

Hybrid Mass Spectrometers for Tandem Mass Spectrometry

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Mass spectrometers that use different types of analyzers for the first and second stages of mass analysis in tandem mass spectrometry (MS/MS) experiments are often referred to as “hybrid” mass spectrometers. The general goal in the design of a hybrid instrument is to combine different performance characteristics offered by various types of analyzers into one mass spectrometer. These performance characteristics may include mass resolving power, the ion kinetic energy for collision-induced dissociation, and speed of analysis. This paper provides a review of the development of hybrid instruments over the last 30 years for analytical applications. (J Am Soc Mass Spectrom 2008, 19, 161–172) © 2008 American Society for Mass Spectrometry

Tandem mass spectrometry (MS/MS), in a very generic description, is a process in which an ion formed in an ion source is mass-selected in the first stage of analysis, reacted, and then the charged products from the reaction are analyzed in the second stage of analysis. The type and quality of data that is obtained can vary greatly depending upon the type of analyzer used in the first and second stages of analysis, and the type of reaction performed between the stages of analysis. The reactions that can be done also can depend upon the type of analyzer. Over the years there have been a variety of means developed to measure the mass-to-charge ratio of gas-phase ions. The most common methods involve: dispersion based on ion momentum or kinetic energy (magnetic and electric sector instruments); separation in time based on ion velocity (time-of-flight); transmission through an electrodynamic field (quadrupole mass filter); and periodic motion in a magnetic or electrodynamic field (ion traps). There are differences in the experimental parameters associated with these various analysis methods that are pertinent to the MS/MS experiment. Some parameters are obvious, typically related to the performance of the mass analyzer while others are more subtle, related to the reactions/chemistry occurring between the stages of analysis. Many times these different parameters are used to categorize MS/MS experiments.

One parameter is the ion kinetic energy. Sector and time-of-flight (TOF) instruments typically operate at

“high” ion kinetic energies (5–20 keV), whereas “low” ion kinetic energies (<50 eV) are typical in quadrupole mass filters and ion traps. The ion kinetic energy is an important parameter in MS/MS experiments because the most common reaction involves colliding the ion of interest with a target gas atom or molecule. When performing ion-neutral collision experiments, the possible reactions that can be accessed (e.g., collision-induced dissociation, collisional cooling, charge permutation, ion/molecule reaction) depends upon the ion kinetic energy. The appearance of the MS/MS spectrum can change drastically as a function of the collision (ion kinetic) energy. A related factor that is equally important, but often not considered, is the time frame of the experiment, that is, the elapsed time between the collision event and the second (or next) stage of analysis. With high kinetic energies, the experimental time frame is typically quite short (i.e., microseconds). Short dissociation times mean a greater kinetic shift. A large kinetic shift typically favors dissociations that occur faster, but that also require more internal energy to dissociate fast enough to be observed on the time scale of the experiment. Not only does this lead to differences in the appearance of high-energy and low-energy MS/MS spectra, but also to reduced MS/MS efficiency for higher kinetic energy CID.

Another distinguishing feature by which tandem mass spectrometry experiments can be classified or categorized is whether the analysis and excitation events are separated spatially or temporally. Techniques in which the ions are separated “in space”—sector, TOF analyzers, and quadrupole mass filters—are commonly referred to as “beam” techniques because ions traverse the analyzer as a contin-

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Table 1. Comparison of mass analyzers with respect to key performance attributes

Analyzer type	Kinetic energy	Resolving power		Mass accuracy		Measurement time ^a (seconds)
		MS-1	MS-2	MS-1	MS-2	
Magnetic (B) sector	High	Medium	Medium	ppt	ppt	10 ⁻⁵
Electric (E) sector	High	na ^b	Low	na ^b	ppt	10 ⁻⁵
Electric and magnetic sector ^c	High	High	Medium	ppm	ppt	10 ⁻⁵
Time-of-flight (TOF)	High	Low	Medium ^d	ppm	ppm	10 ⁻⁵
Quadrupole mass filter (Q)	Low	Low	Low	ppt	ppt	10 ⁻⁴
Quadrupole ion trap (QIT)	Low	Low	Low	ppt	ppt	10 ⁻²
FTICR	Low	High	High	ppm	ppm	10 ⁻¹
Orbitrap	High	na ^b	High	na ^b	ppm	10 ⁻¹

^aThe time, after activation, for the ions to react prior to the second stage of analysis.

^bna: not applicable; this analyzer has not been used for the first stage of an MS/MS experiment. There is currently no mode of operation in which a parent ion can be mass selected for a subsequent stage of analysis.

^cWhen electric and magnetic sectors are used as a double focusing mass spectrometer for one stage of analysis, either prior to (MS-1) the reaction, or subsequent to (MS-2) the reaction.

^dThe resolving power is medium if the TOF ion axis is orthogonal to the first stage of MS; if the axes are coaxial, the resolving power is low.

uous or pulsed beam (analogous to a laser beam). For the beam techniques, every stage of mass-to-charge analysis is done in a separate analyzer, such that the two (or more) stages of analysis are separated (physically) in space. Conversely, trapping instruments such as quadrupole ion traps, Fourier transform ion cyclotron resonance (FTICR) spectrometers, and orbitraps, characterize ions based upon the frequency of their motion in a defined space. In the MS/MS experiment using quadrupole ion traps and FTICR spectrometers, all stages of the experiment can be performed in the same analyzer, with the different stages being separated in time rather than spatially. The overall experimental efficiency is almost always higher because 1) the ions do not have to be transferred from one analyzer to another, and 2) there is typically a much longer time period for reaction and dissociation, so the kinetic shift is small. However, the overall experiment can take significantly more time to complete compared with beam-type instruments.

The last two attributes that can be used to classify the various mass analysis techniques are resolving power [$(m/z)(\Delta m/z)^{-1}$] and measurement accuracy. Mass measurement accuracy is either “high”, expressed in parts per million (ppm), or “low,” expressed in parts per thousand (ppt). FTICR spectrometers, orbitraps and TOF analyzers can routinely achieve low- or sub-ppm mass accuracies, while the other analyzers (i.e., quadrupole mass filters or ion traps) are typically in the ppt range. In terms of mass resolving power, analyzers of various types are capable of either low, medium, or high resolving power. Clearly, relative terminology such as low, medium, and high can be debated. That being said, for the purpose of this discussion, the following definitions apply to those terms: “low”, less than 1000; “medium”, 1000 to 10,000; “high”, greater than 10,000. It should also be noted that while the terms “resolving power” and “resolution” are often used interchangeably in the mass spectrometry literature, they are not equivalent; resolving power = resolution⁻¹. The resolving power achieved when using any of the aforementioned mass analyzers for the first stage

of an MS/MS experiment is no different than that measured for a normal mass spectrum when using that analyzer. However, that is not necessarily true for the resolving power in the second stage of mass analysis. For example, because of the kinetic energy release associated with dissociation of an ion, a single magnetic sector or electric sector exhibits low mass resolving power if CID occurs at high kinetic energies. Conversely, if a double focusing electric/magnetic sector combination is used medium resolving power is observed. Table 1 summarizes the performance parameters for the various analyzers.

Hybrid MS/MS instruments use various combinations of these analyzers to obtain desirable performance characteristics for the phenomena being investigated. Typically, resolving power and measurement accuracy in each stage of the mass spectral analysis are of primary importance. However, the kinetic energy used for CID can also be a critical parameter, depending on the information being sought. Additionally, the speed of analysis (duty cycle) can also be an important parameter. The development of many early hybrid instruments was motivated by the desire for fast MS/MS spectral acquisition times required by the time scale of a chromatographic separation. The early hybrid instruments (1980s) all used beam type analyzers (beam-beam instruments) because these were the standards of the day, with trapping instruments just being introduced as commercially viable mass analyzers. Two of these beam-beam type hybrid instruments evolved into commercial instruments, sector/Q and Q/TOF, with the latter one still being a popular instrument today. Subsequently (1990s), beam-trap type instruments were explored, followed by trap-beam instruments. A handful of beam-trap instruments (sector/QIT) have been commercialized. The trap-beam instrument closely related to the Q/TOF, the QIT/TOF, has become commercially available. Most recently (2000s), trap-trap type hybrid instruments have been commercially developed. Not surprisingly, a general trend in the evolution of hybrid instruments is that their development is driven by ad-

vances in the component mass analyzers, particularly recent breakthroughs in ion trapping instruments.

The remainder of this account will trace the history of the development of hybrid instruments for MS/MS experiments. As noted previously, each decade has been characterized by its own “signature” combination of analyzers (i.e., beam/beam, beam/trap, and trap/trap). The following discussion will be structured according to the general analyzer categories (e.g., beam-beam, beam-trap, trap-beam, and trap-trap), as this description generally coincides with the development timeline (by decade) of hybrid instruments.

Beam-Beam Hybrid Instruments

Hybrid instruments for analytical applications of MS/MS got their start in January of 1979 at a breakfast meeting of Graham Cooks’ research group at Purdue University. MS/MS as an analytical technique was still in its infancy, with the research groups of Cooks and McLafferty at the forefront of the development [1–12]. For all this early work, sector instruments were used exclusively and CID was performed at high kinetic energies. There was a lot of research effort focused on MS/MS sector instrumentation at this time [13–22]. However, in 1978, Yost and Enke published the first results using CID in a triple quadrupole system for MS/MS [23]. The key aspect of this experiment was the CID, as triple quadrupole instruments had already been used in photodissociation studies [24, 25]. This work was seminal in motivating the development of new hybrid MS/MS instrumentation, the first being a hybrid instrument in the Cooks group [26, 27]. At the 1979 breakfast meeting, different performance characteristics of various analyzers were considered. The low-energy CID used in the QqQ instrument was much more efficient than the high-energy CID [28] used in sector instruments (the lower case q indicates a quadrupole used as an ion guide in the rf-only mode; in current instruments this is often a hexapole or octapole ion guide). Using a Q as MS-2 provided much better product ion resolution than sector instruments because the Q was insensitive to the kinetic energy release that accompanies ion dissociation. The advantage of sector instruments over the QqQ was in the parent ion resolution and transmission efficiency. Thus, it was decided to construct a hybrid BqQ mass spectrometer to capitalize on the advantages of both analyzer types.

A schematic of the BqQ constructed in the Cooks laboratory, with support from Finnigan Corporation (today Thermo Scientific, San Jose, CA), is shown in Figure 1. One notable barrier that had to be overcome with an instrument in which one analyzer operates on ions having high kinetic energy (B) and the other analyzer on ions having low kinetic energy (Q) is that one of the sections of the instrument has to be electrically isolated and floated at high voltage. In Figure 1, there are shown two “Lexan electrical isolation flanges”. The vacuum chamber between these two

flanges is floated at 10 kV. This allows the qQ section of the instrument to be operated in a normal manner (i.e., the power supplies operated relative to ground potential) and also keeps the ion source at a low electrical potential (this is in contrast to normal sector instruments in which the ion source is held at high voltage and the sector(s) at ground potential). This design is quite logical for a BqQ because the magnetic field is independent of the system electrical potential. Thus, even though the vacuum chamber passing through the magnetic field was held at a potential of 10 kV, the magnetic sector itself was at ground potential. The situation becomes more problematic if an electric sector is also used because the electric field is dependant upon the electrical potential of the instrument. Thus, either the electric sector voltage supplies have to be floated at the high electrical potential, or the sector portion of the instrument must be operated at ground potential while the quadrupoles and associated electronics are floated at the high electrical potential.

While the BqQ ion optics were being fabricated, a makeshift collision cell was placed between the quadrupole mass filters, and the entire assembly was installed in a temporary vacuum system. This crude QQ instrument worked surprisingly well, showing how forgiving quadrupoles can be. Five publications resulted from work using this apparatus before it was formally installed as part of the BqQ [29–33]. The major concern about the performance of the BqQ centered around the efficiency of ion deceleration from the high kinetic energy (10 keV) needed to traverse the magnetic sector down to the low kinetic energy needed for analysis in the quadrupole mass filter. Once demonstrated that ion deceleration could be accomplished with good transmission efficiency, a collaborative effort between Finnigan and the Cooks group resulted in the first commercial sector hybrid instrument. This instrument employed a double focusing BE sector combination to provide even higher MS-1 resolution [34]. Vacuum Generators (VG, subsequently, Micro-Mass, and now part of the Waters organization), also produced hybrid instruments, using both a forward geometry EB sector mass spectrometer (EBqQ) and a reverse geometry BEqQ.

While these early hybrid instruments emphasized parent ion resolution (resolving power) through the use of double focusing sector instruments for MS-1, MS-2 was still limited to unit mass resolution. To address the issue of product ion resolution, a group at Oak Ridge National Laboratory built a hybrid QEB instrument [35, 36]. This instrument used a high-resolution Kratos Analytical (formerly Associated Electrical Industries, AEI) MS-50 mass spectrometer as MS-2, allowing isobaric product ions to be resolved from one another. This QEB instrument had several advantages over previous sector/quadrupole geometries, the foremost being that the high kinetic energy analyzers (E and B) were at the detector end of the instrument. Thus, ions were accelerated (and focused) through each successive stage of analysis within the instrument, rather

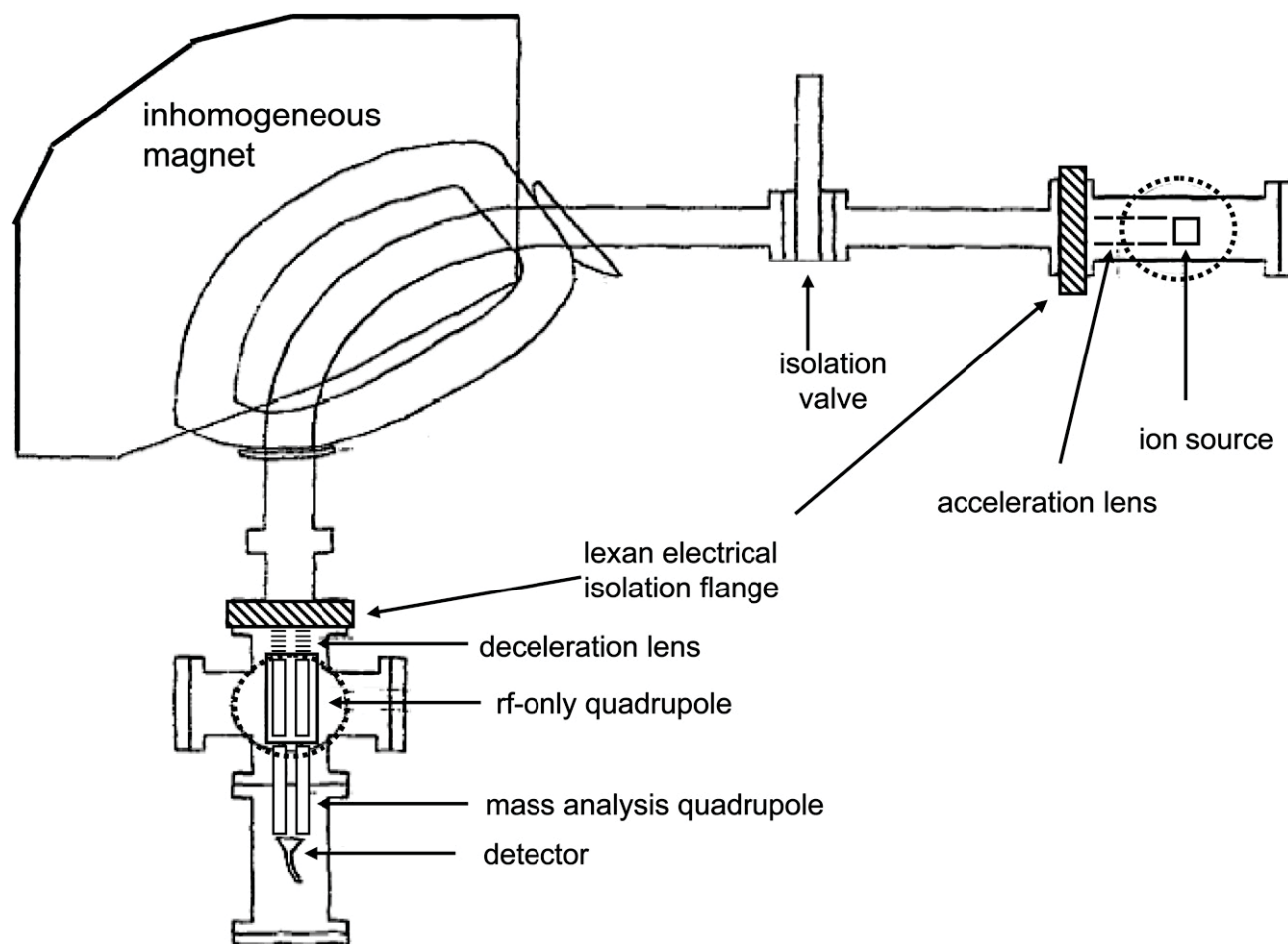


Figure 1. Schematic of the first hybrid MS/MS instrument, a magnetic sector/quadrupole mass filter (BqQ). (Adapted from reference [14]).

than experiencing the deceleration that occurred in the sector/quadrupole geometry. Another important result of this acceleration scheme is that CID can be performed at either low or high kinetic energy. This instrument was the first and only hybrid that easily accessed both kinetic energy regimes for CID.

While one area of attention in the development of hybrid instruments was mass resolving power, a second direction of pursuit was increasing the speed of MS/MS analyses so that it could be coupled effectively with chromatographic separations [37]. Several groups at Michigan State were working together toward this goal and developed instruments based on sector/time-of-flight combinations [38–42]. Both magnetic and electric sectors were coupled with a TOF analyzer to obtain momentum or kinetic energy dispersion of the ions before TOF analysis. Figure 2 shows the schematic of the B/TOF instrument. All product ions from a given parent ion arrive at the detector at the same flight time but have different radius of flight through the magnetic sector. With a point detector such as shown in Figure 2, a complete scan of the magnetic field, with concurrent acquisition of the TOF spectra is necessary. MS/MS spectra are then extracted from this two-dimensional

data array of momentum and time-of-flight. A key enabling development that facilitated this instrument configuration was the availability of higher speed TOF detectors. This was a major focus of the Michigan State work and they developed what was termed a time array detector (TAD). While the TAD is very limited in its capabilities compared with current detection systems for TOF instruments, it was a major development in the early part of the renaissance of TOF mass spectrometry [43–46]. Recent advances in position sensitive detection technology could make this an interesting configuration to explore for current applications needing high speed data acquisition.

About a decade later, sector/TOF hybrid instruments based on commercial sector mass spectrometers became available [47–49]. The goal in designing such systems was not, however, high speed MS/MS combined with chromatography, but instead combining pulsed ionization techniques (MALDI) with MS/MS. The sector portion of the instrument was set to pass the parent ion and then all the product ions generated by the collisional activation event could be detected by the TOF analyzer for every laser pulse. This design did not become popular, as the performance did not justify the

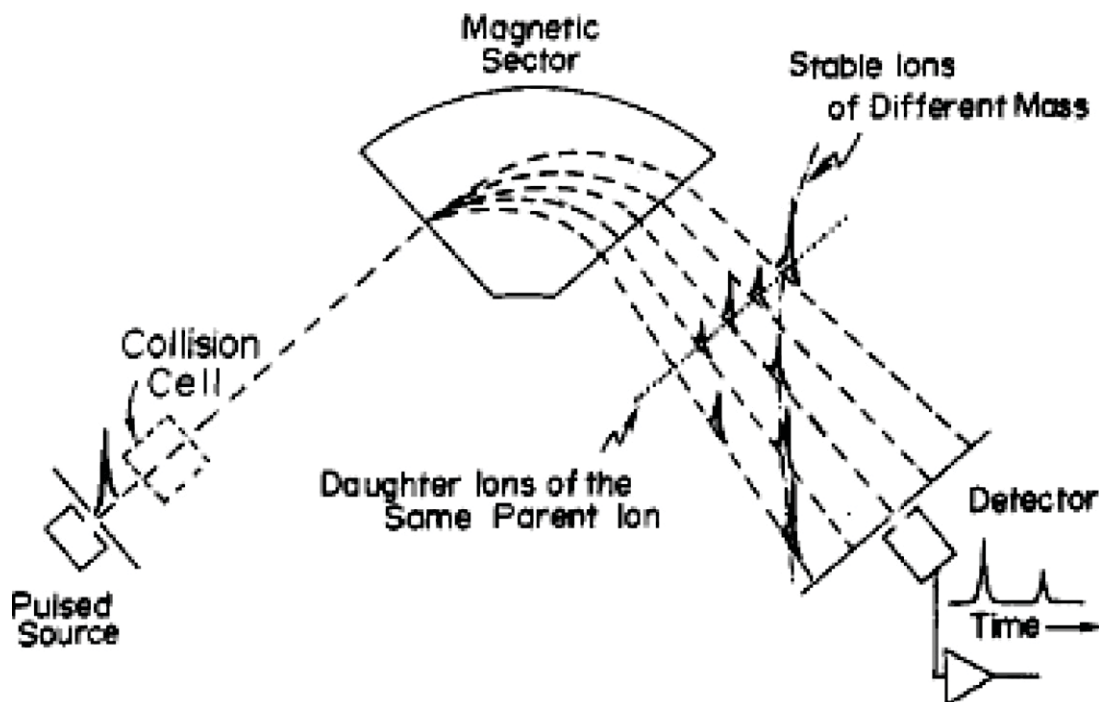


Figure 2. Schematic of a hybrid magnetic sector/time-of-flight (B/TOF) hybrid instrument used for high speed MS/MS applications. (Reprinted with permission from Stults, J. T.; Enke, C. G.; Holland, J. F. *Mass Spectrometry/Mass Spectrometry by Time-Resolved Magnetic Dispersion*. *Anal. Chem.* 1983, 55, 1323–1330. Copyright 1983 American Chemical Society.)

cost and size of the sector instrument when compared with alternative mass analyzers, and only a few were ever produced. Recently, an EB/TOF instrument has been constructed to study surface induced dissociation (SID) [50].

The lack of interest in the sector/TOF hybrid concept during the 1980s was probably due in part to modest (mediocre) TOF performance attributed to the electronic components available at that time. Other limitations of the approach, related to conducting CID at keV collision energies, included low MS/MS efficiency, a wide spread of kinetic energies for the product ions that made ion optics design quite challenging, and the amplification of kinetic energy release [51]. To address the issues associated with high-energy CID, a group at Oak Ridge National Laboratory combined a quadrupole mass filter with a TOF analyzer (Q/TOF) [52, 53]. This combination of analyzers took advantage of the higher MS/MS efficiency demonstrated for triple quadrupole instruments with the analysis speed and sensitivity of a TOF analyzer. This first Q/TOF appears to have been slightly “before its time” since nearly a decade passed before Q/TOF instruments were offered commercially. Interestingly, this instrument geometry has evolved into one of the most common mass spectrometers currently used, and is produced commercially by most major mass spectrometry vendors. As seen in Figure 3, which compares the schematic drawing of the first QTOF with that of a more recent version [54], the initial design has evolved into a very sophisticated instrument

capable of low ppm mass measurement accuracies and resolving powers $>10,000$. The main design advance has been attaching the TOF orthogonally to the Q rather than co-linearly. This improves the time resolution and duty cycle. However, much of the advancement from the modest performance characteristics of the original design to the modern-day models can be correlated with the advances in electronics and computers that make precise time resolution and storage of enormous quantities of data routine. Figure 4 compares the type of data obtained with the first Q/TOF to that obtained today. Certainly, the analyzer advances have been driven in part by the development of ionization techniques capable of generating ions from large biomolecules.

Beam-Trap Hybrid Instruments

The quadrupole ion trap was commercialized in 1984 by the Finnigan Corporation [55], but much of the subsequent development has occurred in academic research groups. The Cooks group has been at the forefront of ion trap and hybrid instrument development, so it was no surprise when they designed instruments combining ion traps with other mass analyzers [56, 57]. These instruments used the beam-type analyzers for the first stage of mass analysis, followed by an ion trap for the second stage of the measurement. The sector/ion trap (S/IT) combination [56] offers the dual advantages of eliminating deleterious space charge effects attributable to background and matrix ions formed in the ion

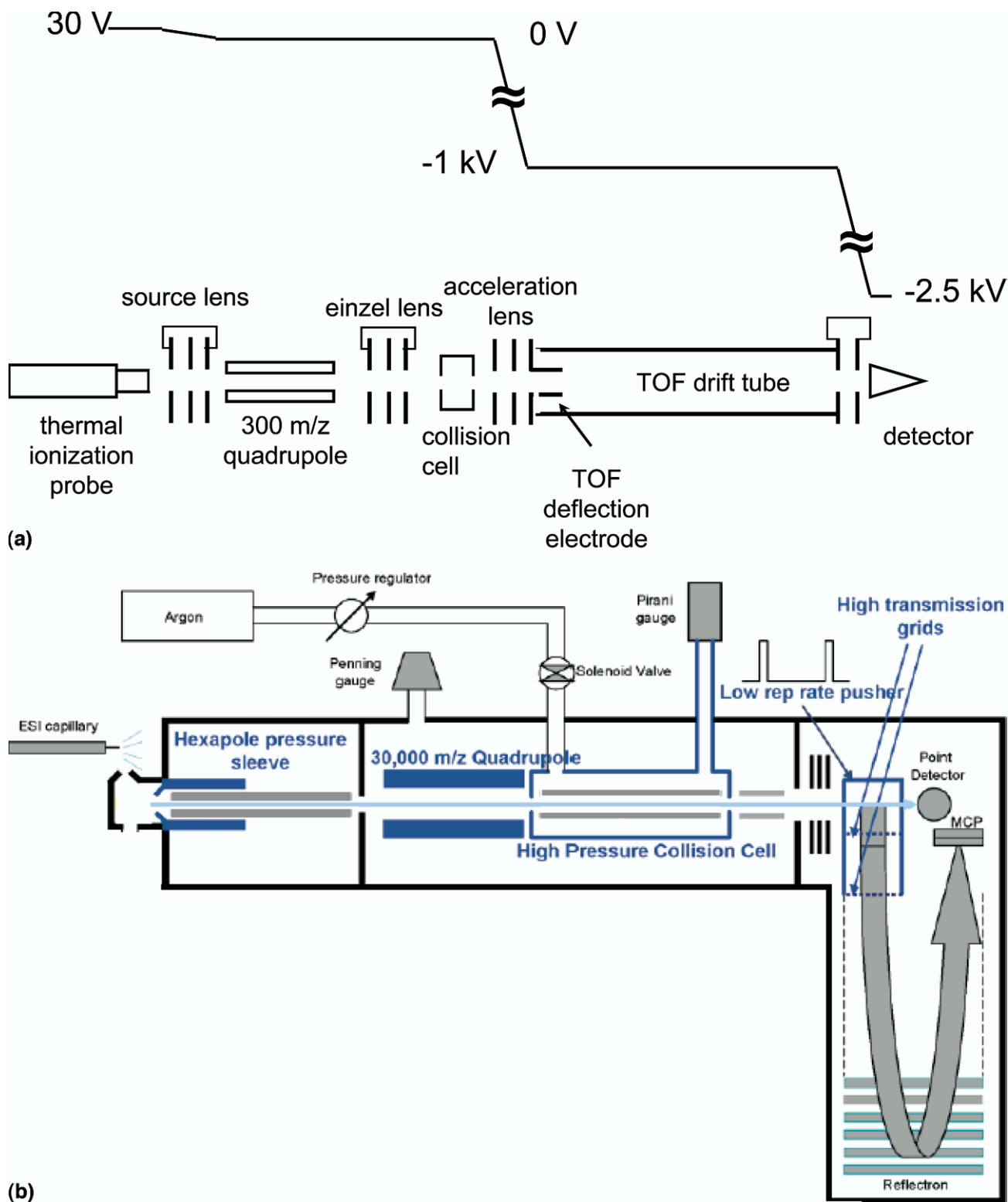


Figure 3. (a) Schematic of the original quadrupole/time-of-flight (Q/TOF) hybrid instrument built in 1984. (Reprinted with permission from Glush, G. L.; Goeringer D. E. Tandem Quadrupole/Time-of-Flight Instrument for Mass Spectrometry/Mass Spectrometry. *Anal. Chem.* **1984**, *56*, 2291–2295. Copyright 1984 American Chemical Society.) (b) Schematic of a current generation Q/TOF that has been modified to optimize analysis of macromolecular complexes. (Reprinted with permission from van den Heuvel, R. H. H. et al. Improving the performance of a quadrupole time-of-flight instrument for macromolecular mass spectrometry. *Anal. Chem.* **2006**, *78*, 7473–7483. Copyright 2006 American Chemical Society.)

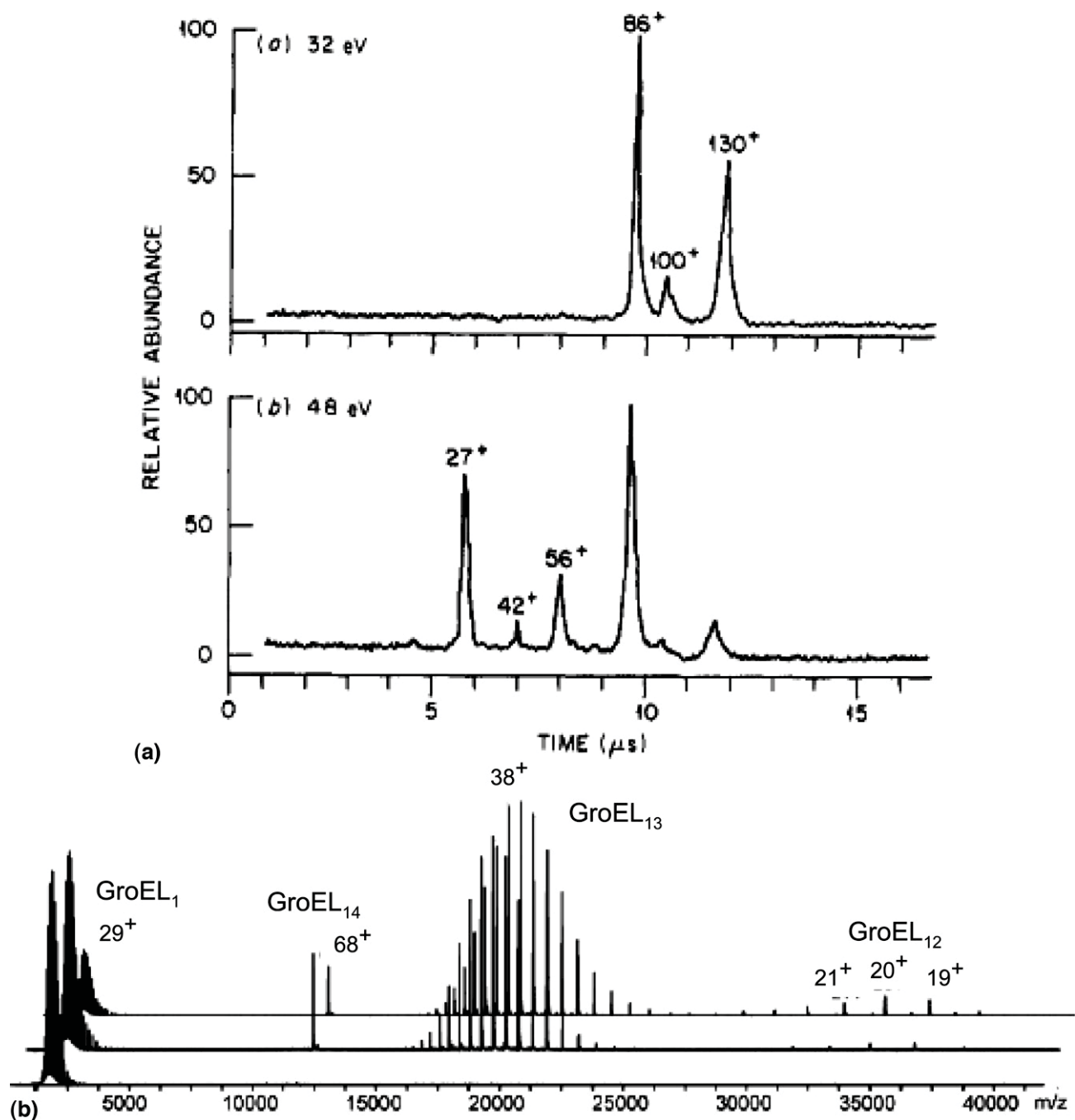


Figure 4. (a) The Product ion spectrum of tetraethylammonium (m/z 130) obtained on the Q/TOF shown in Figure 3a. (Reprinted with permission from Glish, G. L.; Goeringer, D. E. Tandem Quadrupole/Time-of-Flight Instrument for Mass Spectrometry/Mass Spectrometry. *Anal. Chem.* **1984**, *56*, 2291–2295. Copyright 1984 American Chemical Society.) (b) The Product ion spectrum of the macromolecular complex GroEL₁₄ (m/z 11,780, mass 801,000) obtained on the Q/TOF shown in Figure 3(b). Three spectra are shown that were obtained at different collision gas pressures. (Reprinted with permission from van den Heuvel, R. H. H. et al. Improving the Performance of a Quadrupole Time-of-Flight Instrument for Macromolecular Mass Spectrometry. *Anal. Chem.* **2006**, *78*, 7473–7483. Copyright 2006 American Chemical Society.)

source, while providing parent ion selection with high resolving power thus enabling selection/separation of isobaric parent ions. A major disadvantage of this geometry is the requirement that ions must be decelerated from keV to eV kinetic energies after exiting the

sector but before injection into the ion trap. A S/IT instrument was subsequently available commercially, but this timing coincided with declining interest in sector instruments as the capabilities of other mass analyzers were increasing rapidly. Thus, few S/IT in-

struments were sold and those that were mainly used just the sector portion of the instrument.

The Q/ion trap (Q/IT) combination offered the advantages of reduced space charging problems and a compatible (low) kinetic energy regime for the two analyzers [57]. More recently, a variation of the Q/IT has been developed commercially [58]. This instrument evolved from a very successful triple quadrupole instrument by operating the last quadrupole in a novel fashion, as a linear ion trap [59]. The front-end of the instrument is operated as a conventional triple quadrupole for normal CID experiments. Performing CID in the Qq portion of the instrument has the advantage of minimal discrimination in m/z range of product ions (i.e., no low mass cut-off problem associated with ion traps) along with more energetic collisional activation. Using the linear ion trap for the second stage of mass analysis provides greater sensitivity and speed of analysis, compared with a quadrupole mass analyzer operated in its normal mode. In addition to this mode of operation, the conventional triple quadrupole modes of operation are also available (e.g., neutral loss and parent ion scans). The ability to exploit the advantages of ion trap performance while retaining triple quadrupole capabilities makes this instrument a popular choice.

An alternative trapping instrument to the quadrupole ion trap is the Fourier transform ion cyclotron resonance mass spectrometer (FT-ICR MS) [60]. This instrument offers significantly greater mass resolving power and mass measurement accuracy than the quadrupole ion trap, but has the added complexity of a cryogenically cooled magnet and the need to operate at very high vacuum (10^{-8} Pa). Early quadrupole/FT-ICR (Q/FTICR) work was done by the groups of Hunt and McIver [61–63]. While this combination of analyzers showed promise, it did not become popular immediately, in part because the magnetic field strengths and data storage capabilities were much more limited at that point in time. It took 15 years before other researchers started constructing custom Q/FT-ICR instruments [64–66]. Today, higher magnetic field strengths and significant advances in computing and data storage technology combine to give much higher performance compared with the early instruments. A common design goal in recent instruments is the improvement of both duty cycle and dynamic range through selective accumulation of ions from the source during the time necessary to record the FT-ICR spectrum. Q/FT-ICR instruments are now available commercially from two vendors, Bruker Daltonics [67] and Varian [68].

Trap-Beam Hybrid Instruments

All trap-beam analyzer combinations to date have used a quadrupole ion trap for the first stage of MS/MS analysis and a time-of-flight for the second stage. In some cases the quadrupole ion trap is a conventional three-dimensional ion trap (QIT) while in others it is a

linear quadrupole ion trap (LIT). A key feature of this general configuration is the MS/MS (and MS^n) capabilities of ion traps. However, as noted previously, ion traps possess modest resolving power and mass measurement accuracy. These limitations can be overcome by coupling an ion trap with a TOF analyzer, thereby providing better mass accuracy and much higher resolving power in the analysis of product ions.

The first trap/beam combination was initially operated using a QIT only as a storage device to decouple the ionization event from the TOF analyzer [69]. Subsequently, complex waveforms were applied to the end-cap electrodes, in addition to the normal drive rf applied to the ring electrode, so matrix ions from MALDI could be ejected from the trap and analyte ions trapped, isolated, and analyzed [70].

Further development of a QIT/TOF system for MALDI MS/MS occurred in the Cotter laboratory, being a logical extension of their work in quadrupole ion trap and time-of-flight instrument development [71]. Improved performance over earlier systems was obtained by introducing a reflectron ion mirror into the TOF analyzer design. At about the same time, the Douglas group was developing a hybrid ion trap/TOF combination using a linear quadrupole ion trap (LIT) to isolate and dissociate parent ions, followed by product ion analysis with an orthogonal TOF analyzer [72]. A schematic of the LIT/TOF instrument is shown in Figure 5. As can be seen, it is very similar to a Q/TOF, except there is no collision multipole. While the parent ions could be mass-selected and dissociated in this linear quadrupole ion trap, it did not possess the mass analysis capabilities of current linear quadrupole ion traps [58, 73].

Several years later, a system was reported in which ion isolation and dissociation were performed in a QIT, with product ion analysis by TOF [74]. That work emphasized the use of 266 nm photodissociation, which was compared with conventional CID in an ion trap. It was also demonstrated that due to the speed of TOF analysis short-lived ions could be detected that otherwise would not be observed in conventional MS/MS experiments using a QIT. Later experiments with this same instrument demonstrated the feasibility of infrared multiphoton dissociation [75].

QIT/TOF instruments have subsequently been commercialized. Shimadzu followed the early work involving MS/MS of MALDI generated ions, ultimately developing a QIT/TOF [76]. A subsequent generation of this instrument has LC/MS/MS capabilities [77]. Hitachi has taken an alternative development pathway, producing a LIT/TOF [78, 79]. They have also reported results from a QIT/TOF, but this instrument is not currently available commercially [78]. In all cases, an important feature is the MS^n capability of the ion trap mass analyzer.

Trap-Trap Hybrid Instruments

The most recent type of hybrid instrument is the trap-trap combination where two different types of

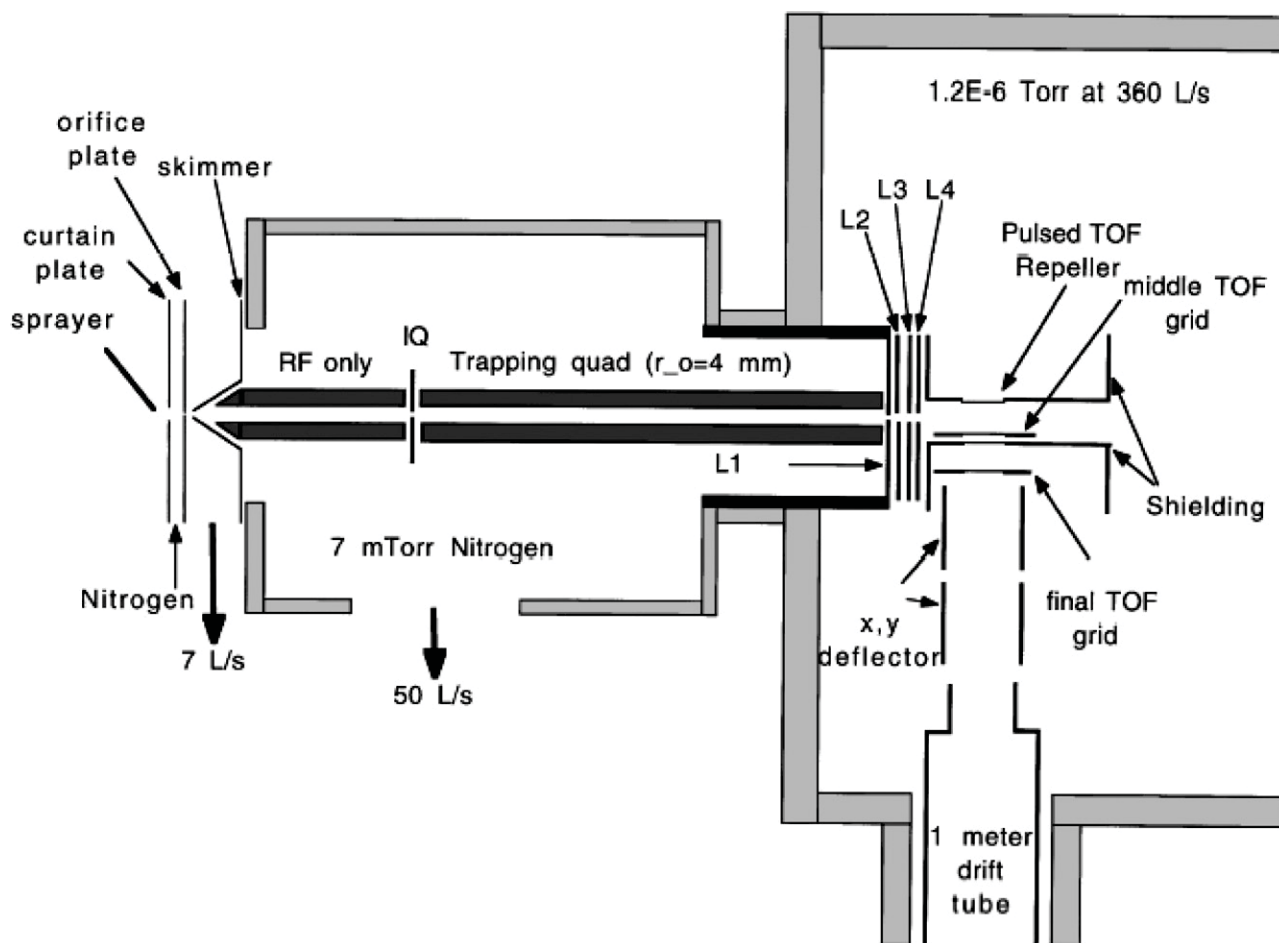


Figure 5. Schematic of the first linear ion trap/time-of-flight (LIT/TOF) hybrid instrument. (Figure 1 from Douglas, D. J.; Campbell, J. M.; Collings, B. A. A New Linear Ion Trap Time-of-flight System with Tandem Mass Spectrometry Capabilities. *Rapid Commun. Mass Spectrom.* 1998, 12, 1463–1474. Copyright 1998 John Wiley and Sons Ltd. Reproduced with permission.)

trapping mass spectrometers are combined. The general goal of this configuration is to achieve even better mass measurement accuracy and resolving power than that obtained by employing a TOF analyzer for the second stage of mass analysis in the MS/MS experiment. Thus, the second trap is not a quadrupole ion trap but either a Fourier transform ion cyclotron resonance (FT-ICR) mass spectrometer or an orbitrap mass analyzer [80]. The trade-off of replacing the TOF with either of these analyzers is the significantly longer measurement times required to obtain the product ion spectrum.

In contrast to the initial development of other types of hybrid instruments, conducted primarily by research groups in academia or national laboratories, the trap-trap combinations have been the result of the efforts of an instrument company, Thermo Scientific (formerly Finnigan Corporation). The first of the trap-trap combinations used a commercial linear quadrupole ion trap (LIT) [73] combined with an FT-ICR mass spectrometer [81]. This platform takes advantage of the high MS/MS efficiency of the LIT and the high mass

resolving power and high mass measurement accuracy features of FT-ICR instruments. A unique attribute of having the LIT as the first stage of analysis is the ability to obtain multiple low resolving power MS/MS spectra using just the LIT, while the FT-ICR is acquiring a separate spectrum at high resolving power and mass accuracy. This capability improves the duty cycle and allows increased dynamic range, in a similar fashion to the Q/FT-ICR geometry. A further advantage of the LIT/FT-ICR is the ability to use ion activation techniques other than CID, primarily electron capture dissociation (ECD) and infrared multiphoton dissociation (IRMPD).

The most recent hybrid trap-trap instrument is also being developed by Thermo Scientific. It has many parallels with the LIT/FT-ICR, substituting the orbitrap mass analyzer for the FT-ICR spectrometer [82]. A schematic [83] of the LIT/orbitrap is shown in Figure 6. This design has some analogies to the beam-beam instruments (e.g., Q/TOF) in that the ions are transferred from one analyzer to another, but rather than being a continuous stream, the ions are moved in packets after they have been accumu-

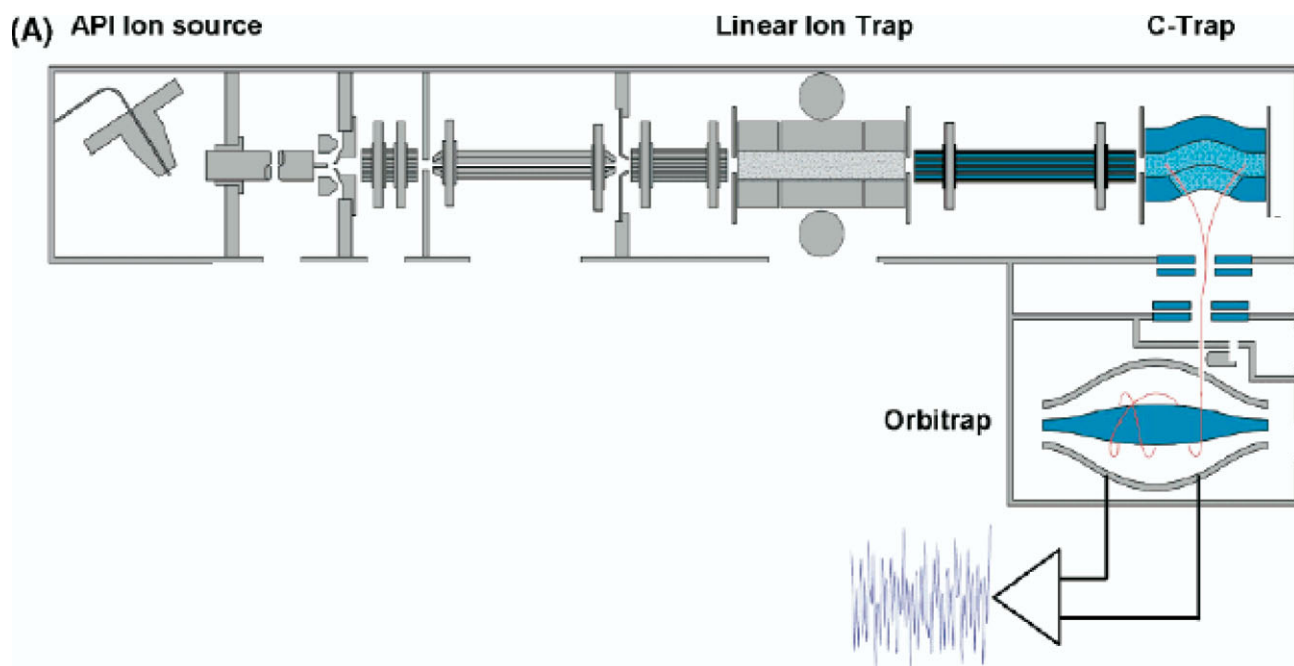


Figure 6. Schematic of the linear ion trap/orbitrap hybrid instrument. (Adapted with permission from Figure 1 published in *J. Am. Soc. Mass Spectrom.* **2006**, *17*, 977–982. Makarov, A.; Denisov, E.; Lange, O.; Horning, S. *Dynamic Range of Mass Accuracy in LTQ Orbitrap Hybrid Mass Spectrometer*. Copyright American Society for Mass Spectrometry).

lated in the LIT. Thus, while one packet of ions is being detected in the orbitrap another packet of ions can be manipulated in the LIT. Note that the “C-trap” is not an ion analyzer but a device used to transfer the packet of ions into the orbitrap. A major advantage of the orbitrap over the FT-ICR spectrometer is not one of performance, but rather of convenience, with the replacement of a large cryogenically cooled super-conducting magnet by an electrostatic trapping device. The mass resolving power and mass measurement accuracy of the orbitrap are currently not quite equivalent to those attributes of the FT-ICR instrument, but it is still a developing instrument. Also, currently it is not possible to conduct MS/MS experiments within the orbitrap (e.g., CID, ECD, IRMPD, etc.); however this situation may change as further development occurs.

Conclusions

Hybrid mass spectrometers have played and continue to play an important role in today’s analytical laboratory. There have been many different configurations and not surprisingly, the history and development of MS/MS hybrid instruments closely follows the development of individual mass analyzers. Sector instruments were the standard platform in mass spectrometry in the 1980s and all the early hybrid instruments incorporated sectors in some way. However, as sectors have faded from the scene, so have hybrid instruments utilizing those analyzers. Interestingly, only one hybrid configuration from the early years has withstood the

test of time, the Q/TOF. While quadrupole mass filter technology has not advanced much since the 1980s, time-of-flight analyzers have undergone tremendous improvement in capabilities. This reality has been fostered in large part by the tremendous advances in computer processor speed and data storage capabilities. Current Q/TOFs have evolved into high-performance instruments with analysis speed being a primary feature. The closely related QIT/TOF and LIT/TOF instruments are likely to cut into the market share of the Q/TOF because of their impressive MS/MS and MSⁿ performance compared with quadrupole mass filter-based systems, and because of and their improved duty cycle.

The other growing area in hybrid instrumentation is the trap-trap configuration. These instruments do not exhibit the speed of analysis demonstrated by the TOF based instruments, sacrificing that capability for superior mass measurement accuracy and mass resolving power. In particular, it seems that the LIT/orbitrap has a promising future given that the orbitrap analyzer is still an evolving mass spectrometer and requires less care and maintenance compared with its FT-ICR mass spectrometer counterpart. While the FT-ICR mass spectrometer currently has the advantage of being able to perform ECD and IRMPD experiments, these and other features (e.g., electron-transfer dissociation, [ETD]) are likely to be incorporated into the LIT/orbitrap, being performed external to the orbitrap analyzer.

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