Fourier Transform Ion Cyclotron Resonance Mass Spectrometry

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In 1965, Cooley and Tukey introduced a fast algorithm which made possible the discrete Fourier transform of a large data set (ca. 10 000 points) by a minicomputer in less than 1 min.[1] Their paper has since become the most highly cited article in all of mathematics.[2] Some of the reasons are evident from Table I, which lists the major advantages of Fourier methods for infrared, nuclear resonance (NMR), and ion cyclotron mass spectrometry.

The versatility and unique analytical capabilities of Fourier transform spectrometry in general[3,4] and Fourier transform ion cyclotron mass spectrometry (FT/ICR) in particular[5-7] have recently been reviewed. Stated most simply, the main advantage of the FT approach is that one obtains the whole spectrum at once, rather than just one frequency at a time. We are biased by our eyes and ears to classify our experiences in terms of *frequency*: light according to its color or sound according to its pitch. However, we can hear all pitches at once in the *time* domain, as when an orchestra plays. The Fourier transform converts data from the *time* domain into the more familiar *frequency* domain. Fourier transform (FT) spectrometry therefore consists of acquistion of data points as a function of time, followed by discrete FT to yield the more familiar frequency-domain spectrum.

Fourier transform ion cyclotron resonance mass spectrometry (FT/ICR) has also been called simply "Fourier transform mass spectrometry" (FT/MS). However, in view of the recent development of Fourier transform time-of-flight (FT/TOF) mass spectrometry,[8] the ion cyclotron experiment is best designated as FT/ICR.

The development of the FT/ICR technique was a combination of insight, circumstances, and timing. More than for most new analytical methods, the scope and advantages of the technique were predictable in advance. It is therefore instructive to begin by tracing the thinking which led to the conception and first experimental demonstration of the FT/ICR method late in 1973.[9]

An ion cyclotron[10] relies on the use of a fixed magnetic field, $\vec{B}$, to deflect an ion of charge, q, moving at velocity, $\vec{v}$, according to the Lorentz force, $\vec{F} = q\vec{v} \times \vec{B}$. For spatially uniform $\vec{B}$, a moving ion of mass, m, will be bent into a circular path in a plane perpendicular to the magnetic field, with a natural angular frequency, w_0.

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$$w_0 = qB/m \quad \text{(mks units)} \tag{1}$$

Thus, if the magnetic field strength is known, measurements of the ion cyclotron frequency in eq 1 suffices (in principle) to determine the ionic charge-to-mass ratio, q/m. In other words, a static magnetic field effectively converts ionic *mass* into *frequency*. Because the cyclotron frequencies for singly charged ions ($12 < m/q < 5000$) in a magnetic field of ca. 3 T span a radiofrequency range (10 kHz $< \nu_0 <$ 4 MHz) within which frequency can be measured with high precision, the ion cyclotron clearly offers the prospect of ultrahigh mass resolution.

Excitation and Detection of Ion Cyclotron Motion

Figure 1 shows a schematic ion cyclotron. Ions may be formed by irradiation of a neutral gas or solid by an electron beam (or laser or ion beam) directed along the magnetic field direction. The ions are trapped in the rectangular "cell", because the static magnetic field, B, constrains the ions from escaping anywhere in a plane perpendicular to the paper, and a small (ca. 0.3 V/cm) static "trapping" voltage on the two end plates, T, prevents the ions from escaping in a direction parallel (or antiparallel) to the magnetic field.

However, even ions of the same m/q and initial velocity are created at random time intervals, and therefore with random phase (i.e., at random points on their circular path)—thus, their incoherent motion cannot produce a detectable macroscopic signal. In order to detect the ions, it is necessary to move them "off center", by applying an electric field oscillating at w_0 to plates E of Figure 1. The rf electric field pushes the ions continuously forward in their orbits, and the original ion packet spirals outward.

By 1973, two general methods for detecting the excited ion cyclotron motion were in use. The first was the 1949 "omegatron",[11] which measured the current

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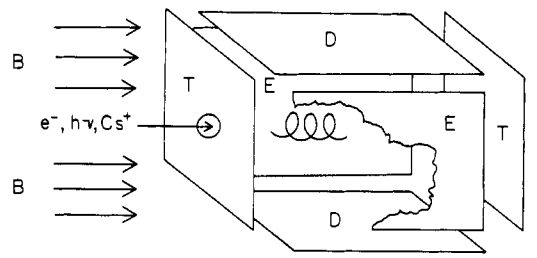

Figure 1. Schematic diagram of the sample chamber ("cell") in an ion cyclotron mass spectrometer. See text for distinctions between omegatron, ICR, and FT/ICR.

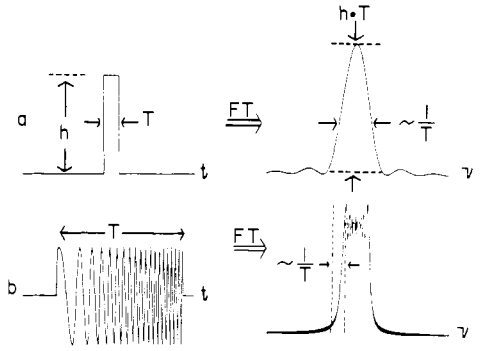

Figure 2. Time-domain excitation waveforms (left) and their corresponding frequency-domain magnitude-mode spectra (right). FT/ICR experiments were first performed with a rectangular rf pulse (a), are currently done with a fast frequency sweep (b), and may be performed in future with tailored excitation (see text).

produced as ions continuously spiralled outward onto a detector plate (labeled "D" in Figure 1). The omegatron proved to have relatively low mass resolution and was used mainly for gas analysis. The second was Wobschall's "resonant" detection of the power consumed as ions were excited to larger orbits,[12] which appeared commercially as Llewelyn's "ion cyclotron resonance" (ICR) spectrometer.[13]

Broad chemical interest in ICR dates from the 1966 demonstration by Baldeschwieler and co-workers that double-resonance ICR[14] (i.e., heating and/or ejecting ions of one m/q ratio while observing another m/q ratio) could be used to establish ion-molecule reaction connectivity in much the same way that double resonance had been used to determine spin-coupling connectivities in nuclear resonance.[15] An early application was Brauman and Blair's demonstration[16] that toluene was more acidic than water in the gas phase—startling, because in the liquid phase, the equilibrium acid dissociation constant for water was known to be 20 orders of magnitude larger than for toluene. Subsequent ICR results made it possible to compare gas-phase (i.e., intrinsic) molecular acidities and basicities[17] in the absence of the solvent effects which had previously obfuscated such comparisons. ICR is now generally acknowledged as the method of choice for study of gas-

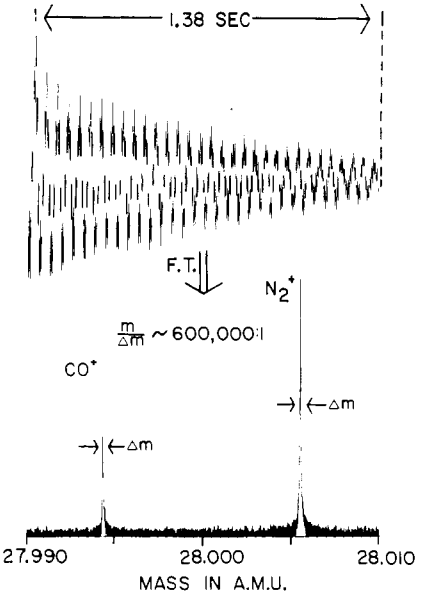

Figure 3. Time-domain (top) and frequency-domain (bottom) ion cyclotron signals for ions of two m/q ratios. Note that the slow oscillation due to ions of higher mass and the rapid oscillation due to ions of lower mass are seen simultaneously in the time-domain heterodyne "beat pattern" (left). Thus, digitization followed by discrete Fourier transform of the time-domain data gives a frequency-domain representation in which the whole mass spectrum is obtained at once (right). Note that FT/ICR performed at a modest magnetic field strength (3.0 T) can produce both high sensitivity (sample pressure was only 6×10^{-9} torr) and high mass resolution (N_2^+ and CO^+ differ in mass by only about 0.011 amu) simultaneously. (Data obtained by T.-C. L. Wang.)

phase ion-molecule reaction rate constants and equilibria, as evidenced by the four American Chemical Society awards in Pure Chemistry that have gone to researchers using ICR (Baldeschwieler, Brauman, Beauchamp, and Freiser).

In spite of its great utility for ion-molecule chemistry, the single-frequency ICR spectrometer was badly limited with respect to mass resolution and speed. Consider first the speed problem, which was very similar to that for continuous-wave carbon-13 NMR. Only one m/q ratio could be excited and detected at a time, much as in a scanned single-slit optical spectrometer. For example, acquisition of an ICR spectrum with fixed-frequency detection required slow (ca. 30 min) scanning of the magnetic field strength. By the early 1970's, Fourier transform methods for exciting and detecting a whole spectrum at once were becoming widely available for infrared[18] and nuclear magnetic resonance (NMR)[19] spectroscopy. It seemed to me that similar FT methods ought to apply to ICR. I broached the idea late in the summer of 1973 to Melvin Comisarow, who had joined me on the faculty at the University of British Columbia 2 years earlier. Comisarow had just finished building a state-of-the-art single-frequency ICR instrument, and we decided to pursue the idea experimentally.

FT/ICR required two principal conceptual innovations: exciting the whole spectrum at once and detecting the whole spectrum at once. My first idea for excitation, by analogy to FT/NMR, was rectangular rf (radio frequency) pulse (see Figure 3a). Its frequency spectrum spans a range of about $1/T$ Hz, in which T

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is the duration of the pulse. Pulsed excitation is therefore suitable for irradiation of a narrow frequency range (i.e., narrow mass range) and was used for the first FT-ICR experiment.[9] However, the frequency-domain *amplitude* of such an excitation is proportional to the *area* of the time-domain pulse.[3,4] For example, in order to excite a wide frequency range (ca. 2 MHz), the pulse must be so short (ca. 0.1 μs) that its amplitude becomes unreasonably high (>10^4 V).[20] It was therefore necessary to lengthen the time-domain excitation in order to reduce the required excitation power. By analogy to continuous-wave ICR, Comisarow reasoned that if a slow frequency sweep with a few millivolt rf amplitude could excite a spectrum one peak at a time during ca. 20 min, then the same excitation should be achieved via a fast (ca. 1 ms) frequency sweep (or "chirp") excitation with an amplitude of a few tens of volts. Chirp excitation, followed by detection *after* the excitation is turned off, was then implemented for wide-band excitation[21] and is still found in all 30-odd FT/ICR instruments now in use. Its power spectrum is shown in Figure 3b and is described in detail elsewhere.[20,22]

By analogy to FT/NMR I knew of two lower-power excitation waveforms, both involving detection *during* the excitation period. The first is a rapid sweep across the frequency range of interest, as in correlation NMR.[23,24] We rejected this method, later pursued by McIver,[25] for the same reasons it was abandoned in NMR: difficulty in suppressing the excitation received at the detector, even when excitation and detection are provided by separate plates in ICR (or crossed coils in NMR); and difficulty in tuning for a relatively sharp optimum in sweep rate, sweep range, and sweep amplitude. The second method is time-shared stochastic excitation/detection, a related version of which had just been demonstrated in NMR.[26] However, the electronic requirements for stochastic excitation/detection could not be met in 1973, and the experiment has only recently become feasible (see below).

The second new aspect was broad-band detection. The prevailing ICR detector was a marginal oscillator,[27] which is a device that detects power absorption at a single frequency. This device is not readily tunable over a wide frequency range. On the basis of the theory of dielectrics,[28] ICR motion can be modeled as a rotating monopole (or rotating electric polarization) which induces an oscillating charge (and hence an electric image current) in the detector plates (D in Figure 1).[29] Comisarow built a broad-band amplifier which could simultaneously amplify such currents from ions of widely different m/q ratios. The new detector provided both absorption and dispersion spectra,[30] whereas a marginal oscillator could give only an absorption spectrum. Thus, just as FT/NMR detection is based upon the magnetization signal induced in a detector coil, FT/ICR detection is based upon the oscillating electric current induced in a pair of detector plates.

The multichannel advantage of FT/ICR is apparent from Figure 3. The oscillating voltages induced by excited ions of different mass-to-charge ratios add together to give the time-domain digitized envelope shown in Figure 3a: a slowly oscillating signal from ions of higher mass, plus a rapidly oscillating signal from ions of lower mass. A discrete Fourier transform of the digitized time-domain data gives the frequency-domain spectrum (which can be rescaled as a mass-domain spectrum) of Figure 3b.

At this stage, one might wonder why FT/ICR was not developed until eight years after introduction of the Cooley–Tukey algorithm[1] which made FT computations feasible for minicomputers, whereas FT/IR[18] and FT/NMR[19] appeared almost immediately after publication of that algorithm in 1965. Apart from the considerations already mentioned, one necessary prior development was the "trapped-ion" cell,[31] which made it possible to retain ions for the 100+ ms period needed for high-resolution detection. A second critical component was a fast 8-bit analog-to-digital converter, since the range of ICR frequencies typically spans a few MHz, whereas most NMR spectra spans a few tens of kilohertz; such devices were only becoming available in the early 1970's.

Spectral Line Shape and Mass Resolution

A valuable feature of the FT/ICR experiment is the wide range over which the system is linear: i.e., the detected signal amplitude is proportional to the excitation amplitude. When such a linear relationship holds, it is not necessary to compute the detailed trajectories of the ions in order to predict the spectral line shape. We therefore began by deriving the line shape in the "zero-pressure" limit that ions undergo essentially no ion-molecule collisions during the detection period[32] and then generalized the theory to include the effects of ion-molecule collisions at finite pressure.[33] Effects of noise are also predictable.[34]

For example, once it was recognized that mass resolution and frequency resolution in FT/ICR are the same,[32] then it was straightforward to compute mass resolution as a function of magnetic field strength, ionic mass/charge ratio, data acquisition period, and time-domain signal damping constant (which is proportional to sample pressure).[33] Mass resolution was predicted to vary directly with magnetic field strength and inversely with sample pressure, as later confirmed experimentally.[35,36]

In NMR, the static homogeneity of the applied magnetic field largely determines spectral resolution, which is thus comparable in both continuous-wave NMR and FT/NMR. However, an unanticipated ad-

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Table I.
Advantages of Fourier Transform over Continuous-Wave Spectrometry

feature	improvement factor	applicable to
speed	10000	IR, NMR, MS
signal-to-noise	100	IR, NMR, MS
automation		IR, NMR, MS
double resonance	no. of coupled spins or ions	NMR, MS
resolution	10000	MS
upper mass limit	30	MS

vantage of FT/ICR was that the observed mass resolution was not only substantially higher than for continuous-wave ICR with the same magnet but was much higher than the measured static homogeneity of the applied magnetic field at the sample.[37,38] For example, mass resolution of 100 000 000:1 has been reported at m/q 18.[39] The explanation is that the magnetic field gradients are mainly radial. Thus, in continuous-wave ICR, ions travel spiral paths during detection and experience various magnetic field values along the way, whereas ions during FT/ICR detection circulate at a fixed radius over which the magnetic field is more homogeneous. The phenomenon resembles spinning the sample in NMR, except that the spinning is due to the intrinsic cyclotron motion itself rather than to any external forces.

In magnetic-deflection mass spectrometers, mass resolution is increased by narrowing the detector slit, with concomitant loss in signal-to-noise (S/N) ratio. However, FT/ICR S/N ratio depends on the number of ions, which can be kept constant as the sample pressure is lowered.[37,40] Thus, FT/ICR is inherently capable of high S/N ratio and high mass resolution at the same time (e.g., Figure 3), a unique analytical advantage.

A magnetic field-swept mass spectrometer (e.g., magnetic sector or continuous-wave ICR) gives fixed mass resolution throughout its mass range by "throwing away" mass resolution at low m/q. In contrast, an FT/ICR instrument operates at fixed magnetic field and thus produces the maximum possible resolution at all m/q values. As a result, FT/ICR mass resolution is inversely proportional to m/q.[32] Thus, one will ultimately reach a mass limit for which two peaks separated by 1 amu are barely resolved.[33] For a 1-in. cubic cell[41] at 3 T and a limiting sample pressure of about 10^{-9} torr, this upper mass limit is about 3000 amu; the limit can readily be raised by using higher magnetic field strength, lower sample pressure, and/or larger ion cyclotron radius.

The principal analytical interest in high mass resolution is for mass calibration and precise mass measurement of unknown species to determine the chemical formula (as demonstrated in Figure 3 for N_2^+ and CO^+). Because no mass spectrometer is linear over a wide mass range at the ppm level required for such measurements, it is necessary to calibrate the mass scale by use of ions of known mass.[36,42,43] However, an important FT/ICR advantage over magnetic-deflection mass spectrometers is that the FT/ICR instrument can be calibrated with high precision (±0.001 amu) over a wide mass range *simultaneously*, as shown in Figure 4.

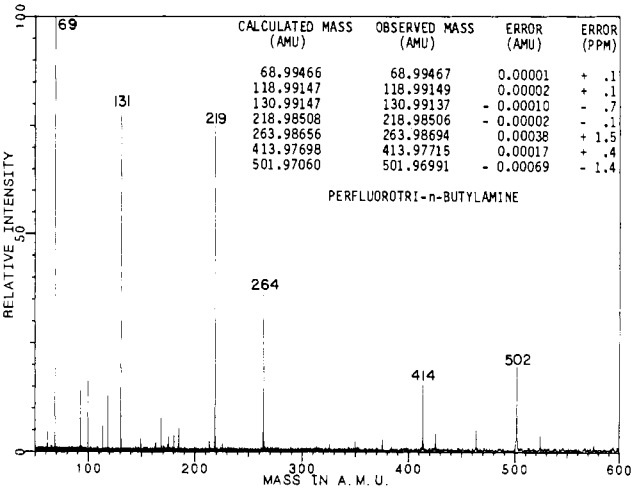

Figure 4. Fourier transform mass spectral calibration over approximately one decade in mass, for time-domain data obtained in approximately 0.1 s, using a Nicolet FT/MS 1000 instrument with 1-in. rectangular cell. For observed peak frequencies, ν, mass calibration was based on least-squares best-fit to an equation of the form[43,44] $m = (A/\nu) + B/(\nu^2)$. The calculated mass for each singly charged positive ion peak was obtained by subtracting the mass of an electron from the total mass of the most abundant isotopes for each peak. [Reprinted with permission from Marshall, A. G. Texas A&M ICCP Symp., April 1985 (Texas A&M University Press).]

Table II.
FT/ICR Features for Analytical Mass Spectrometry

sample pressure	(0.1–1000) × 10^{-9} torr
mass resolution	to 4 000 000 at m/z 131
speed	0.01 –1 s/scan
EI/CI/laser/Cs^+	one source
chemical ionization	no reagent gas
MS/MS/...	one spectrometer
+/− ions	one switch
upper mass limit	ca. 100 000 amu
slits	none
high voltage	none
GC/MS	high dynamic mass resolution
automation	

Low-Volatility Samples

The vast majority of mass spectra are produced by electron ionization of a gaseous sample. Most mass spectrometers require a sample pressure of ca. 10^{-5} torr in the ion "source". Unfortunately, heating a low-volatility compound to 200–300 °C to reach that vapor pressure often leads to pyrolysis of the neutral molecule before the necessary vapor pressure of the parent molecule can be attained. Because the FT/ICR instrument inherently operates at about 1000 times lower sample pressure, it is now possible to obtain mass spectra of low-volatility samples from an ordinary solids "probe".

For example, Figure 5 shows the FT/ICR mass spectrum of a large mixed-metal cluster, obtained at 95 °C at a sample pressure of about 2 × 10^{-8} torr. The parent peaks corresponding to the various isotopes of

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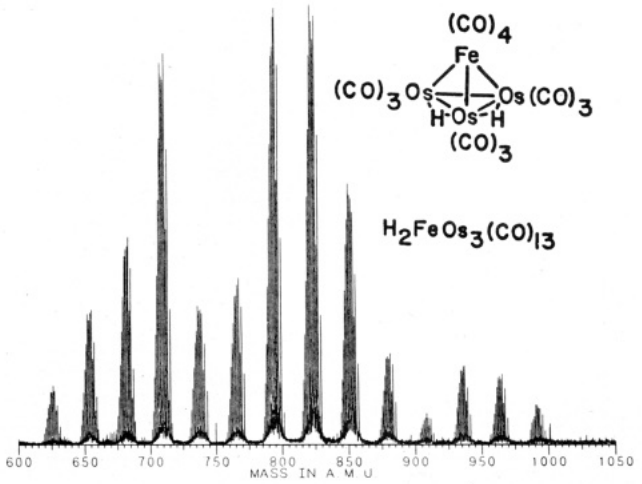

Figure 5. FT/ICR positive ion mass spectrum (50-eV electron ionization energy) of $H_2FeOs_3(CO)_{13}$, run at 95 °C as a probe sample in a Nicolet FTMS-1000 spectrometer. The spectrum was obtained with the help of S. L. Mullen from a sample kindly furnished by S. G. Shore.

$H_2FeO_3(CO)_{13}^+$ are clearly visible in the vicinity of 990 amu. In addition, there are fragment multiplets corresponding to loss of each of the 13 carbonyls. This result is representative of a series of more than a dozen triosmium and other mixed-metal clusters.[5,44,45]

Self-Chemical Ionization

Electron ionization (EI) often produces extensive fragmentation in a positive-ion mass spectrum, so that the peak for the parent ion, M^+, may be small or even absent. In such cases, chemical ionization is a well-known technique for producing, for example, $(M + H)^+$ ions by transfer of protons from some other reagent ion to the parent neutral of the unknown compound. However, the method requires relatively high reagent gas pressure (ca. 1 torr) and usually an ionization source of different geometry.

However, in many instances it turns out that a parent neutral has a higher proton affinity than the neutrals formed by proton loss from some of the daugher fragment ions produced by electron ionization. The cubic trapped-ion cell[31,41] used in FT/ICR can trap ions for as long as several hours. Thus, after formation of ions by traditional electron beam ionization, ion-molecule reactions act to transfer protons from daughter ions to parent neutrals to yield a prominent $(M + H)^+$ peak which facilitates sample identification. At typical FT/ICR operating pressure (10^{-7} to 10^{-8} torr), the reaction period need be only a few seconds. This experiment has been called "self-chemical ionization" or self-CI.[46] (For cases in which self-CI is not successful, a pulsed-valve technique[47,48] may be used to introduce a conventional CI reagent gas.) The important new feature here is that both EI and self-CI spectra can be obtained from the same source geometry and sample pressure, simply by changing the time sequence for the experiment, without the introduction of a reagent gas.

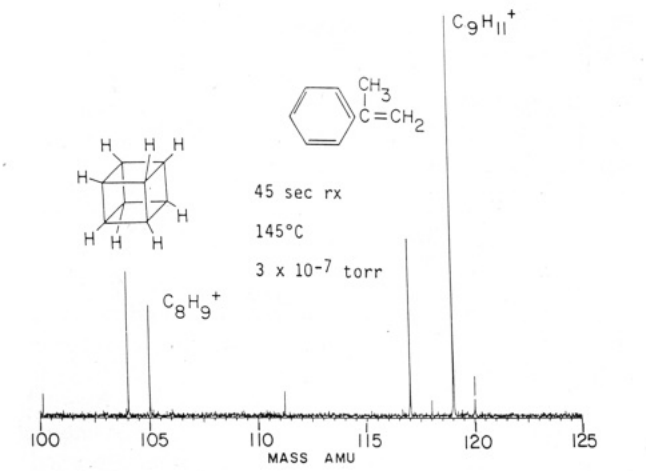

Figure 6. Positive-ion Fourier transform mass spectrum from a mixture of cubane and α-methylstyrene at approximately equal partial pressures. Ions formed by electron impact were allowed to equilibrate for approximately 45 s before this spectrum was taken. Cubane has the lower gas-phase basicity, as determined from the relative intensities of the two protonated molecular ions ($C_8H_9^+$ and $C_9H_{11}^+$). (Spectrum obtained by I. Santos; cubane was provided by L. A. Paquette.)

Ion-Molecule Reactions and Gas-Phase Acidity and Basicity

A traditional application of (non-FT) ICR has been the determination of gas-phase ion-molecule reaction rate constants and equilibrium constants, particularly gas-phase acidities and basicities.[7,17,49] For example, a gas-phase basicity (namely, $-\Delta G°$ for the reaction $M + H \rightleftharpoons MH^+$) can be determined simply by ionizing (by electron impact) a mixture of known partial pressures of an unknown and a compound of known basicity, waiting a few seconds for the ions to equilibrate, and measuring the relative mass spectral peak areas of the two protonated molecular ions. Figure 6 shows such an experiment for (unknown) cubane ($-\Delta G°$ = 198.7 kcal/mol) mixed with (known) α-methylstyrene ($-\Delta G°$ = 200.0 kcal/mol).[50]

Laser Desorption/Ionization

Several techniques previously well-developed for other types of mass spectrometers have been adapted to FT/ICR, including: laser desorption,[51,52] gas-chromatograph mass spectrometry,[53,54] secondary ion mass spectrometry,[55] double-resonance,[56] and collision-activated dissociation.[57] Ion ejection and collisional activation have been combined to yield MS/MS[58,59] up

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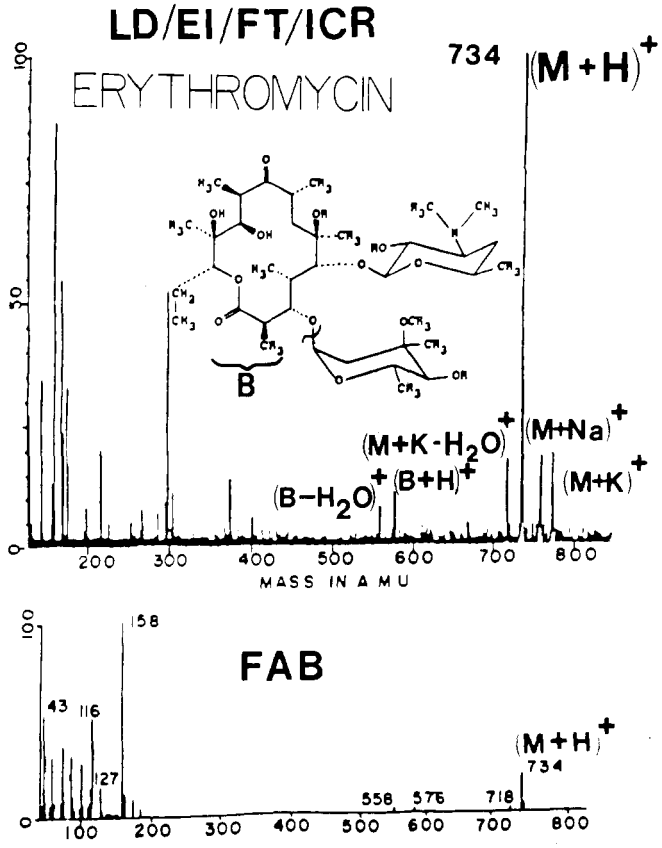

Figure 7. Positive-ion mass spectra of erythromycin. (a) Fast-atom bombardment with a Kratos MS-30 double-focusing mass spectrometer. (b) Laser desorption with a Nicolet FTMS-1000 spectrometer. (Reprinted with permission from ref 61.)

to *four* stages $(MS/MS/MS/MS)^{60}$ using a *single* spectrometer.

For involatile samples, laser desorption/ionization affords a simple and practical means for generating high-mass ions with a minimum of fragmentation. Typically, 100 ng of sample is dissolved in about a microliter of solvent containing a potassium salt, and the solution is then smeared on the tip of a stainless-steel probe. The solvent is allowed to evaporate, and a pulsed CO_2 laser beam (ca. 1 J in 50 ns) is directed to a spot about 1 mm^2 in area. A single laser pulse volatilizes essentially all of the sample at the spot and can produce a very clean mass spectrum, with ca. 2 orders of magnitude less sample than FAB/MS. Figure 7 compares laser desorption/ionization FT/ICR and fast-atom-bombardment mass spectra of erythromycin.[61] The pseudomolecular $(M + H)^+$ ion at m/q 734 is barely visible by FAB but is prominent in LD/EI/FT/ICR (note also $(M + K)^+$ at 772). The laser spectrum also contains a peak corresponding to the amino sugar fragment at m/q 158. This sort of spectrum is typical of a wide range of other large organics and organometallics: e.g., amoxicillin, daunorubicin, and digoxin. Finally, four classes of mass spectra can be obtained from a single sample and mechanical configuration: positive or negative ions produced directly by the laser and electron-impact positive or negative ions formed from neutrals desorbed by the laser.

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GC/FT/ICR

At first inspection, gas chromatography would not appear to be compatible with FT/ICR, because FT/ICR requires relatively high vacuum ($\leq 10^{-8}$ torr) for optimal operation. In fact, GC/FT/ICR experiments to date have had to sacrifice sensitivity by using an open split, jet separator, or pulsed valve to reduce the effluent GC gas load on the FT/ICR detector. A better solution which regains high mass resolution without losing sensitivity is the dual-cell recently designed by Littlejohn and Ghaderi.[62] Their system should make feasible the first GC/MS with high chromatographic resolution as well as excellent "dynamic" mass resolution (30 000:1 at m/q 174),[62] so that chemical formulas of GC peaks may be determined "on the fly" during the GC run.

Problems and New Developments

The advantages of FT/ICR follow from the highly *linear* behavior of ions in crossed magnetic and electric fields. The principal disadvantages derive from relatively small but important *nonlinear* effects in the excitation and in the response.

Virtually all FT/ICR experiments have been performed by using a short (ca. 1-ms) frequency sweep ("chirp") to excite the ion cyclotron motion.[21] A major problem with the "chirp" excitation[20,22] is its nonuniform power spectrum (Figure 2b), which in turn affects the detected FT/ICR relative peak heights, whose accuracy is important for ion concentration ratios (especially isotope ratios). A frequency-sweep "chirp" would have to be swept infinitely slowly in order to produce the perfectly flat power spectrum which would yield correct relative peak heights.[20] However, at typical operating pressures, ions undergoing excitation may begin to react before they can be detected if the "chirp" excitation lasts longer than a few milliseconds.

The above dilemma is readily resolved by methods of the type shown in Figure 8.[63] First, the desired spectral excitation frequency profile is specified as a frequency-domain spectrum sampled at (say, 4K) equally spaced points (e.g., Figure 8a). Then an inverse discrete Fourier transform is used to generate the equivalent discrete time-domain waveform (Figure 8b), which can be subjected to digital-to-analog conversion, amplified as a voltage signal, and applied to the transmitter plates of a rectangular trapped-ion cell. The excitation signal can be detected (sampled, digitized, amplified) simultaneously (Figure 8c) by the receiver plates and subjected to discrete (forward) Fourier transform to yield its power spectrum (Figure 8d). Although the actual power spectrum seen by the sample (Figure 8) is not as perfect as the initial profile (Figure 8a), it is capable of producing highly selective excitation. Figure 8f shows the effect of the "Fourier synthesized" excitation of figure 8d on an electron-ionized mixture of perfluorotri-*n*-butylamine and styrene, whose "normal" FT/ICR spectrum is shown in Figure 8e. The synthesized excitation is clearly highly selective in picking out just the peaks at m/q 78 and 104 without exciting any of the other m/q values (e.g., 77, 79, 103

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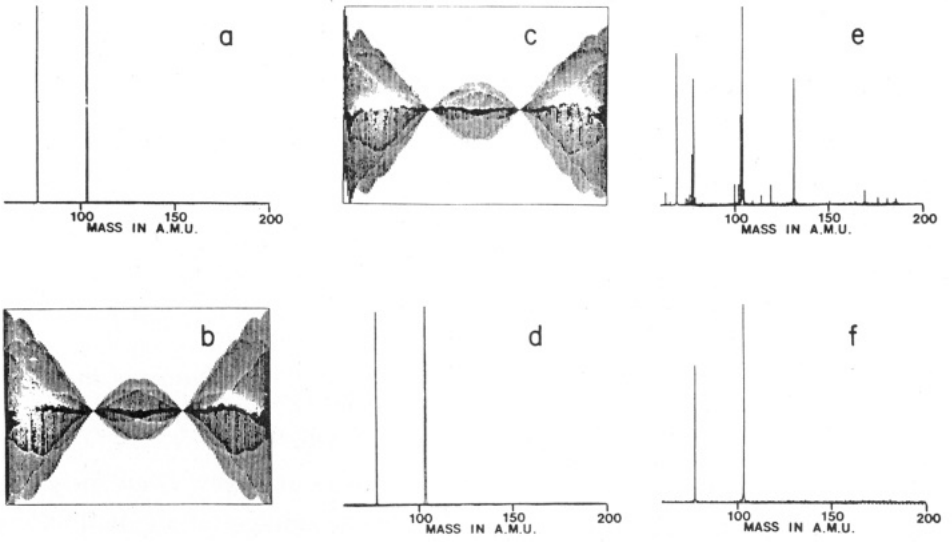

Figure 8. Fourier synthesized two-ion monitoring—see text for description. The effect of this procedure is to excite simultaneously the peaks at m/q 78 and 104, without exciting other peaks in the spectrum. Note that the relative intensities at m/q 78 and 104 are the same in (f) and (e), showing that the two peaks have been extracted without distortion. (Data from T.-C. L Wang and T. L. Ricca.)

or 105). Even better results are possible using heterodyne techniques.[64]

Three general types of excitation can be produced in this way: flat power (for more accurate peak heights), flat power with windows (e.g., for ejection of ions of all but a selected m/q ratio, as in ultrahigh-resolution MS/MS), and power at several selected m/q values (e.g., multiple-ion simultaneous monitoring, as in flow analysis). We believe that such "tailored" waveforms will soon become the excitation method of choice in FT/ICR.[64-66]

Apart from problems due to imperfect electric fields in the cell, two fundamental problems arise from having too many ions in the instrument. First, the macroscopic charge ("space" charge) from a large number of ions actually distorts the electric potentials in the cell and shifts the ion cyclotron frequencies.[67] Second, Coulomb repulsion between ions distorts the cyclotron orbits and broadens the mass spectral peaks. We are currently examining ion trajectories to quantitate the Coulomb effects.

Another problem is the storage of large amounts of digitized data. For example, because of the high available mass resolution over a wide mass range, a GC/FT/ICR experiment can generate ca. one 32K time-domain data set per second for an hour, which is enough to fill a 160-Mbyte storage module from a single GC run. We have recently demonstrated the advantages of storing FT/ICR results in representations that have been "clipped" to as little as to one bit per word, saving up to a factor of 20 in data storage.[68]

Concluding Remarks

Some advantages of FT/ICR for analytical mass spectrometry are listed in Table II. The two features which have most intrigued the mass spectrometry community are the wide mass range and ultrahigh mass resolution. The detection speed follows from the multichannel advantage[3,4] of detecting the entire spectrum at once. Because of the absence of slits and high voltages and low sample pressure, the instrument is safe and reliable—our instrument has operated continuously for as long as 8 months without changing the electron filament. Operation is highly automated—all but a handful of adjustments can be entered from a keyboard. The FT/ICR instrument is structurally simple, because ion formation, reaction, and detection all occur in a single sample chamber consisting essentially of a rectangular box of flat plates whose planarity and spacing are noncritical. At this writing (11 years after the first FT/ICR publication), approximately 30 FT/ICR spectrometers are in use throughout the world. It seems safe to predict that this number will double in the next 2 years, because the technique is extraordinarily versatile, mechanically simple, and uniquely suited for solving some of the most difficult chemical problems in mass spectrometry.

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