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Review

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Advances in Ionization for Mass Spectrometry

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CONTENTS

SCOPE

Integral to advances in mass spectrometry (MS) are developments in ionization technology, which is constantly evolving because of advances in fundamental understanding, enhancements in instrumentation and optimization, and the evolution of novel techniques for ionizing analytes of interest. With the rapid, almost continual emergence of new developments, staying up-to-date can be a significant challenge. This review, therefore, is intended to provide a concise summary of advancements in MS ionization from January 2015 through September 2016. There are a number of helpful review articles and book chapters on specific aspects of ionization that have been published in the last 2 years, which will not be covered here.[1−15] The reader is encouraged to consult them for further study. Because of overlaps with recent reviews on the topics "imaging" and "SIMS", respectively, these areas are not covered in this review if the focus was not specifically on the improvements surrounding an ionization method. The authors of this review have attempted to be as comprehensive as possible on new developments in terms of fundamentals, instrumentation, and key applications, and any omission of papers from the literature on MS ionization is unintentional. It should be noted that searching for key novelties on "ionization" using "mass spectrometry" is ultimately difficult because these two search terms are intrinsic to nearly every paper published on MS. Therefore, searches have also included names, technologies, or methods surrounding well established groups and newcomers to the field.

EMERGING DEVELOPMENTS RELATED TO NEWER IONIZATION TECHNOLOGIES

A relatively new means of transferring small, large, volatile, and nonvolatile compounds from the solid or solution state directly into the gas phase as ions, falling under the general term *inlet ionization* and individually termed matrix-assisted ionization (MAI), solvent-assisted ionization (SAI), or laserspray ionization inlet (LSI) if a laser is used, continues to be developed as a sensitive and robust ionization method in MS. In MAI, specific small molecule matrix compounds have been discovered which require only exposure to subatmospheric pressure conditions, by default available with all mass spectrometers, to produce gas-phase ions of peptides, proteins, lipids, synthetic polymers, and carbohydrates for analysis by MS.[16] Some MAI matrixes produce abundant ions without the need to apply thermal energy. Out of over 40 such matrixes, the top 10 have been categorized for positive and negative mode measurements. These matrixes sublime when placed under subatmospheric pressure so that, similar to solvents, they are pumped from the mass spectrometer eliminating matrix contamination.[17]

Several studies related to MAI were published in this period by Trimpin and collaborators. MAI was used with MS/MS including electron transfer dissociation (ETD) by Marshall and co-workers to characterize components in tissue and labile posttranslationally modified peptides.[18] They also observed a membrane-associated protein directly from nonsprayable electrospray ionization (ESI) solution. Fischer et al. reported that a Europium-PEG complex, potential magnetic resonance imaging (MRI) contrast agents, difficult to observe using ESI or matrix-assisted laser desorption/ionization (MALDI), was readily observed by MAI because the complex ionized especially well in MAI using 1,2-dicyanobenzene as matrix but not the other components in the mixture.[19] The multiply charged ions separate better in the ion mobility spectrometry (IMS) gas-phase separation than singly charged ions. Chakrabarty et al. demonstrated quantification of illicit drugs using MAI with internal standards on two different manufacturers' mass spectrometers and obtained quantification similar to that obtained on the same instruments using ESI.[20] Drugs were detected and quantified directly from tissue samples with excellent sensitivity by Wang and co-workers using MAI and SAI.[21] High throughput analyses were demonstrated by Woodall et al. with the MAI method using various different samples holders.[22] Lu et al. demonstrated low

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femtomole sensitivity for peptides and drugs using a customized probe to insert a MAI matrix (3-nitrobenzonitrile (3-NBN))−analyte (Figure 1) into the intermediate pressure

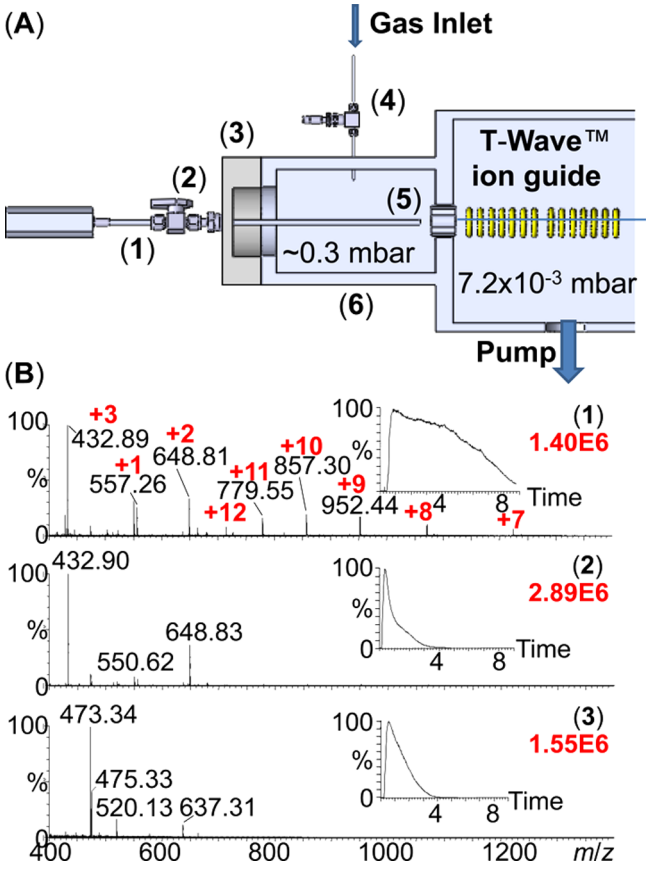

Figure 1. (A) Scheme of the modified vacuum housing to perform MAI: (1) probe, (2) vacuum lock, (3) flange, (4) gas control valve, (5) commercial inlet cap, and (6) hexapole housing. (B) A solution containing a mixture of leucine enkephalin (MW 555.3), angiotensin I (MW1295.6), and ubiquitin (MW 8559) with 6 pmol each and combined with 3-NBN solution, applied to the probe, and dried before insertion into the vacuum housing. Mass spectra and insets of the duration (in minutes) based on the total ion chronogram of ion formation/detection: (1) 1st acquisition, (2) 4th acquisition in which only 3-NBN matrix solution (9:1 ACN−H_2O) was added to the probe successively suggesting that little analyte is lost during sublimation, ubiquitin remains on the probe surface after exposure to high acetonitrile matrix solution and after cleaning the probe surface no contamination from analyte is observed. Reproduced from Simplifying the ion source for mass spectrometry, Lu, I. C.; Pophristic, M.; Inutan, E. D.; McKay, R. G.; McEwen, C. N. *Rapid Commun. Mass Spectrom.* Vol. *30*, Issue 23 (ref 23), 2568. Copyright 2016 Wiley.

MALDI housing of a Waters SYNAPT G2 mass spectrometer but without the laser, ion extraction lens, or hexapole ion guide.[23] The authors demonstrated that by placing matrix−analyte solution on the probe and drying before inserting into the ionization chamber, analyte ions were spontaneously produced in good abundance for over 8 min before the matrix was depleted by sublimation. Interestingly, just loading matrix solution onto the probe thereafter produced nearly equal abundant analyte ions even repeating the ionization and loading several times without adding analyte.

MAI was also employed by other groups. Chen and co-workers presented the utility of interfacing MAI vacuum (MAIV) with a MALDI-LTQ-Orbitrap XL, a high-resolution, accurate mass instrument.[24] The softness of MAI ionization allowed labile post-translational modification (PTM) analysis as well as extended mass range of protein detection due to multiple charging. MAI also yielded more information-rich MS/MS spectra. The sensitivity of MAI was demonstrated by Hoang et al. using a 1 μL syringe method on a Thermo Q-Exactive mass spectrometer. Only ~5 fmol in 50 nL of analyte solution produced a clean mass spectrum of angiotensin I (Figure 2) using the syringe method developed by MSTM. The

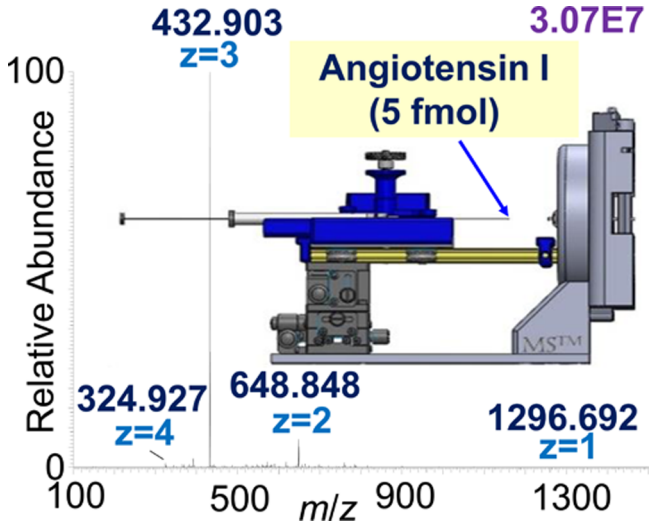

Figure 2. Matrix-assisted ionization (MAI) mass spectrometry from a few femtomoles of the peptide angiotensin I acquired on an Orbitrap Q-Exactive using the MSTM platform which is shown in the inset as a scheme. Abundant multiply charged ions are observe even at this low amount of sample used in the analysis. Springer *Journal of the American Society for Mass Spectrometry*, High Sensitivity Analysis of Nanoliter Volumes of Volatile and Nonvolatile Compounds using Matrix Assisted Ionization (MAI) Mass Spectrometry, *27*, **2016**, 1591, Hoang, K.; Pophristic, M.; Horan, A. J.; Johnston, M. V.; McEwen, C. N., (original copyright notice as given in the publication in which the material was originally published). With permission of Springer.

drug azithromycin was detected in urine diluted 5× with water 12 days after the final dose was administered. Interestingly, neither sodium nor potassium adducts are observed in the salty urine sample which underwent no cleanup.[25] Chubatyi and McEwen reported that for basic compounds, adding ammonium salts to the MAI matrix solutions significantly increased the analyte ion abundance or lowered chemical background or both. Addition of ammonium salts also suppressed ionization of compounds without basic functionality.[26] MAI was used by McLaughlin and co-workers as a means to ionizing 2-methoxydiphenidine (MXP) directly from the surface of a tablet.[27]

An interesting use of the 3-NBN matrix was reported by Santos and coauthors in Eberlin's group.[28] These authors added 10 μg mL^{-1} of 3-NBN as a dopant to the solvent used with easy ambient sonic-spray ionization (EASI) and achieved a 2 to 4-fold gain in total ion current and signal-to-noise for the analyte. The sensitivity of DESI was also improved with the 3-NBN dopant in the tested vegetable oil sample. Interestingly, with 3-NBN EASI and DESI had comparable sensitivity.[28] In inlet ionization, the matrix can be a solvent, but unlike with solid matrixes, so far, no solvent has shown high sensitivity analyses

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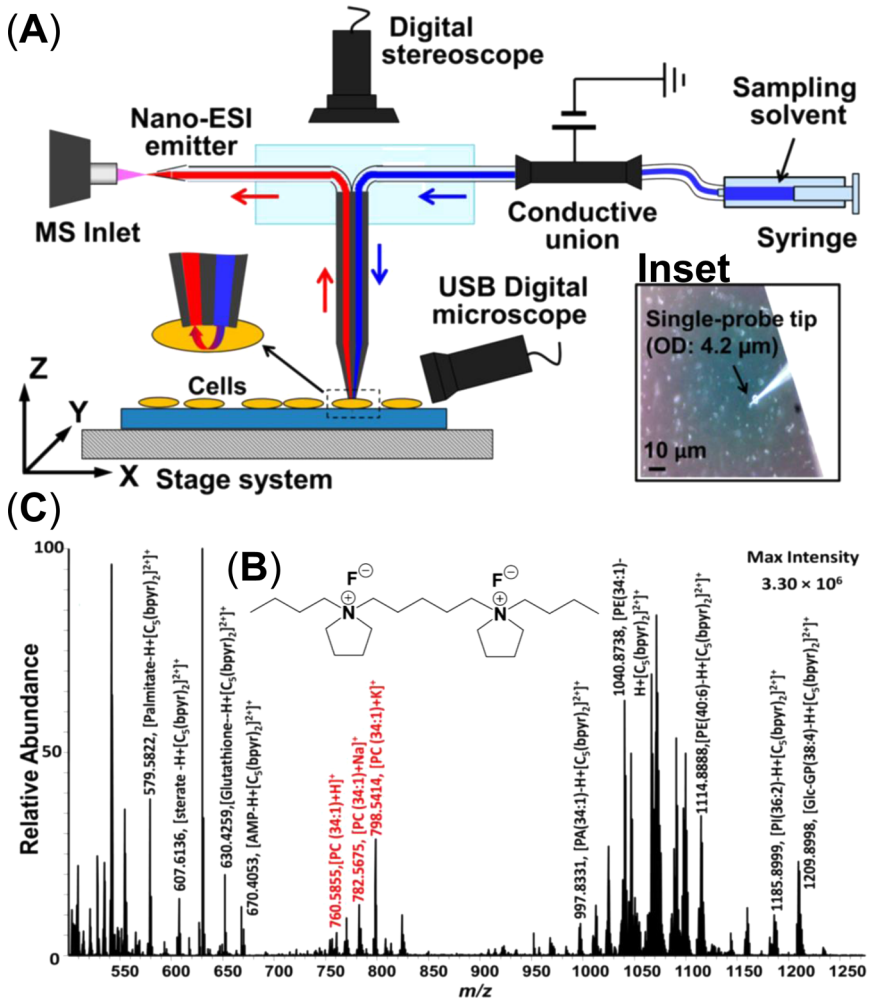

Figure 3. (A) Schematic of single cell mass spectrometry (SCMS) using a single-probe setup. The inset depicts the insertion of a single-probe tip into a cell. (B) Molecular structure of the dicationic compound $C_5(bpyr)_2F_2$ used to ionize negatively charged lipid species. (C) Mass spectrum of a HeLa cell in the positive ionization mode with tentative assignment based on a mass error <5 ppm. The signals labeled with black text are adducts of $[C_5(bpyr)_2]^{2+}$ and those in red text are ions also found in control positive ionization mode (without using $[C_5(bpyr)_2]^{2+}$). Reproduced from Pan, N.; Rao, W.; Standke, S. J.; Yang, Z. B. *Anal. Chem.* **2016**, *88*, 6812. Copyright 2016 American Chemical Society.

without applying heat to the inlet. Fenner and McEwen compared the softness of SAI with ESI using thermometer ions produced from benzylpyridinium salts and found SAI to be significantly softer than ESI under similar instrumental conditions.[29] In SAI, analyte in solution enters the heated inlet tube where charge separation occurs upon droplet formation without application of an electric field. The softness with SAI was interpreted to be related to the protection afforded by solvation, both in traversing the heated inlet and voltage elements in the intermediate pressure region of the inlet.[29]

Rapid evaporative ionization mass spectrometry (REIMS) was developed by Takats et al. as an imaging platform and high-throughput method.[30] In this REIMS approach, ionization of the generated aerosols occurs within the inlet to the mass spectrometer. Belog et al. used an endoscopic REIMS method for in vivo analysis of aerosols created during electrosurgical dissection in order to distinguish healthy gastrointestinal tissue from cancerous tissue.[31] A somewhat similar approach was used by Fatou et al. for real-time surface analysis of even human skin by applying infrared (IR) laser ablation.[32] However, unlike the current REIMS approach, the authors suggest ions are produced remotely and transferred into the mass spectrometer.

Paper spray ionization (PSI) is another method which is gaining attention. PSI uses paper cut into a wedge to aid ionization of compounds in solution that is placed on the paper and wicked to the "V"-tip where electrospray is induced by a high voltage. Wleklinski and co-workers in Cooks' group delved into the details of zero-volt paper spray ionization (zvPSI) and its mechanism.[33] The authors suggested that in zvPSI, pneumatic forces form droplets, which are initially broken up by aerodynamic forces in a statistical charge separation process and the ensuing charged droplets then undergo evaporation and Coulombic fission. The paper suggested several possible modes of ionization of the progeny droplets, including classic ESI models. zvPSI is capable of producing ions similar in charge state to voltage PSI (ESI) but without use of a voltage and with lower ionization efficiency. This work suggested that zvPSI is more sensitive to compounds with higher surface activity relative to those with lower surface activity. Motoyama and Kihara demonstrated the applicability of zvPSI to a wide variety of analytes.[34] The studies included compounds that varied in size and composition, including amino acids, dried peptides,

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lipids from skin imprints, and synthetic polymers in cosmetic lotion. These authors suggested that zvPSI has the same mechanism of ionization as SAI. Wei et al. used zvPSI to discriminate between bacterial species. While the method produced lower signal than voltage PSI, it also produced less background ions.[35]

Two microfluidic techniques on paper for PSI were explored by Bereman et al.[36] Photolithography was not ideal due to significant background noise caused by the photoresist chemicals. However, wax patterning on the paper substrate was quite successful. The wax formed a hydrophobic barrier which confined the sample/solvent to a particular area and thus had a concentrating effect. Yang and colleagues investigated the use of paper substrates modified with mesoporous graphene foams (MGF) for the analysis of drugs in saliva.[37] Since MGFs have high electrical conductivity, less voltage was required for ionization in the PSI experiments. The high surface area of the modified substrate facilitated better separation compared to unmodified chromatography paper, and the linear dynamic range was reported to increase 10×. 3D printing was employed by Duarte et al. to produce microfluidic devices for use with paper tips in PSI experiments.[38] Zhang et al. introduced a technique to minimize interactions between polar functional groups in analytes and cellulose paper substrates.[39] By coating the paper with ZrO_2 the PSI signal intensity was increased for therapeutic drugs in dried blood spots. Vega and coauthors probed ion suppression and recovery in PSI experiments of urine, whole blood, and plasma.[40] They also studied the effects of spray solvent and sample position (relative to the paper tip) on ionization efficiency. Reactive paper spray formed imine derivatives of aldehydes during the ionization process for subsequent mass spectrometric analysis in a study by Bag et al.[41] Modification to paper spray was also introduced by Ren et al.[42] Sensitivity and reproducibility were improved by adding a capillary emitter to the paper substrate. Direct biofluid analysis was reported by Damon et al. using hydrophobic PSI.[43] An interesting paperless paper spray method was introduced by Meher and Chen in which, with application of a voltage to a dielectric substrate, electrospray was induced to monitor fast reactions occurring in a droplet placed on the substrate.[44]

Surface acoustic wave nebulization (SAWN) was further developed during the last 2 years. Yen et al. added a polydimethylsiloxane (PDMS) microchannel to a SAWN wafer which eliminated the need for fused-silica ESI emitter tips and provided a continuous flow of analyte solution to the mass spectrometer.[45] In addition, Monkkonen, and co-workers took a sheet of polyimide, and screen printed electrodes onto it in order to fabricate a digital microfluidic chip. This was then interfaced with SAWN and used to study hydrogen/deuterium exchange in peptides.[46] Huang et al. of Goodlett's group also experimented with a dual interdigitated transducer (IDT) and compared signal intensity to data from a single IDT. The dual IDT produced a signal that was 100× stronger than that of the single IDT.[47] Analysis of lipids using the SAWN technique combined with a unique interpretation algorithm was also highlighted by Yoon and co-workers.[48]

Other relatively new approaches reported during this period include thermal bursting ionization (TBI), reported by Pei et al.[49] In TBI, unlike SAI in which solution droplets experience a pressure drop along with heat and surface contact, TBI has drops impinging a heated surface at atmospheric pressure near the inlet to the mass spectrometer. An ultrasonic vibrating blade was reported by Usmanov and co-workers to produce analyte ions from ionic compounds by dynamic frictions between microdrops and the vibrating blade.[50] An interesting approach for high-resolution surface sampling was reported by Pan et al. in which a miniature single probe surface extraction approach was used for surface sampling at high spatial resolution (Figure 3).[51]

■ ELECTROSPRAY-BASED AMBIENT IONIZATION

Desorption electrospray ionization (DESI) is still an evolving technique for the analysis of surfaces. The method involves electrospray droplets aided by nebulizing gas flow impinging a surface and collecting ions into the mass spectrometer inlet that are produced primarily from the secondary droplets leaving the surface. Penna et al. studied several aspects of the DESI surface and its preparation (e.g., surface wettability, sprayer potential, surface chemistries) and their impact on ion formation.[52] The results indicate that surface wettability plays a crucial role in DESI ion formation efficiency. Dong and co-workers investigated the formation of dicarboxylate dianions in DESI and ESI from dicarboxylic acids in alkaline conditions.[53] The group theorized that the surface in the DESI experiment trapped counterions during desorption, thus forming dianions. In ESI, counterion trapping was hypothesized to be due to an excess of hydroxyl ions. Lubin et al. introduced a novel way to derivatize metabolites for identification by DESI-MS.[54] By simply placing a drop of analyte solution on a glass plate (with Teflon spots to confine the liquids), letting it dry, and dropping derivatization reagent on top of the dried analyte. The dried drop was then ready for DESI-MS analysis. The authors successfully employed the use of several derivatization reagents and could even reuse spots for multiple, successive derivatization steps. Dulay et al. introduced a novel surface for DESI-MS and nanoDESI-MS for the on-surface, in situ digestion of proteins.[55] The Zare group used immobilized trypsin on an organosiloxane (T-OSX) polymer substrate and found that the more hydrophobic T-OSX yielded better sequence coverage. Droplet spray ionization from a glass slide was introduced by Jiang et al.[56] to monitor ethylene polymerization. Wu and Zare developed a laser desorption lamp ionization source for use with an ion trap (LDLI-ITMS).[57] Brown et al. developed a method for detecting fleeting electrochemical reaction intermediates, based on DESI technology.[58] Cheng and co-workers extended the utility of sampling liquids using DESI by replacing the fused silica capillary used to supply the liquid to the spray with a trap column in order to desalt and enrich the analyte. The same approach was used with an enzyme-containing capillary for fast digestion of proteins before DESI analysis.[59] The trap column simplified the analysis of low-level analytes in complex mixtures, while the latter modification hastened the identification of proteins. A novel electrochemistry/liquid sample (EC/LS) DESI-MS system was introduced by Looi et al.[60] A simple electrochemical thin-layer flow-through cell enabled online monitoring of electrochemical reactions, e.g., oxidation.

Lipid profiling of cultured cells was successfully acquired using filter paper as a DESI substrate by Srimany and coauthors.[61] Their study compared the efficacy of four substrates: glass, Teflon-coated glass, thin layer chromatography (TLC) plates, and Whatman filter paper. The filter paper promoted fast drying of the analyte solution, produced uniform distribution of sample on the spot, and yielded good signal intensity. Hemalatha et al. published on the utility of electrospun nylon-6 nanofiber mats as DESI substrates.[62]

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Many properties of nanofibers are "tunable" by modifying spinning parameters, which makes them quite versatile. In this study, examples included DESI-MS of discrete analytes, like periwinkle flower extract, and DESI-MS imaging of dyes and imprints. Elviri et al. also explored the use of novel substrates for DESI-MS.[63] In this study, 3D-printed polylactic acid (PLA) provided enhanced ionization vs PTFE. Various surface configurations were employed in order to accommodate different sample types. Abbassi et al. compared signal intensities of glycerophospholipids in DESI-MS and UPLC−ESI-MS.[64] Differences in relative abundances of the analyte ions appeared to be related to adduct formation and not the actual abundance of analytes present. Angolini et al. imaged metabolites on thin, dehydrated agar cultures using DESI-MSI and easy ambient sonic-spray ionization (EASI) MSI.[65] The dehydration step generated a reliable surface for the experiments. A publication by Pirro et al. used medical swabs as collection devices and means of ionization in a touch-spray ionization (TS) MS study of drugs of abuse.[66] DESI-MS and TS-MS were also successfully used to differentiate cancerous prostate tissue from normal tissue at surgical margins.[67] Meanwhile, Dong et al. studied the effect of tissue surface properties on DESI-MSI and showed that quantitation is not as straightforward as one might expect.[68] Tillner and coauthors explored sprayer geometry in DESI-MSI and discovered that changes in geometry can have a positive effect on reliability of the data.[69] Notably, the study demonstrated that positioning of the solvent capillary is critical.

A miniature capillary electrophoresis (CE) was interfaced with a custom-made nano-DESI and a miniature MS system by He and co-workers.[70] Cai et al. combined probe electrospray ionization (PESI), electrochemistry (EC), and MS to introduce EC-PESI-MS for the analysis of electrochemical reaction products.[71] Lu et al. combined electrochemistry with DESI-MS to gain understanding in electrochemical reaction mechanisms.[72] In addition, Cai et al. in Chen's group studied peptides containing disulfide bonds by combining electrochemistry with ultraperformance liquid chromatography (UPLC)−MS.[73] Hsu et al. presented label-free tissue imaging of proteins using nanoDESI-MSI.[74] According to the authors, the only sample preparation required was mounting the tissue on a sample stage. Lostun et al. utilized dicationic ion-pairing compounds for positive ion reactive DESI-MSI of lipids in biological tissues.[75] Kononikhin et al. reported on a direct spray-from-tissue method, which in some respects is similar to DESI, but with potential advantages for analysis of human brain tumors.[76]

Laser-based ionization methods continued to attract attention from researchers. Lee and co-workers published on laser desorption/ionization droplet delivery (LDIDD) MS, which was used for live-cell imaging.[77] There were four papers from Muddiman's group on IR matrix-assisted laser desorption electrospray ionization (MALDESI). In the first, a drug and its metabolites in liver tissue were imaged by Barry et al. using IR-MALDESI-MSI coupled to a Fourier transform ion cyclotron resonance (FTICR) MS.[78] The results were compared to UV-MALDI-MSI and found to be very similar. Nazari and coauthors demonstrated an application of their oversampling technique in IR-MALDESI-MSI analysis of cholesterol in cervical tissues.[79] Rosen et al. examined the influence of desorption conditions[80] and C-Trap ion accumulation time[81] on IR-MALDESI-MSI. Laser microdissection-liquid vortex capture (LMD-LVC) ESI/MS was highlighted by Cahill and co-workers in Van Berkel's group, reporting three different sampling modes.[82] The research, which included analysis of single cells of *Chlamydomonas reinhardtii*, presented the advantages and disadvantages of laser ablation spot sampling, laser ablation raster sampling, and laser "cut and drop" sampling. They demonstrated the utility of the "cut and drop" sampling by quantifying propranolol in thin tissues.[83] These authors also published a study comparing internal energy distributions of ions in ESI-MS versus LVC-ESI-MS (Figure 4).[84] Interestingly, the energy distributions of both techniques

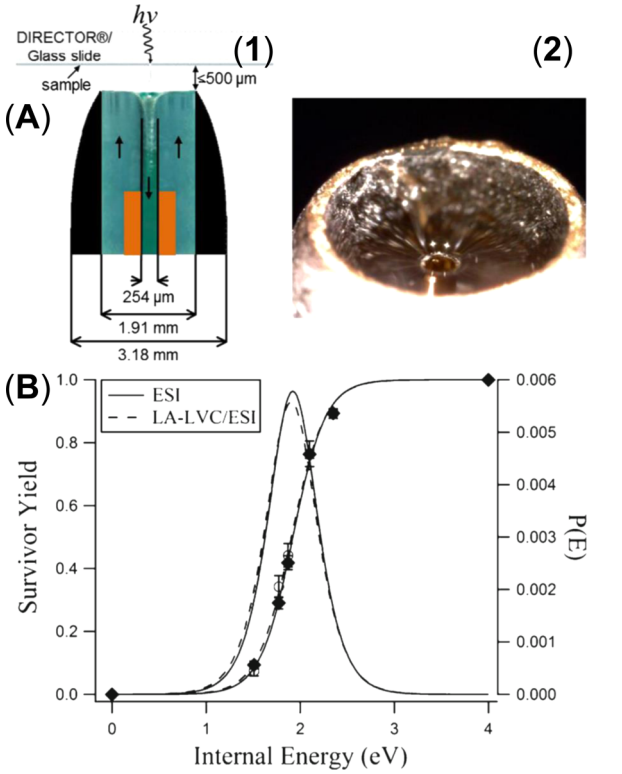

Figure 4. (A) Schematic of the experimental setup for laser ablation (LA) liquid vortex capture (LVC) ESI (1) and (2) photo of the sampling end of the LVC probe. (B) Survival yield plot of the Boltzmann and internal energy distributions of LA-LVC/ESI (dashed lines) and ESI (solid lines) using a glass slide sample substrate at 160 V declustering potential. Springer *Journal of the American Society for Mass Spectrometry*, Comparison of Internal Energy Distributions of Ions Created by Electrospray Ionization and Laser Ablation-Liquid Vortex Capture/Electrospray Ionization, *26*, **2015**, 1462, Cahill, J. F.; Kertesz, V.; Ovchinnikova, O. S.; Van Berkel, G. J., (original copyright notice as given in the publication in which the material was originally published). With permission of Springer.

were identical, indicating that the primary ionization is ESI and is not related to the laser. Cahill et al. also achieved submicrometer pixel size when using a slightly modified setup for imaging.[85] An interesting open port sampling interface (OPSI) was constructed by Van Berkel and colleagues.[86] With no sample preparation, the *self-cleaning* OPSI uses a continuous stream of liquid for direct sampling of analytes. This versatile interface can be combined with numerous types of sources and mass spectrometers.

A 3D printer was used to fabricate various ablation chambers with different geometries by Compton and co-workers in their study of remote laser ablation electrospray ionization (LAESI).[87] Tissue samples were ablated in a sampling chamber,

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then the ablated constituents flowed through a transfer tube to the ESI plume using nitrogen as a carrier gas. When combined with optical microscopy, the technique is a valuable tool for simultaneously examining morphological features and chemical composition of specific areas of biological tissues. Li et al. also in Vertes' group used LAESI in combination with IMS in order to distinguish between isobaric species, decrease ion interferences, and improve metabolite coverage in imaging experiments.[88] In other imaging studies, Stopka and colleagues utilized laser desorption ionization on a silicon nanopost array (NAPA) in order to eliminate the need for matrix.[89] Transmission geometry LAESI was employed by Jacobson et al. to obtain mass spectra with high spatial resolution from a small group of cells (Figure 5).[90] Donnarumma and Murray used transmission geometry mid-infrared laser ablation to transfer biological material to nanoflow LC-MS/MS for profiling of biological tissues.[91] Tata and coauthors successfully used MRI contrast agent as a disease marker in contrast agent (CA) MSI of breast cancer tissue.[92] Zou et al. introduced picosecond IR laser (PIR) LAESI, which capitalized on the advantage of a picosecond IR laser's ability to slice into biological tissue with minimal damage.[93] The team compared the technique's imaging capabilities to both LAESI-MSI and DESI-MSI. The PIR-LAESI results show promise for intraoperative applications. Shi et al. used low energy femtosecond IR laser ablation of flower petals affixed to a stainless steel substrate with postionization using nanoESI (Figure 6).[94]

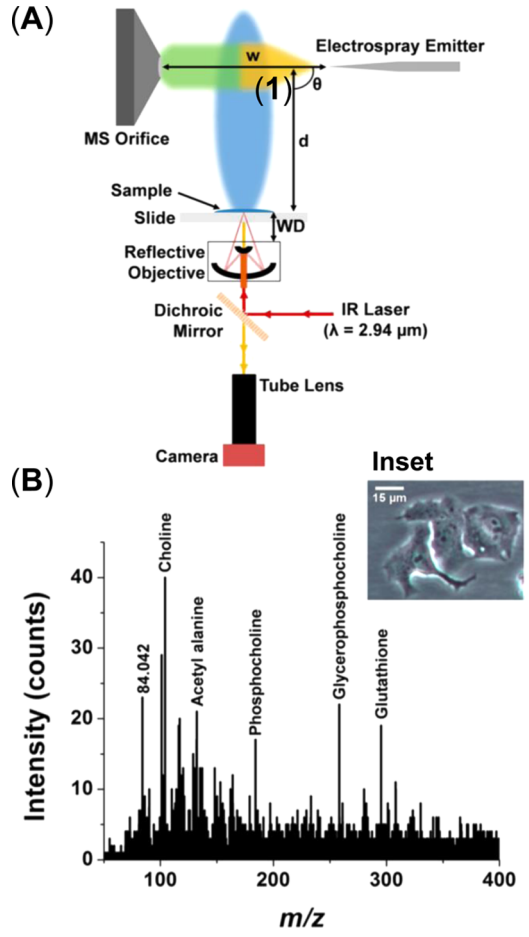

Figure 5. (A) Schematic of transmission geometry laser ablation ESI (LAESI) depicting the interception of the ablation plume with the electrospray plume. Parameters evaluated for MS signal included the angle between the axes of the two plumes (θ = 90°) and electrospray emitter (ESI) to sample distance (d = 19 mm). Other instrumental parameters adjusted include focusing of the dual use reflective objective, with a working distance (WD) of 7.8 mm, for ablation was achieved by adjusting for a sharp microscope image. For optimal signal intensity, the sample ablation occurred at half the distance (w) between the ESI emitter tip and the MS orifice. (B) Mass spectrum of five mammalian cells detected in the positive mode. Inset: optical image of five hepatocytes taken with the long distance microscope. Reproduced from Jacobson, R. S.; Thurston, R. L.; Shrestha, B.; Vertes, A. *Anal. Chem.* **2015**, *87*, 12130. Copyright 2015 American Chemical Society.

Ross et al. applied induction based fluidics (IBF) to inject charged nanodroplets directly into the inlet of a mass spectrometer for the analysis of nanomolar concentrations of oligonucleotides.[95] Forbes et al. acoustically actuated droplet ejection combined with extractive ESI for the rapid detection of inorganic compounds.[96] Interlayer spray ionization for analysis of small volumes of liquid (<2 μL) with no pretreatment was proposed by Chen and co-workers.[97] The method places the sample between two nonporous substrates and applies voltage to form a plume (with no additional solvent). Sensitivity compared to a porous substrate was improved for large molecules.

DISCHARGE-BASED AMBIENT IONIZATION

Methods which use a matrix, including solvents, are limited by the matrix relative to ionization of many low polarity compounds. Gas-phase ionization methods, while not amenable to nonvolatile compounds, fares well with a wide range of compounds which ionize poorly or not at all by, e.g., ESI and are generally easier to use and more robust. Atmospheric solids analysis probe (ASAP) is one such technique which uses atmospheric pressure chemical ionization (APCI) to ionize compounds vaporized from a probe, typically a melting point tube, using the heated nitrogen stream available with APCI or ESI commercial ionization sources. ASAP was applied to the analysis of drug related compounds in several publications. Eikel et al. used thin layer chromatography extraction with direct ESI analysis, ASAP-MS, and HPLC–MS to analyze cannabis related compounds.[98] The ASAP method required only rubbing the melting point tube over the cannabis material or over the index finger of a cannabis user. Amphetamine-type stimulants frequently used in illicit drugs were analyzed in whole urine samples by ASAP interfaced with tandem MS and multiple reaction monitoring by Crevelin et al.[99] The limit of detection directly from urine without cleanup is pg μL^{-1} suggesting the method's utility in clinical and forensic toxicology. Jagerdeo et al. demonstrated the use of ASAP in the analysis of forensic samples, specifically analyzing a rodenticide, black tar heroin, crack cocaine, and dyestuff.[100] In this vein, direct screening of tobacco use indicators in urine and saliva were analyzed using ASAP-MS by Carrizo and coworkers.[101] Nicotine and its metabolites were readily detected from heavy smokers. The skin irritant p-phenylenediamine was rapidly and directly analyzed in henna products used for temporary skin staining using the ASAP approach.[102] Determination of minute amounts of indigoid colorants were characterized in less than 1 min from ancient historic fabrics by Kramell et al. using ASAP-MS.[103]

The ASAP method was also used in the analysis of polymers, oils, and coal tar pitch. Fouquet et al. compared ASAP-MS with ESI-MS/MS and found the methods to be complementary for

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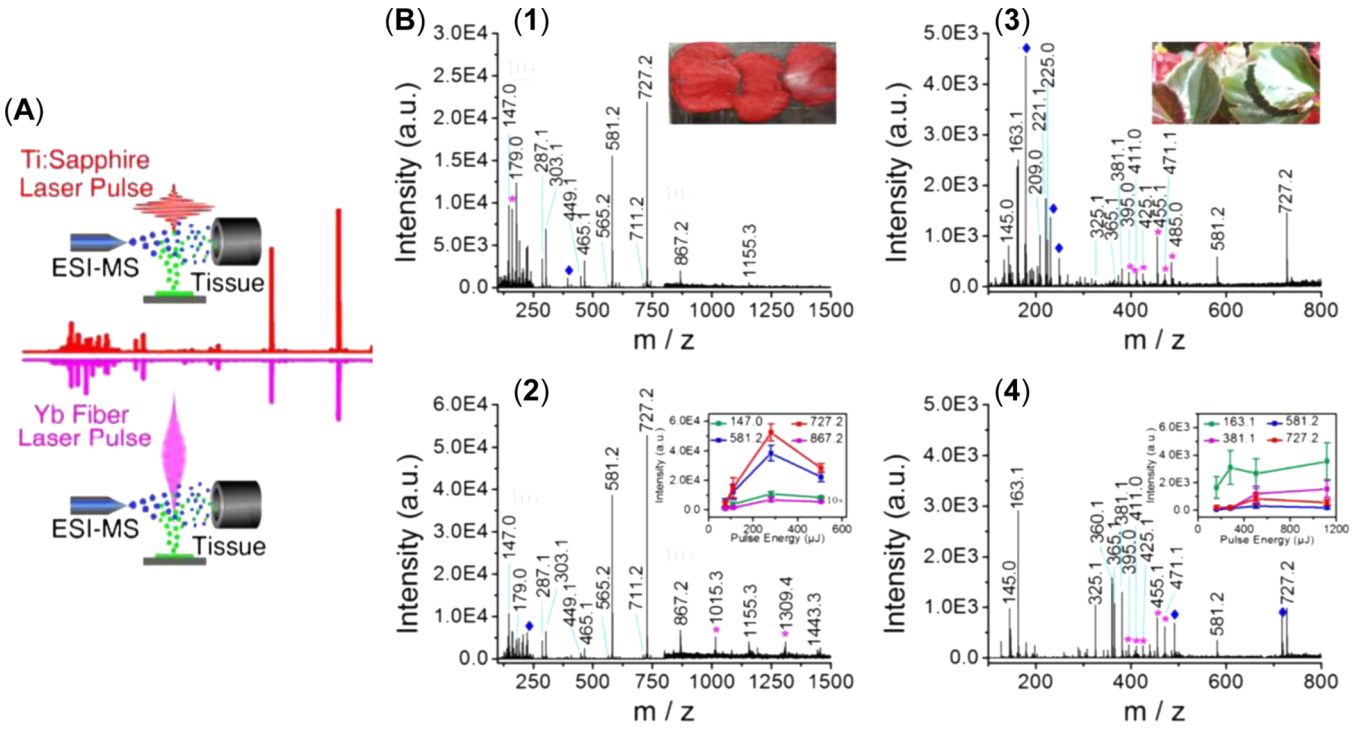

Figure 6. (A) Schematic representation of femtosecond laser electrospray mass spectrometry (F-LEMS). (B) Blank-subtracted mass spectra for a flower petal affixed on a stainless steel substrate: (1) F-LEMS with 46.5 μJ pulse energy and (2) Ti:sapphire-LEMS with 280 μJ pulse energy. Blank-subtracted mass spectra for a flower leaf affixed on a glass substrate: (3) F-LEMS with 46.5 μJ pulse energy and (4) Ti:sapphire-LEMS with 505 μJ pulse energy. Insets: (1) and (3) photos of flower petal and leaf being analyzed by LEMS. Inset: (2) intensity of representative ions (m/z 147.0, 581.2, 727.2, and 867.2) plotted as a function of pulse energy (75, 110, 280, and 500 μJ) for the flower petal using Ti:sapphire-LEMS. Inset: (4) intensity of representative ions (m/z 163.1, 381.1, 581.2, and 727.2) plotted as a function of pulse energy (160, 280, 500, and 1120 μJ) for the flower leaf using Ti:sapphire-LEMS. Signals labeled with ∗ are associated with solvent and unidentified plant features, respectively. Springer *Journal of the American Society for Mass Spectrometry*, Ambient Molecular Analysis of Biological Tissue Using Low-Energy, Femtosecond Laser Vaporization and Nanospray Postionization Mass Spectrometry, *27*, **2016**, 542, Shi, F. J.; Flanigan, P. M.; Archer, J. J.; Levis, R. J., (original copyright notice as given in the publication in which the material was originally published). With permission of Springer.

polydimethylsiloxanes with M_w between 18 000 and 110 000 due to the fragmentation produced during the ASAP thermal vaporization and ionization processes.[104] ASAP IMS-MS was evaluated as a method to characterize poly(ether ether ketone) polymers by Cossoul et al.[105] This solvent-free approach produced almost identical end group assignments and relative ion abundances as MALDI which, unlike ASAP, requires use of strong solvents such as sulfuric acid to first dissolve the polymer. A cyclic olefin copolymer grafted with aryl layers was characterized by Vieillard et al. using ASAP in combination with IMS-MS among other analytical methods.[106] Lebeau applied ASAP to characterize polyurethanes and additives.[107] Rapid characterization of heteroatomic molecules in a bio-oil produced from pyrolysis of rice husk was reported by Fan et al.[108] Petroleum components were characterized by Wu and co-workers using tandem MS with ASAP ionization.[109] ASAP was also used in combination with gas chromatography (GC)-MS for the analysis of carbon disulfide extractable portions from coal tar pitch. Xie et al. demonstrated that ASAP is especially effective for characterizing high molecular weight compounds.[110] Xiao et al. showed ASAP to be useful for rapid identification of pollens which have health implications for large parts of the world's population. The approach used involved the semiquantification of flavonoid fingerprints.[111] Thermal degradation of β-carotene was also studied by Xiao et al. using ASAP and IMS.[112] Determining degradation products in lithium ion batteries also used the ASAP method.[113] During this time period, Advion introduced inert (i) ASAP for the analysis of air-sensitive catalysts.[114] The iASAP approach was developed by Krossing's group at the Albert-Ludwigs-University of Freiburg.

Direct analysis in real time (DART) differs from ASAP in that the discharge producing the ionizing reagent gas is produced in a separate chamber and heated gas from the chamber vaporizes the sample, typically placed on the exterior of a melting point tube, with ionization by the reagent ions in the gas plasma. Cody and Dane added dopants to the argon gas stream in DART.[115] When using this setup, ionization mechanisms were reported to be similar to those in dopant-atmospheric pressure photoionization (APPI). Mass spectra were simplified and provided supplemental information to conventional DART methods. Schlieren photography was employed in order to view the flow of helium gas at the atmospheric pressure interface of a DART ion source by Curtis and colleagues.[116] Effects of various DART parameters and sample probe configurations on disturbances or disruptions of gas flow were studied. As a result, recommendations were made for optimizing efficiency of DART experiments. Häbe and Morlock were also interested in improving the efficacy of the DART ion source.[117] During surface scanning of TLC plates, they examined the effects of numerous different configurations. Ultimately, these authors achieved their goal by introducing several modifications to the DART source and sample gap. Lu et al. improved ionization efficiency of three analytes by

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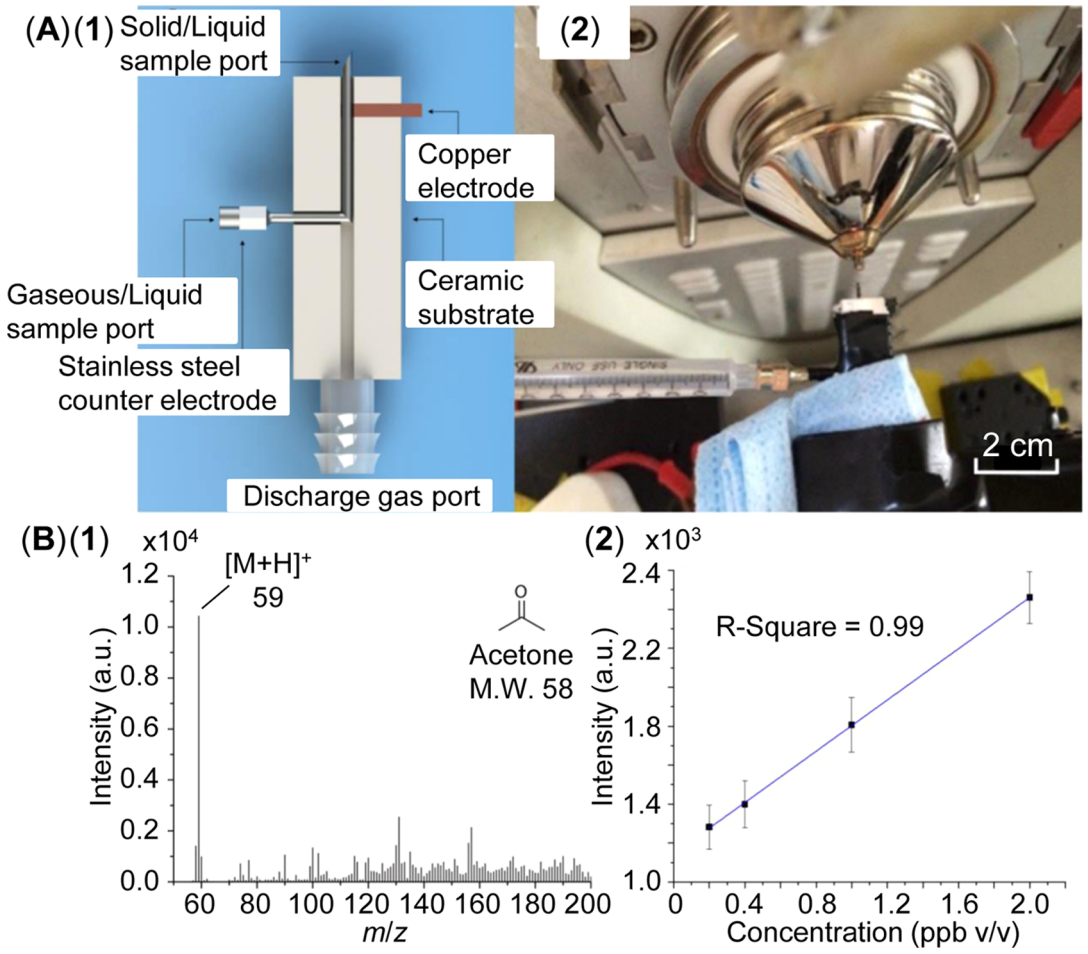

Figure 7. (A) (1) Cross-sectional view of the interior structure and (2) photograph of the microplasma probe desorption/ionization for use in MS. (B) (1) Mass spectra and (2) quantitative curve for gaseous acetone sample. Reproduced from Zhao, Z. J.; Wang, B.; Duan, Y. X. *Anal. Chem.* **2016**, *88*, 1667. Copyright 2016 American Chemical Society.

incorporating a continuous wave (CW) IR laser in their DART ion source.[118] Combining DART and laser desorption, CW-LA-DART-MS yielded significantly stronger signal-to-noise than using DART-MS alone. High-throughput DART was used by Lesiak et al. to detect adulteration of commercially available *Sceletium tortuosum*, a mind altering plant-based drug known as Kanna.[119] DART was also used for trace detection of the explosive erythritol tetranitrate in mixtures by Forbes and Sisco.[120] These authors also studied matrix effects related to the desorption process and compound volatility. Sisco and Forbes reported on the use of DART for the rapid detection of sugar alcohol precursors and the corresponding nitrate ester explosives.[121] Wu et al. combined solid-phase microextraction and DART with ultrahigh-resolution MS to rapidly determine 15 phthalate plasticizers in beverages.[122] Lobodin et al. used DART in combination with FTICR-MS for the analysis of complex mixtures of volatile organic compounds.[123] Newsome et al. studied the effects of humidity on DART and flowing atmospheric pressure afterglow (FAPA) ionization and saw differences in fragmentation and ion abundance.[124]

A variety of other discharge methods of ionization were also reported during this time period. A 3D printer produced a novel ion source with polymeric electrodes in which Baird and coauthors could manipulate ions and study their behavior.[125] Jjunji et al. interfaced a hand-held mass spectrometer with a desorption atmospheric pressure chemical ionization (DAPCI) source for rapid detection of nitroaromatic explosives[126] and polycyclic aromatic hydrocarbons.[127] Wang et al. used micro-fabricated glow discharge plasma (MFGDP) for direct screening for pesticide residues in foodstuff. An advantage of this method is its small size and operation at low temperature.[128] Microplasma probe desorption/ionization (MPPDI) was demonstrated by Zhao et al. for the study of biological samples (Figure 7).[129] This approach also uses a glow discharge for ionization. Shelley and colleagues studied reagent−ion interactions in a flowing atmospheric pressure afterglow (FAPA) ion source by examining the effects on ionization of discharge current, discharge gas flow rate, and spatial location within the afterglow.[130] The authors were able to "tune" the source to create protonated ions (proton-transfer mode) or radical cations of intact molecules (charge-transfer mode). This led to more efficient ionization as well as detection of analytes that are not amenable to protonation. Wolf and co-workers reported on studies relative to mechanistic aspects in dielectric barrier discharge ionization using active capillary plasma ionization and various reagent gases.[131] The dielectric discharge source was directly coupled to solid-phase microextraction by Mirabelli et al. and achieved subpg/g sensitivity.[132] The approach ionized analytes after thermal desorption from a SPME fiber.

The capabilities of the miniature mass spectrometer developed by Zhai and coauthors was extended to include

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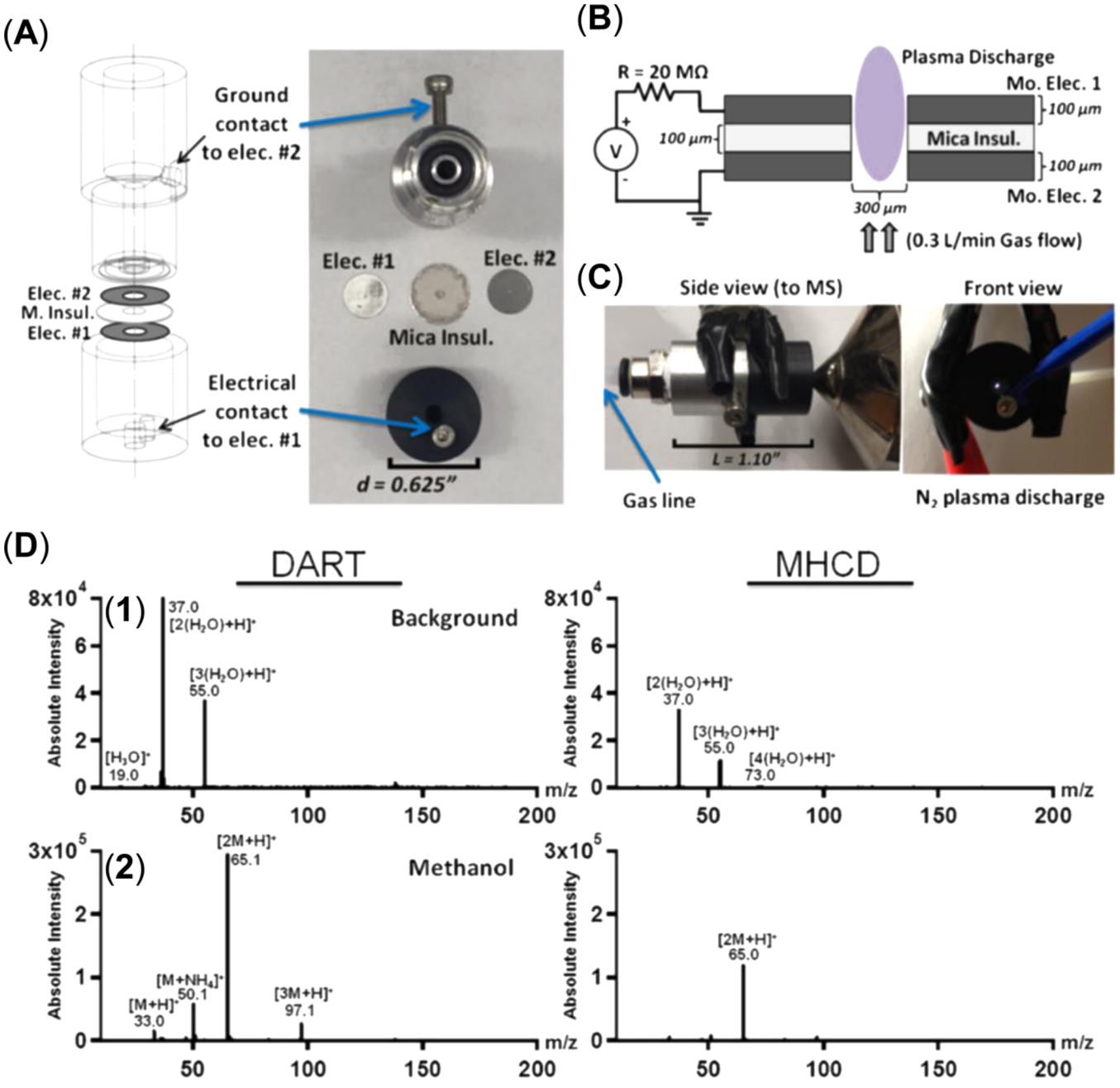

Figure 8. Schematic of and images of the metal−insulator−metal (MIM)-type microhollow cathode discharge (MHCD) microplasma ion source with (A) details of the components of the MHCD assembly; (B) a side- and front-view of the device during plasma discharge operation using 0.3 L min^{-1} high-purity nitrogen gas. (C) Mass spectra of select target analytes acquired using both DART (left column) and MHCD microplasma (right column) ion sources with nitrogen at 2.2 L min^{-1} and 0.5 L min^{-1}, respectively, with (1) background spectra and (2) methanol, as examples. Acquisition parameters were selected to prevent activation in the transfer ion optics:orifice lens 1 at 10 V, ring lens at 6 V, orifice lens 2 at 2 V, bias at 29 V, pusher bias voltage at −0.28 V. Springer *Journal of the American Society for Mass Spectrometry*, Microplasma Ionization of Volatile Organics for Improving Air/Water Monitoring Systems On-Board the International Space Station, *27*, **2016**, 1203, Bernier, M. C.; Alberici, R. M., Keelor, J. D.; Dwivedi, P.; Zambrzycki, S. C.; Wallace, W. T.; Gazda, D. B.; Limero, T. F.; Symonds, J. M.; Orlando, T. M.; Macatangay, A.; Fernandez, F. M. (original copyright notice as given in the publication in which the material was originally published). With permission of Springer.

volatile samples.[133] Addition of an in-vacuum plasma ionization source minimized ion transfer loss in the continuous atmospheric pressure interface. Another interesting coupling of techniques came from Famiglini et al.[134] These authors highlighted a direct interface of electron ionization (EI) with LC for direct flow injection-MS/MS of small molecules in alcoholic beverages. Benham et al. coupled laser-induced acoustic desorption (LIAD) with APPI and demonstrated its utility by analyzing a number of low-polarity organics.[135] Keelor et al. also published the development of a vacuum-assisted plasma ion (VaPI) source.[136] This source can be switched between transmission mode and laser ablation sampling mode in order to accommodate different sample types. Plasma-based ionization was also the focus of Zhou et al. in a paper that presented nanotip ambient ionization mass spectrometry (NAIMS).[137] This technique, in which plasma is created

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when high voltage is applied between a metal surface and a tungsten nanotip, can be structured to favor either sensitivity or resolution. Imaging experiments produced a 5 μm pixel size.

Parshintsev et al. presented a method for analyzing atmospheric aerosols without sample pretreatment.[138] Their desorption APPI protocol measured the correct particle number but detected different compounds when compared to the typical LC-MS aerosol method. Thus, it provides supplemental information on atmospheric aerosols. Spencer and co-workers used low-temperature plasma ionization MS for aerosol analysis.[139] Haapala et al. introduced solvent jet desorption capillary photoionization (DCPI), which is an inexpensive ambient technique that can ionize polar and nonpolar analytes with femtomole sensitivity.[140] The setup combines the advantages of APPI and SAI. Another new approach for ionization came from Wu and coauthors, who developed carbon fiber ionization (CFI).[141] This technique works with analytes capable of being steam-distilled with subsequent ionization by corona discharge. Its compatibility with supercritical fluid chromatography (SFC) was demonstrated.

Small molecules were captured from laser desorption and transferred to a solid phase microextraction (SPME) fiber for subsequent GC-MS analysis by Seneviratne et al.[142] Their technique was reported to simplify ambient ionization of complex mixtures of small molecules. Bernier et al. developed an instrument (Figure 8) that was capable of analyzing both air and water samples to improve air quality monitoring onboard the International Space Station.[143] To accomplish this, the group combined an electrothermal vaporization sample introduction unit with GC differential mobility spectrometry.

TRADITIONAL IONIZATION METHODS FOR MS

Field desorption (FD), plasma desorption, fast atom bombardment (FAB), laser desorption, and thermospray ionization made inroads into converting nonvolatile compounds into the gas phase as ions. However, it was the inventions of ESI and MALDI for use with MS in the 1980s that led to exceptional advances in science because of their ability to characterize minute quantities of nonvolatile compounds even in complex mixtures without any fragmentation.

Technologies Using a Laser for Ionization. An excellent series of papers on "Next Generation Laser-Based Biological Mass Spectrometry edited by Cramer and Rainer has recently been published.[144] This volume is recommended for more detailed coverage of specific topics. In addition, several research groups published papers related to understanding the mechanism of MALDI and laser desorption/ionization (LDI). Zeegers et al. monitored LDI signal intensities of fullerene anions and cations as a function of target plate material and laser fluence.[145] Targets with high electrical resistivity yielded significantly higher anion signal intensities. This provided insight into LDI ionization mechanisms, which was extended to MALDI mechanisms. Silina et al. used Pd nanostructured surfaces to study the effect of melting point, availability of reagent ions, and surface morphology on ionization in LDI.[146] These authors demonstrated that the most efficient ionization was obtained from a surface with lower melting point, accessible K^+ ion, and rough texture. Moskovets proposed an explanation for the ionization of residual peptides in the inlet of the mass spectrometer after atmospheric pressure MALDI experiments.[147] A linear ion trap with a three-stage high pressure ion funnel was used to detect the peptides without laser irradiation. The ions appeared with decreased background pressure in the first funnel, which may indicate matrix-assisted hypersonic-velocity impact ionization of the peptides. Lou et al. described a sample preparation method for MALDI that ameliorated ion suppression.[148] Analyte solutions were dropped on top of a dry target plate that had been preloaded with α-cyano-4-hydroxycinnamic acid (CHCA) matrix. Solvents used for the analytes do not dissolve the CHCA. Thus, analytes were located on the matrix surface, and their incorporation in matrix crystals was minimized. Using mixtures of peptides, synthetic polymers and lipids, the authors showed the detection of analyte ions that had been suppressed with the traditional dry-drop method. Mass discrimination has always been a serious problem in MALDI-TOF MS. Engler et al. devised a free module for COCONUT software to overcome mass discrimination when analyzing polymers.[149] The authors illustrate the improvements of applying the software to spectra of three different styrene/isoprene copolymers, as well as their corresponding homopolymers. Lu et al. measured the ion-to-neutral ratios of four common MALDI matrixes at 355 nm using a TOF-MS.[150] These authors noted that the ion-to-neutral ratios are similar to those predicted by the thermal proton transfer model.

The mechanism by which MALDI produces gas-phase ions received some attention during this period. Kirmess et al. investigated the mechanism of MALDI using a comparison of results from dihydroxybenzoic acid (DHB) isomers. The results agreed with the coupled chemical and physical dynamics (CPCD) model but not a thermal equilibrium model.[151] Knochenmuss used experimental measurements to constrain the CPCD model and obtained better agreement of yield vs fluence for 2,5-DHB compared to the polar fluid model.[152] On the other hand, Bae et al. reported that the abundance of each ion appearing in a mass spectrum is fixed at a fixed effective temperature. The authors suggest that this is best explained by a thermal process governing primary ion formation.[153] Further, Lee et al. determined that earlier theoretical results relative to ion-to-neutral ratios in MALDI were incorrect, especially for analyte ions (Figure 9).[154] According to these authors, the new results best fit a thermal proton transfer model. A series of articles commenting on a 2014 article on "Energetics and Kinetics of Thermal Ionization Models of MALDI" by Knochenmuss,[155] which criticized an earlier publication by Ni's group[156] demonstrating the contentious nature of ionization models in MALDI.[157−160]

Quite a few publications have proposed new MALDI matrixes over the past 2 years. Wang et al. introduced (E)-propyl alpha-cyano-4-hydroxyl cinnamylate (CHCA-C3) as a highly effective matrix for protein ionization, even in the presence of salts and in complex mixtures.[161] These authors ascribed the success of the novel matrix vs traditional matrixes to better ablation capability and increased hydrophobicity. Similarly, Fukuyama et al. also studied the ionization of hydrophobic analytes with novel matrixes.[162] His group discovered that 1-(2,4,6-trihydroxyphenyl)octan-1-one (alkylated trihydroxyacetophenone (ATHAP)) is an excellent matrix for the analysis of hydrophobic membrane proteins containing transmembrane domains. Five coumarins were used as MALDI matrixes and compared to traditional matrixes for the ionization of several hydrophobic analytes with low ionization efficiency by Wang and colleagues.[163] One coumarin in particular, 6,7-dihydroxycoumarin-3-carboxylic acid (DCA), was found to be notably effective. The sensitivity of the detection of

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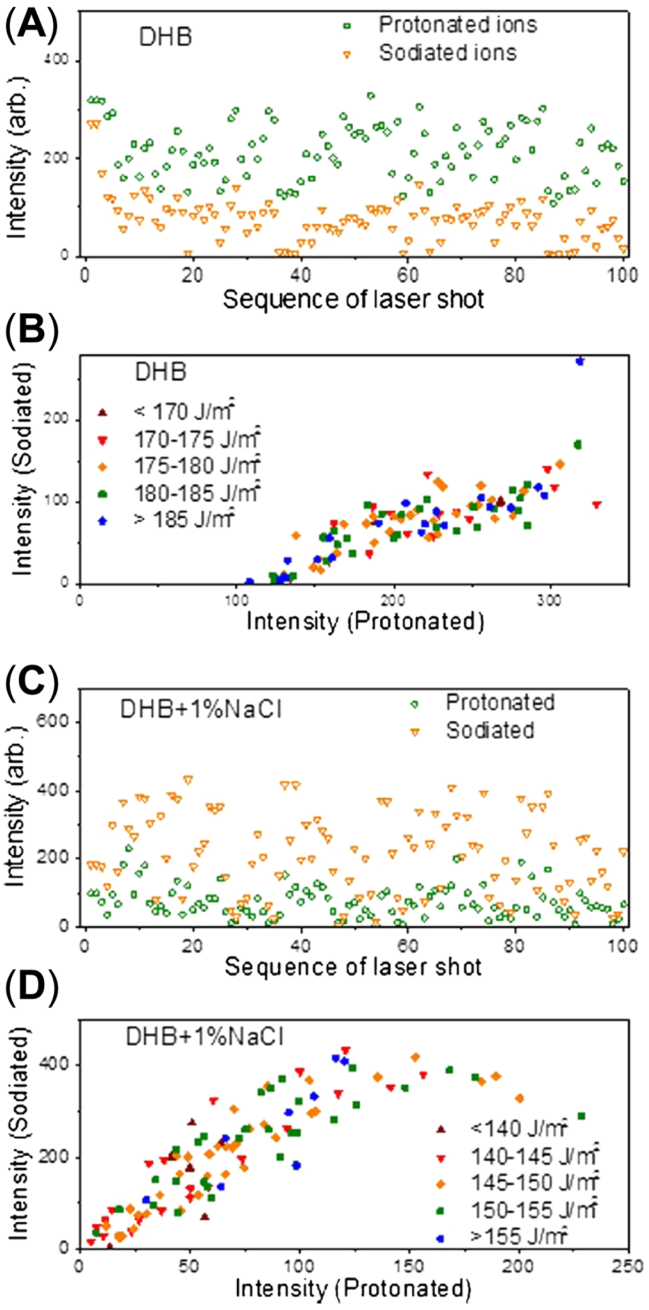

Figure 9. Plots in parts A and C: function of the sequence of laser shots from the same spot of the sample relative to intensity of sodiated and protonated ions acquired by matrix-assisted laser desorption/ionization (MALDI) MS. Both sodiated and protonated ions show shot-to-shot ion intensity fluctuations (~15%). Plots in parts B and D are reblotted and divided into five groups with each group representing a small region of laser energy. Data from the different laser energy regions in parts B and D overlap suggesting that the increase in the sodiated and protonated ion intensities is not prompted by the increase (fluctuation) in laser energy. The observed correlation between the sodiated and protonated ions suggests that these ions are generated from a related ionization mechanism. Springer *Journal of the American Society for Mass Spectrometry*, Formation of Metal-Related Ions in Matrix-Assisted Laser Desorption Ionization, *27*, **2016**, 1491, Lee, C.; Lu, I.-C.; Hsu, H. C.; Lin, H.-Y.; Liang, S.-P.; Lee, Y.-T.; Ni, C.-K., (original copyright notice as given in the publication in which the material was originally published). With permission of Springer.

oligosaccharides was significantly improved by using hydrazinonicotinic acid (HYNIC) as a MALDI matrix in an investigation by Jiao and co-workers.[164] Zhao et al. discovered that humic acids make effective matrixes by ionizing rhodamine B successfully with almost no interfering low mass ions.[165] Work by Chen and colleagues demonstrated that a binary MALDI matrix made from carbon dots with 9-aminoacridine (9AA) ionized a wide variety of small molecules with excellent sensitivity and reproducibility. The binary matrix showed a marked improvement in ionization efficiency compared to 9AA alone.[166] Bibi and Ju studied the use of quantum dots (QD) as MALDI matrixes for qualitative and quantitative carbohydrate analysis.[167] The QD materials enhanced sensitivity and reduced background interference. Zhen et al. investigated the use of various surface capping agents on QDs for proteomics.[168] These authors found that CdTe QD surfaces yielded strong LDI signals and enhanced protein digestion. Bernier et al. found that inorganic metal oxides, namely, tungsten oxide and rhenium oxide microparticles, ionized small molecules (e.g., cocaine, glucose) more efficiently and with less background/matrix interference versus CHCA.[169] *N*,*N*′-bis(4-hydroxylsalicylidene)-*p*-phenylenediamine (BSPD-OH) and other aggregation-induced emission (AIE) compounds were employed as new MALDI matrixes for small molecules (e.g., amino acids, fluoroquinolones) by Yao and co-workers.[170] Gabriel et al. investigated several matrix−cation combinations for the ionization of polystyrenes.[171] The group successfully ionized 1.1 MDa polystyrene using a combination of 2-[(2E)-3-(4-*tert*-butylphenyl)-2-methylprop-2-enylidene]malononitrile (DCTB) matrix with CsCl cationization reagent. Effective deprotonation of weakly acidic, difficult-to-ionize compounds was performed using a superbasic proton sponge, 1,8-bis(trispyrrolidinophosphazenyl) naphthalene (TPPN), as a MALDI matrix in negative ion mode by Calvano and colleagues.[172] Examples of analytes in the study include cholesterol, sterol, steroids, fatty alcohols, and saccharides. Fukuyama et al. reported using 3-hydroxy-4-nitrobenzoic acid (3H4NBA) as an oxidizing matrix for in-source decay of peptides.[173] The matrix yielded more complete sequence coverage and less matrix interference at low mass-to-charge (m/z), compared to conventional matrixes. Interestingly, Calvano et al. simultaneously digested proteins and extracted lipids on a MALDI target that was precoated with conductive graphite paint.[174] On-plate protein digestion took place in just 15 min, compared to hours for traditional digestion, and yielded comparable results. Even hydrophilic phosphorylated peptides could be detected without further treatment. Lipids were readily extracted on-plate and detected. The presence of colloidal graphite appeared to enhance the proteolysis and allowed for desalting by simple target washing. The ability to simultaneously prepare and detect protein digests and lipids on a MALDI plate with this simple protocol can be quite useful, as it integrates proteomics and lipidomics and can work with as little as 1 μL of analyte solution.

Modification and replacement of the MALDI target plate surface were the focus of several publications. Nanoparticles are of particular interest, due to their large surface area and minimal interference at low m/z. Three publications discussed the use of gold nanoparticles (AuNPs) as matrixes. Sekula et al. coated a target plate with AuNPs that were enriched with sodium for the ionization of small molecules without interference at low mass.[175] Marsico and coauthors also used AuNPs as alternative matrixes for small molecule analysis.[176] These authors used

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inkjet-printing to deposit the AuNPs at various densities onto the target plate and discovered that the greatest sensitivity is achieved when AuNP clusters are present. Chau and coauthors took AuNP coating to the next level by coating KBr pellets that contained over-the-counter (OTC) drugs and Chinese herbal medicine granules.[177] The authors then could perform FTIR and MS on the same samples. The approach detected minor components of the samples that were not observed in the FT-IR spectra. The group cleverly exploited AuNPs' transparency in the IR range but strong absorbance in the UV in order to accomplish this result. A novel surface for small molecule analysis was made of ultrathin graphitic carbon nitride (g-C3N4) nanosheets by Lin et al.[178] In negative ion mode, signal intensity and background interference were improved, compared to graphene and traditional MALDI matrixes.

Nanoporous carbon (NPC) matrixes derived from metal−organic frameworks (MOFs) were the focus of a SALDI-MS study by Shih et al.[179] The new preparation protocol yielded NPCs that exhibited superior performance over previous NPC matrixes. Remarkably, Huang and coauthors used ordered mesoporous carbon (OMC) as a surface-enhanced laser desorption/ionization time-of-flight) (SELDI-TOF) MS probe in order to screen a single drop of whole blood for toxins.[180] Sensitivity at parts per trillion levels and good reproducibility were achieved. Other successful tests of the novel SELDI probe involved human urine and environmental water. OMC was found to be an effective MALDI matrix as well. Juang et al. found that microwave irradiation of tea leaves with TiO_2 and graphene flakes enhanced sensitivity of detection for catechins in surface-assisted laser desorption/ionization (SALDI) MS, compared to TiO_2 alone.[181] These authors believe the graphene improves LDI efficiency, while TiO_2 acts as a "probe" to help enrich the tea leaves during the microwave step. Hong et al. developed a layered substrate for SALDI-MS analysis of carboxyl-containing small molecules.[182] These authors used layer-by-layer (LBL) electrostatic self-assembly to make hybrid nanoporous structures of silver nanoparticles (AgNPs) and reduced graphene oxide (rGO). This hybrid substrate inhibited background interference caused by cluster formation of Ag^+ and carbon. Arakawa and colleagues up the ante by sputtering a platinum film onto the surface of a leaf that had been treated with insecticide.[183] The insecticides were ionized using Pt-SALDI, while traditional MALDI-MS was not successful. Pt-SALDI-MSI showed distribution and movement of the insecticides on and within the leaf.

Three papers in the literature investigated the use of inexpensive, disposable MALDI surfaces. Bondarenko and colleagues used small pieces of aluminum foil to grow melanoma cells and subsequently attached the foil to a MALDI plate for whole cell analysis.[184] Using the Al foil substrate eliminated contamination of the cells, and the small size allowed less growth medium and fewer cells, compared to on-plate growth. As an alternative to colloidal silver nanoparticles for ionization, Schnapp and co-workers proposed the use of silver foils that have been made porous by etching with nitric acid.[185] The technique worked well for analyzing long-chain hydrocarbons and other difficult-to-ionize lipids. Bugovsky et al. designed a disposable MALDI plate by taking polypropylene with carbon black and sputtering a nanoscale layer of stainless steel (SS) onto it.[186] The carbon black was used for its conductivity, and sputtering of the SS formed a smooth surface. The novel target performed as well, if not better than, a traditional MALDI target plate. Two research groups published novel techniques of forming more homogeneous spots on MALDI target plates by modifying the droplet drying process. Kudina et al. used ac-electrowetting to excite fluids as they evaporated.[187] This led to a considerable reduction in spot variations and significant improvement of signal intensity. The process was coined "e-MALDI." Lai and colleagues, however, employed thermal means of decreasing MALDI spot heterogeneity.[188] Marangoni flows were created by changing the temperature of the drying droplets, thereby producing thermal gradients. An increase in Marangoni velocities caused a decrease in heterogeneity of the spot. A 65−80% spot heterogeneity decrease was observed when the MALDI substrate was chilled to 5 °C while the surrounding environment was kept at ambient conditions. Warschat et al. used an IR laser to excite the OH stretch vibration band at atmospheric pressure to obtain mass spectra from levitated droplets. While the process would appear to be atmospheric pressure MALDI, the mechanism of ion formation is likely similar to ESI.[189]

API Ionization. The number of publications using ESI and APCI is beyond the scope of this review; therefore, we are especially forced to select only papers that we deem to have advanced the ionization technology. Pure applications of ESI are not considered. Ji et al. used a ballpoint pen to make a simple ESI probe.[190] These authors reported that "BP-ESI" achieved higher ionization efficiency than traditional ESI, presumably because the ball on the tip has a larger surface area than a sharp end. In addition, the ball could be scraped on the surface of an analyte for analysis of solids by ESI. Inkjet printing technology was used by Lin and colleagues to drop suspensions of single cells onto an ESI probe for lipids profiling.[191] The single-probe, a miniaturized sampling and ionization device, was used by Rao et al. and Pan et al. for MSI.[51,192] The probe tip uses surface microextraction to sample intracellular components for real-time MS as reported. Rao et al. were also involved in the analysis of negative ions in positive ion mode via the use of dicationic reagents with the single-probe.[193] Takaishi et al. reported on nanoESI in vacuum using silica tip emitter at a flow rate of 22 nL min^{-1}. No external heating was required for this configuration.[194] Li and co-workers demonstrated that relay ESI (rESI), which employs charge pulses, can be used for high-throughput screening of polar and nonpolar analytes.[195]

CE was combined with ESI and a high-resolution mass spectrometer (HRMS) by Banek and co-workers in order to apply single-cell proteomics to study 16-cell frog embryos.[196] This method has the potential to enhance our knowledge of the processes involved in embryonic development. García-Fonseca and Rubio addressed the nuisance of matrix affects in LC-MS.[197] Their study of toxins in cereal used an oleic acid-based supramolecular solvent with restricted access properties (SUPRAS-RAM). By using the SUPRAS-RAM, they were able to extract the analytes of interest while excluding interfering macromolecules.

Ionization of analytes in nonfriendly ESI solvents was explored by Jiang and Lucy.[198] They found that the use of a makeup solvent worked very well, and using continuous flow extractive DESI (CF-EDESI) was also successful. Guo et al. combined the advantages of ESI and IMS with energy resolved (gradient) tandem MS (gMS^2) for the analysis of metallosupramolecular polymers.[199] The information-rich data set provided thorough understanding of the polymer.

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Consta et al. reported on advances in theoretical and molecular simulation studies of ion chemistry in droplets (see Figure 10).[200] Constas' work provides insights into the mechanism of disintegration of charged nanodroplets.[201] McAllister and co-workers reported on molecular dynamics simulation of the release of native-like protein structures from gaseous charged droplets.[202] Metwally et al. followed up with simulations of salt induced signal suppression of proteins from droplets, concluding that loss of charge through emission of metal cations leads to the suppression effect. The Konerman group also used molecular dynamics simulations to unravel the mechanism of supercharging in ESI.[203,204] Douglass and Venter assessed the role of reagent gas-phase basicity in supercharging during ESI of proteins.[205] Their experiments included negative and positive ion modes, as they sought a model to explain the supercharging phenomenon. Interestingly, adding dimethyl sulfoxide (DMSO), a supercharging reagent, to the electrospray solvent was reported to enhance data quality, improve precision and the number of proteins identified in top 3 label-free proteomics quantitation.[206] The increase in sensitivity is reminiscent of the addition of 3-nitrobenzonitrile,[207] a weak supercharging reagent, to solvents in sonic spray ionization.[28]

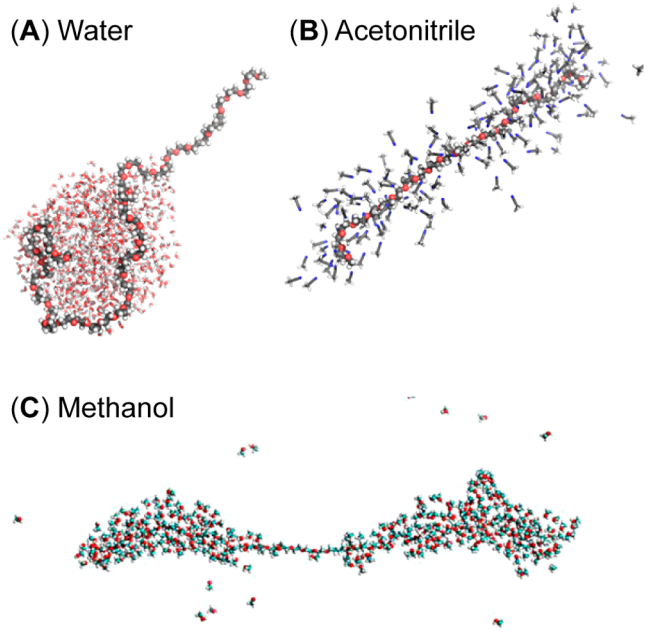

Figure 10. Simulated snapshots of solvation of a charged PEG chain in a droplet depending on the solvent used to perform ESI. Reprinted from *Int. J. Mass Spectrom.*, Vol. 377, Consta, S.; In Oh, M.; Soltani, S. Advances in theoretical and molecular simulation studies of the ion chemistry in droplets, pp. 557−567 (ref 200), Copyright 2015, with permission from Elsevier).

Cheng et al. combined ESI and APCI sources using a concentric geometry, which ensured that ionization of polar and nonpolar analytes occurred simultaneously in both sources.[208] Other modifications of the APCI source include work by Shiea's group modifying a commercial APCI source by installing a flame in place of the corona discharge needle.[209] This new flame-induced APCI (FAPCI) MS technique uses the charged species present in flames to ionize analytes via ion−molecule reactions. The group also doped the flame with alkali chloride solution to form ions with metal adducts.[210] High ion transfer efficiency was attained with the fabrication of a pulsed pinhole (PP) atmospheric pressure interface by Wei et al.[211] The interface worked well with nano-ESI and APCI sources on an ion trap instrument. Zhou and Ouyang studied the trajectory of ions traveling from an atmospheric pressure ion source into a mass spectrometer using simulations and experimentation.[212,213] An APCI alternating current corona discharge ion source was used by Usmanov et al. for explosives detection.[214] Usmanov and Hiraoka also reported on the use of a soleniod pulsed valve for reducing the gas load on the mass analyzer using atmospheric pressure ionization methods.[215] Winter and co-workers characterized a direct sample analysis (DSA) source that is a modified APCI.[216] Wachsmuth et al. redesigned an APCI source for coupling to gas chromatography and achieved a 4-fold decrease in detection limits and narrower elution peaks relative to earlier versions.[217] This improvement led to more than a doubling of peaks above a S/N of 20 extracted from metabolite fingerprints of pancreatic cancer cell supernatants.

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Notes

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research and teaching and was named one of the top 100 Analytical Scientists in 2015 and 50 Women Analytical Scientists in 2016. Dr. Trimpin holds several patents and authored over 80 peer reviewed publications, reviews, book chapters, and a book.

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