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Chapter 1

Principles and Features of Fourier Transform Mass Spectrometry

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Fourier transform mass spectrometry (FTMS) is a rapidly growing technique of increasing analytical importance. Foremost among its many attributes are its high mass resolution and wide mass range capabilities, as well as its ability to store ions. This relatively new technique has been employed in a wide variety of applications, ranging from the exact mass measurement of stable nuclides to the determination of peptide sequences. The future holds considerable promise both for the expanded use of FTMS in a diverse range of chemical problems, as well as advances in the capabilities of the technique itself.

Fourier transform mass spectrometry (FTMS) is an exciting technique that combines the operating features of several different types of conventional mass spectrometers into a single instrument and possesses a number of unique capabilities, as well. Originally developed by Comisarow and Marshall in 1974 (1-3), FTMS is derived from scanning ion cyclotron resonance mass spectrometry (ICR) (4) by the application of Fourier transform (FT) techniques. It should be noted that both in this book and in the general literature, the terms Fourier transform ion cyclotron resonance (FT-ICR) mass spectrometry and Fourier transform mass spectrometry are used synonymously. Although ICR has historically been a valuable tool for the study of gas-phase chemical reactions (5), prior to the introduction of FTMS, the analytical applications of ICR had been restricted by low mass resolution, limited mass range, and slow scanning speeds (6-8). By employing Fourier transform techniques (9) in conjunction with a trapped ion cell (10, 11), FTMS has circumvented these limitations and, in fact, has the potential of becoming an important analytical technique.

This chapter is intended to serve as an overview of the general principles and features of FTMS. Capabilities pertinent to analytical studies will be specifically highlighted. In addition

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to the papers cited in this chapter, the reader is referred to a number of other reviews (12-16) which provide additional references to detailed reports of applications and research in the field of FTMS.

Principles of Fourier Transform Mass Spectrometry

Figure 1 is a schematic of a trapped ion cell with cubic geometry, which is commonly used in FTMS (8, 11). The cell is contained within a high-vacuum chamber (pressures of 10^{-6} torr or less) which is centered in a homogeneous magnetic field. Magnetic field strengths used for FTMS are typically 1-7 T, with 2-3 T fields generated by superconducting magnets being the most common. Like conventional mass spectrometry, ions may be formed in the FTMS cell by a number of methods, including electron impact (1), chemical ionization (17-20), laser ionization and desorption (21-23), and particle induced desorption, such as secondary ion mass spectrometry and plasma desorption (24-27). After formation, ions are trapped in the cell, held in the radial direction (xy plane) by the magnetic field and along the axis of the magnetic field (z-axis) by small voltages (0.5 to 5 V) applied to the trapping plates. Either positive or negative ions may be trapped in the cell simply by changing the polarity of the voltage applied to the cell plates.

The frequency of the cyclic motion of ions, ω, within the cell is given by the cyclotron equation:

$$\omega = KqB/m \qquad (1)$$

where K is a proportionality constant, q is the charge of the ion, m is its mass, and B is the magnetic field strength. Because the magnetic field strength is constant in the FTMS experiment, ions of different mass will have unique cyclotron frequencies. For example, at a magnetic field strength of 3 T, an ion with a mass to charge ratio (m/z) of 18 will have a cyclotron frequency of 2.6 MHz, while an ion at m/z 3,000 will have a frequency of 15.6 KHz.

Because of momentum conservation, the initial ion velocity upon ion formation is the same as the velocity of its neutral precursor. For a macroscopic ensemble of ions, there is no net coherent cyclotron motion even though the ion orbits are nonzero. Without coherent motion, a signal cannot be detected. By applying a very short, high intensity, broadband radiofrequency signal (2) ("chirp") to the excite (or transmitter) plates of the cell, the ions absorb energy, which accelerates them into larger orbits and causes them to move together (coherent motion). The orbiting packet of ions induces a small alternating current ("image current") in the receiver plates (28). This signal is converted into a voltage, amplified, digitized and stored in a computer (28). The frequency components of the image current correspond to the cyclotron frequencies of the ions present in the cell. If ions of only one mass to charge ratio were present in the cell, the detected signal (time domain signal) would resemble a single frequency sine wave. However, in the FTMS experiment, all ions in the cell are excited virtually simultaneously (3) and detected simultaneously (2, 3, 7). The resulting time domain spectrum is very complex because the signals of all ions are superimposed. In order to recover the frequency information, the complex time-domain spectrum is subjected to a Fourier transform algorithm. This generates a frequency domain spectrum, which can be readily converted to the familiar mass spectrum using the cyclotron relationship given above, Equation 1 (3, 29, 30). Another advantage of the Fourier transform technique is that data acquisition time is greatly reduced because ions of all masses are detected simultaneously (7).

Because frequency can be so precisely measured, the exact mass of an ion can be determined very accurately in the FTMS experiment (8). Typically, low parts-per-million accuracy can be achieved in the presence or even in the absence of an internal mass calibrant (13). In addition, a high degree of mass accuracy can be maintained for days without recalibration provided that the magnetic field remains stable. More detailed information on the theory of FTMS (1, 16, 28, 31-33) and the principles of Fourier transforms applied to spectroscopic techniques (9, 34) may be found in the literature.

The Basic FTMS Experiment

In practice, the basic FTMS experiment is conducted using a series of computer-controlled pulse sequences, as depicted in Figure 2. In this experiment, ion formation and detection are separated in time. This is in contrast to conventional mass spectrometers, which rely on spatial dispersion of ions. In the simplest case, the initial pulse involves the formation of ions, whether by electron ionization or another technique. The second is the frequency sweep (2) excitation pulse which brings the ions into coherent motion, as described previously. This is followed by a detection period during which the signal (image current) (28) from the ions is received. A quench pulse is then applied to the cell to remove all the ions from the cell prior to starting the next pulse sequence. The entire experiment sequence can take less than a second (a minimum of about 10 ms for an electron ionization experiment), and the series of pulses may be repeated as many times as desired for signal averaging and enhanced signal-to-noise ratio. Additional pulses or delays between pulses may be inserted in this basic pulse sequences in order to perform more complex experiments, as will be discussed later.

In addition to the cubic cell geometry (11) depicted in Figure 1, a variety of other cell geometries have been devised (4, 35, 36). One that has attacted considerable interest for analytical purposes is the dual cell (37), depicted in Figure 3. In this design, two differentially pumped cubic cells share a common trapping plate which contains a small (2 mm) orifice. This arrangement allows the cells to be operated at a pressure differential of 10^3. Ions may therefore be formed at higher pressures in the "source" cell and transferred to the "analyzer" cell for detection under low pressure conditions. In the FTMS experiment, low pressures are required for high resolution mass measurement and other high performance capabilities, as outlined below.

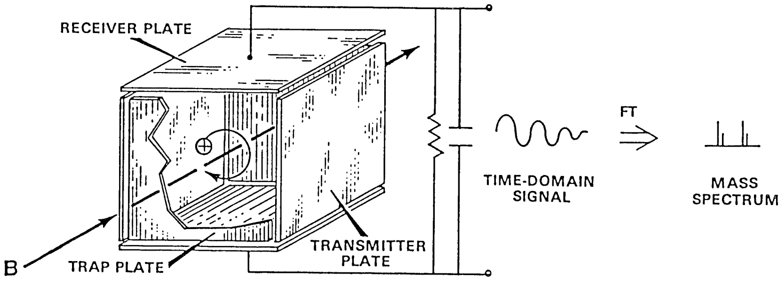


Figure 1. Schematic representation of a cubic trapped ion cell commonly used in FTMS. Coherent motion of ions in the cell induces an image current in the receiver plates. The time domain signal is subjected to a Fourier transform algorithm to yield a mass spectrum.

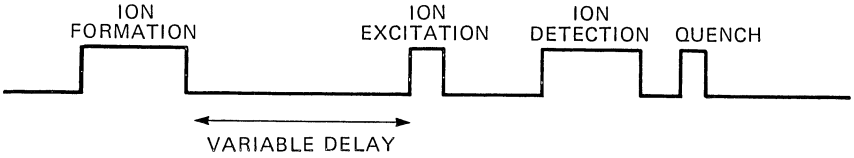


Figure 2. Simple pulse sequence used in elementary FTMS experiments, including ion formation, excitation, and detection. A quench pulse is used to eject ions from the cell prior to repeating the sequence. The variable delay between ion formation and excitation can be used for ion storage and manipulation, as described in the text.

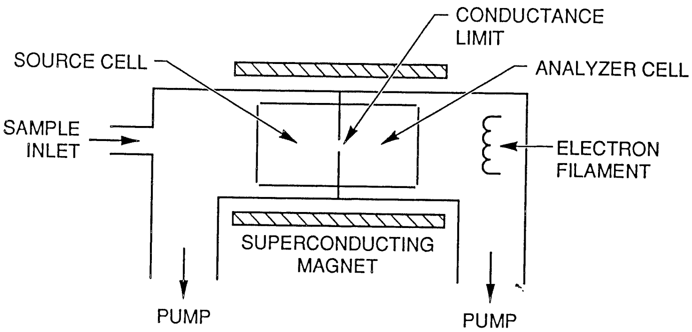


Figure 3. Schematic representation of a dual cell used for FTMS. The two differentially pumped cells are joined by a trapping plate containing a small orifice that is capable of supporting a 10^3 pressure differential. Ions may be detected in either cell. However, if desired, ions formed in the "source" region under higher pressure conditions may be transferred to the "analyzer" cell for detection under lower pressure conditions, as described in the text.

Features of FTMS

FTMS is mechanically simple, yet remarkably versatile. The instrument can be operated in any number of modes simply by changing the pulse sequences used to control the spectrometer. As a result, a wide variety of experiments can be performed with a sample in a very short period of time. For example, by altering just a few parameters using the computer keyboard, one may switch from positive to negative ion detection, from electron ionization to chemical ionization, and from a single stage experiment to a multiple stage experiment (e.g., MS/MS). In addition, a number of features makes FTMS particularly well-suited for analytical studies, including high mass resolution and wide mass range, ability to store, manipulate and selectively detect ions, and compatibility with a variety of ionization techniques. Examples of these features are given below and additional examples may be found in previous reviews of analytical applications of FTMS (13-15, 38).

High resolution and wide mass range. One of the most outstanding features of FTMS is its ability to achieve very high mass resolution, which was predicted early in the development of the technique (7, 39). Mass resolution in the FTMS varies inversely with mass and increases proportionally to observation time and magnetic field strength (8, 40). An increase in operating pressure causes collisional damping of the coherent motion of the ions within the cell and a rapid decay of the image current signal, resulting in a decrease in resolution. Therefore, very low pressure (10^{-8} torr or lower) is required in order to monitor the signal for a sufficiently long period of time to obtain high mass resolution.

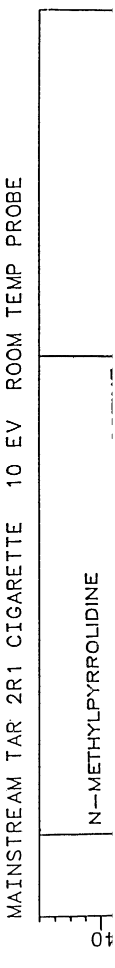
Mass resolution in excess of 500,000 (FWHM) at mass 100 can be readily obtained with most commercial FTMS instruments and resolution of 200,000,000 at m/z 40 (41) has been reported. This compares with the highest mass resolution of commercial sector instruments of about 120,000. In addition, high resolution measurements can be made in a matter of seconds with an FTMS and the instrument can be switched between medium and high resolution modes simply by changing a few parameters through the computer. With conventional magnetic sector instruments, which must be mechanically adjusted (14), this change can be very time-consuming. Further, with conventional mass spectrometers, high mass resolution is achieved by narrowing the ion transmission slits, which results in a decrease in the signal. In FTMS, increased resolution is achieved simply by accumulating the signal for longer periods of time and results in an increase in the signal to noise ratio (S/N) as well (42). Thus, high resolution spectra can often be obtained on very small quantities of sample using FTMS.

In addition to high mass resolution, another important feature of FTMS is its wide mass range (7,8). From examination of the cyclotron equation (Eq. 1), the mass range of FTMS appears to have no upper limit. However, an instrumental upper limit in excess of 100,000 has been suggested (16), based on a detailed study of ion motion (30). From a practical standpoint, the cyclotron frequencies of high mass ions (> 5,000 daltons) are low enough that environmental (1/f) noise can severely interfere with their detection. Improved electronics have been devised to help circumvent this problem, and ions at mass 16,241 from cesium iodide clusters have been detected using an FTMS equipped with a 3 T magnet (43). Alternatively, as higher field magnets are developed and employed, the upper mass range of FTMS will be extended as well. The low mass limit is governed by the rate of signal digitization. For example, according to Nyquist theory, if a 5.2 MHz digitizer is used, the highest frequency signal which can be processed without distortion is 2.6 MHz. As previously mentioned, at a field strength of 3 T, this frequency corresponds to about 18 daltons. Lower masses can be obtained, however, by use of a faster signal digitizer or with lower magnetic fields. Alternatively, a special narrow-band excitation (heterodyne) technique which reduces the digitization requirements of the signal can be used to obtain lower masses (7,8).

The combination of high mass resolution, wide mass range, and exact mass capabilities makes FTMS an important tool for determining the chemical formula of an unknown molecule. This can be especially important for higher molecular weight compounds such as polymers and biological molecules. Resolution of 150,000 at m/z 1180 has been reported (37). High resolution is also required for the separation of isobaric ions and can be of importance in the analysis of mixtures. For example, Figure 4 is a spectrum obtained from cigarette smoke tar, which contains many thousands of compounds. The sample was deposited on a direct insertion probe, and the spectrum was collected using medium resolution conditions. Closer inspection of the area around mass 124 (expansion shown in Figure 5) reveals three well-resolved isobaric ions. Under the moderate resolution conditions used to acquire the spectrum (resolution of 24,000 at m/z 124) molecular formulae for the three compounds can readily be established. Using the high resolution capabilities of FTMS, the same approach can be used to identify isobaric species at much higher masses.

The requirement of low pressure for high resolution mass measurement can limit the performance of FTMS when used in conjunction with chromatographic techniques, such as gas chromatography or supercritical fluid chromatography, or with ionization techniques that require higher source pressures, such as fast atom bombardment or high pressure chemical ionization. Using a jet separator to reduce the pressure within the ion cell, mass resolution for benzene (m/z 78) of 24,000 has been obtained, compared to 8000 without the jet separator (44). Pulsed valves have also been used to limit the gas load in the ion cell by admitting the GC effluent only during the ionization event and allow the gas to be pumped away prior to the ion detection step (45).

Separation of the ionization region from the analyzer region is another means of increasing mass resolution by reducing the pressure in the analyzer region and has the advantage of retaining high mass resolution with little or no loss sensitivity (12). This separation can be accomplished using a tandem quadrupole-FTMS arrangement (46, 47), an external ionization cell (48, 49) or the



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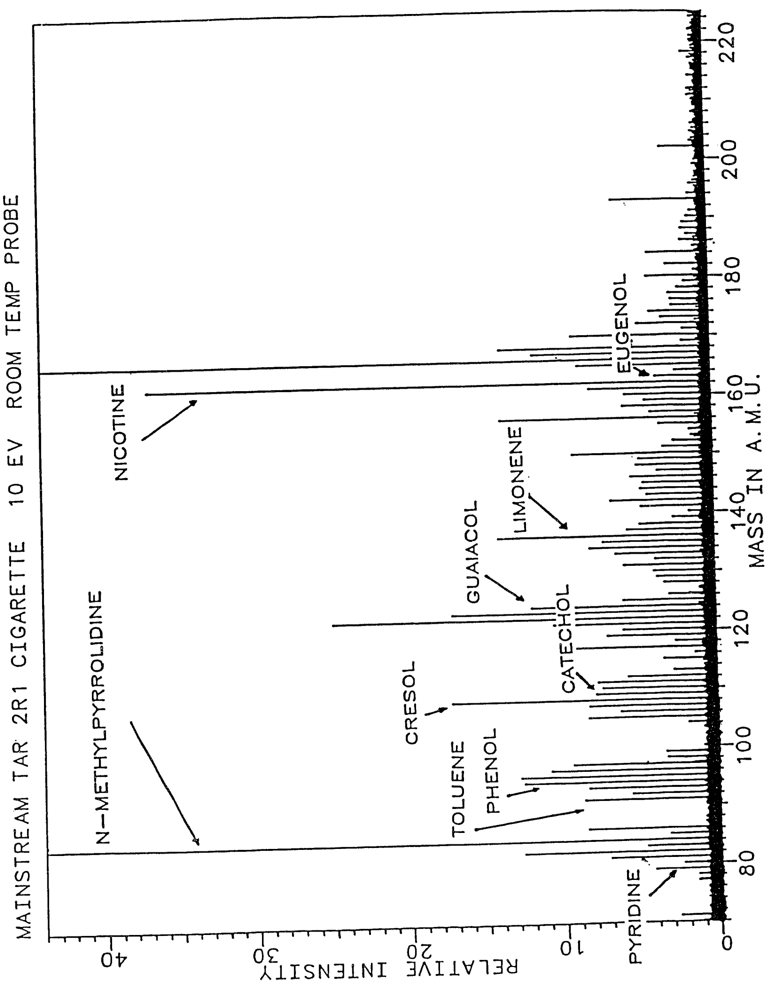


Figure 4. Medium resolution low energy (10 eV) electron ionization spectrum of tobacco smoke tar desorbed from a heated solids probe.

dual cell design (37) described earlier. Using a differentially pumped dual cell interfaced with a GC, mass resolution of 30,000 at m/z 174 has been reported (37). This is sufficient to allow chemical formulae of GC peaks to be determined. Recently, supercritical fluid chromatography has been successfully interfaced to an FTMS equipped with a dual cell (50).

Ion storage and manipulation. Once formed, ions may be trapped within the ion cell for as long as 5 x 10^4 seconds (51) prior to detection. During this time and prior to the excitation pulse and subsequent detection, a number of processes can be used to probe molecular structure. For example, if a short delay (tens to hundreds of msec) is introduced after ion formation, the low mass fragment ions formed from a molecule can react with neutrals to yield ionic products (17, 52). These ions, in turn, can serve as proton transfer agents to ionize remaining neutrals (18). This phenomenon has been called "self-CI" or reagentless CI because no reagent gas is required as in conventional chemical ionization (CI) techniques.

Low pressures (10^{-6} torr) of a reagent gas may be introduced during the delay between ion formation and excitation to provide more selective CI reactions, such as hydrogen/deuterium exchange reactions (18) or to provide a source of low energy electrons for electron capture negative ion CI reactions (53, 54). As in the case of "self-CI", the extent of these CI reactions may be controlled by changing the delay time between ion formation and excitation.

CI reactions using reagent gas pressures of greater than 10^{-6} torr have also been performed using pulsed valve introduction of the reagent (55), in a manner similar to pulsed valve GC/FTMS discussed previously. The CI products can be detected with higher mass resolution because the reagent gas is pumped away prior to the detection step. The dual cell (37) and external source designs (35, 46-48) are particularly well-suited for high pressure CI reactions. In the case of the dual cell, the reagent gas may be introduced into the source cell using either pulsed valves or a static pressure of reagent gas. After a specified delay time to allow the CI reactions to occur, the product ions are transferred to the lower pressure analyzer cell, where they are detected.

Chemical ionization reactions using so-called non-conventional reagents have also been performed using FTMS. These would include compounds with limited volatility that are not amenable for use in conventional high pressure CI sources. Chemical ionization in the FTMS experiment is accomplished by multiple collisions obtained by introducing longer delay times after ion formation, eliminating the need for high concentration of CI reagent ions. For example, metal ions can be readily formed by laser impact on metal targets (56). These ions have been shown to react selectively with organic compounds and have great potential for providing structural information (57, 58).

Ions can also be manipulated after formation by selective excitation using a radiofrequency pulse. A high-power rf pulse may be used to excite an ion (or group of ions) to a sufficiently large orbital(s) to cause neutralization on the cell plates (52). This process, called double resonance (52, 59), has a number of applications. For example, suspected reactant ions may be selectively ejected from the cell using double resonance to confirm their participation in observed ion-molecule reactions (17, 52). Another important application of double resonance is to increase the dynamic range of FTMS, which is generally limited to about 10^3 to 10^4. By ejecting a major ion in a spectrum, the dynamic range of the measurement can be increased, allowing the less abundant components to be observed.

Double resonance can also be used to isolate ions of a single mass in the cell so that additional gas phase reactions may be performed. An important example of this type of process is collisional activation (60, 61), or MS/MS, a technique of increasing analytical importance (62, 63). After the ion of interest is isolated, a second radiofrequency pulse (lower in energy than the ion ejection pulse) is used to excite the ion to a higher kinetic energy. The excited ion undergoes collisions with a suitable target gas, such as argon, which causes the ion to fragment. The mass spectrum of these fragment ions is characteristic of the original ion. At present, the resolution with which a parent ion may be selected is generally limited to unit mass. However, as will be discussed later, new excitation techniques should overcome this limitation.

With conventional MS/MS instruments, several types of mass analyzers are linked together to perform the isolation and analysis steps (62). FTMS performs these steps in one trapped ion cell. In addition, the isolation and excitation steps may be repeated to obtain MS^n. Recently, four stages of MS/MS or MS^5 has been reported using FTMS (64). The ultimate limitation of the number of MS/MS stages possible by FTMS is loss of the ion signal (due to collisional inefficiencies, ion-molecule reactions, and ion ejection), not hardware or software (15). Therefore, in extended multiple MS/MS experiments, such as the MS^5 experiment, it is advantageous to utilize conditions that minimize the number of different daughter ions produced. Extensive fragmentation reduces the percentage of the ion current carried by the daughter ion to be collisionally dissociated in the next step.

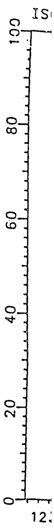
FTMS has several advantages for selected MS/MS experiments. First, the energy of the collision can be varied with the power of the excitation and is proportional to B^2r^2, where B is the magnetic field strength and r is the radius of the cyclotron motion. The ability to alter the energy of the collision can be of particular use in structural studies because collisional spectra are sensitive to energy (60). Typical collisional energies used in FTMS range up to a few hundred electron volts, which is considerably lower than for conventional tandem sector instruments, which can attain several thousand electron volts. In addition, the collisional energies obtainable with FTMS decrease as mass increases (15). However, by using larger cells and greater magnetic field strength, higher collisional energies can be acquired. For example, by employing a larger cell, high-energy charge stripping of benzene has been performed (65).

One distinction of FTMS for collisional dissociation is that these reactions proceed by multiple collisions, which can enhance the occurrence of rearrangement processes. After excitation, the population of ions has a finite kinetic energy distribution and this spread in ion kinetic energy is greater at lower excitation energies (66). Because of this, the daughter ion spectra obtained with FTMS can be less reproducible than with higher energy sector instruments.

Another advantage of FTMS for MS/MS experiments is that high resolution daughter ion spectra can be obtained. Using a single cell and narrow band (heterodyne)(7, 17) detection, daughter ion resolutions of several thousand have been reported (67, 68). A ten-fold increase in resolution for daughter ion spectra was reported when pulsed valves were used to introduce the collision gas and allow it to be pumped away prior to mass analysis (12). Use of a differentially pumped dual cell has allowed much higher resolution daughter ion spectra to be obtained (69). Figure 6 shows a spectrum obtained on the m/z 105 ions obtained from the dissociation of the m/z 120 ions from 1,3,5-trimethylbenzene (mesitylene) and acetophenone. The parent ions were formed by electron impact at 10 eV in the high pressure source cell, and ions of lower mass were ejected by double resonance pulses. The m/z 120 ions were excited to an energy of 125 eV (laboratory frame of reference) and collided with argon, present in the source cell at a pressure of 6 x 10^{-6} torr. The daughter ions were then pulsed across the conductance limit into the lower pressure (1 x 10^{-8} torr) analyzer cell, where they were detected with a resolution of 211,000 (FWHM). Similar experiments with negative ions have yielded daughter ion spectra with resolution in excess of 320,000 (FWHM) at m/z 46 from 2,4-dinitrotoluene.

Other means of manipulating ions trapped in the FTMS cell include photodissociation (70-74), surface induced dissociation (75) and electron impact excitation ("EIEIO")(76) reactions. These processes can also be used to obtain structural information, such as isomeric differentiation. In some cases, the information obtained from these processes gives insight into structure beyond that obtained from collision induced dissociation reactions (74). These and other processes can be used in conjunction with FTMS to study gas phase properties of ions, such as gas phase acidities and basicities, electron affinities, bond energies, reactivities, and spectroscopic parameters. Recent reviews (4, 77) have covered many examples of the application of FTMS and ICR, in general, to these types of processes. These processes can also be used to obtain structural information, such as isomeric differentiation.

Ionization of Non-volatile Samples. In addition to electron impact ionization and chemical ionization, which were discussed earlier, FTMS can be used in conjunction with a variety of other ionization techniques. The wide mass range and high mass resolution capabilites of FTMS make it particularly well-suited for the analysis of high molecular weight compounds, such as polymers and biological samples. These compounds typically have limited volatility due to high molecular weight and/or polarity and are



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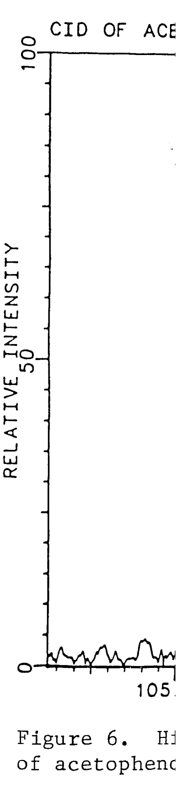

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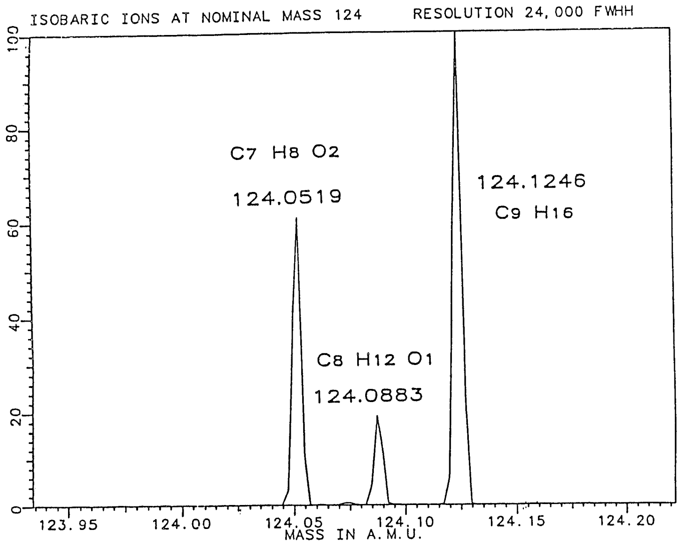

Figure 5. Expansion of the region around m/z 123 of Figure 4 showing three well-resolved isobaric ions.

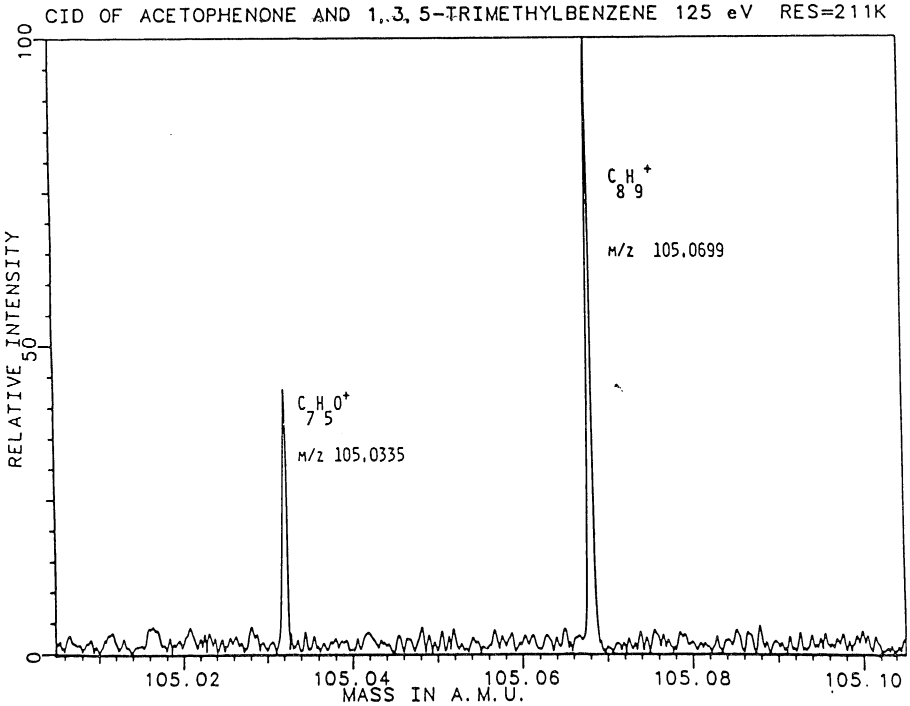

Figure 6. High-resolution CAD daughter ion spectrum of a mixture of acetophenone and 1,3,5-trimethylbenzene from m/z 120 parent ions.

difficult to ionize using conventional techniques. A number of so-called "soft ionization" techniques have been developed for the analysis of high molecular weight compounds by mass spectrometry, including laser desorption, secondary ion methods, and plasma desorption. All of these techniques are applicable to FTMS. In addition, field desorption, one of the first "soft ionization" techniques, has recently been used with FTMS (78).

The combination of FTMS and lasers (79) is particularly well-suited for ionization of non-volatile samples (80) because the FTMS experiment is amenable to non-continuous ion production provided by pulsed lasers. Further, laser desorption offers a means of generating high mass ions with a minimum of fragmentation. After ionization, the versatile features of FTMS can be used to obtain structural information on these high mass ions.

Metal ions have been produced from metal targets using a pulsed Nd/YAG laser and reacted with organics for subsequent study by FTMS (21, 81, 82). Further, cluster ions can be formed by laser desorption and subsequently studied by FTMS (49, 83). In an early study, FTMS spectra of polar and zwitterionic compounds were obtained using a pulsed TEA CO_2 laser (22). Since that time, pulsed lasers have been employed for the ionization of non-volatiles in a number of studies (19, 37, 84-86). For example, the molecular weight distributions of polymers with average molecular weights of up to 6000 daltons have been determined using a pulsed CO_2 laser (87). Solutions of the polymers were doped with either KBr or NaCl and the resulting spectra revealed no significant fragmentation, simplifying molecular weight characterization.

Laser desorption has been employed to ionize nucleosides, oligosaccharides and glycosides, generating both positive and negative ions in the resulting FTMS spectra (88). Laser desorption FTMS has also been used to obtain sequence information on mixtures of peptides (89). Selective excitation of the molecular ions produced by laser desorption was followed by collisional activation to yield complete sequence information on a cyclic decapeptide and for 12 of 15 amino acids of a linear peptide. Oligonucleotides have been studied using laser desorption FTMS and collisional activation, as well (90). Figure 7 shows a negative ion daughter spectrum obtained from the adenine base originally contained in the tetranucleotide d(AGCT), or deoxy(adenosine-guanosine-cytidine-thymidine). This tetranucleotide, which has a molecular weight of 1173 daltons, was ionized using the fundamental line of a Nd/YAG laser at 1064 nm. The fragment anion at m/z 134 was isolated and identified as adenine, based on collisional dissociation, forming a daughter ion at m/z 107, which corresponds to a loss of HCN.

Structural information on ions produced by laser desorption has also been obtained by using infrared multiphoton dissociation processes (73). A pulsed CO_2 laser was used to form the ions, which were further fragmented either by using sequential pulses from the same laser or by using a gated continuous wave infrared laser.

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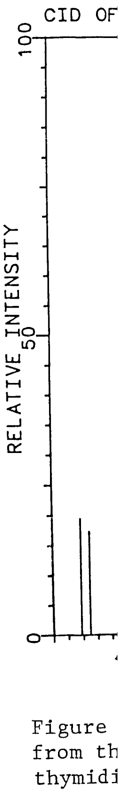

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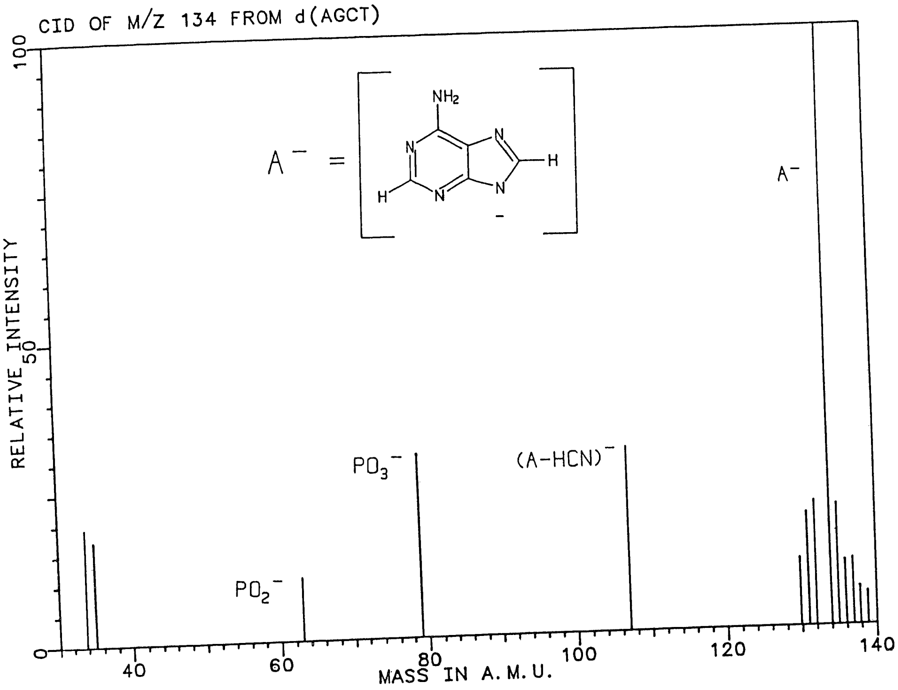

Figure 7. Daughter ion spectrum from the m/z 134 anion isolated from the tetranucleotide deoxy(adenosine-guanosine-cytidine-thymidine). Ions were generated by laser desorption from a direct insertion probe.

ionize erythromycin (91) and produced a very clean spectrum with about two orders of magnitude less sample than fast atom bombardment (FAB). In addition, greater molecular weight information was obtained with the LD/EI/FTMS spectrum than with the FAB spectrum.

Particle induced desorption methods are commonly used to ionize low-volatility compounds. Cesium ion desorption (or cesium ion secondary ion mass spectrometry, SIMS) uses a primary beam of cesium ions to desorb and ionize a non-volatile sample. This technique has been used with FTMS to produce pseudomolecular ions of vitamin B_{12}, $\{(B_{12})_2 + Cs - 2CN\}^+$, at m/z 2792 (24) and molecular ions of *beta*-cyclodextrin (m/z 1135) (92, 93). Detection limits of 10^{-13} mol for the peptide gramicidin S has been demonstrated using Cs^+ SIMS with FTMS (25), and additional structural information was obtained using MS/MS processes.

Fast atom bombardment has been used with an FTMS instrument equipped with an external source (46, 94), and protonated molecules of cytochrome C at m/z 12,385 have been observed. Recently, ^{252}Cf plasma desorption (PD) (95) has been used in conjunction with FTMS (27, 75, 96, 97), and spectra of compounds with molecular weights up to 2000 daltons have been observed (27, 75). This technique has generally been used only with time-of-flight (TOF) mass spectrometers because the ion currents obtainable are typically too low for scanning instruments. PD ionization with FTMS offers a number of advantages over PD/TOF, including higher mass resolution and the capability of ion manipulation to probe molecular structure.

Future Developments and Applications of FTMS

Two important features of FTMS that will be widely exploited in the future are the ultra-high mass resolution and the wide mass range of the technique. It should be noted that to a considerable extent, the need for greater mass range and higher mass resolution has been stimulated by the development of specialized ionization techniques such as laser desorption, fast atom bombardment, plasma desorption, and secondary ion (SIMS) methods. As these and other processes for the production of gas phase ions from involatile solid samples are developed and refined, FTMS will be exceptionally useful for the mass analysis of these materials. For example, the analysis of biopolymers by mass spectrometry is an area that is growing rapidly at present (98). For ordinary protein and nucleotide sequencing, mass spectrometry can be used as an adjunct to traditional biochemical techniques. However, for modified or N-terminus blocked proteins, for which the conventional Edman degradation method often fails, mass spectrometry will be important in its own right (98). Similarly, FTMS could be used to sequence modified nucleotides.

The ultra-high mass resolution capabilities of FTMS will also be used in the future for accurate determination of nuclide masses. It is possible that all the known stable nuclides will have their masses reexamined by FTMS. A recent example of this type of measurement is the determination of the difference in mass between $^{3}He^{+}$ and $^{3}H^{+}$ by FTMS (99), which may be used in conjunction with other data to establish the mass of the antineutrino. Another interesting use of ultra-high resolution FTMS is the direct determination of the relativistic mass difference between the ground state and metastable excited state of ions, such as Ar^+ (100).

FTMS also has the potential of becoming an important tool for determining molecular structure. Traditionally, mass spectrometry has been rather limited in its ability to determine the structure of an unknown compound unambiguously. Additional structural methods, such as nuclear magnetic resonance or crystallography, are commonly used in conjunction with mass spectrometry to elucidate the identity of a molecule. However, when the amount of sample is severely limited or when the sample is a component in a complex mixture, mass spectrometry is often one of the few analytical techniques that can be used.

The ability to trap and manipulate ions in the FTMS makes this a potentially powerful tool for structural determination. The FTMS has been described as a "complete chemical laboratory" (101, 102), where reactions can be used to "pick apart" a molecule systematically using sequential CAD, photodissociation, chemical reactions, or other techniques. As selective and sensitive processes for these reactions are developed, FTMS has the potential of yielding detailed information on the structure of a molecule which is currently only obtainable using techniques that require considerably larger sample sizes. It should also be noted that reactions of trapped ions with neutrals can be also be devised for the step-wise synthesis of a particular species in the FTMS (102, 103).

As noted earlier, the development of the dual cell (37), tandem quadrupole-FTMS (46, 47) and external ionization cell (48, 49) has facilitated the coupling of FTMS and chromatographic methods. Advances in interfacing separation techniques with FTMS will be important in the analysis of mixtures, especially where high mass resolution is required. For example, liquid chromatographic introduction of mixtures isolated from biological systems directly into an FTMS for analysis would eliminate the need for laborious sample clean up.

The future of FTMS from an instrumental standpoint also shows considerable potential. The performance of any FTMS instrument is dependent upon the performance of the computer, magnet, and the vacuum system. While no substantial improvements are on the horizon for the price/performance ratio of vacuum components, the price/performance ratio of computers and magnets improve each year. It is reasonable to expect that the steadily decreasing price of computers and magnets will lower the cost of FTMS instruments and promote their more widespread application. In addition, with the recent surge of research in higher temperature superconducting magnets, it is possible that much smaller, less expensive, and easier to maintain magnets might be available in the future. The commercial development of small, lower performance FTMS instruments based on lower field magnets or other means of ion trapping are also a possibility in the future.

Finally, in addition to computers becoming more powerful, faster, and less expensive, new mathematical- and computer-based concepts are being developed to increase the capabilities of FTMS. One example, which is outlined in a subsequent chapter in this volume (104), is Stored Waveform Inverse Fourier Transform techniques, or SWIFT. These new techniques have the potential to reduce substantially the previous limitations of FTMS with respect to areas such as dynamic range, accurate isotopic ratios, and high resolution parent ion selection in MS/MS experiments.

The high performance capabilities of FTMS, combined with the ability to manipulate trapped ions, makes the FTMS an extremely versatile and powerful tool. The future promises to bring even greater capabilities to this relatively new technique. More applications of FTMS to diverse fields will be seen, as well as the maturation of FTMS into a routine analytical technique.

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