interest can be "isolated" and the ion abundance dynamic range expanded. The second method of manipulation is excitation to promote interactions with a collision gas but not to eject. If the translational energy is high enough, collisional activation followed by fragmentation will occur. The spectrum of the resulting fragment ions can be used as a structural probe.

Ion excitation and detection. Excitation of the cyclotron mode is also used to facilitate observation of the quantity and mass-to-charge ratio of each ion species in the ion trap. This is accomplished by applying an excitation waveform to the cell electrodes marked "transmitter plates." For each excited ion species, coherent cyclotron motion produces a net component image current on the cell electrodes; the current alternates at the ion species' characteristic cyclotron frequency. Following excitation, the superposition of many component image currents on the two cell electrodes marked as receiver plates is amplified, digitized, and stored in a computer for discrete Fourier transformation. This simultaneous observation of all the ion species gives the multichannel advantage. From the areas and frequency centroids of the peaks in the resulting frequency spectrum, one can deduce the quantity and mass of each ion species.

Quench and repeat. At the end of the sequence, the cell is usually purged of all ions either by applying a large potential to one of the trap electrodes to eliminate the trapping potential well or by inverting the polarity of the trap potential. The sequence is then repeated for signal averaging if necessary.

The various operations can be combined in a temporal sequence to perform different experiments such as mass spectrometry, ion-molecule reaction, double resonance, and mass spectrometry–mass spectrometry (MS-MS). Mass spectrometry sequence occurs as ion formation, ion excitation, detection, and quench. The ion-molecule reaction sequence is identical to the MS sequence except that a variable time delay is added between ion formation and detection. Addition of

one or more ion ejection events during the time delay between ion formation and detection gives the double-resonance sequence. If all mass ions but one are ejected, followed by a collisional excitation event and then excitation and detection, the MS-MS experiment is realized.

Instrumental Capabilities and Limitations

Resolution. With low background pressures and long detection times, FTMS is a high-resolution technique (*22*). The resolution of 100,000,000 at m/q 18 cited earlier was obtained by observing the transient response for 51 seconds in a nonroutine experiment where the background pressure was 5×10^{-11} torr and the magnet field strength was 4.7 teslas. In general, resolution, R, is limited by the time of observation, T (Eq. 3), and the collisional damping frequency, ξ/n (Eq. 4):

$$R = m/\Delta m \leq kqBT/m \quad (3)$$

$$R = m/\Delta m \leq k'qB/(mP)\ (\xi/n) \quad (4)$$

were q is in multiples of electronic charge, B is the magnetic field strength (tesla), P is the pressure (torr), k is 1.27×10^7 amu tesla^{-1} sec^{-1}, k' is 8.65×10^{-10} amu cm^3 torr tesla^{-1} sec^{-1} per molecule, and ξ/n is typically 1×10^{-9} cm^3 sec^{-1} per molecule. Note resolution decreases as mass increases.

Based on more routine experiments undertaken in the low 10^{-8} torr range where transient responses last for approximately 1 second, resolving powers of about 100,000 for m/q 1000 at 5 teslas would not be difficult to obtain (*23*). Extrapolation to higher masses may not be valid because as mass increases, electric forces become relatively more important than the decreasing magnetic forces. Electric fields in the cell are nonideal, and their effect on mass resolution is not completely understood. However, magnetic field homogeneity does not appear to be an issue in limiting resolution (*24*).

Present limitations on the size of fast memory and the speed of computation in laboratory computers require that high-resolution spectra be taken in a narrow-band or mixer mode with some loss of the multichannel advantage (*8, 9*). The higher the resolution sought, the more narrow the band. Narrow-band spectra are acquired by mixing the transient response with a reference frequency and digitizing the resultant difference or low-frequency signal. This is less demanding

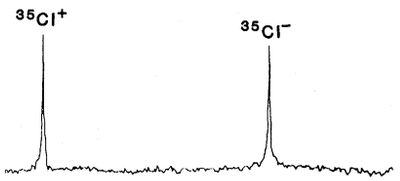


Fig. 1. FT mass spectra of $^{35}Cl^+$ and $^{35}Cl^-$ at a pressure of 10^{-8} torr and a mass resolution of ~1,500,000. The Cl^+ and Cl^- ion signals were alternately acquired, stored, and transformed. The FT mass spectrometer cannot simultaneously store positive and negative ions. [Reprinted from (*11a*) with permission]

of computer performance than digitizing and transforming the original, high-frequency transient response.

High mass limit. The upper mass limit of FTMS has not been adequately tested to date because of difficulties in generating high-mass ions in a trap maintained at low pressure. However, it is known that the ion trap is not capable of trapping ions with masses greater than a critical mass, m_c. For a cubic cell, m_c is given by

$$m_c = qB^2a^2/8V_{eff}\alpha \quad (5)$$

where a is the length of the cell, V_{eff} is the trapping voltage corrected for space charge effects, and the geometry constant $\alpha = 1.3869$ (*21*). A calculation of m_c for an FTMS equipped with a 2.5-cm cubic cell operated with a trap of 1 volt in a 13-tesla magnetic field yields a value of 950,000 amu. It is our opinion that at least 10 percent of the critical mass limit should be useful for FTMS.

Dynamic range. The upper end of the ion abundance dynamic range is bounded by the number of ions the cell can hold. For studies of ion chemistry or other situations that require only low-resolution spectra, the ion trap is operated with ~10^6 ions. Exact mass measurements, however, are best done with ~2×10^4 ions in a 2.5-cm cubic cell in a magnetic field of 1.2 teslas. The lower end of the dynamic range is limited by amplifier noise; specifically, 50 to 1000 ions is the detection limit, depending on the instrument. Thus, a crude estimate of the dynamic range for refined experiments involving exact mass determinations is ~100. In contrast, conventional mass spectrometers equipped with electron multipliers have dynamic ranges of greater than 10^5 under favorable conditions.

Ion storage time and dynamics. Penning traps used in the FTMS are capable of storing ions for extended periods of time. This is illustrated in the example cited previously, where 30 percent of the ions remained in the trap after 13.5 hours at a pressure of 1×10^{-8} torr with a magnetic field strength of 4.7 teslas (*14*). The loss of ions from the trap is due to a number of mechanisms, which are affected by mass, pressure, trap voltage, and magnetic field strength. If an ion is stable and does not react with neutrals present in the ion trap, it can be radially transported to the trap walls by ion-neutral collisions (*25, 26*). The effect of experimental parameters on storage times is exemplified by Eq. 6, derived for an oblong trap (*27*).

$$t_{1/2} = 1.57 \times 10^{-28} (aB)^2/P(V_T + 0.81)\ (\alpha\mu)^{1/2} \quad (6)$$

Here, μ is the reduced mass (grams) of the ion-molecule collision, α is the polarizability of the neutral gas (cubic centimeters), and the other parameters are given elsewhere in this article. At the low pressures and low trap voltages used for exact mass measurement, ion-ion collisions can produce ions with enough axial kinetic energy to overcome the confining electric fields (*21*). This "evaporation" in the z direction is evident (*28*), although not completely understood (because the ensemble of ions is usually not thermal) in the transitory FTMS experiment.

The radial transport and ion evaporation mechanisms contribute to temporal changes of the ion distribution in the trap. As a consequence, electric fields also change to effect changes in the relation between observed frequencies and ion masses (*21, 29*). This nonstationary behavior may account for some of the small but troublesome systematic errors that occur with the use of contemporary mass calibrations, which are based on stationary models.

Accurate mass assignments. The observed ion frequencies can be measured to nine significant figures, but the relation of frequency to mass remains an unsettled question and a subject for further study. A number of calibration procedures have been proposed (*29–32*). The most recent (*33*), which was derived to include the space charge effects of the model ion distributions of Jeffries *et al.* (*21*), is given by

$$m = a/f_{obs} + b/f^2_{obs} \quad (7)$$

where m is mass, f_{obs} is the observed ion frequency, and a and b are calibration constants.

A test of the equation was made by fitting it to frequency measurements for six ions in the range m/q 117 to 135. The average error was +0.4 ppm (the standard deviation or precision was ±4 ppm) for 15,000 ions in the cell. The individual errors were largely systematic and increased as the number of ions was in-

creased, which indicates that space charge effects are not fully accounted for. Nevertheless, electric field effects decrease as the square of B, which suggests that mass measurement errors should be less at higher field strengths. This was confirmed in recent unpublished investigations. As mentioned earlier, electric field effects are more important at high mass and may adversely affect accurate mass determinations of high-mass ions.

Accurate mass assignments are routine on conventional sector instruments, but the most accurate calibration procedures for scanning experiments are empirical and require a mass calibrant ion approximately every 14 amu. FTMS, on the other hand, is capable of reasonably accurate (±10 ppm) measurements without any calibrant (*34*) and should work well with minimal calibrant ions provided the total number of ions is kept small. Furthermore, FTMS should be applicable to accurate mass measurements in chemical ionization and desorption ionization modes, which present problems for the extensive use of calibrants in conventional mass spectrometry.

Sample Introduction and Ionization

The first of three broad classifications of analytical applications centers on sample introduction and ionization. The applications benefit principally from the multichannel advantage of FTMS. Their implementation is often designed so that low pressure can be achieved and ions detected at high mass resolution.

Gas chromatography–mass spectrometry (GC-MS). The first successful coupling of an FTMS and a capillary column gas chromatograph was achieved in 1980 (*35*) and elaborated and then linked with Fourier transform infrared in 1982 (*36, 37*). It has been proposed that FTMS is well suited for high-resolution multiple ion monitoring (*35*). The obstacle for high resolution in the GC-MS mode is the high pressure in the trap, which results from admitting GC eluent and carrier gas. Therefore, the first spectrometer employed a 7.6-cm air gap magnet and a high-speed turbomolecular pump (500 liters per second), which gave a pumping speed of 360 liters per second at the cell. A resolution of 23,000 for m/q 78 was attained.

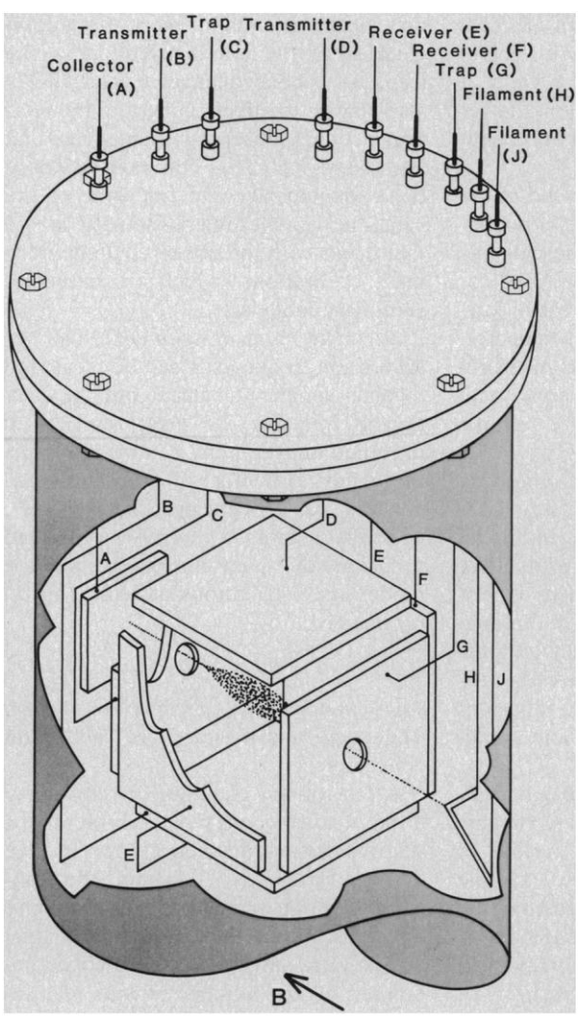


Fig. 2. The cubic ion trap located in a vacuum chamber and between the pole caps of an electromagnet. Ions are formed along the electron beam and probably assume the distribution shown in the cell.

A strategy for obtaining even higher mass resolution in the GC-MS experiment is to admit sample to the FTMS only during the ionization mode. Therefore, the GC was connected to the FTMS through a pulsed valve (*38*). A few hundred milliseconds after the pulse, the neutral gases had been pumped from the cell, and the trapped ions were excited and detected at low pressure and higher resolution. Naphthalene (m/q 128) was monitored routinely at resolving powers of 32,000 and occasionally at 63,000 (see Fig. 3) to 90,000 with detection limits of ~1 ng.

A potentially better strategy was recently developed at Nicolet Instruments. A system based on a superconducting magnet was equipped with two side-by-side cells that share a common center trapping plate containing a tiny orifice, which is the only connection between the two cells. The spectrometer is differentially pumped so that one cell operates in the low 10^{-8} torr range while the other cell remains connected to a GC. Ions are formed in the higher pressure cell, drift along the magnetic field lines (z axis) through the orifice, and are partitioned between both cells. Low-resolution spectra were obtained with the higher pressure cell, and higher resolution spectra with the lower pressure cell. This arrangement should give better detection limits than a pulsed GC FTMS because the time needed for pump-down between GC pulses can now be used for ion observation.

Multiphoton ionization (MPI). It is clear that MPI has both fundamental and analytical applications (*39, 40*). When combined with a mass spectrometer, MPI and particularly resonance-enhanced MPI are highly efficient and selective ionization methods. The first MPI-MS experiments were performed with sector and quadrupole mass spectrometers (*39*), but these are inefficient instruments because several laser shots are required to observe each ion mass. The TOF is a better choice because, like the FT mass spectrometer, it enjoys the multichannel advantage. However, the TOF does not permit high resolution, ion storage, or ion manipulation.

The combination of MPI and FTMS was first demonstrated by McIver and co-workers (*41*). Following those experiments, Carlin and Freiser (*42*) showed that azulene molecular ions (m/q 128) could be detected at mass resolving powers of 21,000 (full width at half height, FWHH) at a magnetic field of ~0.9 tesla. The ability to store and manipulate ions was demonstrated by collisionally activating the *n*-butylbenzene molecular ion.

GC-MPI-MS. Multiphoton ionization is well suited for complex mixture analysis particularly when coupled with gas chromatography, as has been demonstrated by using TOF mass spectrometry (*43*). More recently, MPI has been coupled with the pulsed GC introduction for FTMS high-resolution targeted compound analysis (*44*). Multiphoton ionization gives one dimension of selectivity, which is increased dramatically when coupled with capillary column GC and high-resolution MS. The combination was used for the analysis of the aromatic constituents in unleaded gasoline. No MPI ionization of the aliphatic constituents was observed; only the aromatics were detected with 266-nm ionizing radiation. A targeted constituent such as naphthalene was monitored in a narrow-band mode at a mass resolution as high as 90,000 (1.2-tesla field) with a detection limit of 10 pg and a linear dynamic range for quantification of 2.5 orders of magnitude.

Laser desorption. A laser may also be coupled with FTMS for laser desorption (*45*). Freiser and co-workers (*46*) showed that free metal ions (for instance, Fe^+ or Cu^+) could be desorbed with a laser pulse focused on a metal target in an ICR or FTMS cell. This observation has opened up the study of reactions of metal ions with organic molecules. The first use of laser desorption to produce gas-phase organic ions of polar and zwitterionic molecules in an FT mass spectrometer was by McCrery *et al.* (*47*). The incentive for the research was to take advantage of the high resolution and ion manipulation capabilities of FTMS. For example, the carboxylate anion of adipic acid was directly desorbed and detected at a mass resolution of 10,000. More recently, Ph_3P–N(Ph)=PPh_2^+ (*m/q* 538) was desorbed and detected at a mass resolution of 22,000. These measurements were made at 1.2 teslas, and it is expected that improved resolution will be attained by using higher field superconducting magnets. Although laser desorption is not as routine as fast atom bombardment, it has been used recently to desorb molecules with masses as high as 3628 (*48*).

Secondary ion methods. In its present state, fast atom bombardment cannot be used directly with FTMS because the excess gas from the atom gun and the vapor pressure of the matrix cause intolerable increases in the background pressure. Cesium ion desorption may be a solution because Cs^+ beams, which are produced from solid-state filaments, contribute insignificantly to the background of the spectrometer. The first experiments were conducted by Castro and Russell (*13*).

Two approaches were taken. In one, the sample was placed on a gold trap plate grid and irradiated with a Cs^+ beam from a filament located outside the cell and directly behind the trap grid. A sample of vitamin B_{12} was desorbed to give first $(B_{12} + Cs - CN)^+$, *m/q* 1462, and later $[(B_{12})_2 + Cs - 2CN]^+$, *m/q* 2792. One explanation for the time delay for *m/q* 2792 is that the Cs^+ is implanted on the surface and reacts with the B_{12} to give cationized B_{12}, which is desorbed later. The second approach involved placing the sample on the trap plate across the cell from the entrance for the Cs^+ beam. After longer irradiation, *m/q* 993, a fragment from $[B_{12} + Cs - CN]^+$, and then *m/q* 1966 (a fragment from a Cs^+-bound dimer) were observed. Although the production of these unexpected fragment ions may be viewed as troublesome with real samples, the experiment suggests that solid-state chemistry can be conducted in a controlled fashion to produce high-mass ions, either Cs^+-bound "dimers" or fragments thereof.

Ion Storage: Applications

Unique applications of FTMS are due to its ability to store ions. For example, ions in the trap can be reacted in highly specific ways (chemical ionization) or activated by using lasers to give photodissociation spectra.

Chemical ionization (CI). Unlike conventional mass spectrometers, which require 1 torr of pressure, FTMS chemical ionization is conducted at 10^{-6} torr of reagent gas and $\sim 10^{-8}$ torr of sample. Following the lead of Hunter and McIver (*49*), who showed the advantages of chemical ionization with ICR mass spectrometry, Ghaderi *et al.* (*50*) conducted a systematic investigation of usual CI reagent gases and FTMS. The concept of reagentless CI or "self-CI" was also introduced. Deuterium exchange with D_3O^+, ND_4^+, and so on, an important method for counting active protons (*51*), is advantageously applied with FTMS. Finally, ion-molecule reactions involving condensation rather than proton transfer are readily conducted. Ghaderi *et al.* showed that methyl vinyl ether radical cation could be used to locate the double bond in two insect sex pheromones.

Reagent gas pressures of even 10^{-6} torr preclude high mass resolution in the CI mode. Therefore, the pulsed-valve method for GC-MS was applied for pulsing the reagent gas (*52*). Long time delays between the valve pulse–ionization and detection permit extensive proton transfer to the neutral sample molecules, which leads to many more sample ions than could be prepared by using electron ionization. Mass analysis is conducted at low pressure, which affords high mass resolution; 145,000 for *m/q* 85 and 38,000 for *m/q* 299 (protonated methyl stearate) were demonstrated for single scans.

Photodissociation. Photodissociation of gas-phase ions is a relatively mature field of scientific inquiry, principally because of the pioneering efforts of Dunbar (*53, 54*), who has used ICR as a mass analyzer for fragment ions formed by irradiating parent ions with photons. Measurements in this area have contributed significantly to the understanding of

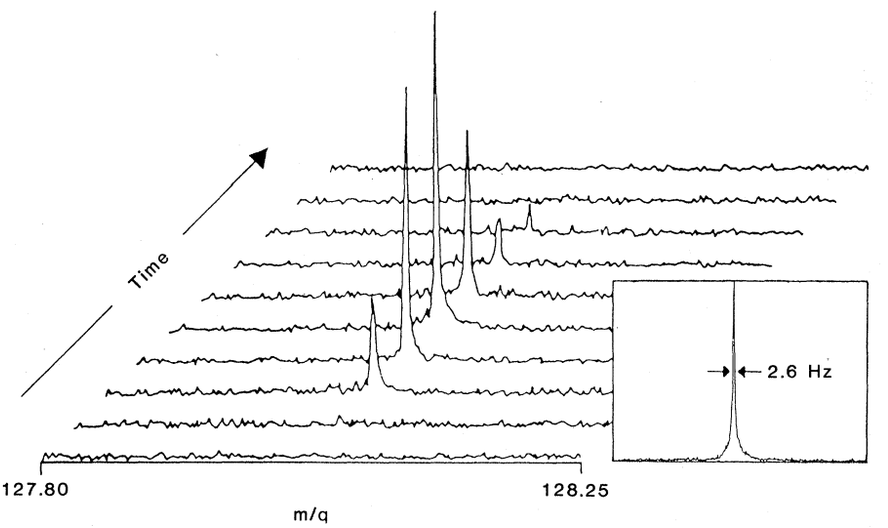


Fig. 3. Elution profile of 20 ng of naphthalene as observed by monitoring the molecular ion at a resolution of 32,000 FWHH. Each spectrum is the result of one 1-second scan. Inset is a higher resolution experiment at 63,000. [Reprinted from (*38*) with permission. Copyright 1983 American Chemical Society]

structure and properties of gas-phase ions.

An example of an analytical application is the photodissociation of a small peptide in an FTMS to give fragments that contain sequence information (*55*). This demonstration may foreshadow many more in which sufficient energy for fragmentation is deposited in biomolecules by multiphoton absorption. The extent of collisional activation of high-mass biomolecules, on the other hand, will undoubtedly be limited by the inefficiency of energy transfer in collisions with lower mass inert collision gases.

Ion Manipulation: Applications

Analytical applications that result from the ability to manipulate ions by using FTMS involve ion ejection, collisional activation (*56*), and the combination of ejection and activation or MS-MS (*57, 58*). There are advantages and limitations of FTMS for these experiments. The energy transferred can be varied with the power of the excitation, and this adds another dimension of information because spectra are sensitive to energy deposition. The same sensitivity causes FTMS collisional spectra to be less reproducible than high-energy collisional spectra obtained with tandem sector instruments. Moreover, the dynamic range of the FTMS is lower, and the maximum energy available for collision is less than for tandem sector instruments and decreases as mass increases. This problem can be remedied in part by using larger cells and greater magnetic field strengths (energy is proportional to B^2r^2, where r is the radius of the cyclotron motion and B is the magnetic field strength). For example, high-energy charge stripping of the stable benzene molecular ion has been accomplished in a larger cell (*59*).

The two most noteworthy advantages of FTMS for MS-MS experiments are in high-resolution daughter ion analysis and the linkage of many sequences of ion ejection and excitation, called $(MS)^n$. Early experiments produced mass resolution of 3250 FWHH at m/q 43 in a 0.9-tesla field (*60*) and 9200 at m/q 866 in a 1.9-tesla field (*61*). Addition of the collision gas through a pulsed valve so that mass analysis could be accomplished at low pressure allowed a factor of 10 increase in the mass resolution (*62*).

The number of stages of ion ejection and collisional activation is not limited by hardware or software but rather by the collisional efficiency. N. M. M. Nibbering and J. C. Kleingeld (*63*) have demonstrated four stages of MS-MS—that is, $(MS)^5$—by collisionally activating first the acetophenone molecular ion and then the various generations of offspring ions (Eq. 8).

$$PhCOCH_3^{+\cdot} \rightarrow PhCO^+ \rightarrow Ph^+ \rightarrow C_4H_3^+ \rightarrow C_4H_2^{+\cdot} \quad (8)$$

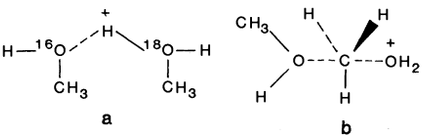
It should be noted that this experiment is applicable for systems where only one or small number of daughter ions result in each stage of collisional activation.

Ion Chemistry Applications

Ion cyclotron resonance mass spectrometry has been a tool in an immensely productive effort to understand the chemistry and spectroscopy of gas-phase ions. The field is too extensive to review here, and the interested reader is directed to specialized reviews (*64–66*). New light has been cast on the intrinsic acidities, basicities, and other properties of organic substances by studies of gas-phase ion equilibria. Important contributors have been McIver, Taft, and Hehre (University of California–Irvine), Beauchamp (Caltech), Bowers and Aue (University of California–Santa Barbara), and Brauman (Stanford). Brauman also pioneered the measurement of electron affinities by using photodissociation of negative ions with ICR. Photodissociation of positive ions has been investigated by Dunbar (Case Western), Beauchamp and van der Hart (Leiden), and Eyler (Florida). Structures and reactivities of ions have been studied by Jennings (Warwick), Nibbering (Amsterdam), Bursey (North Carolina), Lias and Ausloos (National Bureau of Standards), and Gross (Nebraska). A new area of reactivity of metal ions and organic molecules has been opened by Beauchamp and Ridge (Delaware) and Freiser (Purdue). An example of Freiser's work is shown on the cover of this issue. All of this research can be expedited by using FTMS.

The results of systematic investigations of ion reactivity and spectroscopy are examples of channels of information that have not been conveniently available to the analytical chemist. The development of these channels is not only feasible but also highly attractive research with FTMS. In the following paragraphs, only a few highlights of ion chemistry research will be presented to show the power of the FTMS method.

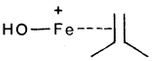
An elegant example of the use of naturally occurring oxygen-18 (~0.2 percent in nature) and FTMS is the study of the mechanism of protonated methanol reacting with methanol to form protonated dimethyl ether (*67*). The reaction product must form through intermediate **a** or **b** (an S_N2 process).



a **b**

If the reacting ion bears an ^{18}O and reacts through the symmetric intermediate **a**, half the products will contain ^{16}O and the other half ^{18}O. If the reaction proceeds by the S_N2 route, the product will contain ^{16}O only. All reactant ions except $CH_3{}^{18}OH_2^+$ were ejected from the cell by using a double-resonance pulse, and the low-abundance $CH_3{}^{18}OH_2^+$ ions were allowed to react with neutral methanol (which contains principally ^{16}O). The predominant product was $CH_3{}^{16}OH^+$, which is expected if an S_N2 mechanism prevails.

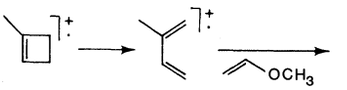
Laser desorption, ion ejection, collisional activation, and gas pulsing have been used in a study of the reactions of FeO^+ and hydrocarbons (*68*). Gas-phase Fe^+ was formed by laser desorption from solid Fe and allowed to react with a pulse of N_2O to give FeO^+ and N_2. Reaction of FeO^+ with $C(CH_3)_4$, for example, gave an ion for which structure **c** was proposed.



c

This structure is consistent with the pattern of collisionally induced decomposition products which was obtained as a function of the translational energy of **c**. Another example of this research strategy is presented on the cover of this issue.

The determination of the approximate energy barrier for the electrocyclic ring opening of the 1-methylcyclobutene radical cation (1-MCB$^{+\cdot}$) to isoprene ion (Eq. 9) required the use of double gas pulsing (*69*).



$$C_7H_{10}^{+\cdot} + CH_3OH \quad (9)$$

The amount of energy imparted to 1-MCB$^{+\cdot}$ was controlled by pulsing into the cell a charge exchange reagent (for example, CS_2) and ionizing it by electron ionization. The charge exchange reagent then ionized 1-MCB ($P = 4 \times 10^{-8}$ torr) and deposited an amount of energy approximately equal to the differences in ionization potentials. After the charge exchange gas was pumped away, a sec-

ond pulse of gas was added, this time of methyl vinyl ether, and all ions except 1-MCB$^{+\cdot}$ were continuously ejected. The evidence for the onset of ring opening is production of $C_7H_{10}^{+\cdot}$, a characteristic reaction of the isoprene radical cation and neutral methyl vinyl ether (see Eq. 9).

Future

The research described here demonstrates that FTMS is capable today of very high mass resolution and accurate mass measurement under conditions that represent only a fraction of its anticipated operating range. To extend FTMS, research is being focused on two areas: concatenated instruments and improved operation of the ion trap. However, storing and manipulating ions are the most noteworthy functions of FTMS because they will permit ion reactivity to be utilized for determining molecular structure.

Concatenated instruments. The most expeditious way to make FTMS more suitable for routine analytical applications is to link it in series with another instrument, preferably another mass spectrometer. In this way, the problems of pressure and dynamic range can be skirted and the features of FTMS emphasized. This was recognized by Smith and Futrell (*70*) and more recently by Kemper and Bowers (*71*), who linked the ICR mass spectrometer with 180° sector mass spectrometers. However, this concatenation is more apropriate for electromagnet-based than for superconducting magnet–based systems.

The successful linkage of a quadrupole mass spectrometer and the FTMS (*72*) is a demonstration that the problems of injecting ions from a conventional MS operating outside the superconducting magnet and at higher pressures into the FTMS can be solved. Ions from the quadrupole were trapped and analyzed by using the FT mass spectrometer (4-tesla magnet) at a resolving power of 101,000 at *m/q* 202. More recently, small peptide $M+H^+$ ions (up to eight amino acids) were desorbed by using FAB in the quadrupole and successfully injected into and analyzed by using the FT mass spectrometer (*73*).

The double-cell design with differential pumping which has been implemented by Nicolet Instruments is another example of concatenation in which two FTMS ion traps are connected. We believe that even more useful concatenations will involve multiple cell designs in which one cell serves for ionization, another for ion storage, and another for mass analysis. Ions can be moved from one cell to another by taking advantage of *z*-mode oscillation, and the entire spectrometer can be arranged to fit within the bore of a single superconducting magnet.

Improvement of ion trap. Some of the problems of dynamic range, resolution, and accurate mass measurement have been met by using higher magnet fields (*11*), larger ions traps (*18*), or low-noise amplifiers. These methods reduce the overall effect of the trapping and coulombic fields which complicate the motion of the ions. However, there are practical limits to making stronger magnetic fields to accommodate ever larger ion cells as well as limits in designing amplifiers with lower noise. An alternative approach to eliminating the electric field complications is to simplify the mechanics of ion motion, an approach that removes the complication rather than simply reducing it.

There are a number of degrees of freedom in the design and use of the ion trap that might be used to achieve some simplification—for example, trap electrode shape, initial ion distribution, and excitation waveform. The motion of even a single ion is complicated by the electric trapping fields, which are a nonlinear function of position in all rectangular and cylindrical ion traps. This is not the case for the hyperbolic Penning trap of Byrne and Farago (*15*), where the motion of an ion is harmonic. Traps of this form have been applied in situations suitable for FTMS (*17, 19*). Neglecting the effect of image charges on the electrodes of the trap, Jeffries *et al.* (*21*) demonstrated certain model charge distributions which produce linear contributions to the electric fields. This is the basis for the hope that changing the distribution of ions in the trap can improve FTMS performance. Although it will be difficult to modify the time evolution of the ion distribution, it may be possible to control the initial ion distribution by changing, for example, the cross section of the ionizing electron beam passing through the trap. Finally, it appears that excitation methods are capable of modifying the ion spatial distribution in ways that have not been anticipated (*28, 74*). Improved excitation waveforms may become available and lead to a better understanding of the collective behavior of the trapped ions during and after the excitation.

New information channels. It is expected that the development of FTMS will enable chemists to use mass spectrometry in new ways. Not only will high molecular masses be measurable, but also, through the use of ion manipulation (MS-MS), the molecules will be degraded into more manageable pieces for which accurate mass measurement is tractable. Moreover, long ion storage will allow lasers to be used for photodissociation and ion-molecule reactions to be employed for production of structurally specific products. These are the new information channels which build on the knowledge of ion chemistry amassed over the past two decades. Automatic procedures can be forecast in which sequences of reagent gas pulsing, laser pulsing, and ion ejection will enhance mass separation, even high-resolution mass separation, through chemical means. FTMS offers an opportunity, as does no other physical method, to combine in a single instrument the potential for measuring both chemical and physical properties of trace amounts of substances.

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Pyrolysis Mass Spectrometry of Complex Organic Materials

Henk L. C. Meuzelaar, Willem Windig, Alice M. Harper
Stanley M. Huff, William H. McClennen, Joseph M. Richards

High sensitivity, specificity, and speed are widely recognized characteristics of mass spectrometry (MS) which have earned the technique its reputation as one of the most powerful analytical tools for organic materials available today. With the total number of library spectra approaching 100,000 and with novel desorption ionization methods such as fast atom bombardment advancing into the 5,000- to 15,000-dalton range (*1*), it is tempting to credit MS with nearly universal applicability as well. Unfortunately, in reality most organic materials on this planet, whether natural or man-made, consist of molecular assemblies of a complexity and size far beyond the capabilities of direct MS techniques.

As we intend to demonstrate in this article, however, the combined use of advanced pyrolysis techniques, mass spectrometry, and computerized multivariate analysis methods (Py-MS) offers a viable approach to the analysis of extremely complex organic materials. Moreover, Py-MS techniques require minimal sample preparation and can be readily automated (*2, 3*). On the negative side, however, these techniques have not yet attained a satisfactory level of interlaboratory reproducibility and require dedicated equipment and expert personnel.

During the past two years, several comprehensive overviews of the development of Py-MS techniques since Zemany's pioneering work in 1952 (*4*) were published by Irwin (*2*), by Meuzelaar *et al.* (*3*), and by Schulten and Lattimer (*5*). These monographs provide in-depth discussions of the different Py-MS techniques and their applications in the areas of synthetic polymer chemistry, natural product chemistry, biochemistry, pharmacology, microbiology, medicine, fuels technology, organic geochemistry, soil science, and forensic science.

As schematically depicted in Fig. 1, the three basic pyrolysis techniques (filament pyrolysis, direct probe pyrolysis, and laser pyrolysis) may be combined with any of a number of different mass separation techniques and chemometric procedures, which explains the multitude of experimental approaches encountered in the literature. Nevertheless, filament pyrolysis techniques appear to be the method of choice in most current reports and Curie-point Py-MS (perhaps the most widely used form of filament Py-MS today) has achieved a limited degree of standardization and interlaboratory reproducibility (*3*) due to the availability of dedicated Curie-point Py-MS systems from at least two manufacturers (*6*).

The present article will not attempt to provide a comprehensive overview of the many different Py-MS techniques and procedures, such as can be found in the above referenced monographs. In-

Henk L. C. Meuzelaar is a research professor and director of the Biomaterials Profiling Center, University of Utah, Salt Lake City 84108. Willem Windig, William H. McClennen, and Joseph M. Richards are on the staff of the Biomaterials Profiling Center, as research associate, analytical chemist, and research assistant, respectively. Stanley M. Huff is a resident in the Department of Pathology at the University of Utah School of Medicine, and Alice M. Harper is an assistant professor of chemistry at the University of Texas, El Paso 79968.