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Accelerated Articles

Design and Characterization of a Multisource Hand-Held Tandem Mass Spectrometer

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A wireless-controlled miniature rectilinear ion trap mass spectrometer system, total weight with batteries 5.0 kg, consuming less than 35 W of power, and having dimensions of 22 cm in length by 12 cm in width by 18 cm in height, is characterized. The design and construction of the mass spectrometer including mass analyzer, vacuum system, electronics system, and data acquisition and processing systems, is detailed. The mass spectrometer is compatible with various types of ionization sources including a glow discharge electron impact ionization source used in the internal ionization mode, and various atmospheric pressure ionization sources, including electrospray ionization, atmospheric pressure chemical ionization, and desorption electrospray ionization, which are employed for external, atmospheric pressure ionization. These external sources are coupled to the miniature mass spectrometer via a capillary interface that is operated in a discontinuous fashion (discontinuous atmospheric pressure interface) to maximize ion transport. The performance of the mass spectrometer for large and small molecules is characterized. Limits of detection in the parts-per-billion range were obtained for selected compounds examined using both the internal ionization and external ionization modes. Tandem mass spectrometry and fast in situ analysis capabilities are also demonstrated using a variety of compounds and ionization sources. Protein molecules are analyzed as the multiply protonated molecules with mass/charge ratios up to 1500 Da/charge.

Miniature mass spectrometers are useful because they combine the usual advantages of mass spectrometry—broad applicability, high sensitivity, high specificity—with the convenience of fast in situ analysis. These features are important to many applications in the area of public safety, environmental protection, and industrial process monitoring, among others.[1] After a decade of increased attention, progress in the development of hand-portable mass spectrometers is becoming increasingly rapid. Ion traps of a variety of types have been the mass analyzer of choice in most recent miniature mass spectrometers, a choice made mainly because of their inherent tandem MS capability, relaxed requirement for high vacuum, and flexible modes of operation.[2−8] Battery-powered ion trap miniature mass spectrometers with weights below 10 kg have been developed and a few have began to appear as commercial products.[9−12]

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The applications of miniature mass spectrometers are still confined to a few areas, since only limited types of samples can be analyzed. At present, almost all portable miniature mass spectrometers use an electron impact ionization source, and this represents a major limitation on the types of compounds that can be studied. It also means that a most important property of in situ instrumentation, rapid response, often cannot be realized since complex mixtures cannot be analyzed without prior sample workup. Atmospheric pressure ionization (API) sources can solve the restrictions on the types of compounds that can be analyzed, and among them, the ambient ionization methods such as desorption electrospray ionization (DESI) can provide the instantaneous, no-sample-preparation capabilities that are mandatory for in situ analysis. However, API sources are inherently difficult to apply in miniature mass spectrometers, because of the limited pumping capacities of these instruments. In order to use API sources, the flow conductance of the ion-transfer interface must be large enough for ions generated in the atmospheric pressure region to be transferred into the ion trap efficiently. With a traditional ion-transfer interface, a high pumping speed—usually hundreds of liters per second—is necessary to maintain the vacuum manifold pressure at an appropriate level.[7,13] By contrast, the pumping speed obtainable in a miniature mass spectrometer is only a few liters per second due to the restriction of weight, size, and power consumption. While it is possible to use API sources with interfaces having sufficiently low conductances to be compatible with miniature mass spectrometer vacuum systems, sensitivity and resolution are sacrificed.[14] Thus, API sources are still barely used in current miniature mass spectrometers.

A discontinuous atmospheric pressure interface (DAPI) was developed recently to enable the use of API sources with miniature mass spectrometers with limited pumping speed.[15] The DAPI consists of a series of simple capillaries directly connecting the atmospheric pressure ion source to the vacuum mass analyzer region. The interface has no ion optical elements and no differential pumping stages. Gases carrying ionized analytes are pulsed into the mass analyzer for short periods at high flow rates instead of being continuously introduced at lower flow rates. This means that an ion-transfer channel with a much higher conductance can be used for a discontinuous interface than is possible for a traditional continuous interface. The performance of DAPI was demonstrated[15] using a miniature mass spectrometer with a 10 L/s pumping speed mass spectrometer. API sources, including electrospray ionization (ESI),[16] atmospheric pressure chemical ionization (APCI),[17] and DESI,[18] were able to be used effectively. The development of DAPI greatly improves the analytical capabilities of miniature mass spectrometers.

Although the weight, size, and power consumption of miniature mass spectrometers have already reached a level in which handheld operation is possible, the ~20 lb level of current systems make this inconvenient. This paper describes a considerably smaller miniature ion trap mass spectrometer, the Mini 11. One purpose of the study was to test the effects on ion trap mass spectrometer analytical performance of the weight, size, and power consumption limitations. The instrument was designed and built in a "multifunctional/minimalist" fashion as a portable ion trap mass spectrometer. The "multifunctional" characterization stresses the fact that multiple ionization sources can be used and different types of analytes can be analyzed with the instrument using a variety of types of experiments. The term "minimalist" is intended to indicate that the instrument was built as simply as possible, consistent with providing the desired functions. The number of control signals was minimized to just five, so that the electronics system could be compact. Low-power, simple designs were adopted in different parts of the instrument, including the ionization source, ion-transfer interface, and pressure measurement device. The performance of the instrument was characterized and demonstrated with various ionization sources and compounds. The design and the characterization of the instrument are presented.

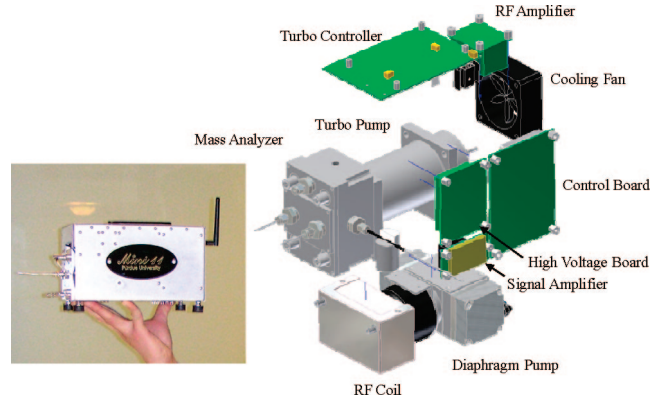

Figure 1. Exploded view of Mini 11 mass spectrometer and its components.

INSTRUMENTATION

The configuration of the Mini 11 ion trap mass spectrometer is shown in Figure 1. The instrument consists of a mass analyzer, vacuum system, and electronics system. It weighs 3.2 kg (without power supply) and 4.95 kg with battery pack. It has a size of 22 × 12 × 18 cm, consumes less than 35 W of power, and can operate autonomously for 2 h. It is wireless-controlled through a remote computer. A micro-turbomolecular pump and a diaphragm pump are used to provide the vacuum of the instrument.

Mass Analyzer and Operational Modes. The configuration of the Mini 11, including the placement of the mass analyzer, is shown in Figure 2a. The instrument consists of a glow discharge electron impact ionization (GDEI) source,[19] a rectilinear ion trap (RIT),[4] an electron multiplier (miniature channeltron, Burle Technologies, Inc., Lancaster, PA), and an optional membrane sample inlet (o.d. 1.19 mm, i.d. 0.64 mm, and length 10.0 cm) Dow Corning, Midland, MI), and an optional DAPI to connect the instrument to one of several possible API sources. The geometry of the RIT is identical to that used in the Mini 10 mass

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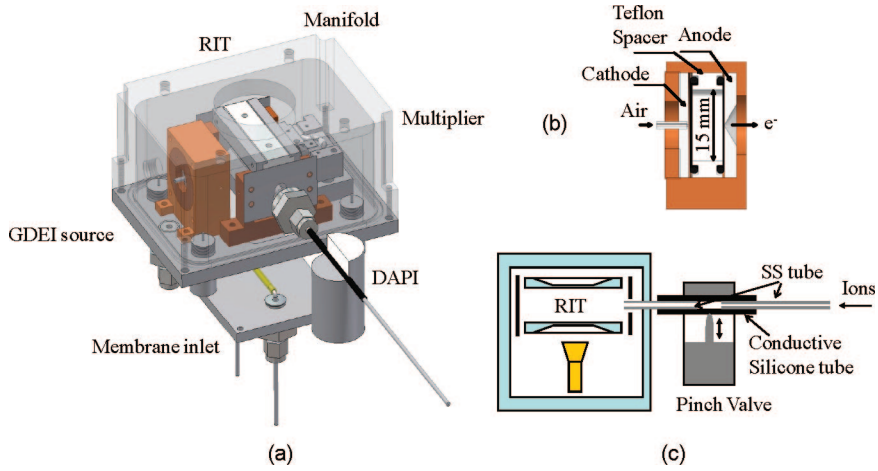

Figure 2. (a) Mini 11 mass analyzer and assembled components including rectilinear ion trap (RIT), glow discharge electron impact ionization (GDEI) source, and discontinuous introduction system (discontinuous atmospheric pressure inlet, DAPI) to allow externally generated ions to be sampled, and a membrane inlet system, (b) GDEI source, which provides electrons for ionization of sample vapors introduced into the ion trap, and (c) DAPI introduction system showing components used for controlled and efficient sampling of externally generated ions.

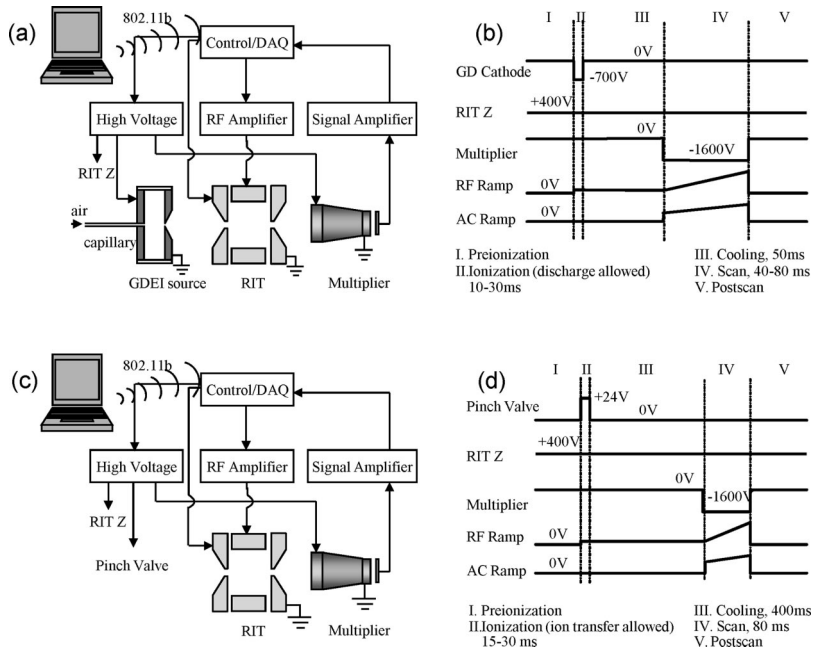

Figure 3. (a) Electrical connections used in internal ionization mode. (b) Control signal sequence in internal ionization mode. (c) Electrical connection in external ionization mode. (d) Control signals sequence in external ionization mode.

spectrometer previously described.[9] The aluminum vacuum manifold has outside dimensions of 9 cm in length by 6.5 cm in width by 4.7 cm in height and inside dimensions of $7.8 \times 5.6 \times 3.6$ cm. The mass analyzer was designed to operate in two modes using different ionization sources: internal ionization and external ionization. The GDEI source is used in the internal ionization mode and API sources including ESI, APCI, and DESI are available for use in the external ionization mode.

The GDEI electron ionization source is used to ionize vapor-phase analytes introduced directly into the vacuum manifold or more usually as permeate through a semipermeable membrane. The GDEI source (shown in Figure 2b) is much more robust than a filament electron source and it uses much less power (<0.1 W) than a resistively heated thermionic filament. The electrical connections and control signal timing sequence in the internal ionization mode are shown in Figure 3a and b. The five control signals needed to operate the instrument include the rf signal, a single-phase ac signal, the glow discharge control signal, a dc lens signal, and a multiplier power signal. During each scan cycle, the anode of the GDEI source is permanently grounded, and a dc voltage switched between −700 and 0 V is applied to the cathode. During the ionization period of a scan cycle, the cathode potential is set to −700 V to ignite the glow discharge and generate electrons. The electric field between the cathode and the anode accelerates the electrons toward the anode. Depending on the location inside the GDEI where the electrons are generated, their kinetic energies range from 0 to 700 V. The cathode potential is set to 0 V during the recovery period of the scan cycle to stop the discharge. The ionization period is typically 10−30 ms in a scan cycle of 150 ms in these internal ionization experiments. After the ionization period and a 50-ms ion cooling period, a −1500-V voltage is applied to the multiplier. Both the rf amplitude and the

ac amplitude are scanned from low to high to eject ions from the ion trap. In order to minimize the number of control signals, only one ac signal is used to cause resonance ejection. With the cathode potential at a constant value of −700 V, a constant discharge current is obtained. The discharge current value is used as an indicator of the manifold pressure through a calibrated relationship between discharge current and manifold pressure. Thus, there is no pressure gauge as such on the Mini 11 mass spectrometer.

In the external ionization mode, any one of several atmospheric pressure ionization sources can be connected to the instrument through the DAPI.[15] Ions generated at atmospheric pressure are transferred into the ion trap through the DAPI in a pulsed fashion. A sketch of the DAPI interface is shown in Figure 2c. The DAPI consists of two stainless steel tubes connected by a conductive silicone plastic tube (i.d. $^1/_{16}$ in., o.d. $^1/_8$ in., and length 2 in, Simolex Rubber Corp., Plymouth, MI). One stainless steel tube has dimensions of 250-μm i.d., $^1/_{16}$-in. o.d., and 4-in. length, and the other has dimensions of 1-mm i.d., $^1/_{16}$-in. o.d., and 2-in. length. The conductive silicone plastic tube goes through a 70-g normally closed pinch valve, (390NC24330, ASCO Valve Inc., Florham Park, NJ), which controls the open/close status of the DAPI. Both stainless steel tubes are electrically grounded during operation. The electrical connections and control signal timing sequence in the external ionization mode are shown in Figure 3c and d. A total of just five control signals are used in the external ionization mode, including the rf signal, the single-phase ac signal, a pinch valve control signal, the dc lens signal, and the multiplier power signal. In the ion introduction period of each scan cycle, a 24-V dc pulse signal is applied on the pinch valve to open the interface. The interface is opened for 15−30 ms to allow ions to enter the ion trap, and then the interface is closed for the remainder of the scan cycle. The manifold pressure rises to 10^{-1}−10^{-2} Torr after the opening of the pinch valve. In the subsequent 400-ms cooling period, the manifold pressure drops to 10^{-3}−10^{-4} Torr, a value which is low enough to allow mass analysis. Next, the multiplier is turned on, and both rf signal amplitude and resonance ac signal amplitude are scanned to record the mass spectrum. The whole scan cycle in the external ionization mode usually takes ~600 ms, which is almost 5 times that of the scan cycle in the internal ionization mode. The change in manifold pressure during the course of each scan cycle is shown in the Supporting Information section.

Vacuum System. The pumping system of the Mini 11 consists of a two-stage diaphragm pump, a miniature hybrid turbomolecular pump, and its controller. The two-stage diaphragm pump (1220-N84.0-9.00, KNF Neuberger Inc., Trenton, NJ) weighs 0.8 kg and consumes 6 W of power during continuous operation. It is able to provide a backing pressure of 3 Torr at a pumping speed of 5 L/min. A customized hybrid turbomolecular pump (Creare Inc., Hanover, NH), backed by the diaphragm pump, is used to evacuate the vacuum manifold. This cylindrical turbomolecular pump has dimensions of 10.5 cm in length and 5.5 cm in diameter and weighs 0.5 kg. The pump provides a pumping speed estimated to be 3 L/s at 10^{-4} Torr at a rotation speed of 100 000 rpm. An ultimate pressure of 10^{-6} Torr can be attained, but much higher pressures are used in these experiments. The turbomolecular pump consumes 10.5 W of power when the instrument is operated in the internal ionization mode and 11.5 W when operated in the external ionization mode.

Electrical System. The electrical system consists of a power supply, a control board, a high-voltage board, a rf power amplifier, a rf coil, and a signal current amplifier. The whole electronics system is controlled by a remote computer with interface software written in Labview 8.2. During each scan cycle, the scan function to be used is sent to the control board using wireless communication 802.11b protocol. Control signals are generated on the control board in the sequence described in the scan function. All dc control signals are modified to appropriate levels through the high-voltage supply board and then sent to the mass analyzer. The rf signal generated on the control board is amplified by the rf power amplifier and the rf coil. During the rf scan, the detected signal received from the electron multiplier is amplified by the signal current amplifier and sent back to the control board for data acquisition. Finally, the acquired data are sent back to the remote computer to generate a spectrum in the interface software. It takes ~4 s from the time of sending the scan function to obtain the mass spectrum for each cycle. This delay is mainly caused by the data transmission rate of the control board.

A choice of power supplies is available, so that users can choose appropriately depending on environmental conditions. The power supply either consists of a removable 110 V/60 Hz ac to 24 V dc convertor (SCS120PW24, Lambda Electronics Inc., San Diego, CA) and five dc to dc convertors (Micro Series, Vicor Corp., Andover, MA), or the ac to dc convertor can be replaced with three 7.2 V 3300 mAhr NiMH rechargeable battery packs (Powerizer, Richmod, CA), which weigh ~1 kg, to support 2−3 h of instrument operation when needed. The power supply outputs includes multiple dc voltages, +5, +24, ± 15, and ± 48 V, no matter what the input.

The control board handles control signal generation, signal detection and communication with the remote computer. A Rabbit3000A microprocessor with a main clock running at 58.98 MHz is used as the processor of the control board. The processor environment circuits consist of two direct digital synthesis components AD9834 used to generate rf and ac signals, a D/A convertor AD5308 used to convert all dc control signals from digital to analog, a 12-bit A/D convertor ADS7870 used to covert diagnostic analog signals to digital, a MAX3378E level translator used to generate trigger signals, a Sipex 3232EB used as RS232 interface to communicate with the turbo controller, a 16-bit A/D convertor AD7621 used to sample the amplified spectrum signal, and a DIGI Connect WI-ME module used as the wireless interface to communicate with the remote computer(s) via the 802.1-1b standard.

The high-voltage board converts the dc control signals to desired values to operate the ionization source and the mass analyzer. The output signals from the high-voltage board include a constant 4-kV dc voltage source used for each of the API sources, a glow discharge control signal switchable between 0 and −700 V, a constant dc lens signal adjustable between 0 and 800 V, a 24-V dc pulse signal used for pinch valve control, and a multiplier voltage source switchable between 0 and −1500 V. The Mini 11 rf system consists of a power amplifier and a resonance coil. An rf signal of 0−5 $V_{p\text{-}p}$ is generated by the control board and amplified to 0−90 $V_{p\text{-}p}$ by the power amplifier, an Op Amp driven class B push−pull amplifier. The output signal from the power amplifier is further amplified through the resonance coil. The coil

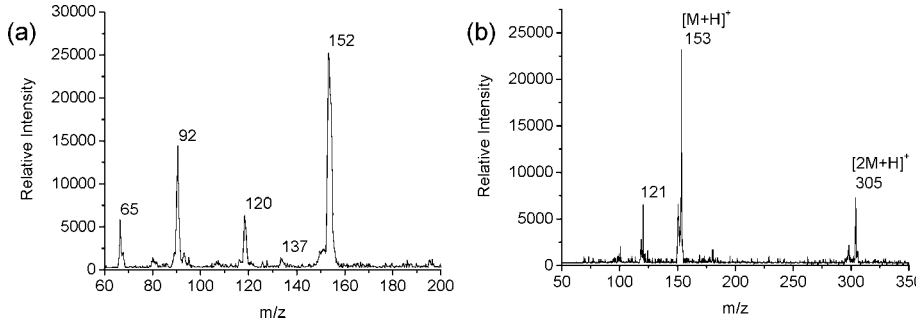

Figure 4. Mass spectrum of methyl salicylate recorded using (a) glow discharge in the internal ionization mode and (b) APCI in the external ionization mode.

was wound around a 25-mm PVC core for 180 turns with 30-gauge magnet wire. The inductance of the coil is ~297 μH, and the capacitance is ~3 pF. Maximum rf amplitude of 4500 $V_{p\text{-}p}$ (maximum power 10 W) can be obtained from the rf system. A signal current amplifier built using Op-Amps is used to convert the output current signal from the multiplier to a voltage signal with a gain of 1.5×10^6 V/A.

EXPERIMENT RESULTS AND DISCUSSION

The Mini 11 mass spectrometer has capabilities for utilizing multiple ionization sources and for analyzing different types of compounds, including high-mass biomolecules. Tandem MS capabilities and fast in situ analysis capabilities are also provided. The performance of the Mini 11 was characterized using various ionization sources and different compounds in regard to each of the capabilities just noted.

Capability for either Internal Ionization or External Ionization. The Mini 11 was designed as a multiple ionization source mass spectrometer. Internal ionization experiments are done using the GDEI ionization source with either direct vapor introduction or sample introduction via a membrane inlet. In the external ionization mode, APCI, ESI, DESI, and other API sources can be used. To test the operation of the instrument in the internal ionization mode using the GDEI source, a vial containing methyl salicylate was placed in front of the membrane inlet entrance for vapor analysis. Air containing the vapor of the ester was forced to flow through the membrane by a sample pump, and the mass spectrum shown in Figure 4a was obtained. From the known saturated vapor pressure of methyl salicylate at room temperature and the volume of sample used, one can estimate the maximum amount of sample used in this experiment as 20 μg. Next, the same sample was analyzed using an APCI source with the instrument operated in the external ionization mode. In the experiment, a stainless steel corona discharge needle with 4-kV dc voltage applied to it was placed 10 mm from the DAPI entrance. The sample vapors wafted into the corona discharge, and the mass spectrum was recorded (Figure 4b). In Figure 4a, besides the molecular ion, m/z 152, abundant fragment ions, m/z 65, 92, 120, and 137 appear in the spectrum due to the high internal energy deposited in ions in the course of electron impact ionization. By comparison, the dominant peak in Figure 4b appears at m/z 153, which corresponds to the protonated molecule while the proton-bound dimer, m/z 305, also appears. Very little fragmentation was observed in the spectrum, consistent with expectation for APCI. These experimental results are a simple verification of the capability to operate the instrument in both the internal ionization and external ionization modes. The differences between the two spectra are also characteristic of the two ionization methods.

Mass Range and Mass Range Extension. The mass range of an ion trap mass spectrometer is determined by the ion trap geometry, rf frequency, maximum rf amplitude, and the Mathieu q value used for resonance ejection. Usually, the rf system utilizes a power amplifier and a resonance coil, with high power output and a high-quality factor coil yielding an appropriately high mass range. After the ion trap and the rf system have been completed, there are at least two ways to increase the mass range of an ion trap mass spectrometer.[20−22] One is to decrease the resonance ac frequency. By doing so, ions with a given mass to charge ratio can be ejected at a lower q value and hence at a lower rf voltage. The other method is to keep the ejection q value constant but decrease the rf frequency, so that ions with the same mass to charge ratio can be given the same q value using a lower rf voltage.[23] Usually, the capacitance of the resonance circuit needs to be increased to decrease the resonance frequency of the rf system, in practice an easy thing to do.

For most of these experiments, the instrument's rf frequency was tuned to 1041 kHz at which value the maximum rf amplitude is 4500 V peak to peak. The mass/charge range is then 700 Da/atomic charge if the ejection point of $q = 0.8$ is selected. The expected high-mass limit was verified with perfluorotributylamine (PFTBA) using the GDEI source in the internal ionization mode; vapor-phase PFTBA was forced to flow through the membrane inlet, and the mass spectrum of PFTBA was recorded by scanning the rf amplitude to eject ions of m/z 60−700. The ac amplitude was scanned from 1.2 to 2.5 V at the same time to maintain the optimum resolution at the higher mass/charge ratios. The mass spectrum recorded is shown in Figure 5a. Fragment ions of PFTBA, with mass/charge ratios up to m/z 614, appear in the spectrum.

A mass range with an upper limit of approximately m/z 650 is adequate for the analysis of many smaller organic molecules. However, it is not suitable for biomolecules like larger peptides and proteins. In order to extend the instrument's mass range, the

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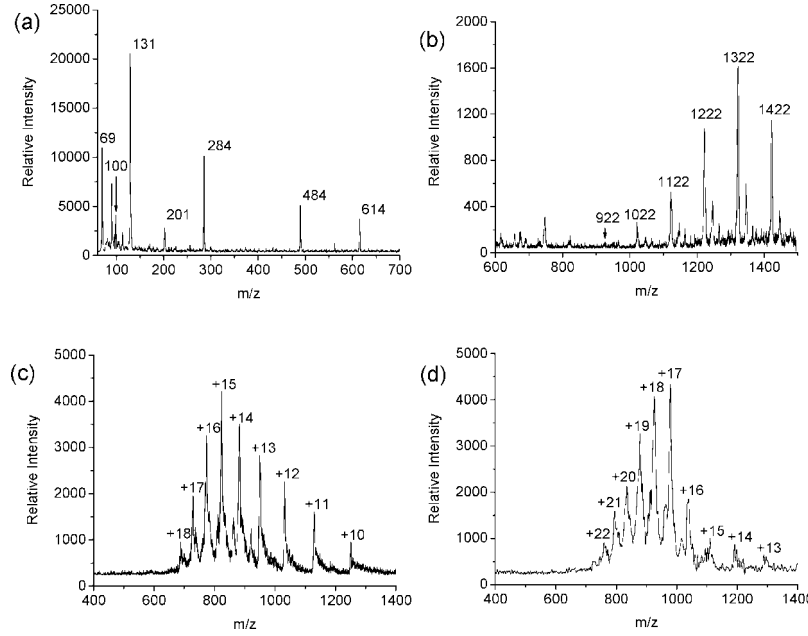

Figure 5. (a) Mass spectrum of PFTBA obtained using GDEI internal ionization with an rf frequency of 1041 kHz. (b) Mass spectrum of 100 ppm Ultramark obtained using a nano-ESI source in the external ionization mode with rf frequency at 695 kHz. (c) Mass spectrum of 200 ppm cytochrome *c* recorded using nano-ESI source with an rf frequency of 695 kHz. (d) Mass spectrum of 200 ppm myoglobin recorded using ESI source in the external ionization mode with rf frequency 695 kHz.

length of the coaxial cable used to connect the rf coil and the ion trap was increased. This added capacitance to the resonance LC circuit, so that the rf frequency tuned at a lower value, 695 kHz. The maximum rf amplitude was similar and the upper limit of the mass range was extended to 1500 Da at the lower rf frequency. A sample solution containing 100 ppm Ultramark was prepared to confirm the mass range. (All sample solutions used for nano-ESI and ESI source were prepared using 1:1 methanol−water with 0.5% acetic acid.) A nano-ESI source using a nanospray tip prepared in-house was used as the ionization source.[24] The spray tip was placed 10 mm from the entrance of the DAPI with a 2.5-kV voltage applied to it. Figure 5b shows the mass spectrum recorded by averaging 20 scans. (The software always averages the latest 20 spectra, so that the refresh rate is same as that of a single scan, which is 4 s.) Ions with mass to charge ratios up to 1422 appear in the spectrum, and the mass resolution at high mass is estimated as 180 ($m/\Delta m$, fwhm definition). Protein molecules too can be analyzed using the Mini 11 after mass range extension, as noted in a preliminary communication,[25] although a different mass range extension method was used here. The nano ESI source was used to spray 200 ppm cytochrome *c* solution, and the averaged mass spectrum (20 scans) is shown in Figure 5c. An ESI source, as opposed to a nanospray source, was used with 80 psi sheath gas pressure and a 4-kV dc voltage. A 200 ppm myoglobin solution was sprayed at 3 μL/min flow rate and the 20-scan mass spectrum is shown in Figure 5d. Although the mass range was increased by decreasing the rf frequency, the sensitivity and resolution of the instrument decreased at the same time, as can easily be noted in Figure 5b−d.

Sensitivity and Limits of Detection, LOD. The LOD and the sensitivity of the Mini 11 were characterized in both the internal ionization mode using the GDEI source and in the external ionization mode using the ESI source. In the internal ionization mode, aqueous solutions of naphthalene at concentrations from 200 ppb to 5 ppm were prepared and pumped through the silicone membrane tube at flow rates of 10 mL/min at room temperature using a peristaltic pump. Mass spectra were recorded for each sample. After the introduction of each sample solution, a blank solution was pumped through the membrane tubing for 5 min to clean the membrane. The intensity of the molecular ion signal (m/z 128) depends on the solution concentration, and a portion of the mass spectrum obtained using the 500 ppb solution is shown in Figure 6a. An LOD of 150 ppb was obtained for this experiment, and a linear response with a R^2 of 0.998 was obtained over the concentration range from 200 ppb to 5 ppm. To characterize detection limits in the external ionization mode, cocaine solutions with concentrations from 200 ppb to 5 ppm were prepared. These samples were analyzed using an ESI source. The intensity of the ion current at m/z 304 is linear with solution concentration, and the mass spectrum obtained for the 500 ppb solution is shown as an inset in Figure 6b. An LOD of 80 ppb was obtained for this experiment, and a linear response with a R^2 of 0.999 was obtained in the concentration range from 200 ppb to 5 ppm.

Tandem MS and Mixture Analysis. Tandem MS, an inherent capability of ion traps, is important for confirmation of specific compounds in complex mixtures, especially when prior separation by chromatography is not used. The most common form of the experiment, the product ion scan, consists of the isolation of a precursor ion and its dissociation, typically by means of gas-phase collisions, to give a set of product ions. There are many ways to carry out the process in practice. In order to simplify the control circuit, the forward-and-reverse ion isolation scan[26,27] and resonance-enhanced collision-induced dissociation[28] were selected so that a single-frequency ac waveform could be used for both the isolation

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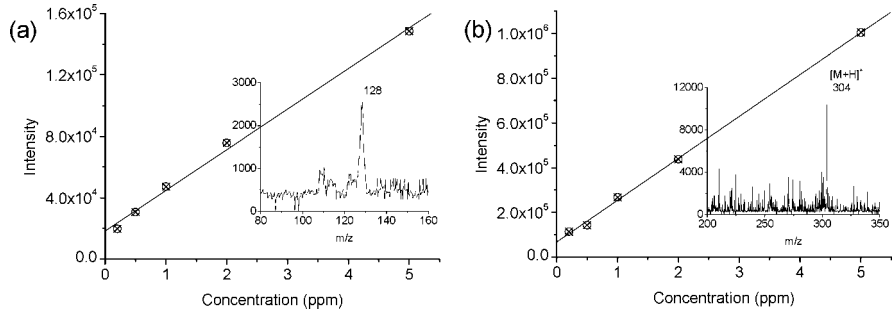

Figure 6. (a) Calibration curve showing intensity of molecular ion of naphthalene examined from aqueous solution by internal ionization using GDEI source. (b) Calibration curve showing intensity of protonated cocaine examined using external ESI.

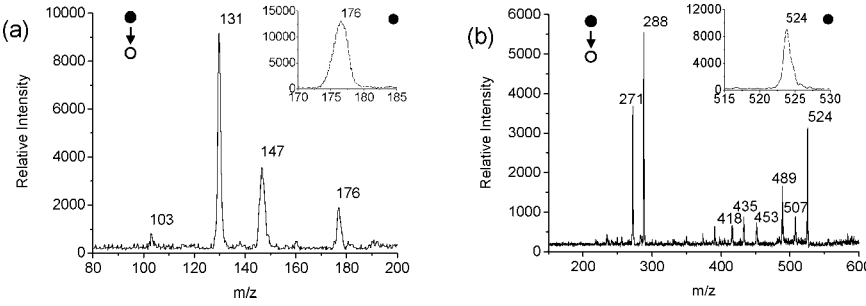

Figure 7. (a) Product ion CID spectrum of ionized ethyl cinnamate, internal ionization mode using GDEI. Inset shows the isolated molecular ion of *m/z* 176. (b) Isolated signal for protonated MRFA, *m/z* 524, (inset) and product ion CID mass spectrum of 1 ppm MRFA solution obtained using external ESI ionization.

and dissociation processes. In the forward-and-reverse scan isolation method, ions with a mass to charge ratio lower than the target parent ions are ejected first by applying a resonance ac signal with a frequency at a high q value and scanning the rf amplitude from low to high value at the same time. Ions with a mass to charge ratio higher than the target parent ions are then ejected from the trap by changing the ac frequency to a lower q value and scanning the rf amplitude from a high value to a low value. After the isolation of the parent ions, fragment ions are generated by applying an ac signal with a frequency equivalent to the secular frequency of the selected precursor ions. The MS/MS product ion spectrum is then recorded by scanning out all ions in order of their mass to charge ratios.

The tandem MS capability of the instrument was verified in both the internal ionization mode and the external ionization mode. In the internal ionization mode, vapors of ethyl cinnamate introduced from the membrane inlet were analyzed using GDEI source. The molecular ion, m/z 176, was isolated and dissociated and the product ion mass spectrum is shown in Figure 7a, where the insert shows the isolated precursor ion. In the external ionization mode, the tandem MS capability was verified using a 1 ppm solution of the tetrapeptide MRFA ionized using ESI. The MS/MS product ion spectrum of protonated MRFA is shown in Figure 7b. To demonstrate the mixture analysis capabilities of the Mini 11, a drug mixture consisting of 5 ppm each of methamphetamine, cocaine, and heroin was analyzed using tandem MS and external ESI source. The result is shown in the Supporting Information section with the mass spectrum of the mixture appearing in Figure S2a. The forward and reverse scan isolation procedure was used to isolate protonated cocaine ions at m/z 304, and their MS/MS product ion spectrum was then recorded using CID by applying an ac signal with an amplitude of 0.3 V at frequency of 160 kHz. A single abundant fragment ion at m/z 182 is observed in this spectrum, Figure S2d.

Rapid In Situ Analysis Using DESI. The development of ambient ionization sources allows the use of a mass spectrometer to analyze samples in their native environment, without prior sample preparation.[29] Fast in situ analysis capabilities are available by combining an ambient ionization source and a miniature mass spectrometer.[30] To demonstrate this, two experiments were done using the Mini 11 instrument equipped with a DESI source.[18] From the DESI source, a methanol/water (9:1) solvent was sprayed at a flow rate of 10 μL/min with a spray voltage of 4 kV to generate charged droplets. A spray angle of ~55° and a takeoff angle of ~10° were selected. A sheath gas pressure of 120 psi was used. The distance between the spray tip and the surface was ~2 mm, and the sampled area was estimated to be 1 mm^2. The first group of samples consisted of four 2 mm × 3 mm dots drawn on a piece of printer paper (Xerox Corp., Rochester, NY). The first three dots were drawn with BIC Round Stic blue, black, and red ballpoint pens, respectively, and the last dot was drawn with both a blue pen and a red pen. The samples on the paper were analyzed using an 18-ms ion introduction time and the mass spectra recorded are shown in Supporting Information Figure S3. Basic violet 3 and basic blue 26, which give rise to the peaks of m/z 372 and 470, occur in the blue ink sample while only basic violet 3 was found in the black ink. Rhodamine, the compound

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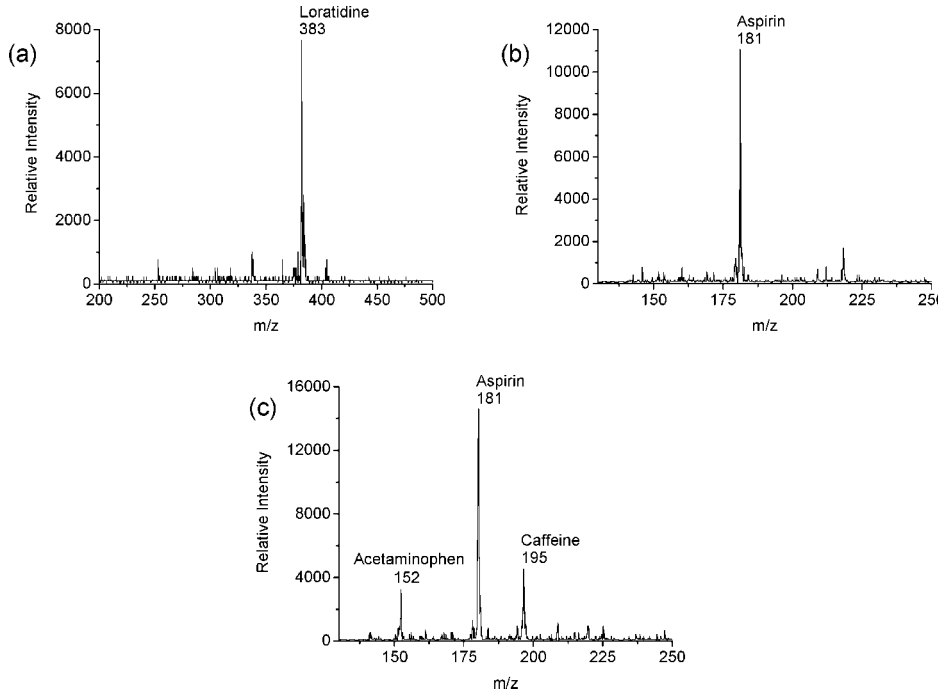

Figure 8. Direct analysis of drugs as tablets using DESI on the Mini 11. (a) Claritin; (b) aspirin; (c) Excedrin.

responsible for the peak at m/z 443, was found in the red ink. All three dyes were found in the last dot. The peaks m/z 358 and 344 observed from both the black and blue ink are reported to be the products of oxidative demethylation of basic violet 3.[31] In the second group of samples, three commercial drugs in tablet form, Claritin, aspirin, and Excedrin, were analyzed using an external DESI source connected by the DAPI interface to the Mini 11. The experimental conditions for DESI were identical to those described above. Mass spectra recorded from the three tablets are shown in Figure 8a−c. The active ingredient loratadine gives rise to the peak m/z 383 in the Claritin tablet spectrum, while the active agent aspirin, m/z 181, was found in the aspirin tablet, and three active ingredients, acetaminophen, aspirin, and caffeine are responsible for the peaks m/z 152, 181, and 195 found in the Excedrin tablet.[32] Taking advantage of the ambient ionization method, it took less than 1 min to obtain these results.

CONCLUSION

A wireless-controlled miniature mass spectrometer, Mini 11, has been designed, built, and characterized. The instrument is able to operate in the external and internal ionization modes, the former through the use of a discontinuous atmospheric pressure interface. Analytes can be ionized by either a GDEI source or one of several API sources. The ability to implement multiple types of ionization sources enables the user to select ionization techniques appropriate to particular samples and to improve the sensitivity and specificity toward selected analytes. By using ambient ionization sources, the fast in situ analysis capability of the instrument was demonstrated with DESI on drug tablets. Samples were analyzed in their native states without preparation, and analytical results were obtained in minutes. Tandem MS capabilities are also available to analyze complex samples by using forward-and-reverse scan isolation and collision-induced dissociation. The mass range of the instrument was characterized using Ultramark and the proteins myoglobin and cytochrome *c*. A mass/charge range with an upper limit of m/z 1500 was achieved. The limits of detection in both internal ionization and external ionization modes were characterized at the ppb level, using GDEI and ESI sources. The simplicity and portability of the instrument were maintained while extending the capabilities of earlier miniature mass spectrometers. Only five control signals were needed to operate the instrument, which weighs 3.2 kg, consumes less than 35 W of power, and has a size of $22 \times 12 \times 18$ cm.

Further development of the instrument will stress continued reduction in weight, power consumption, and size, and further improvement in analytical capabilities. More important, miniature mass spectrometers need to be applied in more areas of science and technology. Significant among the applications that are now being tackled is the implementation of these instruments to analyze reacting chemical systems on the benches of synthetic chemists.

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SUPPORTING INFORMATION AVAILABLE

Additional information as noted in text. This material is available free of charge via the Internet at http://pubs.acs.org.

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