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Miniature mass spectrometer equipped with electrospray and desorption electrospray ionization for direct analysis of organics from solids and solutions

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ABSTRACT

We report on the use of a small light-weight mass spectrometer (MS) for chemical analysis of organic material directly from solution or from the solid state with potential value in future planetary missions. The mass spectrometer used in the experiments reported here is handheld and controlled from a laptop computer through custom software. Detection and identification of small organic molecules, including some that might be prebiotics, was achieved using methods relevant to *in situ* and remote sensing applications. The miniature MS was equipped with a discontinuous atmospheric pressure interface (DAPI) and a home-built electrosonic spray ionization (ESSI) source. Aqueous solutions of molecules of interest were examined using the ESSI technique, while desorption electrospray ionization (DESI) was applied to examine solid samples. The system performance was characterized by direct analysis of analytes belonging to several compound classes including biotic and abiotic amino acids, purines, pyrimidines, nucleosides and peptides. Detection limits in the sub-ppm range for solutions were achieved with the atmospheric pressure sampling/ionization interface. Tandem mass spectrometry (MS^2) was successfully applied to confirm trace detection of target compounds in mixtures. Multiple stage (MS^n) analysis, where $n = 3$–5, was employed for molecular structure confirmation and to demonstrate the high chemical specificity as well as the sensitivity of the instrumentation. The use of improved versions of this type of mass spectrometer on exploration missions could provide detailed chemical information on organic materials in physical states currently difficult to access. The high sensitivity and specificity, combined with rapid detection and the absence of requirements for sample preparation are encouraging features of the instrumentation.

1. Introduction

The search for extra-terrestrial life features prominently in plans for planetary exploration, as exemplified in NASA's mission statement [1–3]. In line with this, we have been working to develop miniature mass spectrometers capable of providing high sensitivity and specificity in the detection of a wide variety of chemical and biological compounds. Simultaneously, we and others have been developing methods of ionization that can be adapted to direct analysis of condensed-phase samples using miniature mass spectrometers [4].

Mass spectrometry (MS) is capable of providing high sensitivity and selectivity in the identification and, with more difficulty, quantitation of a wide range of chemical and biological compounds. Traditionally costly and cumbersome, it has been the subject of rapid recent development [5–9]. Several mass spectrometric systems have been successfully deployed in the field and a number of small instruments have progressed to the point of commercialization [10–13]. These mass spectrometers allow vapor analysis or the analysis of volatiles in aqueous solution and they employ standard electron ionization or chemical ionization methods together with gas or semi-permeable membrane interfaces [5]. Small mass spectrometers that allow direct chemical analysis of molecules in liquid and solid samples are much more rare and are only now becoming available, principally through the use of ambient ionization methods, in which samples are analyzed in the ordinary environment without preparation [14]. Here we explore the applicability of miniature mass spectrometers equipped with these types of ionization sources to the identification of such bio-organic compounds as might be encountered in the exploration of water–ice covered worlds and other extraterrestrial environments.

The partially ice-covered bodies Enceladus, Europa, Mars and from recent observations, the Moon [15], are the solar system locations thought to have the greatest potential as abodes for either

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Table 1
Mini 10.5 mass spectrometer: performance and physical characteristics.

Characteristic	Mini 10.5 MS
Mass range/resolution	m/z 25–550 with unit resolution
Time for spectrum acquisition	1 s
Number of scans averaged (typically)	10
Data volume	120 kbits per spectrum
Mass (system)	~10 kg
Power consumption	50 W average

extant or extinct life. They are targets of interest because there is ample evidence for the presence of liquid water during at least some parts of their history [16–19]. For the Mars exploration program, a strategy of "follow the water" has dominated program planning for over a decade. Now that the history of aqueous processes is becoming better understood, the next step in this strategy would be to "find the carbon" referring to the discovery of organic biomarkers that may be present on Mars and elsewhere in the solar system where life may have existed [20]. Future missions to these objects will have to include instruments that can identify specific chemical compounds directly in the water, ice and soil.

In this context, one of a series of Purdue-built handheld mass spectrometers, the Mini 10.5 [21–26], was used for a systematic investigation of biomolecules, including biotic and abiotic amino acids, purines, pyrimidines, nucleosides and peptides. The miniature instrument was equipped with a discontinuous atmospheric pressure interface (DAPI) [27] to optimize delivery of externally formed ions into a small MS. A home-built electrosonic spray ionization (ESSI) source [28] was used to generate ions from organics in solution. The same ESSI ion source was used to examine solids samples in the desorption electrospray ionization (DESI) mode [29]. We seek to evaluate both sensitive detection of target molecules and specificity in making chemical assignments. Tandem mass spectrometry (MS/MS) was employed to achieve these objectives; it is highly desirable in the case of complex samples and also allows structural verification of target compounds detected at concentrations near the limit of detection (LOD).

2. Materials and methods

2.1. Mini 10.5 MS: instrument design

The Mini 10.5 is a hand-held mass spectrometer based on a rectilinear ion trap (RIT) [30] mass analyzer and aspects of its performance have been reported [21–26]. Table 1, summarizes performance and physical characteristics of this miniature mass spectrometer. The instrument features unit resolution, an upper mass limit defined by access to mass-to-charge ratio (m/z) of 550 Da/charge and detection limits for analytes in solution that range from high parts per trillion to low parts per million for favorable analytes. It is capable of performing multiple stage mass spectrometry experiments (MS^n) using waveform isolation and collision-induced dissociation (CID) of mass-selected precursor ions to generate product ions. All components, including the electronics and vacuum system, are assembled in an aluminum case of length: 34 cm, width: 22 cm and height 19 cm. The total weight of the instrument, including batteries, is 10 kg. The maximum power consumption, when both rough and turbo pumps are running and the RF is continuously being scanned to its maximum amplitude, is ca. 50 W; the instrument can be operated for 3–4 h on batteries, depending on the operating mode selected. The Mini 10.5 MS has a Windows operated on-board computer as well as wireless capabilities to allow communication with remote computers and with other Mini 10 series instruments [21]. The instrument is controlled by and data are processed using software (Version 2.2) from Griffin/ICx Analytical Instruments (West Lafayette, IN).

Mass analysis is performed using a quadrupole ion trap [31] configured in a simple rectilinear geometry (dimensions x_o = 5.0 mm, y_o = 4.0 mm, axial length z_o = 43.2 mm) and operated in the mass-selective instability scan mode to generate mass spectra at a drive frequency of 1000 kHz and 250–4000 $V_{0\text{-}P}$. A supplementary AC signal at 350 kHz and an adjustable amplitude of 0.5–2.1 $V_{0\text{-}P}$, applied between the two x electrodes, allows resonant ejection during the RF mass-selective instability scan [21]. Ions are ejected in the order of increasing mass in the radial direction during the RF amplitude ramp, and then detected using a channeltron electron multiplier (Burle 5903, Burle Industries, Inc., Lancaster, PA) held at high voltage (−1300 to −1800 V, ca. 10^6 gain). Air is used as the buffer gas to cool the trapped ions prior to the mass scan and as the collision gas in the MS/MS experiments.

2.2. Sample delivery and ionization

The capillary inlet of the Mini MS was modified to incorporate a DAPI interface, which allows ions generated externally by atmospheric pressure ionization methods to be admitted into the ion trap in a pulsed fashion. This interface allows efficient sampling of ions from air into a system capable only of a low pumping speed. The discontinuous interface consists of two in-line stainless steel capillaries connected by a silicon tube that is physically pinched shut by a solenoid-operated pinch valve (model 390NC24330, ASCO Valve Inc., Florham Park, NJ). Ions, generated outside of the manifold, as well as surrounding gas from the atmosphere are drawn into the manifold while the pinch valve is held open [27]. The duty cycle for ion introduction is typically 1%, and is largely limited by the pumping speed of the vacuum system.

ESSI [28], a variant of electrospray ionization (ESI) [32], was used in order to produce ions from solution-phase samples. A home-built ESSI source, held at 3.5 kV potential, was operated using nitrogen nebulizing gas at a pressure of 120 psi. Solutions were introduced at a flow rate in the range of 3–5 μL/min. The choice of ESSI and the conditions used allowed the same device to be used to direct ionized solvent droplets at a surface and so perform desorption electrospray ionization (DESI). For these experiments, the capillary inlet was mounted on a movable bracket and tilted toward the surface being analyzed (the incident angle relative to the plane of the surface was 55°; the take-off angle was 10°). Solvent droplets were propelled pneumatically and the sprayer was positioned 3 mm from the surface. The DESI source was held at 5.0 kV potential and operated using nitrogen nebulizing gas at a pressure of 150 psi. Spray solvents, either MeOH/H_2O (50%, v/v) or acetonitrile, were introduced at a flow rate of 3 μL/min.

2.3. MS and MS^n experiments

Ions formed by ESSI or DESI were transferred through the DAPI interface into the mass analyzer where they are trapped while the co-introduced air and solvent vapors were pumped away. Once the pressure had dropped to levels at which mass spectra could be recorded [27], the trapped ions were manipulated using normal ion trap operations available in instruments capable of resonance ejection and mass-selective excitation. These capabilities allowed for tandem and higher-stage mass spectrometry experiments. Multiple stages of mass analysis and fragmentation were accomplished with the individual stages of dissociation and product ion selection being separated in time.

Single-stage MS experiments were conducted using a scan function consisting of four periods: (i) ion introduction (15–20 ms), (ii) pump down and ion cooling period (500–750 ms), (iii) mass analysis (60–100 ms), and finally (iv) a recovery period (200–250 ms). In the case of tandem MS experiments, ion introduction and cooling were immediately followed by two additional operations:

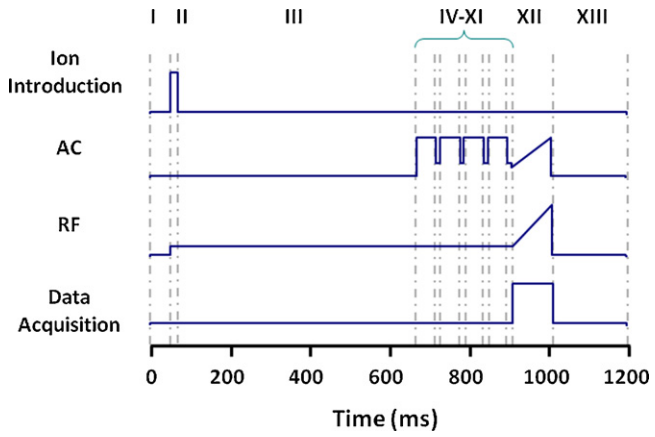

Fig. 1. Scan function (timing diagram) describing experimental sequence for MS^5 experiments using the miniature ion trap MS. The individual stages are: pre-ionization (I), ion introduction (II), pump down and ion cooling (III), ion isolation #1 (IV), collision-induced dissociation (CID) #1 (V), ion isolation #2 (VI), CID #2 (VII), ion isolation #3 (VIII), CID #3 (IX), ion isolation #4 (X), CID #4 (XI), mass scan (XII) and post-scan (XIII).

40–50 ms ion isolation and a 5–15 ms CID period. During the ion isolation stage, ions of interest were selected by application of waveforms in resonance with ions of particular mass/charge ratios (and hence frequencies), i.e., by the stored inverse Fourier transform (SWIFT) method [33]. Mass-selection conditions were optimized for each of the analytes to yield maximum signals for the ions of interest. A supplementary SWIFT pulse at a frequency in the range from 70 to 200 kHz, a 5–10 kHz bandwidth and an amplitude of 1.5–2.0 V, was applied between the two *x*-electrodes. In the next step, CID was performed using a sine wave of a frequency chosen to match the secular frequency(ies) of the ion(s) of interest (in the range 70–200 kHz) and with a low amplitude of 0.1–0.2 V [34]. Implementation of the waveform caused internal excitation of the selected ions, converting some of the translational energy acquired via collision into the internal energy and leading to dissociation in the RIT. The amplitude of the waveform was adjusted to control the degree of dissociation. Mass spectra displaying the product ions were recorded (MS/MS and sequential MS^n spectra, where $n = 3–5$) using one or more steps of MS selection and fragmentation. A 40–50 ms ion isolation step and a 5–15 ms CID step was repeated $n-1$ times prior to performing the final product ion scan to record an MS^n experiment. The sequence of events (scan function) for such an experiment is shown in Fig. 1.

2.4. Samples

All chemicals were commercially available and used without purification. Acetonitrile, adenine, adenosine, caffeine, cocaine hydrochloride, cytidine, cytosine, 1-methyladenine, thymine, uracil, uridine, and L-amino acids (2-aminoadipic acid, arginine, lysine, norleucine, norvaline, phenylalanine, proline, serine and valine) were obtained from Sigma–Aldrich (St. Louis, MO), a synthetic peptide KAAAK–OH (Lys-Ala-Ala-Ala-Lys) was from 21st Century Biochemicals, Inc. (Marlboro, MA), bradykinin acetate salt and tetrapeptide RGDS–OH (Arg-Gly-Asp-Ser) were from Sigma–Aldrich. All working solutions were prepared in methanol/water (50%, v/v in water). For the DESI experiments, amino acid solutions were deposited (0.4 μL) onto filter paper surfaces, air dried and analyzed using typical DESI conditions [29]. Methanol and water, either chromatographic or analytical grade, were obtained from Mallinckrodt (Paris, KY) and used to prepare the spray solvent mixture (50%, v/v in water).

3. Results and discussion

3.1. Analysis of amino acids

It is well established that carbonaceous meteorites contain a wide variety of organic compounds [35,36], including amino acids and nucleobases, compounds which might have played a critical role in terrestrial biochemistry. An extraterrestrial source of these molecules [37–41] and in some cases their probable non-solar system origin [42,43] is indicated through isotope ratio measurements that reveal moderate enrichment in heavy isotopes (e.g., ^{13}C, ^{15}N) relative to their terrestrial counterparts.

Among the key molecules of life, particular interest attaches to the detection and identification of amino acids due to their fundamental importance to terrestrial biology. It is generally assumed that abiotic synthesis of amino acids, for instance on the early Earth, resulted in racemic mixtures. Whether these building blocks were synthesized on earth or imported on meteorites, subsequent chiral enrichment must have occurred to achieve the chiral purity in the biosphere that is a necessary condition for the subsequent development of self-replicating organisms [39,43–46]. L-Enantiomeric enrichment of some of the amino acids found in meteorites has been reported in several recent studies [39–51]. These observations point to the value of detailed examination of organic materials by mass spectrometry, especially amino acids [52]. In the present study, biotic (arginine, lysine, phenylalanine and serine) as well as abiotic amino acids (norleucine, norvaline and aminoadipic acid) were studied individually and in mixtures using ESSI and DESI with a Mini 10.5 mass spectrometer. (Note that the biotic/abiotic distinction is simply based on relationships to current terrestrial biology, it is not used here to imply terrestrial prebiotic processing or molecular chiral discrimination [43].) Limits of detection achieved for solutions of pure amino acids are given in Table 2. The results of MS/MS analysis were employed for: (i) structural verification of target compounds, possible even when detected at concentrations near the LOD, (ii) multistage fragmentation of model compounds which demonstrates the possibility of detailed structural elucidation and (iii) identification of particular target compounds in complex mixtures. These results are presented in the following sections.

ESSI/MS/MS was performed for trace level detection of amino acids. This follows from the fact that using ion trap mass spectrometry, tandem MS experiments are routinely performed for highly specific quantitative analysis of targeted compounds [53]. The mass spectrum of 0.5 ppm (0.5 μg/mL) of L-arginine recorded using the handheld MS is shown in Fig. 2a. The signal/noise ratio for protonated arginine, $[Arg+H]^+$ is low due to the large number and abundance of ions originating from trace impurities in the instrument and the sample matrix. However, the CID product ion MS/MS spectrum of the species selected at m/z 175 (Fig. 2b) reveals a fragmentation pattern characteristic of the ion $[Arg+H]^+$ (compare with Fig. 2d) isolated from a concentrated (a 100-fold higher) arginine sample (Fig. 2c). Ions at m/z 148 (Fig. 2b) are interpreted as fragments originating from isobaric species at m/z 175.

Tandem MS is established as a useful technique for fundamental studies of ion structure and fragmentation [54,55]. In mass spectrometers capable of performing MS^n scans, where $n > 2$, unambiguous assignment of product ions originating from MS^2 experiments is possible. Using the Mini 10.5, ESI/MS^n experiments were performed by sequential trapping and fragmentation of ions of interest permitting one to record fragments arising from the specific ion population. Ion trap mass spectrometers are capable of multiple stage MS experiments (MS^n) but among miniature mass spectrometers, only MS^2 and MS^3 experiments can be found in the literature [21–23]. Here, MS^5 experiments were performed on the protonated dimer of arginine using sequential

Table 2
Detection limits in analysis of amino acids using handheld mass spectrometer.

Sampling/ionization method	Analyte	Molecular weight	Detected species	LOD[a]
ESSI/DAPI of biotic amino acids	Arginine		$[M+H]^+$, $[M+Na]^+$, $[2M+H]^+$, $[2M+Na]^+$, $[3M+Na]^+$	0.5 μg/mL
	Lysine	146.19 g/mol	$[M+H]^+$, $[M+Na]^+$	<1 μg/mL
	Phenylalanine	165.19 g/mol	$[M+H]^+$, $[M+Na]^+$, $[2M+H]^+$, $[2M+Na]^+$	0.5 μg/mL
	Serine		$[M+H]^+$, $[M+Na]^+$, $[2M+H]^+$, $[2M+Na]^+$	>1 μg/mL
ESSI/DAPI of abiotic amino acids	L-2-Aminoadipic acid	161.16 g/mol	$[M+H]^+$, $[M+Na]^+$	~5 μg/mL
	L-Norleucine	131.17 g/mol	$[M+H]^+$, $[M+Na]^+$, $[2M+H]^+$, $[2M+Na]^+$	1 μg/mL
	L-Norvaline	117.15 g/mol	$[M+H]^+$, $[M+Na]^+$, $[2M+H]^+$, $[2M+Na]^+$	0.5 μg/mL

[a] 1.5–2.0 μL samples of selected amino acids in $MeOH/H_2O$ solutions at various concentrations were used to obtain averaged mass spectrum to determine detection limits.

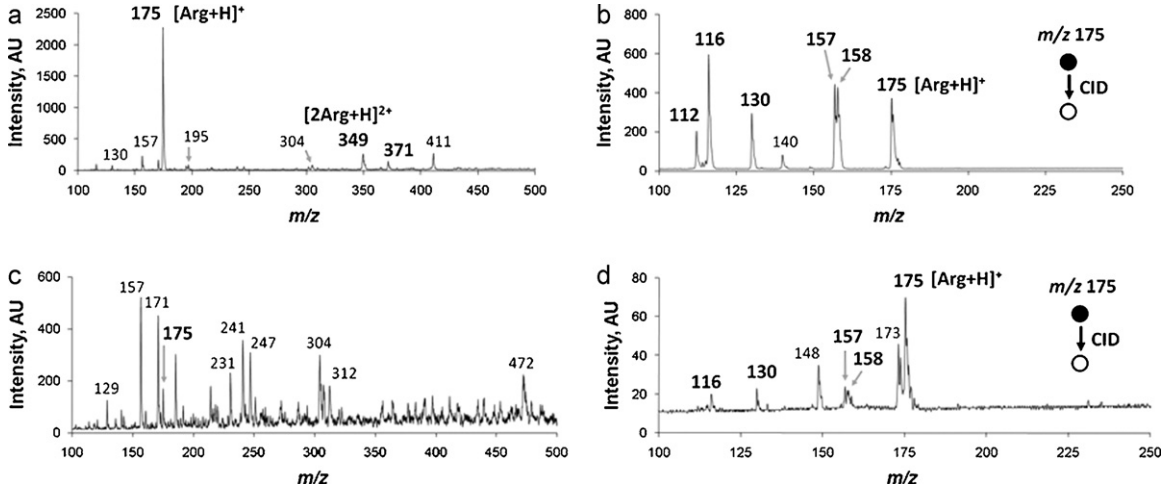

Fig. 2. ESSI/Mini 10.5 mass spectra of arginine in aqueous solution: (a) full scan mass spectrum, (b) MS/MS product ion spectrum of 0.5 ppm L-arginine (Arg), (c) full scan mass spectrum and (d) MS/MS spectrum of 50 ppm L-arginine. For the tandem mass spectrometry experiments, ions at m/z 175, corresponding to the mass-to-charge ratio of protonated arginine, $[Arg+H]^+$, were isolated and fragmented by collision-induced disssociation.

CID and trapping of selected product ions (Fig. 3). These results demonstrate the exceptional performance of the miniature mass spectrometer and its power in recording structurally characteristic fragmentations.

In one demanding experiment, a mixture containing 30 ppm of arginine (Arg), 4 ppm caffeine (Caff) and 30 ppb cocaine (Coc) in methanol/water was analyzed, caffeine and cocaine being chosen as mixture components which can compete with the arginine for

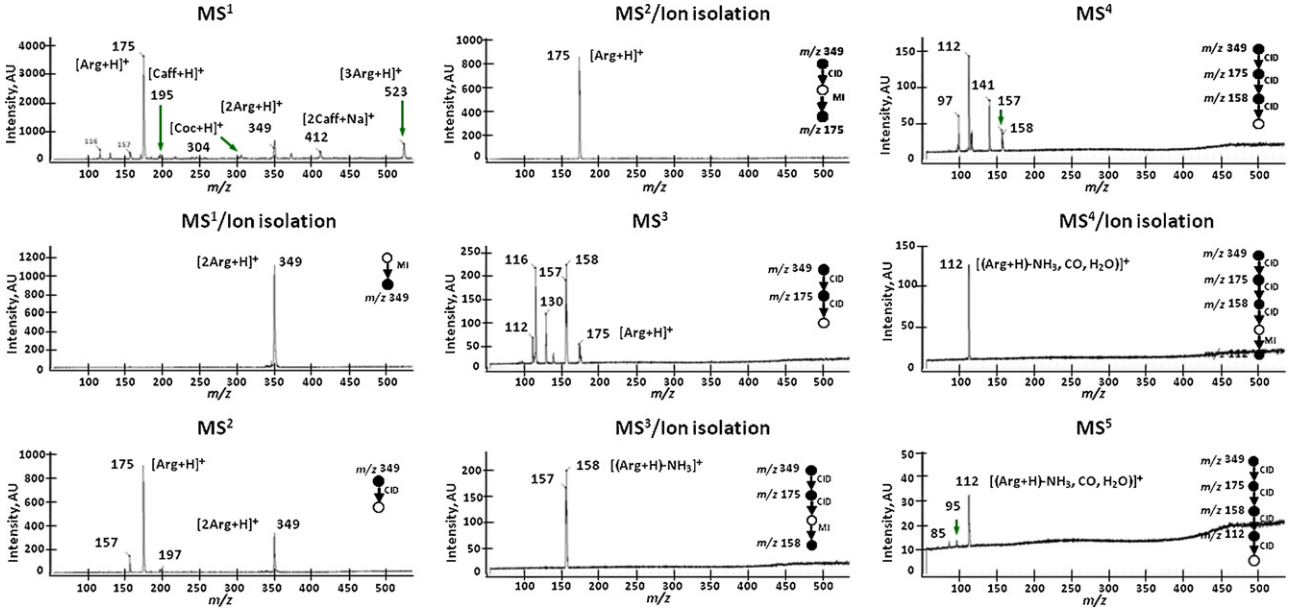

Fig. 3. ESSI/MS^5 study of L-arginine (30 ppm in $MeOH/H_2O$) clusters performed using the Mini 10.5 ion trap mass spectrometer. Ions at m/z 349 $[2Arg+H]^+$ were isolated from the ion population generated by ESSI from a $MeOH/H_2O$ (50%, v/v) solution containing 30 ppm L-arginine (Arg), 8 ppm caffeine (Caff) and 60 ppb cocaine (Coc). Upon isolation, an ion package (m/z 349) was submitted to the indicated steps of fragmentation and mass selection. In the last stage, the MS^5 product ion mass spectrum was recorded. The symbols indicate the various stages of the MS^n experiments; each scan takes approximately 1 s to record. Ten to forty scans were averaged for each mass spectrum presented here.

the proton. The full mass spectrum includes the following ions: $[Arg+H]^+$ m/z 175, $[Caff+H]^+$ m/z 195, $[Arg+Na]^+$ m/z 197, $[Caff+Na]^+$ m/z 217, $[Coc+H]^+$ m/z 304, $[2Arg+H]^+$ m/z 349, $[2Arg+Na]^+$ m/z 371, $[2Caff+H]^+$ m/z 412, $[3Arg+H]^+$ m/z 523, as well as ions that originate from fragmentation of protonated arginine, m/z 116, 130, 157, and ions from trace impurities in the solvent or background in the instrument, namely m/z 171, 240, 246, and 310. The protonated dimer of arginine, $[2Arg+H]^+$ m/z 349, was isolated and submitted to CID. The product ion mass spectrum was dominated by the formation of the protonated arginine monomer, which was in turn mass selected and fragmented further. The product ion mass spectrum of protonated arginine, $[Arg+H]^+$ m/z 175, shows a complex fragmentation pattern. In addition to fragmentation by loss of NH_3 and by loss of H_2O, ions of m/z 112 ($[(Arg+H)–(NH_3, H_2O, CO)]^+$, m/z 116 $[(Arg+H)–(H_2N)_2C{=}NH]^+$ and m/z 130 $[(Arg+H)–(NH_3, CO)]^+$ were observed. This behavior is in agreement with the literature [56,57]. In the following MS stages (MS^4 and MS^5), ions of m/z 158 and m/z 112 were submitted to subsequent steps of mass selection and fragmentation. Finally the MS^5 product ion mass spectrum was recorded. The capability to perform a long sequence of mass isolation and fragmentation steps (MS^4 and MS^5 analysis), to the best of our knowledge, has not been reported before on a miniature mass spectrometer. Such a capability allows for the recognition of the analyte molecule with high specificity based on its consecutive fragmentation patterns.

Dissociation by CID is uniquely simple in terms of its applications but fairly complicated in terms of the energy transfer functions and the dissociation mechanisms involved [55]. Numerous parameters affect the fragmentation pattern [58], including pressure and nature of the collision gas, ion energies within the mass analyzer, applied radiofrequency amplitude and parent ion collision energy. Although some of these parameters can be easily manipulated in commercial instruments (pressure and type of collision gas, collision energy, fill time of the ion trap and the scan rate) [58], they are harder to control on fieldable miniature mass spectrometers. For instance, the pressure of the collision gas within the DAPI/Mini MS when it is interfaced with an ESSI ionization source depends on the ion introduction time (pinch valve opening) and nebulizer gas flow rate of ESSI. Consequently, the regulation of the energy transferred during CID processes is a challenge for miniature instrumentation. What is more, an extensive pump-out and ion cooling (500–700 ms) and ion trapping period (during MS^n experiments) allows for (i) multiple collisions of analyte ions with residual gas and consequently loss of ions due to the charge transfer with colliding background neutrals (e.g., to oxygen molecules), (ii) ion/molecule reactions, e.g., formation of water cluster adducts as well as (iii) ion fragmentation, when sufficient amount of translational energy is converted into internal energy. These factors are important since they control the nature of the data recorded and they mean that a customized reference spectra library of MS and MS/MS spectra is needed for analyte identification using a miniature mass spectrometer.

In each of the stages of the MS^n experiment, trapped ions gain and lose kinetic energy though cooling and activating collisions. During the CID processes some of the energy gained is converted into internal energy and leads to the fragmentation. However, the translational excitation of the ion may result in motion of the ion towards the electrodes and ions escape from the the trapping region. Competition between CID processes and resonance ejection is well known [59].

Because of the factors discussed above, each of the ion isolation and CID steps causes a significant decrease of the ion population. For instance, the isolation of protonated arginine, $[Arg+H]^+$ m/z 175, obtained from the CID of the protonated arginine dimer, $[2Arg+H]^+$ m/z 349, results in a 6% ion abundance loss (depending on the resolution chosen) (Fig. 3). The subsequent isolation of arginine fragments, e.g., $[(Arg+H)–NH_3]^+$ m/z 158, results in ~12% ion abundance loss, then isolation of m/z 112 $[(Arg+H)–(NH_3, H_2O, CO)]^+$, causes ~11% loss of ion abundance of the precursor ion (Fig. 3). High trapping efficiency is required in order to achieve multiple steps of ion selection and CID. In addition, only instruments with sufficient sensitivity are capable of detecting fragment ions whose abundance is lower than the precursor by three orders of magnitude, as it is shown in Fig. 3 for the protonated arginine dimer.

Instrumental analysis of complex mixtures generally involves two operations: separation of components and characterization of the individual compounds [60]. This type of study is performed routinely using a combination of techniques such as gas chromatography (GC) or liquid chromatography (LC) and mass spectrometry (GC/MS or LC/MS). Similarly, high-resolution mass spectrometry [61] and/or tandem MS [54] can be employed for analysis of complex samples. In order to optimize the speed of *in situ* chemical analysis with a miniature mass spectrometer, separation techniques should be avoided if possible. Tandem MS experiments provide some separation (based on ion selection as a surrogate for separation of the neutral molecules) and they can provide unambiguous assignment of the molecule of interest (Fig. 4). Following such a scenario, a single-stage mass spectrum was recorded, then the ions of interest (e.g., protonated amino acid molecules) were isolated from the mixture, and submitted to CID. The results of analysis of a mixture of abiotic amino acids are presented in Fig. 4. Ions of m/z corresponding to the protonated amino acids were selected from the mixture and dissociated. The complexity of the mixture was reduced significantly by mass selection. The assignment of target compounds was achieved based on the characteristic fragmentation patterns recorded.

3.2. *In situ surface analysis of amino acids*

Desorption electrospray ionization is rapidly an increasingly widely used ambient ionization method for organic compounds. The process involves spray solvent droplet impact on a sample surface, creation of a localized surface solvent-layer and its break up resulting in recreation of numerous offspring droplets from the solvent layer including the dissolved analytes [29,62].

DESI is applied here to the *in situ* detection of amino acids directly from surfaces. The principal advantage of this approach is the lack of any requirement for sample preparation. For optimal results two set of solvents were used: $MeOH/H_2O$ (50%, v/v) for the amino acids with electrically charged side chains (L-arginine and L-lysine) and acetonitrile for polar amino acids (L-proline, L-phenylalanine and L-valine). Representative mass spectra are shown in Fig. 5. DESI MS analysis resulted in abundant protonated amino acid molecules, i.e., protonated: L-lysine $[Lys+H]^+$ m/z 147, L-arginine $[Arg+H]^+$ m/z 175, L-proline $[Pro+H]^+$ m/z 116, L-phenylalanine $[Phe+H]^+$ m/z 166 and protonated L-valine at m/z 118 (results not shown). The presence of protonated amino acid dimers was observed in the mass spectra of L-lysine, L-arginine and L-proline. DESI/Mini 10.5 MS analysis of L-phenylalanine samples resulted in a base peak at m/z 120 that was interpreted as an immonium ion originating from phenylalanine, which is in agreement with the literature [63].

3.3. *MS analysis of nucleosides, purine and pyrimidine bases*

Extra-terrestrial identification of the compounds capable of multiplication, inheritance and variation would be a strong indication of both life and evolution. Simpler forms of the compounds now associated with genetic information transfer (occurring in modern RNA, DNA) may have been important in early replication systems [64]. The suitability of the Mini MS for the analysis of

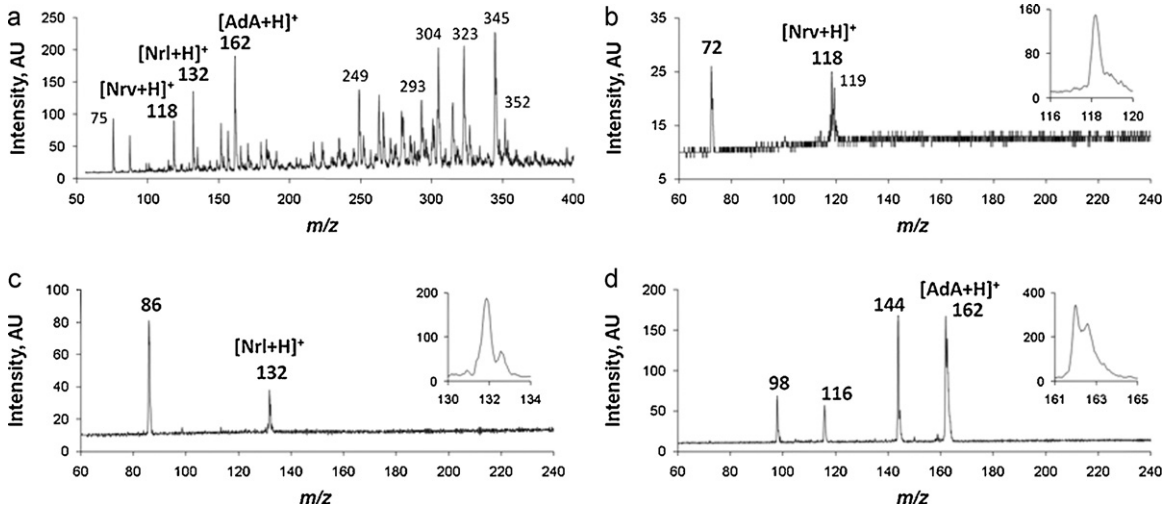

Fig. 4. ESSI/Mini 10.5 study of abiotic amino acids: (a) full scan mass spectrum obtained from MeOH/H_2O (50%, v/v) solution containing 17 ppm L-aminoadipic acid (Ada), 3 ppm L-norleucine (Nrl), 8 ppm L-norvaline (Nrv) and 60 ppb cocaine. Product ion MS/MS spectra of (b) L-norvaline, (c) L-norleucine and (d) L-aminoadipic acid. The inserts in panels (b)–(d) display the *m*/*z* region selected for isolation of precursor ions prior to MS/MS. Note the improved S/N in MS/MS vs. the single stage MS scan.

simple compounds associated with nucleic acids was tested using purines (adenine, 1-methyladenine), pyrimidines (thymine, cytosine, uracil) and nucleosides (cytidine, uridine, adenosine). The results are presented in Table 3. A representative mass spectrum of a mixture containing adenine, adenosine and cytidine, as well as the CID MS/MS spectrum of the protonated nucleoside, cytidine, is shown in Fig. 6. The product ion mass spectrum of protonated cytidine is dominated by protonated base at *m*/*z* 112 as expected from the literature [65,66].

3.4. Mass analysis of peptides

The handheld mass spectrometer used in this study is equipped with the low power RF driving circuit (4000 V_{max}) which provides a mass/charge range up to *m*/*z* 550 using resonance ejection at an AC frequency of 350 kHz. Examination of biomolecules such as peptides and proteins requires a mass/charge range above *m*/*z* 1000 and this extension of the mass range was achieved using resonance ejection at a lower frequency AC signal (ejection frequencies of 120

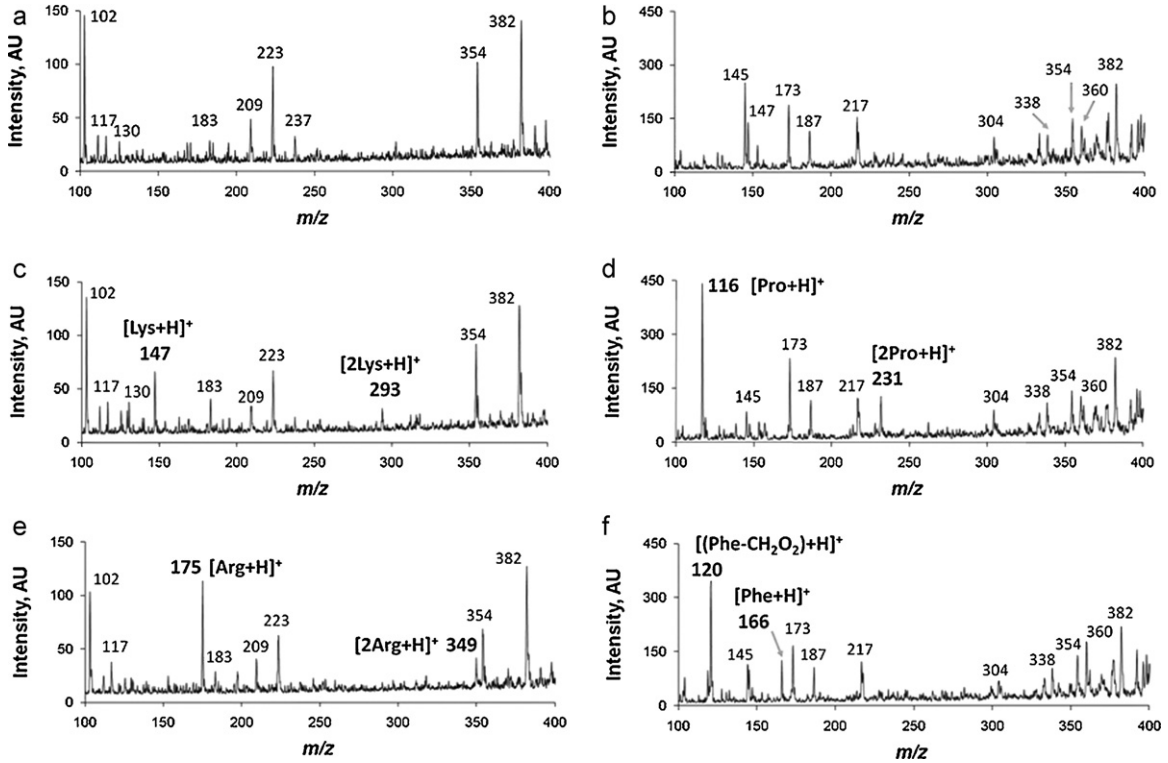

Fig. 5. DESI/Mini 10.5 mass spectra of (a) blank paper surface sprayed with in MeOH/H_2O (50%, v/v), (b) 10 μg of L-lysine (Lys) and (c) 3 μg of L-arginine (Arg) deposited on the paper. Ions of *m*/*z* 102, 183, 209 and 223 are interpreted here as originating from trace solvent impurities. They are commonly observed during the positive ion mode DESI-MS and ESSI-MS analysis of amino acids. Ions of *m*/*z* 117, 130, 354 and 382 are interpreted as due to the trace impurities originally present on the paper substrate. DESI/Mini 10.5 mass spectra of (d) blank paper surface, (e) 10 μg of L-proline (Pro) and (f) 1 μg of L-phenylalanine (Phe) deposited on the paper substrate. Acetonitrile was used as the spray solvent. Ions of *m*/*z* 145, 146, 173, 187, 217, 304, 338 and 360 are interpreted here as originating from trace solvent impurities and trace impurities in the system.

Table 3
Nucleosides, purine and pyrimidine bases examined by ESSI using handheld mass spectrometer.

Compound type	Analyte	Molecular weight	Detected species	LOD[a]
Purines	Adenine	135.13 g/mol	$[M+H]^+$, $[M+Na]^+$, $[M+H_2O+Na]^+$, $[2M+H]^+$, $[2M+Na]^+$, $[2M+K]^+$	0.1 μg/mL
	1-Methyladenine[b]	149.15 g/mol	$[M+H]^+$, $[2M+H]^+$, $[2M+Na]^+$	0.5 μg/mL
Pyrimidines	Cytosine	111.10 g/mol	$[M+H]^+$, $[M+Na]^+$, $[2M+H]^+$, $[2M+Na]^+$	0.1 μg/mL
	Thymine	126.11 g/mol	$[M+H]^+$, $[2M+Na]^+$, $[3M+Na]^+$, $[4M+Na]^+$	0.5 μg/mL
	Uracil	112.09 g/mol	$[M+H]^+$, $[2M+Na]^+$, $[3M+Na]^+$, $[4M+Na]^+$	2.0 μg/mL
Glycosylamines	Adenosine	267.24 g/mol	$[M+H]^+$, $[M+Na]^+$, $[M+H_2O+Na]^{2+}$	0.5 μg/mL
	Cytidine	243.22 g/mol	$[M+H]^+$, $[M+Na]^+$, $[2M+H]^+$, $[2M+H_2O+H]^+$, $[2M+Na]^+$	2.0 μg/mL
	Uridine	g/mol	$[M+H]^+$, $[M+Na]^+$, $[2M+H]^+$, $[2M+Na]^+$	5.0 μg/mL

[a] 1.5–2.0 μL of sample of selected amino acid in MeOH/H_2O solution was used in order to obtain averaged mass spectrum (to determine detection limits).
[b] LOD for the analyte was determined base on the signal-to-noise ratio (S/N = 3).

and 140 kHz) [22]. Trace amounts of several small peptides were examined using single-stage MS (Fig. 7).

Mass analysis of peptides was performed directly from MeOH/H_2O solutions with 0.2% of formic acid added as a source of protons. Representative mass spectra are shown in Fig. 7. The concentration of analyte was either 25 μg/mL (RGDS, Bradykinin) or 50 μg/mL (KAAAK). The sample volume in the range of 0.5–0.7 μL was used to generate a mass spectrum, however, the characterization of detection limits was not attempted. Single and multiple additions of proton to the peptide molecules were observed. Mass analysis of the peptide RGDS yielded protonated ions, $[RGDS+H]^+$ at *m*/*z* 434, as well as the doubly charged molecule, $[RGDS+2H]^{2+}$ at *m*/*z* 217. Peptide fragmentation was observed, e.g., water or ammonia loss from protonated RGDS ($[(RGDS+H)–NH_3]^+$ *m*/*z* 417, $[(RGDS+H)–H_2O]^+$ *m*/*z* 416) and a possible peptide cleavage, which led to ions of *m*/*z* 165 and 232 (presumably b_3^{2+} and $[b_2+H_2O]^+$). Ions of *m*/*z* 445, 456, 462 and 467 are interpreted as due to impurities in the peptide sample (peptide purity ~90%). Mass analysis of the KAAAK revealed its protonated ion, *m*/*z* 488, and doubly protonated form, detected at *m*/*z* = 245. No fragmentation products were noted in the mass spectrum. In case of peptides with molecular mass below 500 Da (KAAAK, RGDS), the protonated molecules dominated the mass spectra. It was not possible to observe the singly charged ion of Bradykinin because its mass to charge ratio exceeds the working range of the miniature mass spectrometer. However, doubly protonated Bradykinin, $[Brad+2H]^{2+}$ at *m*/*z* 531

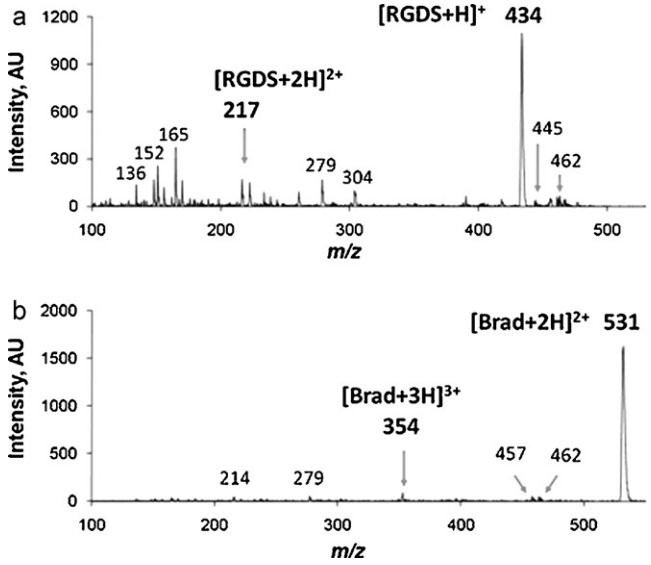

Fig. 7. ESSI/Mini 10.5 mass spectra of (a) 25 ppm peptide RGDS, (b) 25 ppm Bradykinin, each peptide was prepared in MeOH/H_2O solution with 0.2% formic acid added to facilitate positive ion formation. Single and multiple additions of proton to the peptide molecules occur. Ions in the low mass region (*m*/*z* 136, 152, 157, 185, 223, 279 and 304) are due to trace impurities in the system.

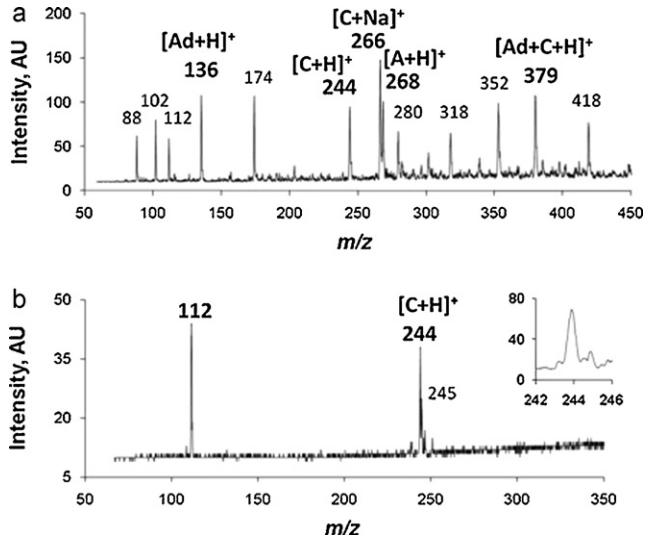

Fig. 6. ESSI/Mini 10.5 mass spectra of 12 ppm adenine (Ad), 12 ppm adenosine and 25 ppm cytidine in MeOH/H_2O (50%, v/v): (a) Full scan mass spectrum, (b) product ion MS/MS spectrum of protonated cytidine, *m*/*z* 224. The insert in panel (b) displays the *m*/*z* region selected for isolation of precursor ions prior to the CID experiment. Note the improved S/N in the MS/MS vs. the single stage MS scan.

and its higher charge state $[Brad+3H]^{3+}$ at *m*/*z* 354 gave abundant signals (Fig. 7).

4. Conclusions

The inclusion of a miniature mass spectrometer on future planetary exploration missions could improve the chemical analysis of organic material due to its high sensitivity and specificity. When equipped with an ambient ionization source (adapted to the Mars atmospheric conditions, i.e., low temperatures, pressure below 1 kPa and an atmosphere different from that of Earth), the capability for ready examination of solids, liquids and gases would be an additional useful feature. In order to explore ice-covered worlds, platforms have to be constructed to melt and drill through the ice. Such platforms, or cryobots, already tested on Antarctic and Greenland ice sheets [67], have been proposed for use on Martian polar caps and Europa [68,69]. As a cryobot descends through an ice cap, the melted liquid can be collected and analyzed to determine its composition. Having a small tandem mass spectrometer of the Mini 10.5 type interfaced to a cryobot would allow for selective detection of compounds of interest as well as for identification of unknowns. (Note that subsequent revisions of the instrument are much lighter (<5 kg) and smaller (length: 22 cm, width: 12 cm and height 18 cm), without sacrificing instrument performance [70].)

The distinctive capability of handheld mass spectrometers to provide sensitivity and high molecular selectivity for biomolecules relevant to extra-terrestrial investigations has been shown. Nevertheless, it is recognized that the analytical performance of the mass spectrometer as well as the design and operating conditions of the ionization source can be improved significantly. Ion transfer efficiency should be improved. In addition, the decrease or elimination of consumables (sheet gas, supplementary solvents), the automation of the entire system, and increasing analysis throughput are of great importance. The entire study was done using the positive ion mode. Recently developed efficient negative ion detection capabilities [71] must be provided to expand the number of molecules that can be detected (e.g., carboxylic acids, some lipids, phenolics, etc.). Enhanced chemical analysis specificity will result from bipolar operation. Specificity could also be augmented by integration of additional appropriate high speed separation methods prior to the mass spectrometer. One possibility is to use ion mobility spectrometry (IMS) to increase the selectivity by including the separation of ions based upon their shape and physical characteristics, especially if used in conjunction with MS/MS. The implementation of differential ion mobility separation on a miniature mass spectrometer has recently been reported [14].

The study presented here shows the sensitivity and high specificity of the MS system especially when tandem MS technique is applied to: (i) target compound analysis, (ii) mixture analysis, and (iii) molecular structure elucidation. Multiple MS stages (up to MS^5) were achieved using the mass analyzer. The handheld mass spectrometer was tested using a variety of compounds, including: biotic and abiotic amino acids, puric and pyrimidic bases, and peptides with detection limits in the sub-ppm range. These results demonstrate applicability to chemical analysis of traces of compounds critical in terrestrial biology. Furthermore, the MS^n capabilities and their high specificities may allow for the identification of compounds unfamiliar in the terrestrial environment. Such findings have the potential to lead to a better understanding of the solar system and the origin of life on Earth.

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