Miniature Mass Spectrometers

Zheng Ouyang[1,3] and R. Graham Cooks[2,3]

[1]Weldon School of Biomedical Engineering, [2]Department of Chemistry, and [3]Center for Analytical Instrumentation Development, Purdue University, West Lafayette, Indiana 47907; email: ouyang@purdue.edu, cooks@purdue.edu

Annu. Rev. Anal. Chem. 2009. 2:187–214

First published online as a Review in Advance on February 19, 2009

The *Annual Review of Analytical Chemistry* is online at anchem.annualreviews.org

This article's doi:
10.1146/annurev-anchem-060908-155229

1936-1327/09/0719-0187$20.00

Key Words

instrumentation, ambient ionization, in situ analysis, ion traps

Abstract

We discuss miniaturization in mass spectrometry in terms of the mass analyzer, the mass spectrometer, and the total analytical system. Mass analyzer miniaturization has focused on ion traps. Decreases in mass analyzer size facilitate reduction of the sizes of the other components of a miniature mass spectrometer, especially the radio frequency electronics and vacuum system. Appropriate sample introduction systems are needed for performance optimization. The criteria by which a miniature mass spectrometer is judged include adequate performance in the traditional areas of resolution, detection limits, and specificity; ruggedness; reliability; and fully autonomous operation. Our discussion of the total analytical system emphasizes the removal of the bottleneck of sample preparation and suggests a solution to the combination of sampling, preconcentration, and ionization: ambient ionization methods. We also describe current miniature mass spectrometers.

1. INTRODUCTION

1.1. Mass Spectrometry and Chemical Analysis

Matrix effects: alterations in mass spectra caused by decreasing or obscuring analyte signal; signaled by the presence of major or minor components of the sample matrix or by the decrease or absence of analyte signal

Tandem mass spectrometry (MS/MS): experiment in which multiple stages of mass analysis allow data to be recorded for chemical species obscured by matrix signal or to enhance structural specificity. Usually precursor ions related to the analyte are mass-selected and energized by gaseous collisions or other means to give characteristic fragment ions

Chemical analysis plays an increasingly important role in our complex natural and postindustrial world by helping to determine the nature of materials of all types. Among analytical methods, mass spectrometry (MS) has the distinctive capability of providing high sensitivity and high selectivity in the detection and quantitation of a wide variety of chemical and biological compounds. In a mass spectrometer, molecules in a sample are ionized, then their mass-to-charge ratios (*m/z*) are measured; both processes occur by one of various available methods. In a typical MS analytical procedure (**Figure 1**), samples are first collected and sent to an analytical laboratory, where components of interest are separated and preconcentrated before the measurement step. Often, special treatments are implemented, such as using chemical reactions to derivatize targeted compounds to optimize their chemical properties with respect to the ionization methods chosen for MS analysis. The samples introduced into the mass spectrometer after such pretreatment usually contain the analytes of interest in a much-simplified matrix, which significantly improves the sensitivity of analysis by increasing the relative concentration of the analytes and minimizing matrix effects. Mass spectrometers produce data that are displayed as mass spectra—plots of intensity versus *m/z*—that must be interpreted and/or correlated with existing data to determine which compounds are present and in what amounts.

Mass spectra provide information about analytes' molecular weights and chemical structures from the pattern of fragment ion abundances. The latter information is obscured when the sample is examined from a complex mixture. However, it can still be acquired using tandem mass spectrometry (MS/MS), a type of experiment in which mass-selection of precursor ions is used to separate them from the ionic mixture before they are excited to increase their internal energy and thereby to induce fragmentation. The first stage of mass analysis serves as a sample separation step and is done after (rather than before) ionization. Fragment ion (MS/MS) spectra can be used for structural elucidation, structure confirmation, and quantitation. MS/MS is routinely used for complex-mixture analysis in drug metabolism and for other studies in the pharmaceutical industry.

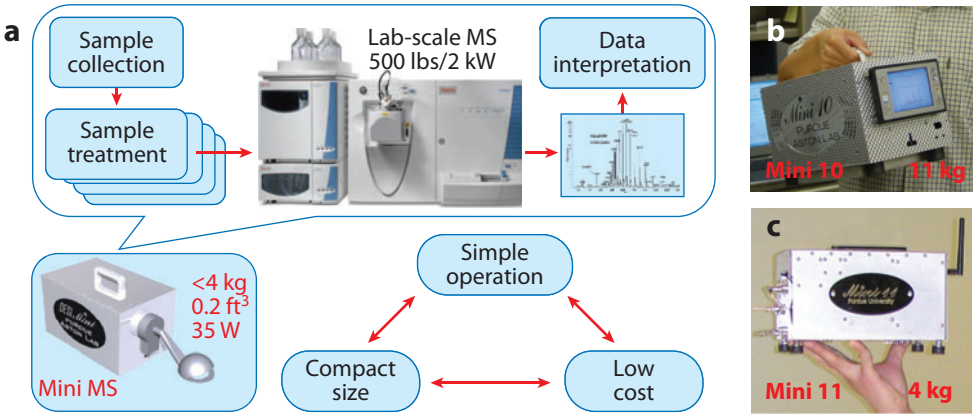

Figure 1

(*a*) Conceptual schematic of a miniaturized total mass spectrometry (MS) analytical system. (*b*) Mini 10 and (*c*) Mini 11 handheld ion trap mass spectrometers. Panels *b* and *c* reprinted from References 3 and 4, respectively, with permission.

A modern mass spectrometer typically employs multiple mass analyzers, often as combinations of different basic types, and is highly versatile in terms of the ionization methods and types of experiments it can be programmed to perform. Various samples can be analyzed using the same mass spectrometer as long as they are compatible with the particular type of ionization sources fitted to the instrument. The total time needed for the mass analysis step is less than 1 s. In contrast, the sample preparation and pretreatment steps, which are critical to convert the sample into an MS-compatible form, can take hours to perform, although parallel operations on many samples are often possible. A lab-scale mass spectrometer weighs hundreds of kilograms and costs from $80,000 to over $1,000,000.

Miniaturization: Various terms are used to describe instrumentation sizes. Transportable refers to devices that require mechanical means; portable devices can be carried by a single person; handheld and palm are anthropomorphic comparisons

1.2. Consequences of Miniaturization of the Total Mass Spectrometry Analytical System

What are the potential consequences of successful miniaturization of the mass spectrometer? Obviously, such a development would encourage in situ applications of MS in a broad area of applications; more subtly, it would be a driving force toward simplified MS systems, targeted operations, and development of high-volume/low-margin instrumentation in a large variety of optimized specialty forms.

In contrast to traditional chemical-analysis procedures, where samples are brought to the laboratory for analysis, the aim of miniaturization in analytical chemistry is to bring the lab to the samples. A common goal is to allow the full process of chemical analysis to be performed in situ for the sake of convenience as well as to increase throughput and to decrease error rates and cost. The whole analytical system should be (*a*) small enough to fit in the environment of the application, (*b*) affordable, and (*c*) operationally simple enough to match the skills of the end users. Different criteria apply to the size, affordability, and simplicity requirements for different applications. Typically, multiple operations are involved in MS analytical procedures, and specialized equipment is required for each specific procedure. The mass spectrometer itself is usually the largest, heaviest, and most expensive and power-consuming component of such an instrumental system. The development of miniaturized and low-cost mass spectrometers would impact MS-based analytical systems in the following respects:

1. Compact size and low power consumption would allow the use of mass spectrometers in physicians' offices, on industrial production lines, as continuous monitors in waste sites, at airport checkpoints, and even in family homes.
2. Simple operation, autonomous data analysis, and direct result reporting are critical for using the miniature device for in situ and/or real-time applications.
3. The low cost and relative simplicity of these instruments should allow their quick adaptation to a wide variety of applications wherein the costs of ownership and maintenance would otherwise be burdensome. Importantly, these features should in turn encourage the development of specialized devices (as opposed to the versatile instruments used in laboratories), which would help simplify the operational procedures for end users.

1.3. History of Mass Spectrometer Miniaturization

A mass spectrometer comprises an ion processing system, a vacuum system, and a control system. The ion processing system includes an ionization source, a mass analyzer, and an ion detector (**Figure 2**). Depending on the type of mass spectrometer, the ion processing system may not constitute the major portion of the weight and power consumption of the instrument, but it may still have a significant impact on the properties of the rest of the instrument. For instance, the location

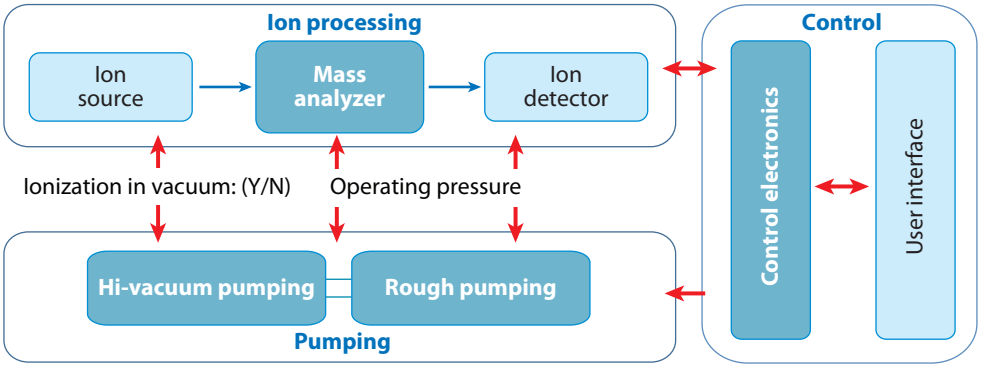

Figure 2

Subsystems of the mass spectrometer.

of the ionization source, whether inside or outside the vacuum, has a large effect on the vacuum system requirements, as it determines whether an atmospheric pressure interface is required.

Miniaturization of the mass spectrometer has proceeded via the following three stages:

1. Miniaturization of mass analyzers. In the early 1990s, the impact of mass analyzer size reduction on the size and power reduction of the mass spectrometer was first explored (1, 2). Research efforts emphasized the development of miniaturized mass analyzers of adequate performance but with simplified geometries for ease of fabrication.
2. Miniaturization of mass spectrometers. From about 2000 onward, increasing attention has been paid to the development of small-size mass spectrometers in addition to small mass analyzers. A better understanding at the system level of the mutual influences between the subsystems was thus obtained. Modern electronics were used to construct the control system, and improvements in the design of the pumping system became necessary. Handheld mass spectrometers weighing less than 10 kg (**Figure 1**) (3–5) were developed. The process of transferring the achievements in mass analyzer miniaturization into the development of small mass spectrometers led to an appreciation of the complex challenges of producing these small devices for in situ applications.
3. Miniaturization of total MS analytical systems. This is a contemporary activity. With the availability of miniature mass spectrometers, the development of in situ analysis using these devices calls for faster sample handling and data interpretation and for further improvement of the miniature MS to allow development of in-field MS labs for real-world applications. We now face significant challenges as well as a variety of choices. Ambient ionization (see Section 4) has emerged as a fast sampling method that is particularly appropriate for in situ miniature MS analysis.

Atmospheric pressure interface: transfer system, including ion optical and pressure differential stages, to transfer an externally generated ionized sample into the high vacuum of the mass spectrometer

1.4. Philosophy of Miniature Instrumentation Development

The community of scientists working to miniaturize mass spectrometers shares an appreciation for the specificity and sensitivity that MS provides. However, the criteria by which MS instrumentation is judged are changing with the development of miniature mass spectrometers. For decades, lab-scale instrument development has aimed to increase mass range, mass resolution, mass measurement accuracy, and sensitivity. With the potential of low-cost miniature mass spectrometers has come the realization that a wider range of performance criteria may be pursued. Mass spectrometers will now become highly relevant to targeted applications. The development of

these instruments will no longer aim solely for high performance, but may instead aim to achieve a balance among adequate performance, affordability, and feasibility for new high-volume applications. Active research programs are under way to define new geometries that provide adequate mass analysis performance and ease of fabrication in miniaturized instruments and to develop mass spectrometers with adequate sensitivities and selectivity but with simplified operating procedures. These new criteria will become increasingly important as the era of low-volume, high-margin, highly versatile analytical instruments gives way to one of specialized high-volume, low-margin, mass-produced instrumentation for niche applications, where rapid, continuous, and cheap chemical analysis for particular analytes is the major objective.

2. MINIATURIZATION OF THE MASS ANALYZER

2.1. Miniature Mass Analyzers of Various Types

Every type of mass analyzer, except for the newly developed orbitrap, has been miniaturized and tested for the purpose of developing portable mass spectrometers. Beam-type mass analyzers, such as time-of-flight (TOF) and sector mass analyzers, are usually much larger than trapping mass analyzers such as quadrupole ion traps (scale a few cm). Some examples are shown in **Figure 3**. Efforts to design a "tiny TOF" instrument yielded a series of miniature TOF mass analyzers (6–8), including a 5-cm endcap reflectron TOF with higher-order kinetic-energy focusing for improved resolution. A *m/z* exceeding 60,000 was achieved, and peptides and proteins were analyzed using matrix-assisted laser desorption/ionization (MALDI) (**Figure 3*a***) (9). Additionally, several miniature double-focusing mass analyzers have been reported (2, 10–14). A nonscanning Mattauch–Herzog geometry sector (2, 10–12) was developed using new materials to construct a lighter magnet (**Figure 3*b***). Numerous ions in a *m/z* range up to 500 can be recorded simultaneously using a discrete focal plane array detector. A resolution better than unity and a mass accuracy better than 0.01 Da per charge have been achieved for krypton, xenon, and hexane using electron impact (EI) ionization. The linear quadrupole mass filter is also proving to be a popular miniature mass analyzer, and it has been utilized as a single analyzer (15–20) and in arrays of identical mass analyzers (21, 22). For example, a 4×4 array of electrode rods forms nine parallel quadrupole mass filters. Two versions of this type of quadrupole array (21, 22), one with rods measuring 0.5 mm in radius and 10 mm in length and another with rods measuring 1 mm in radius and 25 mm in length, were developed and characterized at a radio frequency (RF) higher than 11 MHz. Unit resolution was obtained for volatile organic compounds (VOCs) ionized by EI (22, 23). The much smaller V-groove quadrupole (16) was one of the first mass analyzers to be fabricated using micromachining. The metalized glass electrodes (0.25 mm in radius and 20–30 mm in length) were mounted in silicon to form the quadrupole, and peak widths of 2.7 Da z^{-1} were recorded at *m/z* 40 when an RF of 6 MHz was used (**Figure 3*d***).

New fabrication methods have been used in the development of mass analyzers at small scales, especially for instruments with critical dimensions measuring less than 1 mm for which traditional precision machining is no longer the best choice. MEMS (microelectromechanical systems) processes have been used to fabricate mass analyzers of all types (24, 25), including Wien filters (15, 26), traveling-wave analyzers (27), TOF instruments (28), quadrupole mass filters (29), and ion trap mass analyzers (30–32). Other methods, such as laser machining (33), SLA (stereolithography apparatus) (34, 35) and LTCC (low-temperature cofired ceramics) fabrication (36), have been used to fabricate ion trap mass analyzers of intermediate size and more complex configurations.

The size reduction achieved in the different types of mass analyzers has had a surprisingly varying impact on the design and performance of the resulting mass spectrometers. Some critical

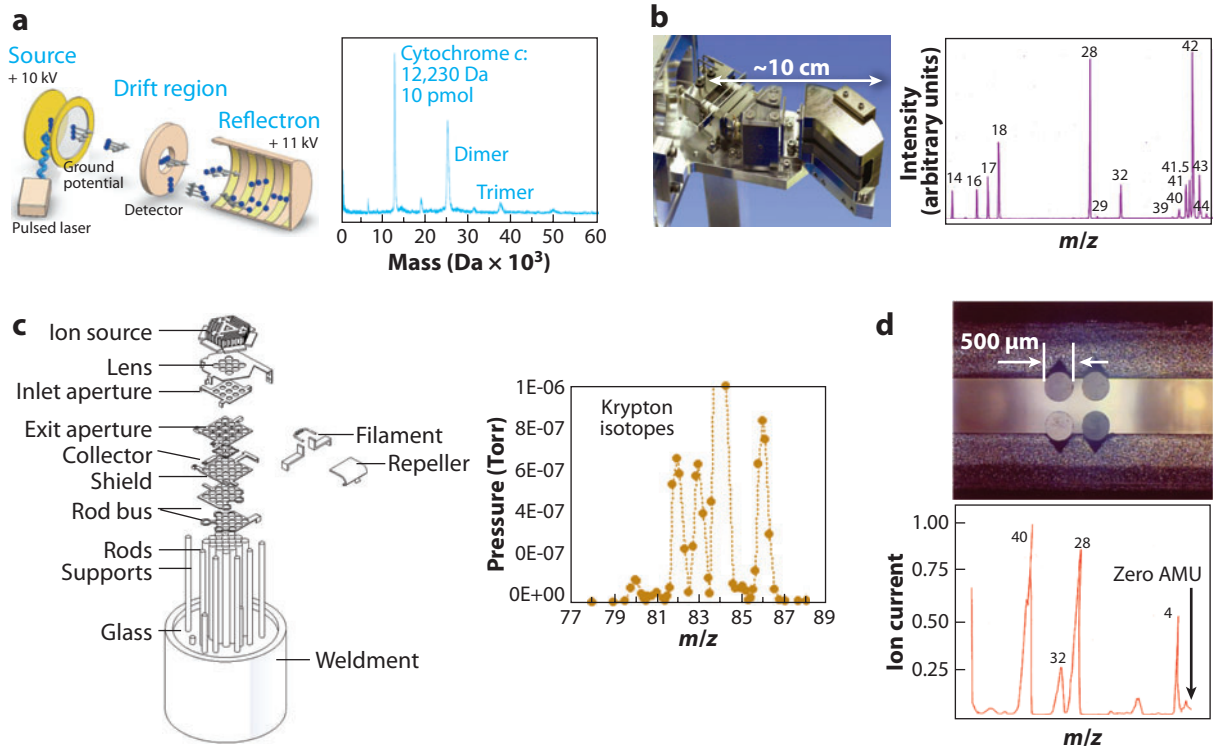

Figure 3

(*a*) "Tiny TOF" (time of flight) mass analyzer with a miniaturized endcap reflectron used to record spectra for peptides and proteins when ionizing by matrix-assisted laser desorption/ionization (MALDI). Reproduced from Reference 9 with permission. (*b*) Mattauch–Herzog sector instrument with focal plane array detector. The lower region of the mass spectrum was recorded when krypton gas was introduced into the chamber. Photo and spectrum reproduced from References 117 and 12, respectively, with permission. (*c*) An exploded view of the micropole quadrupole array mass analyzer and a spectrum of krypton isotopes recorded with a radio frequency (RF) of 14 MHz. Image and spectrum reproduced from References 21 and 23, respectively, with permission. (*d*) V-groove quadrupole mass filter fabricated using micromachining and the spectrum of a mixture of argon, air, and helium recorded using an improved version. Image and spectrum reproduced from References 24 and 18, respectively, with permission.

considerations in the design and selection of miniature mass analyzers for miniaturization of mass spectrometers include

1. Impact on mass analysis. Shrinking a TOF or a double-focusing sector mass analyzer from ~1 m or larger to ~10 cm or smaller influences total instrument size but also inevitably causes degradation in mass resolution, which is intrinsically dependent on the size of the TOF or sector. The resolution of the ion cyclotron resonance (ICR) and quadrupole ion trap depends upon the frequency of the ion motion inside the trap, which in turn depends upon the nature of the electromagnetic field. Theoretically, the electromagnetic field depends solely on the shape, not the size, of these mass analyzers. In practice, it is difficult to maintain undistorted geometries; smaller volumes result in loss of resolution, mostly through smaller trapping capacity, which is crucial for sensitivity.
2. Impact on vacuum system. For beam-type mass analyzers, the required collision-free distance decreases linearly with size reduction. For instance, a 10-fold decrease in the size of a TOF analyzer should allow it to operate at a 10-fold higher pressure, which would lower the

requirement for the compression ratio of the pumping system. For a trap-type mass analyzer, because the ions are trapped in the device for long periods and because the accumulated trajectory length is much longer than the size of the mass analyzer, the size reduction of the mass analyzer may not directly affect the allowable operating pressure. Among mass analyzers, quadrupole ion traps are unique in that their optimal performance occurs at several milliTorr (in contrast to 10^{-5} Torr or less for other analyzers). These devices can trap ions efficiently at high pressures, which is critical for developing an appropriate miniaturized vacuum system (see Section 3.3 for further discussion).

3. Impact on the control system. The separation of ions in the mass analyzer usually depends directly on the magnetic or electric field strength therein. The smaller the mass analyzer is, the lower is the force required to maintain the same field strength, which can result in a smaller driving/control system. The fields inside mass analyzers include static (dc) and dynamic (ac or RF) electric fields and static magnetic fields. For TOFs and electric sectors, where static electric fields are used, the impact of size reduction is relatively small, as high voltages can be provided using fairly compact circuits. For magnetic sectors and for ICR instruments, the use of smaller magnets for miniaturized analyzers reduces the system weight significantly. For RF mass analyzers, such as quadrupole filters and quadrupole ion traps, size reduction results in a quadratic reduction in RF voltage and a biquadratic reduction in power, which is crucial for miniaturization.
4. MS/MS capability. For the analysis of complex mixtures, MS/MS is extremely useful: It (*a*) minimizes chemical noise and (*b*) allows acquisition of information about the chemical structure of the analyte. For applications using miniature analytical systems in which throughput requirements limit sample processing, MS/MS is even more important for compound identification and confirmation. Ion trap mass analyzers can be used to perform multistage MS/MS in a single device, a significant advantage over beam instruments.

Chemical noise: unwanted contribution to a spectrum arising from matrix components

Collision-induced dissociation (CID): increase in an ion's internal energy upon collision, which leads to fragmentation. Activation is achieved using multiple low-energy collisions in ion trap instruments

2.2. Miniature Quadrupole Ion Trap Mass Analyzers

When evaluating mass analyzers for miniaturization in the context of the above considerations, it becomes apparent that quadrupole ion traps have distinct advantages over other instruments. For instance, they have the highest operating pressures, the capability for performing MS/MS in a single device, and the large impact of miniaturization on reducing the instrument size and the power required for the electronics.

2.2.1. Geometry evolution and simplification. The original quadrupole ion trap, invented by Wolfgang Paul in 1953 (37), has electrodes of hyperboloid geometry (**Figure 4**). This device was used for ion storage for decades before it was developed into a mass analyzer. To operate the quadrupole ion trap, an RF is applied between the ring and endcap electrodes, and ions are trapped by the three-dimensional (3D) trapping field. Following work by Todd et al. (38) and March et al. (39), who used the device as a mass analyzer, George Stafford and his colleagues (40) developed the mass-selective instability scan method. In this experiment, ions are ejected from the ion trap in order of their m/z value (from low to high), and the m/z versus ion-abundance information is recorded as a mass spectrum. The trapped ions can be mass-selectively isolated and subsequently fragmented, commonly by collision-induced dissociation (CID) (41), to acquire tandem mass spectra. The 3D quadrupole ion trap has a simplified analog, the cylindrical ion trap (CIT), which has flat electrodes. The CIT was first used for ion storage (42, 43) and was subsequently developed into a mass analyzer, first (44) using the mass-selective stability scan developed by March and later (45) using the mass-selective instability scan developed by Cooks and colleagues. The CIT was

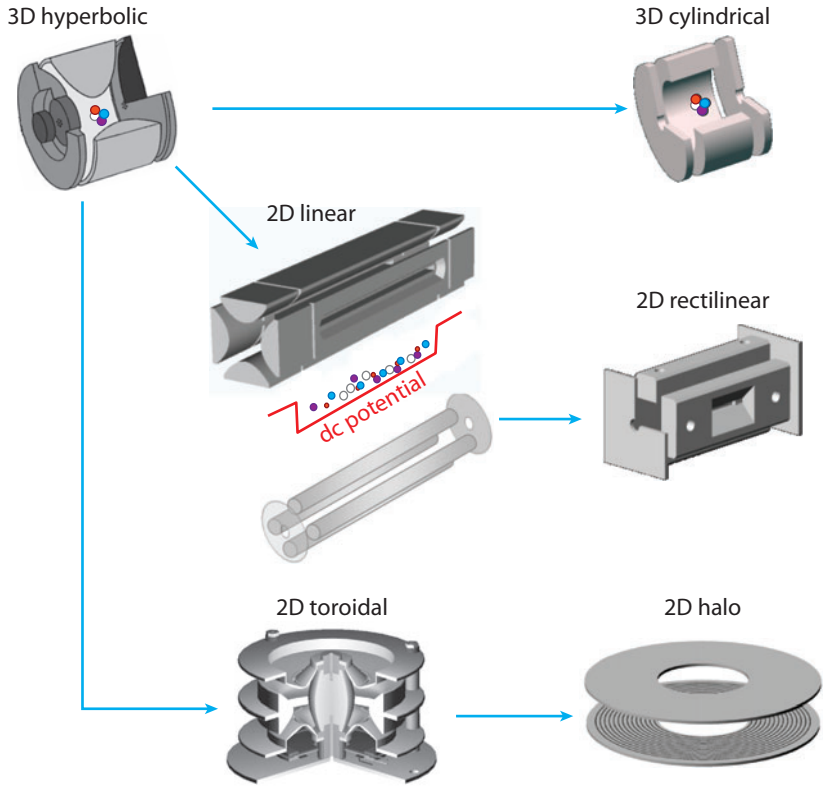

Figure 4

Evolution of quadrupole ion trap geometry toward simplified high-capacity geometries. Images of toroidal and halo ion traps reproduced from References 54 and 33, respectively, with permission. Abbreviations: 2D, two-dimensional; 3D, three-dimensional; dc, direct current.

recognized as a candidate analyzer for mass spectrometer miniaturization due to the ease of its fabrication with adequate precision at small scales (30, 31, 36, 46–49). Many large-scale and small-scale versions of this device have been fabricated using a variety of methods, including traditional precision machining and MEMS micromachining. The CIT has been used in a series of portable mass spectrometers (50–52).

While the simplified 3D CIT ion trap was being developed and implemented as an analyzer in miniature mass spectrometers, revolutionary developments in ion trap geometry led to the enlargement of the trapping capacity (53–56). In a 3D ion trap, the ions are pushed toward the center point of the 3D volume. When too many ions are trapped, coulombic interactions (i.e., space charge effects) degrade the mass resolution as well as the efficiency of mass selection (i.e., the ion isolation efficiency) in CID. It is believed that good-quality spectra can be acquired with minimum space charge effects only when 500 ions or fewer are trapped in a 3D Paul trap with a ring electrode radius (r_0) of 5 mm (57). Two alternative geometries, linear and toroidal, were first proposed in 1996 (53); both allow ions to be trapped along a line instead of at a point, as occurs in a 3D ion trap. In 2002, the linear ion trap was fully developed and characterized by Thermo Electron (now Thermo Fisher™) (56) as well as by MDS Sciex™ (55). In this device, the ions are scanned out through slits in the axial electrodes of the former and through the end electrodes of the latter.

The rectilinear ion trap (RIT), a simplified version of the linear ion trap that uses flat electrodes, was soon developed (58). The RIT has a 40-fold greater trapping capacity than does a CIT of the same nominal size (58). The RIT was used for the development of the 10-kg Mini 10 (3) and the 4-kg Mini 11 (4) handheld mass spectrometers. In addition to their large trapping capacity, linear ion traps can efficiently trap externally injected ions. A large fraction of the ions injected axially into the linear ion trap can be trapped successfully (59), compared with ~5% for 3D ion traps (60). Ion traps with toroidal geometry also have enlarged trapping capacities, as they trap the ions on the circumference of a circle. The performance of these devices was first characterized in 2001 after optimization of the electric field (54). A miniaturized toroidal ion trap (61) was the basis for the development of Torion Technologies' portable gas chromatography (GC) mass spectrometer (5). Also, the halo trap (33), a highly simplified version of the toroidal ion trap, was recently characterized. Like the linear ion trap, the toroidal trap has an enlarged trapping capacity; however, ions cannot be injected orthogonally into the RF field, which is necessary for the highest efficiency in trapping externally injected ions.

2.2.2. Performance optimization. Criteria for performance evaluation include mass resolution, ionization efficiency, and overall mass analysis efficiency, as well as other factors appropriately weighted for particular applications. For instance, a typical objective in the analysis of VOCs is to achieve unit mass resolution over a mass range of 500 Da (hence, *m/z* 500 for singly charged ions). The overall efficiency for mass spectrometric analysis depends on the efficiency of multiple individual steps in the analysis process, which include ion trapping, ion isolation and excitation (for MS/MS), and ion ejection during the mass scan used to acquire the spectrum.

Both the geometry of the ion trap and its operating conditions influence the quality of its performance. In lieu of performing a large number of experimental tests on actual devices fabricated with different geometries, theoretical calculations and numerical simulations have been used as effective tools in the ion trap mass analyzer design process (**Figure 5**). Theoretical calculations were used for the prediction of the best geometry, and numerical simulations were used to optimize the electromagnetic field and select appropriate mass analyzer operating conditions. A typical cycle of the design process uses trial geometries and includes (*a*) mechanically designing the electrode assembly, (*b*) solving the electromagnetic field inside the mass analyzer, (*c*) simulating the trajectories of an ensemble of ions, and (*d*) hence acquiring the mass spectrum (**Figure 5*a***). Often, multiple cycles are implemented to obtain optimal results. Although many software packages for simulating ion motion are available, SIMION® (62) and ITSIM® (Ion Trajectory SIMulation) (63, 64) are the most frequently used in the development of miniature ion traps because they integrate necessary functions and have user-friendly interfaces. SIMION employs an integrated field solver. ITSIM was developed particularly for ion trap simulations and allows one to obtain simulated mass spectra that directly correspond to the performance of the ion trap.

The internal electric field is critical for ion trap mass analyzer performance (65–67). The ideal electric field would be a pure quadrupolar field, but it can only exist in the case of hyperbolic electrodes of infinite length. Theoretically, in such a field all trapped ions with the same *m/z* value would have exactly the same frequency of motion, regardless of their initial conditions and subsequent locations. In practice, higher-order fields are introduced when using real (truncated) electrodes, and they are further complicated by the holes or slits needed for ion injection and ejection. Simplified electrodes, as used in a CIT or a RIT, add even greater proportions of non-quadrupolar fields. The goal of field optimization is to find the electrode structure that gives the best combination of field components so as to optimize mass analyzer performance (68). Two approaches have been implemented to realize field optimization in practice. One is to (*a*) make iterative changes in the dimensions of the electrodes and their relative spacings to vary the relative

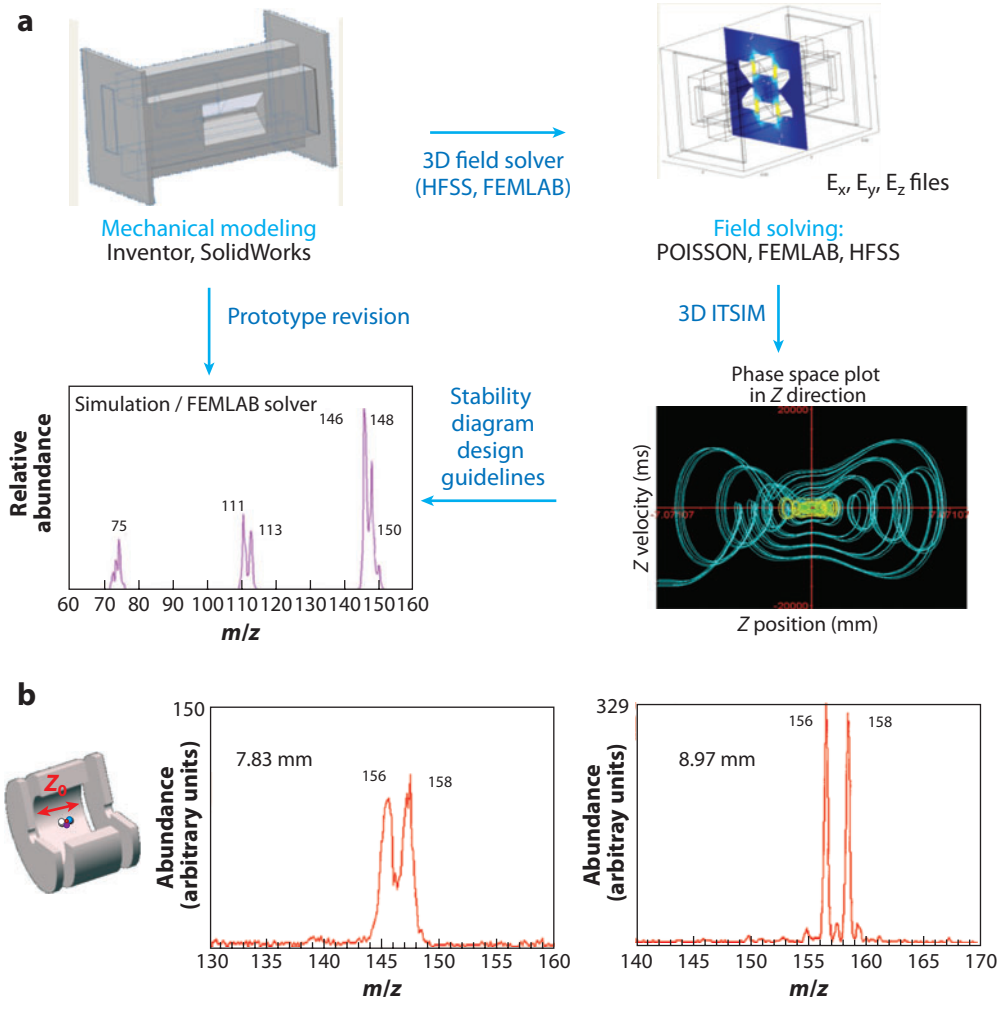

Figure 5

(*a*) Procedure for optimization of ion trap geometry by simulation. (*b*) Performance of a cylindrical ion trap optimized by stretching distance between the endcaps. Spectra reproduced from Reference 45 with permission. Abbreviations: HFSS, high-frequency structural simulator; ITSIM, ion trajectory simulation.

Buffer gas: added to remove energy from ions by collision without scattering them from the trap; also used in CID experiments to add internal energy to translationally excited ions through collisions

strengths of the higher-order components, (*b*) calculate the fields, and (*c*) simulate ion motion to identify and then fabricate the optimum design. This process was applied to the optimization of the CIT (**Figure 5*b***) (45, 47, 68), RIT (58) (**Figure 6*a***), and toroidal ion traps (54) (**Figure 6*b***). The second approach does not emphasize optimization of the electrode geometry, but instead uses electrode arrays to create the desired field by applying individually controllable potentials to the individual electrodes in the array. This method has been applied to the halo trap (33, 69) (**Figure 6*c***) and to a RIT (70). The concept has also been used in the development of a simplified version of a toroidal ion trap with a single planar electrode array (32).

A special feature of ion trap operation is that mass analysis in lab-scale instruments is usually performed using helium as the buffer gas. The buffer gas cools the ions through collisions and so assists in their trapping and in efficient excitation during CID. Ambient air is a particularly

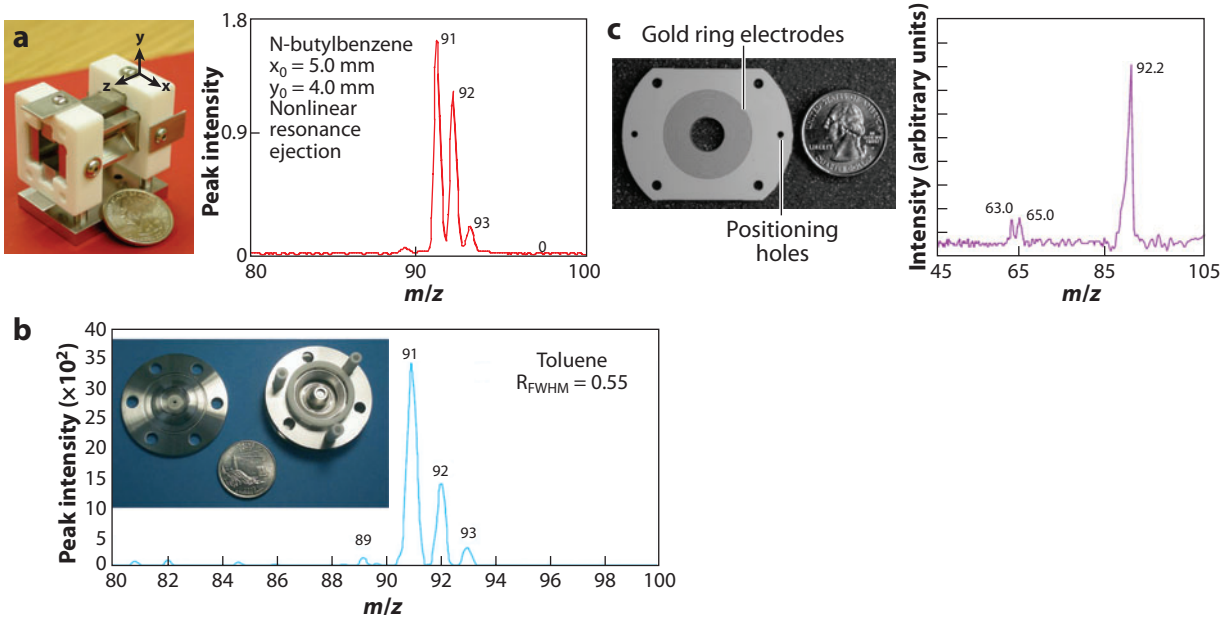

Figure 6

Performance of miniature ion traps of different types. (*a*) Rectilinear ion trap (x_0 = 5.0 mm) optimized to provide unit resolution and improved trapping capacity. Spectrum reproduced from Reference 58 with permission. (*b*) Performance of a miniature toroidal ion trap (r_0 = 2 mm) operated at 3 MHz using resonance ejection and sweeping the frequency of the auxiliary alternating current. Photograph and spectrum reproduced from References 61 and 5, respectively, with permission. (*c*) Trapping plate of a halo trap coated with metal ring electrodes and overlaid with germanium and the spectrum recorded for toluene. Abbreviation: FWHM, full width at half-maximum. Reproduced from Reference 33 with permission.

desirable buffer gas for a miniature ion trap, given the inconvenience of using helium for field applications. However, optimization of operating conditions is important because collisions also excite trapped ions and can lead to their dissociation and/or loss from the trap. Nevertheless, resonance ejection can be implemented at a nonlinear resonance point, and a half-size RIT is capable of providing unit resolution mass spectra and allowing CID when using ambient air at several milliTorr as the buffer gas (3, 71).

2.2.3. Miniature ion trap mass analyzers. The process of ion trap miniaturization requires striking a balance between the advantages of low RF voltage and the performance of the mass analyzer, including mass resolution and the mass analysis efficiency. As noted above, to scan to a given *m/z* value, the smaller the mass analyzer is, the lower (quadratically) is the required RF voltage (**Figure 7**) and the lower (biquadratically) is the power required to perform the scan. However, use of a lower RF voltage decreases the trapping potential well depth, which causes lower ion trapping efficiency and poorer mass resolution. Often, RF signals of higher frequency—in contrast to those below 1 MHz, which are used for lab-scale ion trap instruments—are used for the characterization of miniature ion trap mass analyzers. This approach effectively improves the performance of the miniature mass analyzers because the trapping potential well depth is increased. However, higher-frequency RF signals are used at the expense of an increase in RF voltage (**Figure 7**). If the RF voltage and power used become more similar to those used to operate a larger ion trap, there is far less opportunity to miniaturize the whole instrument.

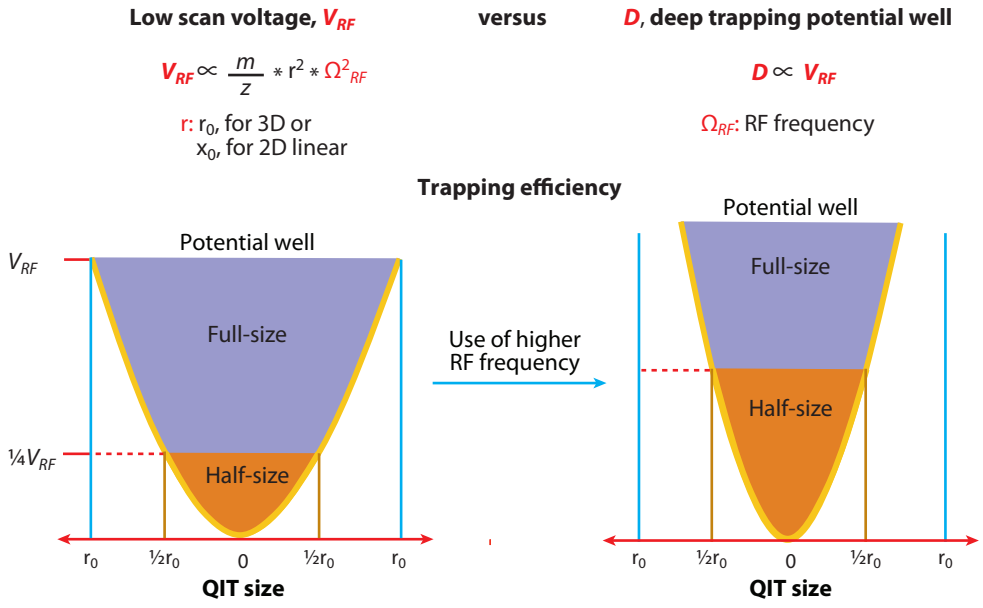

Figure 7

Competing effects of RF frequency, RF voltage (V), and trap size on pseudopotential well depth and hence on trapping efficiency and capacity. Abbreviations: 2D, two-dimensional; 3D, three-dimensional; QIT, quadrupole ion trap. Critical dimensions and nominal sizes for 3D and linear ion trap, r_0 versus x_0: Paul and cylindrical ion (3D) traps are characterized by their internal radii, which have a fixed relationship to their axial dimension z_0. Analogously, linear ion traps are characterized by the dimension x_0, which bears an optimal relationship to y_0, the other critical dimensions of the 2D device.

An effective means of improving the limited ion trapping capacity of miniature ion trap mass analyzers (while keeping the advantage of low RF voltages) is to increase the trapping volume by using an array of traps with identical dimensions. For 3D ion traps, parallel arrays of small-sized CITs have been used (72). CIT arrays with individual ion traps having r_0 as small as 1 μm have been fabricated with standard MEMS technologies (**Figure 8**) (30, 31). Researchers have expended significant effort on lowering the capacitance of the whole device (30) because the ultimate driving power required from the RF supply depends upon it. This objective was achieved with the assembled configuration shown in **Figure 8*b***, which has minimum overlap between the ring and end electrodes. An array of 256 CITs of $r_0 = 20$ μm (**Figure 8*c***) was operated with an RF of 100 MHz, and a xenon spectrum was acquired using an RF amplitude below 90 $V_{0\text{-}P}$ (**Figure 8*d***) (31).

Linear ion traps have another intrinsic advantage in miniaturization. Although the interelectrode distances x_0 and y_0 are decreased, the axial length (z) need not be decreased proportionately; this allows a larger trapping volume. A practical challenge is whether a device with a large aspect ratio (z/x_0) can be fabricated with adequate precision.

The performance of mass analyzers at the 1-mm scale (36, 48) is promising for use in miniature mass spectrometers for chemical analysis applications. CITs with r_0 of 0.5 mm (48), 1.023 mm (52), and 1.375 mm (36) have been fabricated and tested (**Figure 9*a–c***). Relatively high RF frequencies were used in the CITs' characterization, but a *m/z* of 200 could be covered with RF amplitudes of several hundred volts. Notably, unit resolution was achieved using a 1.375-mm-r_0 trap fabricated from LTCC (36). The LTCC process is widely used in electronics packaging and is suitable for mass production at low cost.

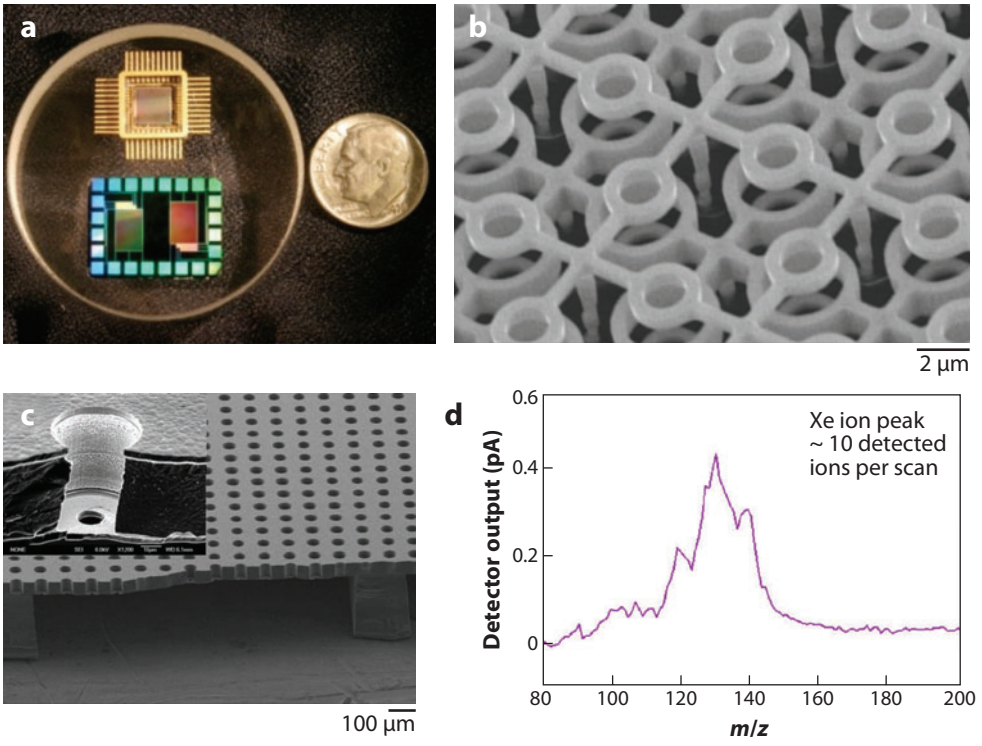

Figure 8

(*a*) Two microarray chips of cylindrical ion traps (CITs). (*Top*) An array of 10^6 CITs of $r_0 = 1$ μm. (*Bottom*) Two CIT arrays. (*b*) Scanning electron micrograph of a CIT microarray. $r_0 = 1.5$ μm; the overlap between the ring and endcap electrodes is minimized. Reproduced from Reference 30 with permission. (*c*) Scanning electron micrograph of a CIT microarray chip with $r_0 = 20$ μm. (*d*) Xenon (Xe) spectrum recorded using the type of chip shown in panel *c* with 256 CITs. Panels *c* and *d* reproduced from Reference 31 with permission.

Recently, RITs (34, 35) and arrays (M. Fico, J.D. Maas, S.A. Smith, W.J. Chappell & R.G. Cooks, manuscript in preparation) have been developed and fabricated using SLA. SLA is a fast prototyping technique that uses a laser beam to "write" complex 3D structures, such as the circular RIT array shown in **Figure 9*d***, via the photopolymerization process (M. Fico, J.D. Maas, S.A. Smith, W.J. Chappell & R.G. Cooks, manuscript in preparation). The x_0 of each RIT in the array is 1.66 mm, and the length is 8.33 mm. A CID spectrum of peptide bombesin doubly charged molecular ions at *m/z* 811 was recorded using one of the channels, and it showed fragment ions in the *m/z* range up to 1200 with peak widths of 2 units. It is encouraging that a linear ion trap on this size scale operating at an RF frequency below 1 MHz has a trapping capacity high enough for efficiently performing MS/MS. Spectra can be acquired for ions in the *m/z* range up to 1200, with RF amplitudes below 100 $V_{0\text{-}p}$.

3. MINIATURIZATION OF THE MASS SPECTROMETER

Miniaturization of mass analyzers alone does not necessarily lead to a straightforward size reduction of the mass spectrometer, which incorporates many other components of the ion processing,

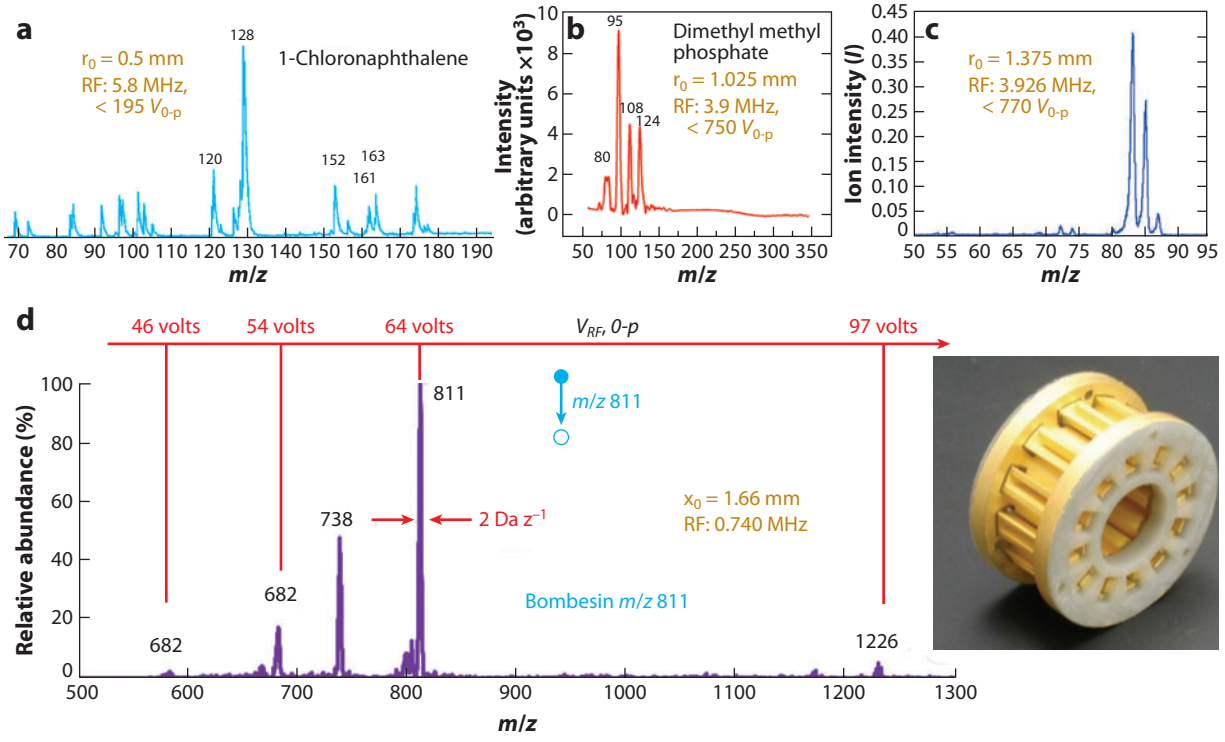

Figure 9

(*a*,*b*) Mass spectra recorded using stainless steel cylindrical ion traps (CITs) of (*a*) $r_0 = 0.5$ mm and (*b*) $r_0 = 1.025$ mm. (*c*) Mass spectra recorded using a low-temperature cofired ceramics (LTCC)–fabricated CIT of $r_0 = 1.375$ mm and (*d*) a stereolithography apparatus (SLA)–fabricated rectilinear ion trap (RIT) of $r_0 = 1.6$ mm, which is one element in the trap array illustrated. Panels *a*, *b*, and *c* reproduced from References 48, 52, and 36, respectively, with permission.

vacuum, and control subsystems. This section considers this larger set of systems and examines further options for miniaturization.

3.1. Challenges

The impact of ion trap miniaturization on the control electronics is quite dramatic. **Figure 10** compares the handheld Mini 11 mass spectrometer using a RIT of $x_0 = 5$ mm with an ion trap mass spectrometer (ITMS) that has a 3D Paul trap of $r_0 = 10$ mm. The small (factor of two) size reduction allows use of a much smaller RF coil to provide a sufficiently high voltage to scan to higher mass (*m/z* 800 for the Mini 11 versus *m/z* 650 for the ITMS) with unit mass resolution. The power consumption of the RF circuit is estimated to be reduced from ~250 W to ~15 W. Using a RIT of $x_0 = 1.6$ mm (**Figure 9*d***) would require even lower voltages and a much lower power consumption. For the low voltage boards in the control system, the technology available for fabricating electronic circuits has been advancing quickly, and compact low-voltage digital/analog boards with complex functions can be made with multilayer printed circuit boards that have surface-mounted components (4, 5). Although further miniaturization of ion trap mass analyzers remains ripe for exploration, with regard to miniaturizing the entire mass spectrometer we should focus on components other than the mass analyzer. The vacuum system is a case in point.

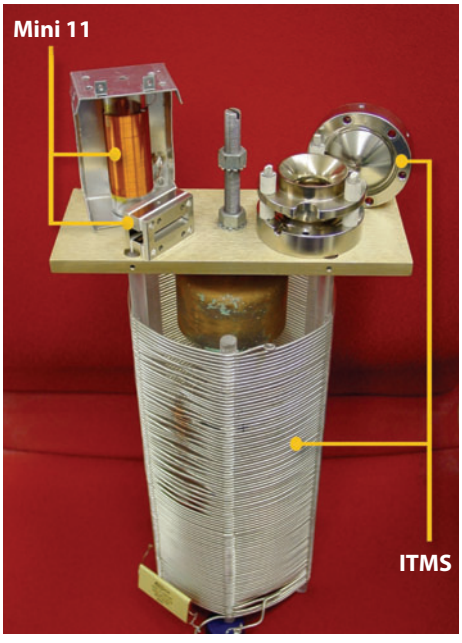

Figure 10

Comparison of the radio frequency coils used to drive the ion trap in the handheld Mini 11 and in the first commercial ion trap mass spectrometer, the Finnigan ITMS^{TM}. A half-size rectilinear ion trap is used in the Mini 11, whereas a full-size Paul quadrupole trap is used in the ITMS. The figure also shows the ion traps in the two instruments.

The vacuum system, including the vacuum pumps and the vacuum manifold with its various interfaces, is almost always the most expensive, the heaviest, and the most power-consuming part of a mass spectrometer. The performance of a mass spectrometer is highly dependent on the design of the pumping system, which determines how much sample can be introduced and how low a vacuum can be maintained. For portable systems, the quality of the miniature pumping systems has a substantial impact on the robustness of the instrument. The turbo pumps used for mass spectrometers are often considered too fragile for in-field applications, where mass spectrometers are moved around during operation.

3.2. Miniaturization of the Vacuum System

An early strategy to make mass spectrometers portable was to remove the rough pumps. In one instance, the vacuum manifold was first pumped down, then the rough pump was detached from the instrument. During operation in the field, vacuum was maintained by a light, low-power ion pump. Implementation of this general strategy allowed the development of a transportable mass spectrometer using ICR (73), a portable instrument using a quadrupole mass filter (74), and recently, a palm portable ITMS (52). The advantage of this strategy is that it allows one to set aside the issues of weight, size, and power associated with the pumping system so that small instruments with low power consumption can be developed. The disadvantages include the limitations on sample introduction and the fact that the system is not self-sustainable. Pulsed gas sample introduction must be implemented to avoid rapid pressure increases. When coupled with a GC system (74), a membrane is effective in limiting input of carrying gas from the GC column

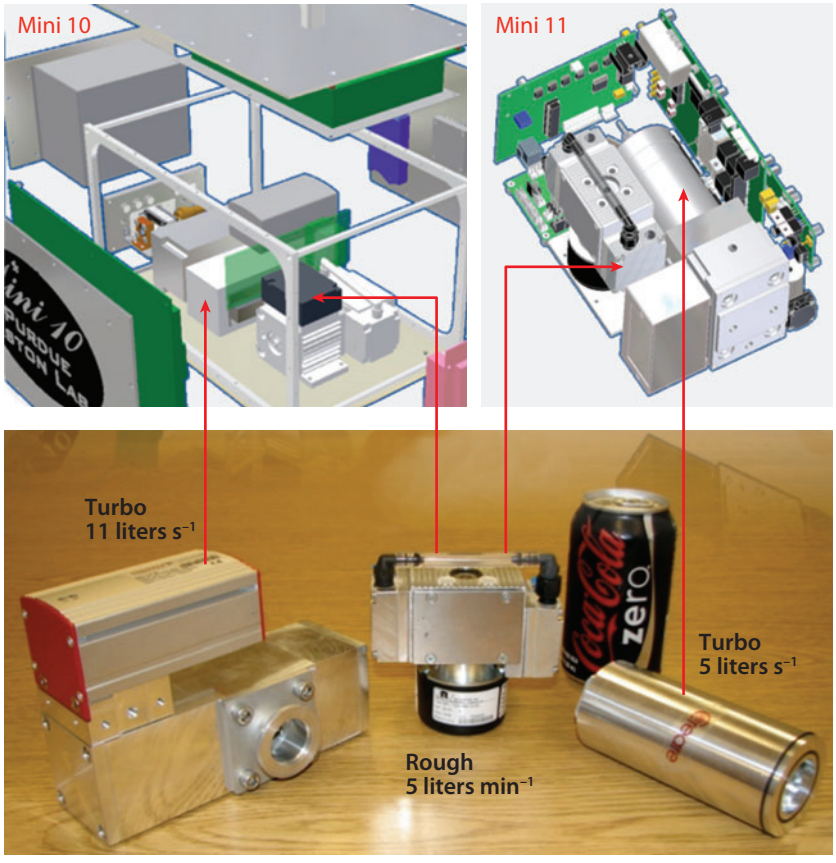

Figure 11

Compact pumping systems using miniature roughing and turbomolecular pumps. Shown are turbo pumps made by Pfeiffer Vacuum, Inc.™ and by Creare, Inc.™ The rough pump is a KnF™ two-stage diaphragm pump.

into the vacuum. The portable system must also be recharged using a nearby rough pumping system.

Self-sustaining portable MS systems that use miniature versions of the traditional rough-turbo pump configurations found in lab-scale instruments have been developed (**Figure 11**). Instead of the rotary vane pumps commonly used for lab-scale mass spectrometers, diaphragm pumps are used exclusively for the roughing stage of portable systems. KnF two-stage diaphragm pumps (5 liters min^{-1}; Model 1091-N84.0-8.99 or similar systems) are used for handheld instruments, and four-stage diaphragm pumps with higher pumping speeds are used in transportable instruments. The ultimate pressures that these pumps provide range from 1 to 2 Torr. For high-vacuum pumping, although some alternative options are being explored, turbo-molecular pumps are still the only reliable choice for portable mass spectrometers. Two types of commercial turbo pumps, the ATH 31 series (1.2 kg, ~30 liters s^{-1}; manufactured by Alcatel Vacuum Technology Corporation™) and the TPD 011 (2 kg, ~10 liters s^{-1}; manufactured by Pfeiffer Vacuum, Inc.™) are commonly used in the development of miniature mass spectrometers. Although the Pfeiffer TPD 011 is not the lighter of the two instruments nor the one with the larger pumping speed, it has proven to be robust enough to operate while in motion (3, 75). Recently, a turbo pump weighing only 500 g

(manufactured by Creare, Inc.™) was used (4) in the development of the 4-kg Mini 11 handheld instrument. The total weight of this miniature pumping system is below 3 lb, and the power consumption is below 18 W. The ultimate vacuum that it can provide is below 10^{-8} Torr, which is much lower than the operating pressure needed for a miniature mass spectrometer system. In fact, miniature quadrupole ion trap mass analyzers, such as a RIT, can provide optimum operation at a pressure above 1 mTorr (75, 76). One strategy in the future development of miniature pumping systems will be to eliminate the unnecessary turbo stage, which has little impact on the pumping speed but a substantial impact on the ultimate pressure. The turbo stages inside a turbo pump represent the most mechanically fragile and the most expensive components of the pumping system.

3.3. Development of Sample Introduction Interfaces

As discussed above, the vacuum system is critical because it is closely related to how sample (or ionized sample, depending on whether internal or external ionization is used) is introduced into the mass spectrometer for mass analysis. A miniature pumping system with one diaphragm and one turbo pump allows the creation of a single-stage vacuum system that is conceptually similar to that used in a lab-scale GC-MS instrument. The neutral gas can be leaked into the manifold, then ionized to achieve mass analysis. Sample introduction methods for lab-scale instruments using this type of vacuum system are readily transferrable to miniature instruments with minimum difficulty, even with their greater restrictions on input flow. These methods include micro-GC (5, 77), solid-phase microextraction (78), and membrane introduction (3, 50, 51, 79–82). The typical ionization method used with these sample introduction systems is EI. A glow discharge EI source has been developed as an alternative to the traditional filaments for miniature mass spectrometers, and it has been demonstrated to be much more durable and much less power consuming than resistively heated filaments (71).

For lab-scale mass spectrometers, the vacuum system configuration is very different in instruments in which atmospheric pressure sample ionization is followed by ion transfer into the mass analyzer. This type of mass spectrometer is widely used in biomedical studies ranging from metabolite analyses in the pharmaceutical industry to peptide analyses for proteomic studies. The ionization methods used include electrospray ionization (ESI) (83, 84), atmospheric pressure chemical ionization (APCI) (85), and atmospheric pressure MALDI (86, 87). Devices capable of analyzing under ambient conditions nonvolatile compounds, such as plastic explosives from solids or biomolecules from solution, would significantly widen the application area for miniature mass spectrometers. However, pumping systems with significantly higher pumping speeds and more differential pumping stages that are currently available are required to establish an atmospheric pressure interface that would allow the transfer of ions from the ambient pressure region to the vacuum for the mass analysis (**Figure 12*a***). So far, no miniature pumping system with a weight, size, and power consumption low enough for portable instruments or a high enough ion transfer efficiency has been successfully developed.

However, a direct leak type of atmospheric pressure interface on the Mini 10 used a capillary to directly connect the ambient and vacuum regions (88). Spectra were acquired for proteins and peptides using ESI, and the mass range was extended through the use of a low-resonance ejection frequency. However, ion transfer was limited by the low conductance of the capillary, and mass resolution suffered from the high pressure in the vacuum manifold. Recently, the barrier to high performance of a small vacuum system was overcome with the development of a discontinuous atmospheric pressure interface (DAPI) for a quadrupole ion trap–based miniature instrument (**Figure 12*b***) (4, 89). The DAPI uses a pinch valve to control the opening of an interface, and

Membrane introduction: system in which a semipermeable but nonmicroporous membrane is used to selectively transfer analytes from an air or water matrix into the vacuum by means of diffusion through the membrane. The experiment protects the cleanliness of the vacuum system but is limited to volatile analytes

Atmospheric pressure ionization: a broader term than ambient ionization that does not imply lack of sample pretreatment (e.g., the sample is often treated with matrix, dissolved in solution, etc.) or full access to the sample during MS

Ambient ionization: involves untreated sample in an open environment; sampling and ionization occur simultaneously

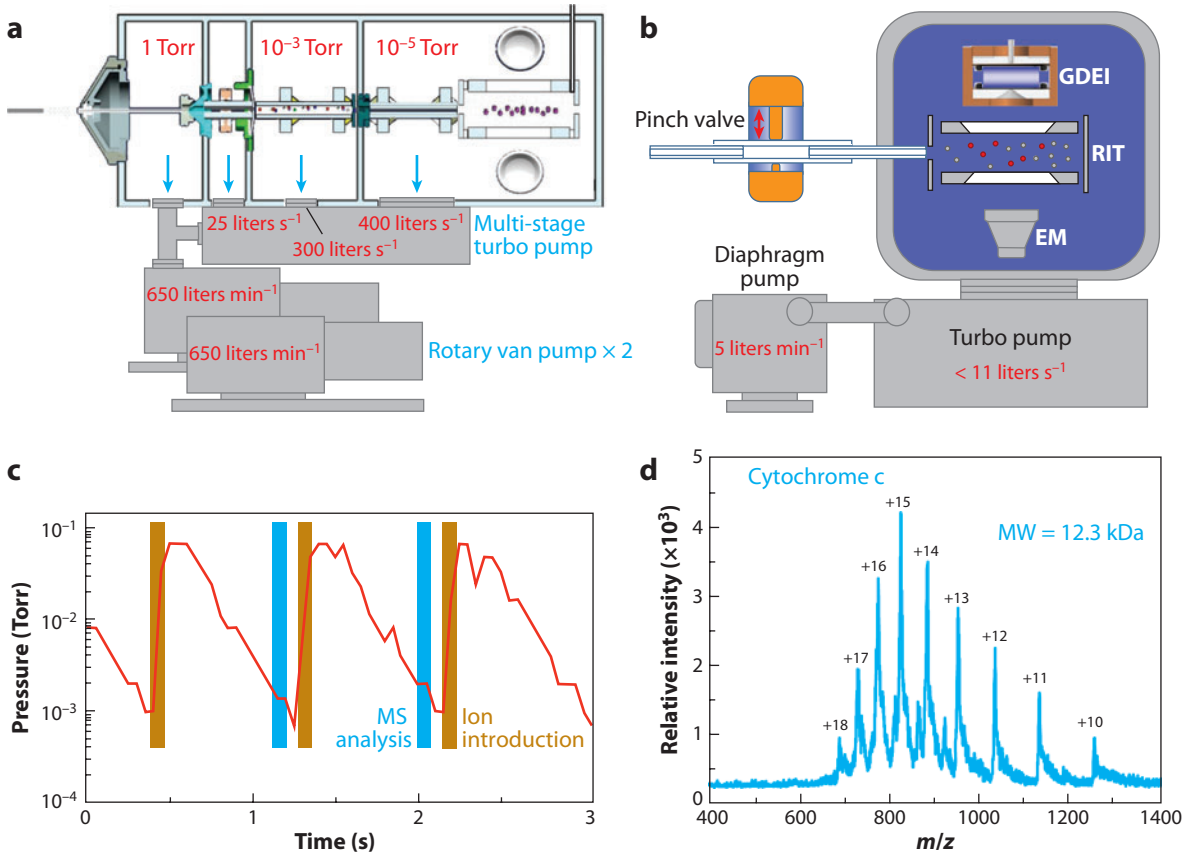

Figure 12

(*a*) Typical configuration of vacuum systems for lab mass spectrometers with atmospheric pressure interfaces. (*b*) Discontinuous atmospheric pressure interface (DAPI) for miniature vacuum systems using a pinch valve for controlling opening. (*c*) Pressure variation inside the vacuum during the operation of the DAPI. (*d*) Mass spectrum of 200 ppm cytochrome *c* recorded using a nano–electrospray ionization (ESI) source with a radio frequency of 695 kHz. Abbreviations: EM, electron multiplier; GDEI, glow discharge electron impact; MS, mass spectrometry; RIT, rectilinear ion trap. Panels *a* and *b* reproduced from References 89; panel *d* reproduced from Reference 4 with permission.

when open, the flow conductance is much greater than the pumping system can tolerate. During each mass analysis cycle, the interface is opened for only ~20 ms. The introduced ions are trapped in the RIT while the introduced gas increases the pressure; then the gas is pumped away (**Figure 12*c***). Mass analysis, including MS and MS/MS, can then be performed after a delay of some 300 ms, when the pressure drops into the low milliTorr range. DAPIs have been implemented on the Mini 10 (89) and Mini 11 (4) devices and have been characterized with ESI, APCI, and ambient ionization methods (90, 91), which include direct-solids analysis by desorption electrospray ionization (DESI) (92) and low-temperature plasma (LTP) probe ionization (93). Chemical analysis has been performed for various solid organic compounds and mixtures (4; 89; M.A. Visbal, G. Huang, J.D. Harper, Y. Zhou, R.G. Cooks & Z. Ouyang, manuscript submitted) and for amino acids, peptides, and proteins in solution (**Figure 12*d***) (4, 89).

4. TOTAL MASS SPECTROMETRY ANALYTICAL SYSTEMS

4.1. Bottlenecks in Analysis Using Miniature Mass Spectrometers

The purpose of miniaturizing mass spectrometers is to enable high-quality in situ analysis. Given the existence of small mass spectrometers of adequate performance such as the Mini 11, where are we in terms of solving the problems of in situ analysis? The answer is: We are not there yet.

The problems associated with the power requirements and weight of the mass spectrometer have largely been solved, and of course, mass analysis itself is already highly automatic and fast. However, the progress described so far in this review highlights the fact that sample preparation still takes too long and requires far too many manual operations. The weak links in in situ analytical protocols include sample collection, extraction, preseparation, and other special treatments that are highly dependent on the nature of the samples and of the analytes of interest. After mass analysis, data analysis is also needed to translate the raw spectral data into the information needed to draw conclusions. The problem that has now moved into sharp focus is: How can we implement these necessary processes into simple, automated, and reliable methods that are compatible with in situ mass analysis?

Great effort has been made toward miniaturizing devices and simplifying the operations associated with almost every step in sample treatment. A micro-GC has been implemented and could be coupled to a portable MS system (**Figure 13*a***) (5, 77, 78, 94). One of the most promising directions in miniaturizing and automating sample preparation is through the use of microfluidics, an approach that provides capabilities similar to laboratory systems for sample separation, but uses miniature chip-based devices with low consumption of sample and solvents and with automated operation. The integration of these devices into miniature mass spectrometers will be useful for many future applications following the success of discontinuous sample introduction (89).

Rather than building devices mimicking standard lab operations, researchers have actively pursued development of alternative methods to provide fast and simple sampling operations. In some cases, the nature of the sample makes this relatively easy: For instance, in the case of real-time analysis of VOCs in air or water, sampling occurs via membrane introduction (3, 4, 50, 51, 79, 80, 95). The most common membrane used for this purpose is the hydrophobic PDMS (polydimethylsiloxane, or simply silicone) membrane, which allows organic compounds in the vapor state or in aqueous solution to diffuse through the membrane and to be released into the vacuum while excluding the matrix, thereby serving as an effective means of analyte preconcentration (81, 82). The greatest advantage of membrane introduction mass spectrometry (MIMS) is its simplicity. Volatile ingredients in human breath, for example, can be directly analyzed (**Figure 13*b*,*c***) (96). Using the Mini 10 instrument with the vacuum system shown in **Figure 11**, the limits of detection for the MIMS instruments are 50 ppb (3) and 3 ppb for naphthalene in air and water, respectively, without heating the membrane. Disadvantages of MIMS include its relatively long clear-time and its limited applicability to less-volatile or polar compounds. Alternative trap-and-release methods allow the monitoring of toxic industrial compounds, and limits of detection well below the permissible exposure limits have been achieved in short (<2 min) total analysis times with the Mini 10 (75).

With the development of the discontinuous atmospheric pressure interface (89), more options for direct, rapid sampling have become possible. Within the past four years, ambient ionization (90, 91) has emerged as a direct sampling method; it allows analytes in untreated samples to be directly ionized and transferred (97) into the mass spectrometer for mass analysis.

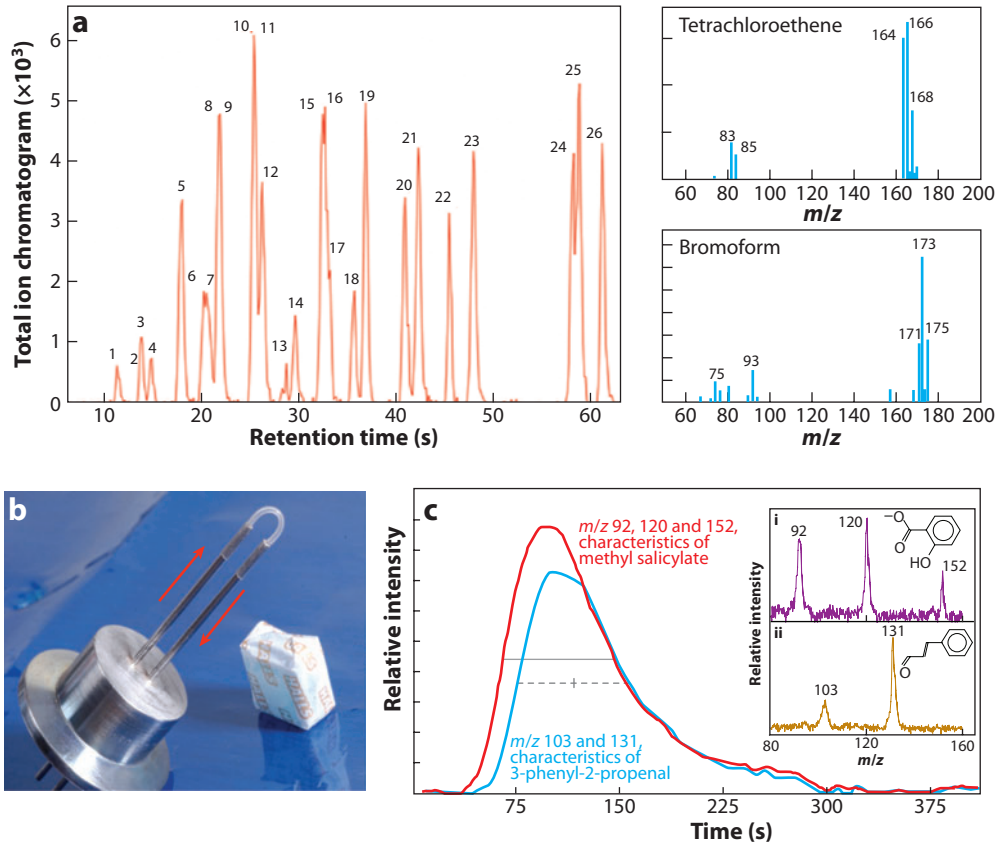

Figure 13

(*a*) Analysis of a 26-component EPA (Environmental Protection Agency) Method 624 volatile halocarbon compound mixture (20 ppm in water) using a miniature gas chromatography mass spectrometer with a toroidal ion trap. Reproduced from Reference 5 with permission. (*b*) A membrane inlet used in miniature mass spectrometers (50, 51, 79, 96). (*c*) Direct analysis of human breath after eating cinnamon and wintergreen candies containing ingredients 3-phenyl-2-propenal and methyl salicylate. Reproduced from Reference 96 with permission.

4.2. Ambient Ionization for Direct Sampling

Since the demonstration of the capabilities of the first two ambient ionization sampling methods, DESI (92) and direct analysis in real time (98), as many as 18 related methods (92, 93, 97–110) for direct ionization of analytes from unprepared samples (91) have been introduced. There is a significant difference between ambient ionization and atmospheric pressure ionization methods such as ESI, although this difference is perhaps obscured by the similar nomenclature. The term ambient ionization designates methods that combine the sampling process with the ionization process and that can (*a*) desorb the analytes directly from untreated samples in the condensed phase and (*b*) ionize them for mass analysis. The ionization occurs simultaneously with (92, 93, 98, 100, 106, 108) or immediately after (101, 109) desorption. DESI (92) and the LTP method (93) have been implemented with the Mini 10 (89; M.A. Visbal, G. Huang, J.D. Harper, Y. Zhou, R.G. Cooks & Z. Ouyang, manuscript submitted) and Mini 11 (4) handheld mass spectrometers for fast sampling and ionization. As shown in **Figure 14*a*** for DESI analysis, charged droplets are sprayed on the

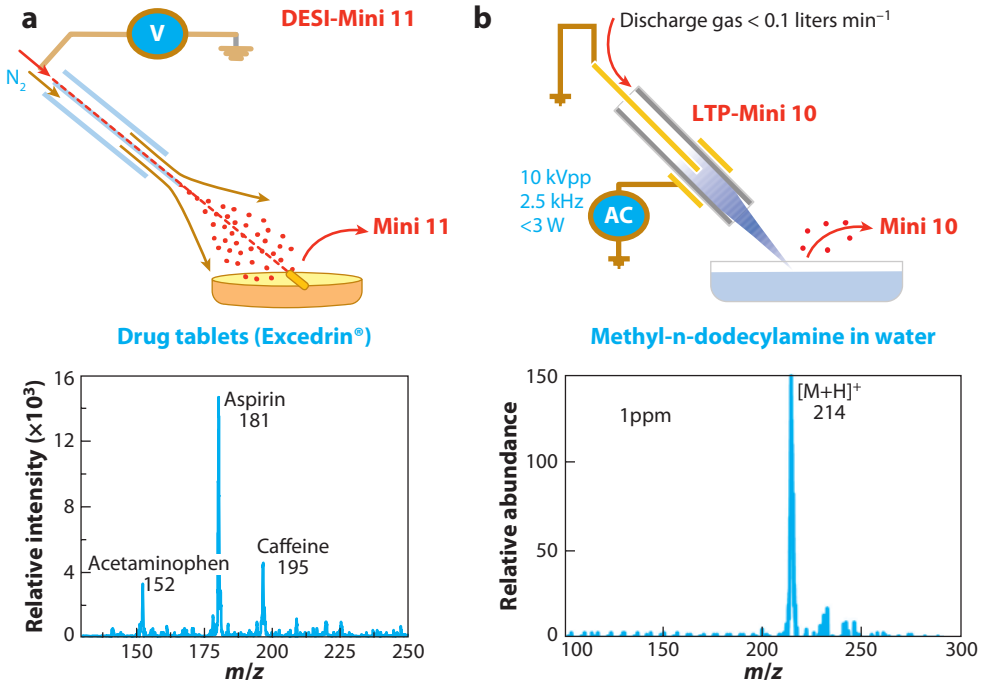

Figure 14

(*a*) Direct analysis of active ingredients in drug tablets using desorption electrospray ionization (DESI) and a Mini 11 handheld mass spectrometer. Spectrum of Excedrin® reproduced from Reference 4 with permission. (*b*) Direct analysis of chemicals in water samples using a low-temperature plasma probe and a Mini 10 device. Reproduced with permission from M.A. Visbal, G. Huang, J.D. Harper, Y. Zhou, R.G. Cooks & Z. Ouyang (manuscript submitted).

surface of the tablets, and the constituent molecules are picked up by secondary microdroplets and are sucked into the vacuum system of the Mini 11 for mass analysis. In contrast to traditional laboratory sample preparation procedures followed by atmospheric pressure ionization (e.g., by ESI or by APCI), the total analysis time using ambient ionization sampling is ~3 s. This includes the time required for (*a*) sample extraction, (*b*) separation of the analytes from the matrix, (*c*) formation of a solution containing the analyte(s), (*d*) ionization, and (*e*) mass analysis. Using LTP, the chemicals in complex liquids can be directly desorbed, ionized, and analyzed by miniature mass spectrometers (**Figure 14*b***).

When not using separation procedures, poor sensitivity to analytes at low concentrations in a complex mixture is always of great concern. Notably, reagents can be added to the spray solution in desorption ionization to allow selective ionization of targeted analytes. This approach has been explored in the form of reactive DESI (111) and has been applied to analyses of steroids in raw urine (112) and of cholesterol in tissues (C. Wu, D.R. Ifa, N.E. Manicke & R.G. Cooks, manuscript submitted), for example, where it results in a significant improvement in sensitivity. Reactive forms of electrospray-assisted laser desorption/ionization (113) and LTP (G. Huang, J.D. Harper, R.G. Cooks & Z. Ouyang, manuscript submitted) were also demonstrated recently. Through the use of reagents that target specific chemical features of the analyte, ionization becomes an important step for improving the specificity of the entire analysis process. Reactive ambient ionization methods are expected to play an important role in future analyses using miniature mass spectrometers.

Table 1 Portable mass spectrometry analytical systems

	Self-sustainable portable systems						Portable systems without rough pumping	
Systems	**Mini 10/Mini 11 (3, 4)**	**ChemCube™ (115)**	**Guardion-7™ (5)**	**Suitcase TOF (9)**	**Griffin 600™ (116)**	**Ion-camera (117)**	**Palm-portable MS (52)**	**HAPSITE® (74)**
Developer	Purdue University	Microsaic Systems	Torion Technologies	Johns Hopkins Applied Physics Lab	Griffin Analytical Technologies, Inc.	OI Analytical	Samyang Chemical Co.	Inficon
Weight	10 kg /4 kg	14 kg	11 kg	N/A	15 kg	18 kg	1.5 kg	18 kg
Power	70 W/30 W	50 W	75 W	N/A	N/A	75 W	5 W	<150 W
Mass analyzer	Rectilinear ion trap	Quadrupole mass filter	Toroidal ion trap	TOF	Cylindrical ion trap	Mattauch–Herzog sector	Cylindrical ion trap	Quadrupole mass filter
MS/MS	Yes	No	Yes	No	Yes	No	No	No
Sampling/ ionization	MIMS, direct leak, GDEI, APCI, ESI, DESI, LTP	SPME, EI	SPME, mini GCEI	MALDI	SPME, MIMS EI	Direct gas leak EI	Pulsed gas leak EI	GCEI
Mass range/ resolution	*m/z* 700, R = 700; *m/z* 1500, R = 750	*m/z* 600, R = 400	*m/z* 500, R = 500	*m/z* 70,000, R = 70	*m/z* 425, R = 400	*m/z* 300, R = 300	*m/z* 300, R = 150	m/z 300, R = 300

Abbreviations: APCI, atmospheric pressure chemical ionization; DESI, desorption electrospray ionization; EI, electron impact; ESI, electrospray ionization; GCEI, gas chromatography electron impact; GDEI, glow discharge electron impact; LTP, low-temperature plasma; MIMS, membrane introduction mass spectrometry; MALDI, matrix-assisted laser desorption/ionization; MS, mass spectrometry; SPME, solid-phase microextraction; TOF, time of flight.

5. CURRENT MINIATURE MASS SPECTROMETER SYSTEMS

Portable mass spectrometers for which relatively complete information has been reported are listed in **Table 1**, which comprises the best-available information. Some other systems have been explored for miniaturization of the mass spectrometers, including a miniature electric/magnetic cross–field mass spectrometer (114), a GC-MS quadrupole ion trap mass spectrometer (94), and a miniature MIMS instrument that uses the microquadrupole filter array as a mass analyzer (80).

6. CONCLUSIONS AND PROSPECTS

The status of miniature mass spectrometer development can be compared to the corresponding stage in the development of the personal computer. In the field of chemical analysis devices, we have the equivalent of a bare-bones personal computer. Instruments of appropriate size and simplicity are now (literally) in hand for direct sampling, introduction, mass analysis, and data acquisition. These hand-held instruments are typically based on single ion trap mass analyzers, which are geometrically simplified versions of the Paul trap or are arrays of such analyzers operating cooperatively to reduce voltage and power requirements and to increase ion signals.

A wide variety of fabrication methods in addition to traditional precision machining is being explored for fabricating mass analyzers with complex configurations at the micrometer scale. Capabilities for data storage, spectral library comparison, and wireless data transmission and instrument control are being pursued or have already been accomplished.

The objective of mass spectrometer miniaturization is to apply the selectivity and specificity of MS analysis to in situ experiments, in locations ranging from the physician's office to the production line; to autonomous and continuous subway, waste dump, and water purification plant monitoring; to trace residue identification in foodstuffs; and to hundreds of other specific tasks in which qualitative and quantitative chemical analysis is essential. Success in creating miniature mass spectrometers may well result in an explosion of specialized instruments that are narrowly suited to particular tasks. The instrumentation may be barely adequate to perform the defined tasks and may have just enough capability to meet the demands of the problem. Extensive optimization is likely to minimize or exclude manual tasks, increase reliability, and minimize instrumentation cost.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

ACKNOWLEDGMENTS

Support of the fundamental work on development of miniature mass spectrometers in our laboratories has been provided by the Office of Naval Research, the National Science Foundation, and the Department of Homeland Security's Advanced Research Project Agency and Transportation Security Agency. We have also benefited from support and collaboration with Thermo Fisher, Inc., ICx, Inc., and Prosolia, Inc.

LITERATURE CITED

1. Kaiser RE, Cooks RG, Stafford GC, Syka JEP, Hemberger PH. 1991. Operation of a quadrupole ion trap mass-spectrometer to achieve high mass charge ratios. *Int. J. Mass Spectrom. Ion Process.* 106:79–115

2. Sinha MP, Tomassian AD. 1991. Development of a miniaturized, lightweight magnetic-sector for a field-portable mass spectrograph. *Rev. Sci. Instrum.* 62:2618–20
3. Gao L, Song QY, Patterson GE, Cooks RG, Ouyang Z. 2006. Handheld rectilinear ion trap mass spectrometer. *Anal. Chem.* 78:5994–6002
4. Gao L, Sugiarto A, Haper J, Cooks RG, Ouyang Z. 2008. Design and characterization of a multisource hand-held tandem mass spectrometer. *Anal. Chem.* 80:7198–205
5. Contreras JA, Murray JA, Tolley SE, Oliphant JL, Tolley HD, et al. 2008. Hand-portable gas chromatograph–toroidal ion trap mass spectrometer (GC-TMS) for detection of hazardous compounds. *J. Am. Soc. Mass Spectrom.* 19:1425–34
6. Bryden WA, Benson RC, Ecelberger SA, Phillips TE, Cotter RJ, Fenselau C. 1995. The tiny-TOF mass-spectrometer for chemical and biological sensing. *Johns Hopkins APL Tech. Dig.* 16:296–310
7. Cornish TJ, Cotter RJ. 1997. High-order kinetic energy focusing in an end cap reflectron time-of-flight mass spectrometer. *Anal. Chem.* 69:4615–18
8. Cotter RJ, Fancher C, Cornish TJ. 1999. Miniaturized time-of-flight mass spectrometer for peptide and oligonucleotide analysis. *J. Mass Spectrom.* 34:1368–72
9. Ecelberger SA, Cornish TJ, Collins BF, Lewis DL, Bryden WA. 2004. Suitcase TOF: a man-portable time-of-flight mass spectrometer. *Johns Hopkins APL Tech. Dig.* 25:14–19
10. Sinha MP, Gutnikov G. 1991. Development of a miniaturized gas-chromatograph mass-spectrometer with a microbore capillary column and an array detector. *Anal. Chem.* 63:2012–16
11. Sinha MP, Langstaff DP, Narayan DJ, Birkinshaw K. 1998. Resolving power enhancement of a discrete detector (array) by single event detection. *Int. J. Mass Spectrom.* 176:99–102
12. Sinha MP, Wadsworth M. 2005. Miniature focal plane mass spectrometer with 1000-pixel modified-CCD detector array for direct ion measurement. *Rev. Sci. Instrum.* 76:025103
13. Diaz JA, Giese CF, Gentry WR. 2001. Sub-miniature ExB sector-field mass spectrometer. *J. Am. Soc. Mass Spectrom.* 12:619–32
14. Burgoyne TW, Hieftje GM, Hites RA. 1997. Design and performance of a plasma-source mass spectrograph. *J. Am. Soc. Mass Spectrom.* 8:307–18
15. Freidhoff CB, Young RM, Sriram S, Braggins TT, O'Keefe TW, et al. 1999. Chemical sensing using nonoptical microelectromechanical systems. *J. Vac. Sci. Technol. A: Vac. Surf. Films* 17:2300–7
16. Syms RRA, Tate TJ, Ahmad MM, Taylor S. 1996. Fabrication of a microengineered quadrupole electrostatic lens. *Electron. Lett.* 32:2094–95
17. Syms RRA, Tate TJ, Ahmad MM, Taylor S. 1998. Design of a microengineered electrostatic quadrupole lens. *IEEE Trans. Electron Devices* 45:2304–11
18. Taylor S, Tunstall JJ, Leck JH, Tindall RF, Jullien JP, et al. 1999. Performance improvements for a miniature quadrupole with a micromachined mass filter. *Vacuum* 53:203–6
19. Taylor S, Tunstall JJ, Syms RRA, Tate T, Ahmad MM. 1998. Initial results for a quadrupole mass spectrometer with a silicon micromachined mass filter. *Electron. Lett.* 34:546–47
20. Holkeboer DH, Karandy TL, Currier FC, Frees LC, Ellefson RE. 1998. Miniature quadrupole residual gas analyzer for process monitoring at milliTorr pressures. *J. Vac. Sci. Technol. A: Vac. Surf. Films* 16:1157–62
21. Ferran RJ, Boumsellek S. 1996. High-pressure effects in miniature arrays of quadrupole analyzers for residual gas analysis from 10(-9) to 10(-2) Torr. *J. Vac. Sci. Technol. A: Vac. Surf. Films* 14:1258–65
22. Orient OJ, Chutjian A, Garkanian V. 1997. Miniature, high-resolution, quadrupole mass-spectrometer array. *Rev. Sci. Instrum.* 68:1393–97
23. Boumsellek S, Ferran RJ. 2001. Trade-offs in miniature quadrupole designs. *J. Am. Soc. Mass Spectrom.* 12:633–40
24. Syms R. 2008. *Miniaturized mass spectrometry*. Presented at Pittsburgh Conf. Anal. Chem. Appl. Spectrom., 55th, New Orleans
25. Syms R. 2009. Advances in microfabricated mass spectrometers. *Anal. Bioanal. Chem.* 393:427–29
26. Sillon N, Baptist R. 2002. Micromachined mass spectrometer. *Sens. Actuators B Chem.* 83:129–37
27. Hauschild JP, Wapelhorst E, Müller J. 2007. Mass spectra measured by a fully integrated MEMS mass spectrometer. *Int. J. Mass Spectrom.* 264:53–60

28. Yoon HJ, Kim JH, Choi ES, Yang SS, Jung KW. 2002. Fabrication of a novel micro time-of-flight mass spectrometer. *Sens. Actuators A Phys.* 97/98:441–47
29. Geear M, Syms RRA, Wright S, Holmes AS. 2005. Monolithic MEMS quadrupole mass spectrometers by deep silicon etching. *Microelectromech. Syst. J.* 14:1156–66
30. Blain MG, Riter LS, Cruz D, Austin DE, Wu GX, et al. 2004. Towards the hand-held mass spectrometer: design considerations, simulation, and fabrication of micrometer-scaled cylindrical ion traps. *Int. J. Mass Spectrom.* 236:91–104
31. Pau S, Pai CS, Low YL, Moxom J, Reilly PTA, et al. 2006. Microfabricated quadrupole ion trap for mass spectrometer applications. *Phys. Rev. Lett.* 96:120801
32. Pau S, Whitten WB, Ramsey JM. 2007. Planar geometry for trapping and separating ions and charged particles. *Anal. Chem.* 79:6857–61
33. Austin DE, Wang M, Tolley SE, Maas JD, Hawkins AR, et al. 2007. Halo ion trap mass spectrometer. *Anal. Chem.* 79:2927–32
34. Fico M, Yu M, Ouyang Z, Cooks RG, Chappell WJ. 2007. Miniaturization and geometry optimization of a polymer-based rectilinear ion trap. *Anal. Chem.* 79:8076–82
35. Yu M, Fico M, Kothari S, Ouyang Z, Chappell WJ. 2006. Polymer-based ion trap chemical sensor. *IEEE Sens. J.* 6:1429–34
36. Chaudhary A, van Amerom FHW, Short RT, Bhansali S. 2006. Fabrication and testing of a miniature cylindrical ion trap mass spectrometer constructed from low temperature cofired ceramics. *Int. J. Mass Spectrom.* 251:32–39
37. Paul W, Steinwedel H. 1953. A new mass spectrometer without a magnetic field. *Z. Naturforsch. Sect. A* 8:448–50
38. Mather RE, Lawson G, Todd JFJ, Bakker JMB. 1978. Quadrupole ion storage trap (quistor) as a low-pressure chemical ionization source for a magnetic-sector mass-spectrometer. *Int. J. Mass Spectrom. Ion Process.* 28:347–64
39. Fulford JE, Hoa DN, Hughes RJ, March RE, Bonner RF, Wong GJ. 1980. Radio-frequency mass selective excitation and resonant ejection of ions in a 3-dimensional quadrupole ion trap. *J. Vac. Sci. Technol.* 17:829–35
40. Stafford GC, Kelley PE, Syka JEP, Reynolds WE, Todd JFJ. 1984. Recent improvements in and analytical applications of advanced ion trap technology. *Int. J. Mass Spectrom. Ion Process.* 60:85–98
41. Louris JN, Cooks RG, Syka JEP, Kelley PE, Stafford GC, Todd JFJ. 1987. Instrumentation, applications, and energy deposition in quadrupole ion-trap tandem mass-spectrometry. *Anal. Chem.* 59:1677–85
42. Grebner TL, Neusser HJ. 1994. Laser-produced ions stored in a cylindrical ion-trap and detected in a reflectron time-of-flight mass-spectrometer. *Int. J. Mass Spectrom. Ion Process.* 137:L1–6
43. Mikami N, Miyata Y, Sato S, Sasaki T. 1990. Ion trap method combined with 2-color laser spectroscopy of supersonic molecular beams—photodissociation of trapped $C_6H_5CL^+$. *Chem. Phys. Lett.* 166:470–74
44. Fulford JE, March RE, Mather RE, Todd JFJ, Waldren RM. 1980. The cylindrical ion trap—a theoretical and experimental study. *Can. J. Spectrosc.* 25:85–97
45. Wells JM, Badman ER, Cooks RG. 1998. A quadrupole ion trap with cylindrical geometry operated in the mass selective instability mode. *Anal. Chem.* 70:438–44
46. Ouyang Z, Badman ER, Cooks RG. 1999. Characterization of a serial array of miniature cylindrical ion trap mass analyzers. *Rapid Commun. Mass Spectrom.* 13:2444–49
47. Badman ER, Johnson RC, Plass WR, Cooks RG. 1998. A miniature cylindrical quadrupole ion trap: simulation and experiment. *Anal. Chem.* 70:4896–901
48. Kornienko O, Reilly PTA, Whitten WB, Ramsey JM. 1999. Micro ion trap mass spectrometry. *Rapid Commun. Mass Spectrom.* 13:50–53
49. Van Amerom FHW, Chaudhary A, Cardenas M, Bumgarner J, Short RT. 2008. Microfabrication of cylindrical ion trap mass spectrometer arrays for handheld chemical analyzers. *Chem. Eng. Commun.* 195:98–114
50. Patterson GE, Guymon AJ, Riter LS, Everly M, Griep-Raming J, et al. 2002. Miniature cylindrical ion trap mass spectrometer. *Anal. Chem.* 74:6145–53
51. Riter LS, Peng YA, Noll RJ, Patterson GE, Aggerholm T, Cooks RG. 2002. Analytical performance of a miniature cylindrical ion trap mass spectrometer. *Anal. Chem.* 74:6154–62

52. Yang M, Kim T-Y, Hwang H-C, Yi S-K, Kim D-H. 2008. Development of a palm portable mass spectrometer. *J. Am. Soc. Mass Spectrom.* 19:1442–48
53. Bier ME, Syka JEP. 1995. *U.S. Patent No. 5,420,425*
54. Lammert SA, Plass WR, Thompson CV, Wise MB. 2001. Design, optimization and initial performance of a toroidal rf ion trap mass spectrometer. *Int. J. Mass Spectrom.* 212:25–40
55. Hager JW. 2002. A new linear ion trap mass spectrometer. *Rapid Commun. Mass Spectrom.* 16:512–26
56. Schwartz JC, Senko MW, Syka JEP. 2002. A two-dimensional quadrupole ion trap mass spectrometer. *J. Am. Soc. Mass Spectrom.* 13:659–69
57. Schwartz JC. 1997. *Do space charge effects limit LC quadrupole ion trap performance*? Presented at Sanibel Conf. Mass Spectrom., Quadrupole Ion Traps, 9th, Sanibel Island, FL
58. Ouyang Z, Wu GX, Song YS, Li HY, Plass WR, Cooks RG. 2004. Rectilinear ion trap: concepts, calculations, and analytical performance of a new mass analyzer. *Anal. Chem.* 76:4595–605
59. Dolnikowski GG, Kristo MJ, Enke CG, Watson JT. 1988. Ion-trapping technique for ion/molecule reaction studies in the center quadrupole of a triple quadrupole mass spectrometer. *Int. J. Mass Spectrom. Ion Process.* 82:1–15
60. Quarmby ST, Yost RA. 1999. Fundamental studies of ion injection and trapping of electrosprayed ions on a quadrupole ion trap. *Int. J. Mass Spectrom.* 190/191:81–102
61. Lammert SA, Rockwood AA, Wang M, Lee ML, Lee ED, et al. 2006. Miniature toroidal radio frequency ion trap mass analyzer. *J. Am. Soc. Mass Spectrom.* 17:916–22
62. Appelhans AD, Dahl DA. 2005. SIMION ion optics simulations at atmospheric pressure. *Int. J. Mass Spectrom.* 244:1–14
63. Bui HA, Cooks RG. 1998. Windows version of the ion trap simulation program ITSIM: a powerful heuristic and predictive tool in ion trap mass spectrometry. *J. Mass Spectrom.* 33:297–304
64. Wu GX, Cooks RG, Ouyang Z, Yu M, Chappell WJ, Plass WR. 2006. Ion trajectory simulation for electrode configurations with arbitrary geometries. *J. Am. Soc. Mass Spectrom.* 17:1216–28
65. March RE. 1997. An introduction to quadrupole ion trap mass spectrometry. *J. Mass Spectrom.* 32:351–69
66. March RE, Todd JFJ, eds. 1995. *Practical Aspects of Ion Trap Mass Spectrometry, Vol. I: Fundamentals of Ion Trap Mass Spectrometry*. Boca Raton, FL: CRC
67. March RE, Todd JFJ. 2005. *Quadrupole Ion Trap Mass Spectrometry*. Hoboken: Wiley. 2nd ed.
68. Wu GX, Cooks RG, Ouyang Z. 2005. Geometry optimization for the cylindrical ion trap: field calculations, simulations and experiments. *Int. J. Mass Spectrom.* 241:119–32
69. Austin DE, Peng Y, Hansen BJ, Miller IW, Rockwood AL, et al. 2008. Novel ion traps using planar resistive electrodes: implications for miniaturized mass analyzers. *J. Am. Soc. Mass Spectrom.* 19:1435–41
70. Ding C-F, Jiang G, Filippov I, Luo C, Yang P, Li X. 2007. *Simulations of the field distributions and the performance of printed circuit board ion trap mass spectrometer (PCB IT-MS)*. Presented at ASMS Conf. Mass Spectrom. Allied Top., 55th, Indianapolis
71. Gao L, Song Q, Noll RJ, Duncan J, Cooks RG, Ouyang Z. 2007. Glow discharge electron impact ionization source for miniature mass spectrometers. *J. Mass Spectrom.* 42:675–80
72. Badman ER, Cooks RG. 2000. A parallel miniature cylindrical ion trap array. *Anal. Chem.* 72:3291–97
73. Rimkus WV, Davis DV, Gallaher K. 2003. *Novel miniature FTMS for analysis of corrosives and chemical warfare agents*. Presented at Workshop Harsh-Environ. Mass Spectrom., 4th, Montreal
74. Spaeder TA, Walton RB. 2003. Hapsite GC/MS analysis of low level chemical warfare agents, toxic industrial compounds and toxic industrial materials in the field by first responders. *Abstr. Pap. Am. Chem. Soc.* 226:U128
75. Keil A, Hernandez-Soto H, Noll RJ, Fico M, Gao L, et al. 2008. Monitoring of toxic compounds in air using a handheld rectilinear ion trap mass spectrometer. *Anal. Chem.* 80:734–41
76. Song Q, Kothari S, Senko MA, Schwartz JC, Amy JW, et al. 2006. Rectilinear ion trap mass spectrometer with atmospheric pressure interface and electrospray ionization source. *Anal. Chem.* 78:718–25
77. Meuzelaar HLC, Dworzanski JP, Arnold NS, McClennen WH, Wager DJ. 2000. Advances in field-portable mobile GC/MS instrumentation. *Field Anal. Chem. Tech.* 4:3–13
78. Patterson GE, Wells JM, Grossenbacher JW, Cochran AJ, Knecht BA, et al. 2004. *GC and direct SPME characterization using a portable cylindrical ion trap (CIT) mass spectrometer*. Presented at Conf. Detect./Sens. Res. Technol. Homel. Natl. Secur., Gatlinburg, TN

79. Riter LS, Meurer EC, Handberg ES, Laughlin BC, Chen H, et al. 2003. Ion/molecule reactions performed in a miniature cylindrical ion trap mass spectrometer. *Analyst* 128:1112–18
80. Janfelt C, Frandsen H, Lauritsen FR. 2006. Characterization of a mini membrane inlet mass spectrometer for on-site detection of contaminants in both aqueous and liquid organic samples. *Rapid Commun. Mass Spectrom.* 20:1441–46
81. Bier ME, Cooks RG. 1987. Membrane interface for selective introduction of volatile compounds directly into the ionization-chamber of a mass-spectrometer. *Anal. Chem.* 59:597–601
82. Bier ME, Kotiaho T, Cooks RG. 1990. Direct insertion membrane probe for selective introduction of organic-compounds into a mass-spectrometer. *Anal. Chim. Acta* 231:175–90
83. Fenn JB, Mann M, Meng CK, Wong SF, Whitehouse CM. 1989. Electrospray ionization for mass spectrometry of large biomolecules. *Science* 246:64–71
84. Yamashita M, Fenn JB. 1984. Electrospray ion source. Another variation on the free-jet theme. *J. Phys. Chem.* 88:4451–59
85. Carroll DI, Dzidic I, Stillwell RN, Haegele KD, Horning EC. 1975. Atmospheric pressure ionization mass spectrometry: discharge ion source for use in liquid chromatograph–mass spectrometer–computer analytical system. *Anal. Chem.* 47:2369–73
86. Laiko VV, Baldwin MA, Burlingame AL. 2000. Atmospheric pressure matrix-assisted laser desorption/ionization mass spectrometry. *Anal. Chem.* 72:652–57
87. Tanaka K, Waki H, Ido Y, Akita S, Yoshida Y, et al. 1988. Protein and polymer analyses up to *m/z* 100,000 by laser ionization time-of-flight mass spectrometry. *Rapid Commun. Mass Spectrom.* 2:151–53
88. Keil A, Talaty N, Janfelt C, Noll RJ, Gao L, et al. 2007. Ambient mass spectrometry with a handheld mass spectrometer at high pressure. *Anal. Chem.* 79:7734–39
89. Gao L, Cooks RG, Ouyang Z. 2008. Breaking the pumping speed barrier in mass spectrometry: discontinuous atmospheric pressure interface. *Anal. Chem.* 80:4026–32
90. Cooks RG, Ouyang Z, Takats Z, Wiseman JM. 2006. Ambient mass spectrometry. *Science* 311:1566–70
91. Venter A, Nefliu M, Cooks RG. 2008. Ambient desorption ionization mass spectrometry. *Trends Anal. Chem.* 27:284–90
92. Takats Z, Wiseman JM, Gologan B, Cooks RG. 2004. Mass spectrometry sampling under ambient conditions with desorption electrospray ionization. *Science* 306:471–73
93. Harper JD, Charipar N, Mulligan CC, Zhang X, Cooks RG, Ouyang Z. 2008. Low temperature plasma probe for ambient desorption ionization. *Anal. Chem.* 80:9097–104
94. Shortt BJ, Darrach MR, Holland PM, Chutjian A. 2005. Miniaturized system of a gas chromatograph coupled with a Paul ion trap mass spectrometer. *J. Mass Spectrom.* 40:36–42
95. Janfelt C, Graesboll R, Lauritsen FR. 2008. Characterization and optimization of membrane inlets for a miniature ion trap mass spectrometer operating at a high background pressure of humid air. *Int. J. Mass Spectrom.* 276:17–23
96. Riter LS, Laughlin BC, Nikolaev E, Cooks RG. 2002. Direct analysis of volatile organic compounds in human breath using a miniaturized cylindrical ion trap mass spectrometer with a membrane inlet. *Rapid Commun. Mass Spectrom.* 16:2370–73
97. Chen H, Venter A, Cooks RG. 2006. Extractive electrospray ionization for direct analysis of undiluted urine, milk and other complex mixtures without sample preparation. *Chem. Commun.* 2042–44
98. Cody RB, Laramee JA, Durst HD. 2005. Versatile new ion source for the analysis of materials in open air under ambient conditions. *Anal. Chem.* 77:2297–302
99. Ford MJ, Van Berkel GJ. 2004. An improved thin-layer chromatography/mass spectrometry coupling using a surface sampling probe electrospray ion trap system. *Rapid Commun. Mass Spectrom.* 18:1303–9
100. McEwen CN, McKay RG, Larsen BS. 2005. Analysis of solids, liquids, and biological tissues using solids probe introduction at atmospheric pressure on commercial LC/MS instruments. *Anal. Chem.* 77:7826–31
101. Shiea J, Huang M-Z, Hsu H-J, Lee C-Y, Yuan C-H, et al. 2005. Electrospray-assisted laser desorption/ionization mass spectrometry for direct ambient analysis of solids. *Rapid Commun. Mass Spectrom.* 19:3701–4
102. Shieh IF, Lee CY, Shiea J. 2005. Eliminating the interferences from TRIS buffer and SDS in protein analysis by fused-droplet electrospray ionization mass spectrometry. *J. Proteome Res.* 4:606–12

103. Takats Z, Cotte-Rodriguez I, Talaty N, Chen HW, Cooks RG. 2005. Direct, trace level detection of explosives on ambient surfaces by desorption electrospray ionization mass spectrometry. *Chem. Commun.* 1950–52
104. Sampson JS, Hawkridge AM, Muddiman DC. 2006. Generation and detection of multiply-charged peptides and proteins by matrix-assisted laser desorption electrospray ionization (MALD-ESI) Fourier transform ion cyclotron resonance mass spectrometry. *J. Am. Soc. Mass Spectrom.* 17:1712–16
105. Haddad R, Sparrapan R, Eberlin MN. 2006. Desorption sonic spray ionization for (high) voltage-free ambient mass spectrometry. *Rapid Commun. Mass Spectrom.* 20:2901–5
106. Ratcliffe LV, Rutten FJM, Barrett DA, Whitemore T, Seymour D, et al. 2007. Surface analysis under ambient conditions using plasma-assisted desorption/ionization mass spectrometry. *Anal. Chem.* 79:6094–101
107. Na N, Zhao M, Zhang S, Yang C. 2007. Development of a dielectric barrier discharge ion source for ambient mass spectrometry. *J. Am. Soc. Mass Spectrom.* 18:1859–62
108. Andrade FJ, Ray SJ, Webb MR, Hieftje GM. 2007. *The helium atmospheric pressure glow discharge: a new ionization source for the direct analysis of solids, liquids and gases*. Presented at ASMS Conf. Mass Spectrom. Allied Top., 55th, Indianapolis, IN
109. Chen H, Yang S, Wortmann A, Zenobi R. 2007. Neutral desorption sampling of living objects for rapid analysis by extractive electrospray ionization mass spectrometry. *Angew. Chem. Int. Ed.* 46:7591–94
110. Nemes P, Vertes A. 2007. Laser ablation electrospray ionization for atmospheric pressure, in vivo, and imaging mass spectrometry. *Anal. Chem.* 79:8098–106
111. Chen H, Cotte-Rodriguez I, Cooks RG. 2006. *cis*-diol functional group recognition by reactive desorption electrospray ionization (DESI). *Chem. Commun.* 597–99
112. Huang G, Chen H, Zhang X, Cooks RG, Ouyang Z. 2007. Rapid screening of anabolic steroids in urine by reactive desorption electrospray ionization. *Anal. Chem.* 79:8327–32
113. Peng IX, Ogorzalek Loo RR, Shiea J, Loo JA. 2008. Reactive-electrospray-assisted laser desorption/ionization for characterization of peptides and proteins. *Anal. Chem.* 80:6995–7003
114. Rohrs HW, Gentry WR, Chhatwal RS, Berger PS. 2002. *Development of a low cost miniature mass spectrometer*. Presented at Pittsburgh Conf. Anal. Chem. Appl. Spectrosc., 54th, New Orleans
115. Wright S. 2006. *Development of the first commercially available mass spectrometer on a chip*. Presented at Pittsburgh Conf. Anal. Chem. Appl. Spectrosc., 57th, Orlando
116. Patterson G, Grossenbacher J, Wells M, Keil A, Gregory M, et al. 2007. *Development of a light-weight integrated direct analysis mass spectrometer*. Presented at ASMS Conf. Mass Spectrom. Allied Top., 55th, Indianapolis
117. Kibelka G. 2005. *A CCD detector array for direct ion measurement*. Presented at Workshop Harsh-Environ. Mass. Spectrom, 5th, Sarasota

Annual Review of
Analytical Chemistry

Volume 2, 2009

Contents

Errata

An online log of corrections to *Annual Review of Analytical Chemistry* articles may be found at http://anchem.annualreviews.org/errata.shtml