13 Ambient Mass Spectrometry

Learning Objectives

- Ion formation under ambient conditions
- Interfaces for ambient mass spectrometry
- Screening techniques for rapid quality control and safety applications
- Real time examination of samples during physical manipulation

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All methods for the generation of ions for mass spectrometry described up to this point require the analyte for ionization to be presented either directly under high vacuum (EI, CI, FI, FD) or contained in a sort of solution from which ions are to be extracted into or generated in the gas phase (FAB, LDI, MALDI). Even the atmospheric pressure ionization techniques employ processes that create ions from dilute (solid) solutions of the sample (ESI, APCI, APPI, AP-MALDI). This chapter deals with the manifold methods and interfaces which are allowing to overcome these limitations, and which have developed at a breathtaking pace within the short time since the publication of the first edition of this book.

Desorption electrospray ionization (DESI) [1] was introduced at the end of 2004, and *direct analysis in real time* (DART) [2] soon after in 2005. The apparent potential of both DESI and DART in high-throughput applications soon led to the development of some "derivatives" with the intention to broaden the field of applications or to adapt the underlying methodology to specific analytical needs. Now, the repertoire of methods includes variations of the DESI theme such as *desorption sonic spray ionization* (DeSSI) [3], later renamed *easy sonic spray ionization* (EASI) [4] or *extractive electrospray ionization* (EESI) [5,6]. Then, there are the DESI analogs of APCI and APPI, i.e., *desorption atmospheric-pressure chemical ionization* (DAPCI) [7,8] and *desorption atmospheric pressure photoionization* (DAPPI) [9].

All these methods have one important characteristic in common: they direct a stream of ionizing or at least ion-desorbing fluid medium onto a sample surface from which analyte ions are withdrawn and transported through air into the mass analyzer via a standard API interface. The beauty of this approach lies in the fact that a sample needs just to be exposed to the ionizing medium under ambient conditions. In other words, DESI, DART and those numerous related methods enable the detection of surface materials like waxes, alkaloids, flavors, or pesticides from plants as well as explosives, pharmaceuticals, or drugs of abuse from luggage or banknotes. These and many more analytical applications are readily accessible by

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plainly exposing the corresponding items to the ionization region of the interface – even without harm to living organisms [10]. This reduced need for sample pre-treatment is key to the success of *ambient MS*. In ambient MS, samples are accessible to observation and may even be subjected to some kind of processing, either mechanical manipulations or chemical treatments, while mass spectra are continuously being measured. Recently, a fieldable ion trap mass spectrometer for use with commercial DESI and DART ion sources has been constructed [11].

Note: Although the features of DESI and DART are in many ways superior and "revolutionary", one should be aware of intrinsic limitations. The detection of a compound largely depends on the matrix, e.g., whether it is *on* or eventually *in* skin, fruit, bark, stone etc. This also results in a lack of quantification abilities. However, also no other single ionization method, especially when used under just one set of conditions, can deliver ions of all constituents of a complex sample. Nonetheless, DESI, DART and related methods can deliver a wealth of chemical information with unprecedented ease.

13.1 Desorption Electrospray Ionization

The novel feature of *desorption electrospray ionization* (DESI) is that it allows ambient MS without sample preparation or sample pre-treatment. Furthermore, "ambient" means here not only the mere operation at atmospheric pressure, e.g., as is the case with AP-MALDI, but the operation in a freely accessible open space in front of the atmospheric pressure interface [12]. DESI is applicable to solids, liquid samples, frozen solutions, and to loosely surface-bound species like adsorbed gases. It can detect low-molecular-weight organic compounds as well as comparatively large biomolecules. The material presented to DESI may be a single compound suitably prepared on a sample target analogous to LDI or it can be a complex biological material like tissue, blood, whole leaves, or fruit [13].

Note: Although it appears that the results of DESI analyses are almost instantaneously available, DESI spectra tend to require more thorough examination than standard ESI spectra in order to draw the right analytical conclusions.

13.1.1 Experimental Setup for DESI

In a standard ESI experiment the spray capillary is set to high voltage in respect to a counter electrode that is essentially represented by the atmospheric pressure entrance of the interface. Sample ions are already contained in the solution that is supplied to the sprayer (Chap. 12). For desorption electrospray, only a solvent or solvent mixture is sprayed under strong pneumatic assistance onto a surface at an impact angle α. Driven by the high-velocity gas stream, the highly charged microdroplets receive sufficient kinetic energy to be forced onto the sample surface

even while an electrostatic charge is constituting there. The resulting interaction may dissolve and take up analyte ions. Local electrostatic charging and the reflected gas stream may now act in concert and transport analyte ions away from the surface at an angle β (Fig. 13.1). A nearby sampling orifice may then inhale a portion of the mist in the same way as it normally would do when the sample is already admixed to the solvent system. To bridge the gap between the sampling area and the entrance into the interface, a transfer line or extension tube is mounted in front of the orifice. This tube, e.g., 3 mm o.d. stainless steel, simplifies handling and particularly accessibility of the sample and also improves desolvation of the ions, probably due to different droplet sizes as compared to standard ESI conditions [1,12]. DESI practice has shown that interfaces with a heated transfer capillary are superior to those employing a counter-current desolvation gas and corresponding modifications have been suggested [14].

Note: In principle, any mass spectrometer equipped with an ESI source can be modified for DESI operation by mounting the sprayer on an adjustable frame and placing a *x*,*y*-movable sample stage between sprayer and entrance of the interface (Chap. 13.1.3) [15]. For safety, a GΩ–resistor should be welded in the high-voltage supply cord. However, for successful analytical application, only sensitive modern instruments are suitable.

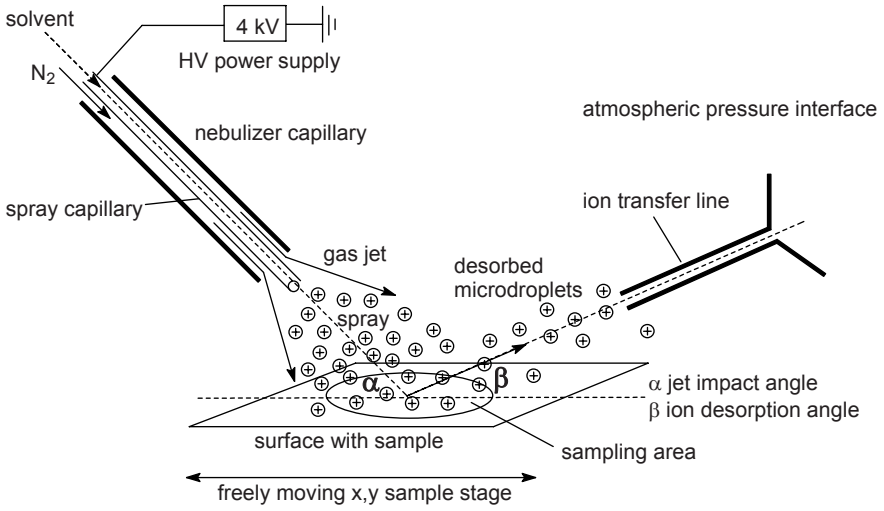

Fig. 13.1. Schematic of a DESI interface. A jet of gas and charged microdroplets is created by means of a standard pneumatic ESI sprayer and directed onto a sample surface at angle α. As a result, charged microdroplets containing ions of the surface material are created and transported away due to the action of the reflected gas stream and electric repulsion at angle β. A portion of the "secondary ESI spray" may be taken up by the atmospheric pressure interface of the mass spectrometer. Although at the expense of optimum sensitivity, an extended ion transfer line is normally employed to bridge the gap from surface to interface sampling orifice [1,12].

Obviously, DESI introduces new parameters to the ESI experiment. In particular, the velocity of the spray gas (represented by the supply pressure), the sprayer-to-surface and sampling orifice-to-surface distances, and the angles of impact and desorption are contributing to the effectivity of ion generation and subsequent uptake into the mass spectrometer. Accordingly, these parameters need to be carefully optimized for any DESI application as they exhibit rather wide variations (Table 13.1) [12,13]. It has also been found that optimum settings differ between API interfaces with counter-current drying gas and those employing the heated desolvation capillary design [16]. The transit of charged particles from the sample surface into the ion transfer line of the interface is determined, among others, by the dragging action of the mass analyzer's vacuum.

Additional parameters associated with DESI are the electrical conductivity, the chemical composition, and the texture of the sample surface. Neutralization of the droplets landing at the surface must be avoided to maintain continuous release of charged particles from the surface. Conductive sample supports need to be either isolated or floated at a potential equal to or slightly lower than the spray voltage. The electrostatic properties of the surface are also relevant for an insulator, because the signal stability depends on its preferred polarity. A highly electronegative polymer like PTFE, for example, yields better signal stability in negative-ion mode, whereas PMMA performs bettter in positive-ion mode. The chemical composition of the surface can affect crystallization of the analyte, and thus, as observed in MALDI preparations, lead to the occurrence of "sweet spots". Therefore,

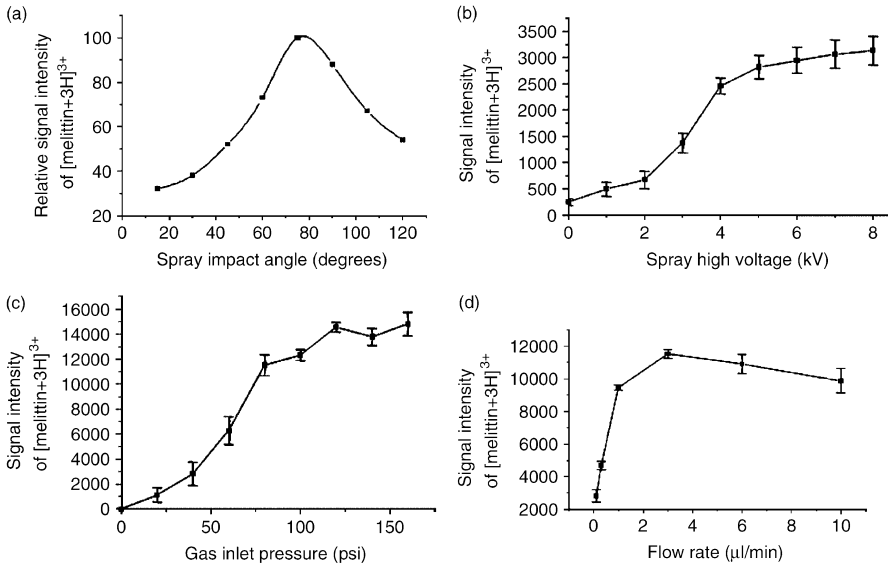

Fig. 13.2. Influence of experimental parameters on the intensity of the $[M+3H]^{3+}$ ion of melittin: (**a**) spray impact angle, (**b**) spray high voltage, (**c**) nebulizing gas pressure (14.5 psi ≈ 1 bar), (**d**) solvent flow rate. Reprinted from Ref. [12] with permission. © John Wiley & Sons, Ltd. 2005.

high affinity of analyte molecules to the surface needs to be avoided as it is detrimental for the release of analyte. Finally, the surface texture plays a role. The use of HF etched glass slides as DESI substrates instead of untreated ones delivered a dramatic increase in signal stability and eliminated "sweet spot" effects. Generally, rough surfaces like paper or textiles give superior sensitivity [12].

Example: Examinations have been carried out on the dependence of the signal intensity of the $[M+3H]^{3+}$ ion of melittin on basic experimental DESI parameters such as spray impact angle, spray high voltage, nebulizing gas inlet pressure, and solvent flow rate. Methanol : water = 1 : 1 was sprayed onto a sample of 10 ng melittin deposited on a PMMA surface at fixed spray tip-to-surface distance of 1 mm. While one parameter was varied, the others were kept constant at about their average value. The results reveal optimum conditions for each parameter that are rather typical for DESI and, as far a flow rate and spray high voltage are concerned, also for ESI (Fig. 13.2) [12].

DESI parameters can be grouped in a compound class-specific manner. It was found that proteins, for example, yield stronger signals when the spray is pointed onto the sample from close to vertical at about 1 mm distance while small molecules such as caffeine work best at an angle around 45° and several millimeters distance from the spray needle (Fig. 13.3) [12].

Early on, commercial DESI sources have become available and have meanwhile reached a level of maturity. They feature ESI sprayers adjustable in both angle and distance towards sample plates that can be operated under data system control (Fig. 13.4).

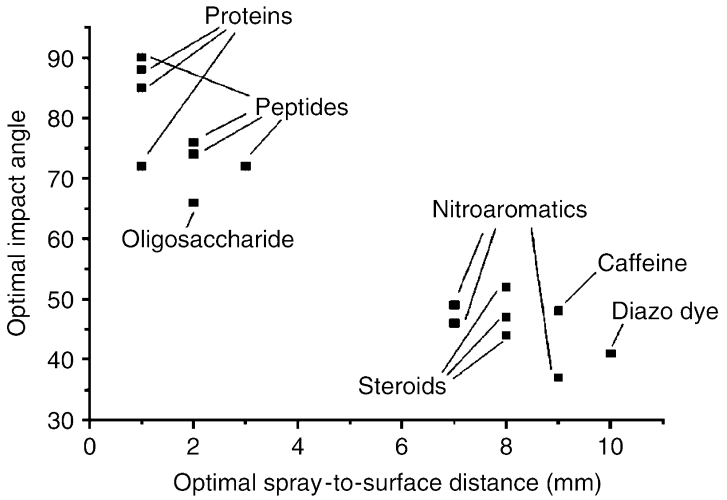

Fig. 13.3. Compound class-specific optima of spray impact angle and spray needle distance to surface. The *upper left* group of analytes would preferably be analyzed by ESI whereas the *lower right* group would rather demand for APCI (cf. Chap. 13.1.2). Reprinted from Ref. [12] with permission. © John Wiley & Sons, Ltd. 2005.

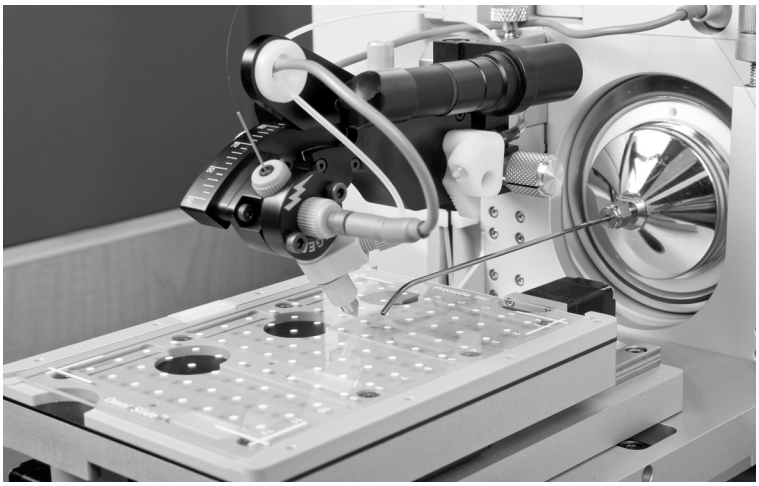

Fig. 13.4. A commercial DESI ion source. This one here is the Prosolia Omni Spray 2D source coupled to a Thermo Fisher LTQ mass spectrometer. The surface shown is a 96-spot Omni Slide HC having the standard microtiter plate dimensions. Note the extended desolvation capillary and the adjustable sprayer. Courtesy Prosolia, Inc., Indianapolis, In USA.

Table 13.1. Typical parameters for DESI

Parameter	Range of useful settings
Solvent flow rate	3–5 µl min^{-1}
Nebulizer gas pressure	8–12 bar
Spray voltage	2–6 kV
Sprayer-to-surface distance	1–5 mm
Sprayer-to-surface angle	30–70°
Surface-to-desolvation capillary distance	1–5 mm
Surface-to-desolvation capillary angle	10–30°
Temperature of desolvation capillary	200–300°C

13.1.2 Mechanisms of Ion Formation in DESI

DESI combines features of ESI with various desorption ionization devices [12], while also obviously displaying a resemblance to spray ionization methods, as an electrospray plume is usually generated by applying a potential of several kilovolts to an electrolytic solution under (strong) pneumatic assistance. The mist comprising charged microdroplets, ionic clusters, and gas phase solvent ions is then directed onto the sample surface. Therefore, the physical state of the sample distinguishes DESI from ESI. In this respect, DESI shows some phenomenological relationships to desorption ionization, because methods such as plasma desorption (PD), (matrix-assisted) laser desorption ionization ((MA)LDI), as well as fast atom bombardment (FAB) and its inorganic variant secondary ion mass spectrometry (SIMS, Chap. 15.5) all involve the impact of projectiles on condensed

phase samples. Depending on the method, these projectiles are either photons, energetic atoms, or ions. In contrast to those desorption methods, DESI is performed in the ambient atmosphere, and therefore, the projectiles in DESI can only possess low kinetic energies.

Three processes of ion formation have been proposed for DESI [17]; depending on the conditions and applied solvent-analyte pair one of these will predominate: *i*) droplet pickup, *ii*) condensed phase charge transfer, and *iii*) gas phase charge transfer.

i) *Droplet pickup* involves impact of electrosprayed droplets on the surface followed by dissolution of the analyte from the surface into the droplets. The droplets are again released from the surface and subsequent evaporation of the solvent and Coulomb fission generates ions by processes analogous to conventional ESI. The droplet pickup mechanism accounts for the similarity of DESI spectra with those of standard ESI in case of proteins. Interestingly, peptide ions can be observed even when the target and the sprayer are held at equal electrical potential. This has been attributed to the effect that offspring droplets will emerge mainly from the edges of a spreading primary droplet. In this case, charged droplet formation would essentially occur by electrospray driven by the potential between the edges and the extended desolvation capillary.

ii) *Condensed phase charge transfer* involves gaseous ions delivered by the electrospray and the analyte on the surface. The desorption of the analyte ions from the surface is thought to occur by a type of *chemical sputtering*. (Chemical sputtering is a process in which ion bombardment induces chemical reactions that finally lead to the formation of volatile erosion products [18].) This way, ions can be formed by transfer of electrons, protons, or other small ions from the impacting microdroplet to the surface bearing the analyte. A surface charge builds up and the momentum delivered from the impact event may then suffice to effect direct release of analyte ions from the surface. This proceeds at very low impact energy if the reactions are exothermic, while somewhat higher energies (adjusted via gas pressure) are required to achieve lift-off in case of endothermic reactions.

iii) *Gas phase charge transfer* means that ion formation occurs after volatilization or desorption of neutral species from the surface into the gas phase through ionization via proton/electron transfer or other ion–molecule reactions at atmospheric pressure. Indeed, the assumption of ion–molecule reactions, eventually purely in the gas phase above the sample, has led to the development of an DAPCI source (Chap. 13.2), in the first place to prove this mechanism of ion formation [7]. The solvent pH can be used to positively affect the vapor pressure of the analyte, e.g., the vapor pressure of volatile plant alkaloids is increased by addition of a base.

13.1.3 Analytical Features of DESI

DESI can serve for the identification of natural products in plant material [1,12,13], of lipids in animal tissue [16,19], for high-throughput analyses of pharmaceutical preparations [20], and for drug metabolite identification or even quan-

titation in blood and other biological fluids [12,14], as well as for the direct monitoring of biological tissue for biomarkers and in vivo analysis [10,16,19]. DESI is applicable to the analysis of proteins, carbohydrates, and oligonucleotides [12], as well as small organic molecules. Potential DESI applications are also in forensics and public safety such as the detection of explosives, toxic compounds, and chemical warfare agents on a variety of common surfaces, e.g., paper, plastics, cloth or luggage [17,21]. Plastic explosives, i.e., formulated explosive mixtures, can also be analyzed [10,17,21]. Even the transfer of ion-loaded gas from the sample to the API source through an up to three-meter-long stainless-steel tubing, termed non-proximate sampling, has been demonstrated [22].

The limit of detection for small peptides is in the order of 1 pg absolute or < 0.1 pg mm^{-2}, for proteins in the order of < 1 ng absolute or < 0.1 ng mm^{-2}; small molecules such as pharmaceuticals and explosives are detectable in the range of 10–100 pg absolute or 1–10 pg mm^{-2} [10,12]. These numbers indicate a footprint of about 10 mm^{-2} roughly corresponding to a circular spot of 3 mm in diameter. Smaller footprints can be realized – sample and sensitivity of the instrument permitting. The number of DESI papers is steadily growing. A few representative examples of DESI applications are compiled below.

Example: The negative-ion DESI mass spectrum of the over-the-counter drug acetylsalicylic acid (aspirin) was measured with a home-built DESI source attached to a seasoned triple quadrupole instrument (Fig. 13.5). The sample was presented on paper to a methanol spray. Whereas this sample even allowed tandem mass spectra of the $[M–H]^-$ ion, *m/z* 179, to be readily obtained, other samples were beyond the instrument's sensitivity limits [15].

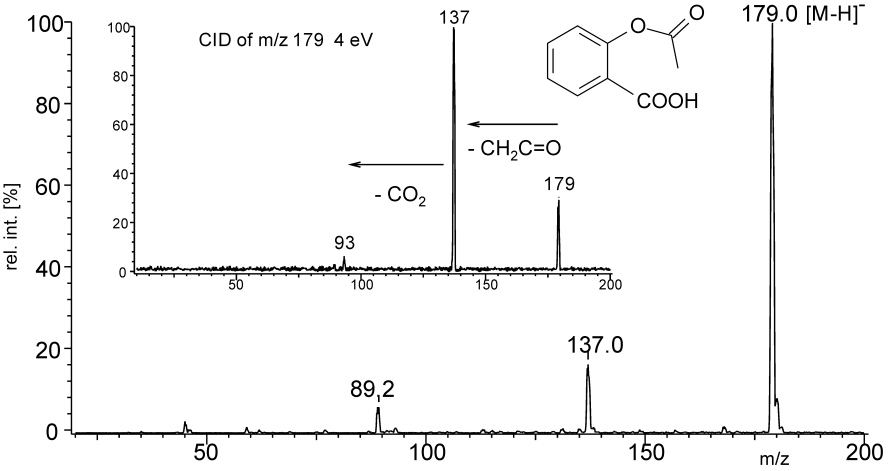

Fig. 13.5. Testing of a home-built DESI source. DESI mass spectrum of acetylsalicylic acid from paper analyzed by negative-ion DESI using methanol spray. The *inset* shows the tandem mass spectrum of the deprotonated ion.

Example: Plant alkaloids can be identified from DESI mass spectra of seeds, leaves, flowers, or roots. Here seeds of deadly nightshade (*Atropa belladonna*) were subjected to DESI for the identification of their principal alkaloids atropine and scopolamine (Fig. 13.6) [13]. (Atropine is the name of the racemic mixture of (R)- and (S)-hyoscyamine. It is a tropane alkaloid also extracted from jimsonweed (*Datura stramonium*), mandrake (*Mandragora officinarum*) among other plants of the Solanaceae family.) The inset in Fig. 13.4 shows tandem mass spectra of the ions at *m/z* 290 and 304, thereby confirming them as corresponding to protonated hyoscyamine and scopolamine, respectively. The confirmation of the ion at *m/z* 304 as $[M+H]^+$ ion of scopolamine was obtained by comparing the tandem mass spectrum with that of the standard alkaloid.

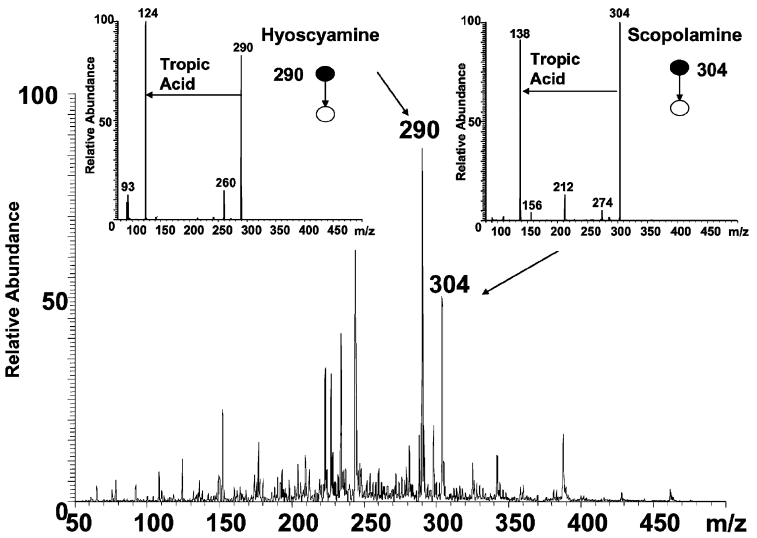

Fig. 13.6. DESI mass spectrum of *Atropa belladonna* seeds using methanol : water = 1 : 1 as spray solvent. The *insets* show tandem mass spectra of the protonated alkaloids hyoscamine, *m/z* 290 and scopolamine, *m/z* 304. Both protonated alkaloids have the characteristic loss of tropic acid, 166 u, in common. Reprinted from Ref. [13] with permission. © The Royal Society of Chemistry, 2005.

Example: Mouse liver sections were analyzed by DESI-FT-ICR-MS. The spectra of the tissue samples exhibited strong signals for phospholipids and lysophospholipids that were detected either as $[M+H]^+$, $[M+K]^+$, or $[M+K]^+$ ions. The mass accuracy of generally 1 ppm of the FT-ICR instrument allowed for assigning unique molecular formulas to most signals (Fig. 13.7) [16].

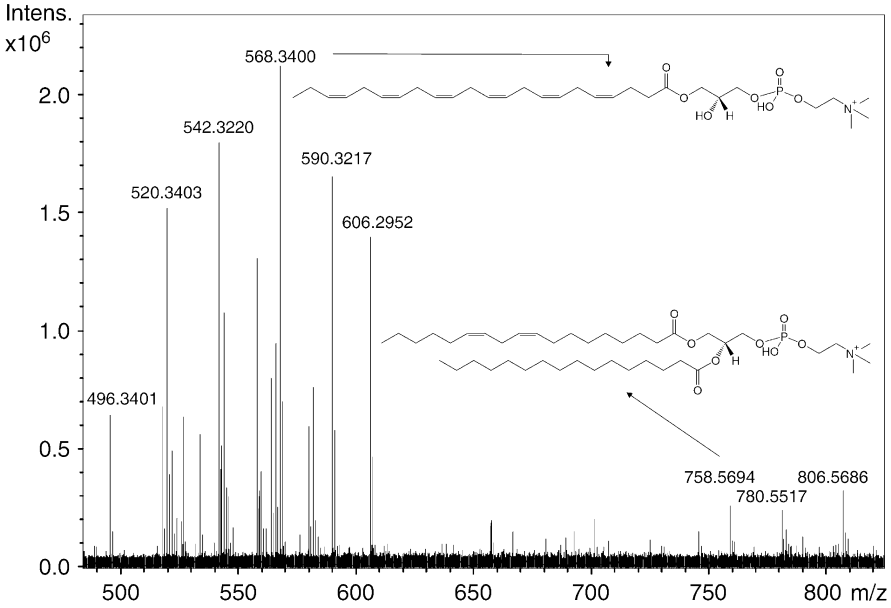

Fig. 13.7. Lipid profile of murine liver tissue sections as acquired by DESI-FT-ICR-MS using methanol : water = 1 : 1 (v/v) with 1% acetic acid as spray solvent. Reproduced from Ref. [16] with permission. © John Wiley & Sons, Ltd., 2008.

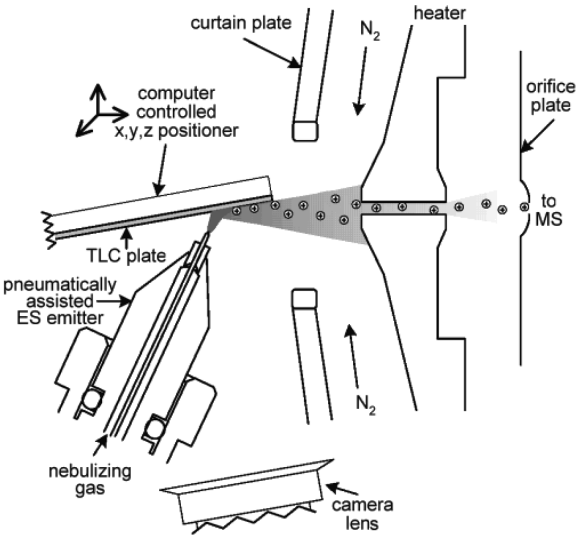

Fig. 13.8. Fully computer-controlled TLC-DESI unit attached to an ESI interface using the curtain gas design. Reprinted with permission from Ref. [23]. © The American Chemical Society, 2005.

Example: TLC-DESI was developed in the van Berkel group [23]. The sprayer was positioned about 4 mm from the curtain plate of the mass spectrometer at a 50° angle relative to the TLC plate surface. The TLC plates were cut to align the sample bands with the DESI plume. Methanol was sprayed at about 5 µl min^{-1} while a *x*-*y*-*z* robotic platform and control software were used to move the TLC plate relative to the stationary DESI emitter at about 50 µm min^{-1}. The position of the TLC plate relative to the sprayer was monitored with a camera, the image of which was output to a PC so as to correlate staining, position, and DESI spectral data (Fig. 13.8).

13.2 Desorption Atmospheric Pressure Chemical Ionization

The first report on *desorption atmospheric pressure chemical ionization* (DAPCI) appeared in a paper on the analysis of nitroaromatic explosives by negative-ion DESI [7]. These molecules all possess high electron affinities and thus they are prone to electron capture and deprotonation. From the positive effect of the DAPCI mode of operation for their detection, it was inferred that a chemical ionization mechanism should be effective if analytes are volatilized in the course of DESI analysis. So the main difference between DESI and DAPCI is the substitution of the charged solvent mist by a (hot) solvent vapor and the application of a corona discharge as the initial source of electric charge in DAPCI [17]. As usual in APCI, the corona discharge is created by applying a high DC voltage (3–6 kV) to a tapered tip stainless steel needle. Reactant ions are created in the solvent vapor upon passing the discharge. Then, the ionized gas streams onto the surface to be analyzed. Obviously, the droplet-pickup mechanism (Chap. 13.1.2) is precluded in DAPCI, while charge transfer to the surface and gas phase ionization of the analyte present the two possible mechanisms of ion formation [22].

It has been shown that addition of solvents can be avoided if the moisture of the ambient air is sufficient to generate H_3O^+ reagent ions [8,24]. The setup for DAPCI (using ambient air only) is shown in Fig. 13.9. A comparison of spectra of Proctosedyl, an ointment containing cinchocaine (M_r = 343 u) and hydrocortisone (M_r = 362 u), as obtained by DESI, DAPCI with ambient air, and DAPCI with solvent is presented in Fig. 13.10.

Applications of DAPCI include the comparative analysis of different teas such as green tea, oolong, and jasmine tea by their chemical fingerprints [24,25] and the direct rapid analysis of melamine and cyanuric acid in milk products delivering detection limits of 1–20 pg melamine mm^{-2} [26]. Furthermore, DAPCI has been successfully employed for the detection of peroxide explosives [21] or of illicit ingredients in food such as sudan red dyes in tomato sauce [24]. Analogous to DESI, DAPCI analyses can be performed with remote sampling [22].

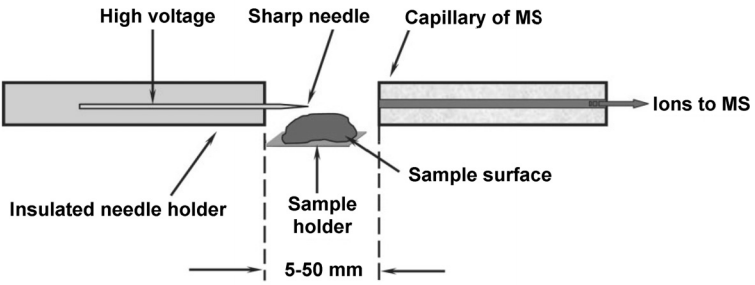

Fig. 13.9. Schematic of a DAPCI source for operation with moist ambient air as reagent gas. The sharp needle discharge electrode is coaxially centered in a capillary of 3 mm i.d. delivering humidified nitrogen gas if the ambient air is below 20% relative humidity. Adapted from Ref. [24] with permission. © John Wiley & Sons, Ltd., 2007.

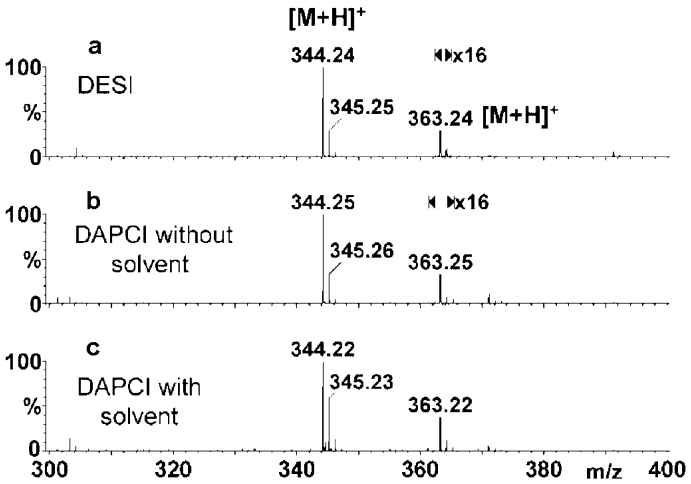

Fig. 13.10. Comparison of DESI, solvent-free DAPCI and DAPCI of Proctosedyl ointment. **(a)** Positive-ion DESI spectrum with the intensity of *m/z* 363, protonated hydrocortisone, 16-fold expanded to show the low-abundant ion. **(b)** Positive-ion DAPCI spectrum of the ointment obtained without solvent and same expansion as above. c) Positive-ion DAPCI spectrum obtained with solvent. Reproduced from Ref. [8] with permission. © John Wiley & Sons, Ltd., 2006.

13.3 Desorption Atmospheric Pressure Photoionization

DESI works best with polar analytes that are easy to protonate or deprotonate, although analytes of low polarity are accessible to a certain extent. This was the rationale for developing DAPCI. In order to improve the efficiency of ambient MS in the regime of low-polarity compounds even further, *desorption atmospheric*

pressure photoionization (DAPPI) has been developed. DAPPI represents the adaptation of APPI for the ambient analysis of surfaces analogous to the conversion of APCI to DAPCI.

In DAPPI, a heated jet of solvent vapor and nebulizer gas desorbs solid analytes from the surface. Using a microchip nebulizer turned out to be advantageous for handling and for highly responsive temperature control of the gas. The microchip nebulizer is a small glass device for mixing gas and solvent flow (dopant) and for heating the fluid medium during its passage along a platinum wire (Fig. 13.11) [9]. A krypton discharge lamp is directed toward the sample so as to irradiate the vapor phase immediately above the surface with UV photons of 10 eV where ionization of the analyte occurs. Like DESI and DAPCI, DAPPI uses a standard API interface to collect the ions [9,27].

The mechanism of ion generation in DAPPI has been proposed to be a combination of thermal and chemical processes. After thermal desorption of the analytes from the surface they can be photoionized in the gas phase. However, analytes with no UV chromophore may only be ionized by ion–molecule reactions with dopant ions. Dopant molecular ions, as formed from toluene for example, may promote charge exchange, while protonated dopant ions will yield $[M+H]^+$ ions.

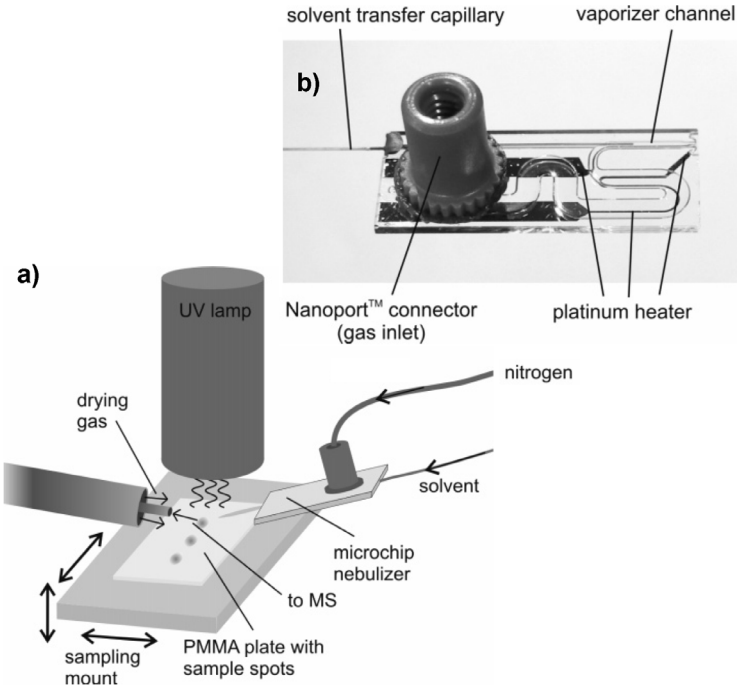

Fig. 13.11. Schematic of (**a**) the DAPPI setup and (**b**) photograph of the microchip nebulizer. The small solvent flow is mixed with nitrogen gas and vaporized in the microchip nebulizer by resistive heating of the platinum wire. The krypton UV lamp irradiates the sample surface that is in contact with the hot reagent gas. Reproduced from Ref. [9]with permission. © The American Chemical Society, 2007.

Acidic analytes can undergo deprotonation, while electronegative molecules are prone to anion addition or electron capture [27]. (The rules governing these processes have already been dealt with in Chap. 7.) The factors influencing the desorption and ionization in DAPPI such as the microfluidic jet impinging geometry, the thermal characteristics of the DAPPI surfaces, as well as chemical aspects like spray solvent have been examined for both positive- and negative-ion mode [27].

Example: DAPPI is capable of analyzing dried sample spots of compounds of different polarities from various surfaces, may serve for the direct analysis of pharmaceuticals and illicit drugs from tablets and other preparations (Fig. 13.12), and of many other applications [9,27-29].

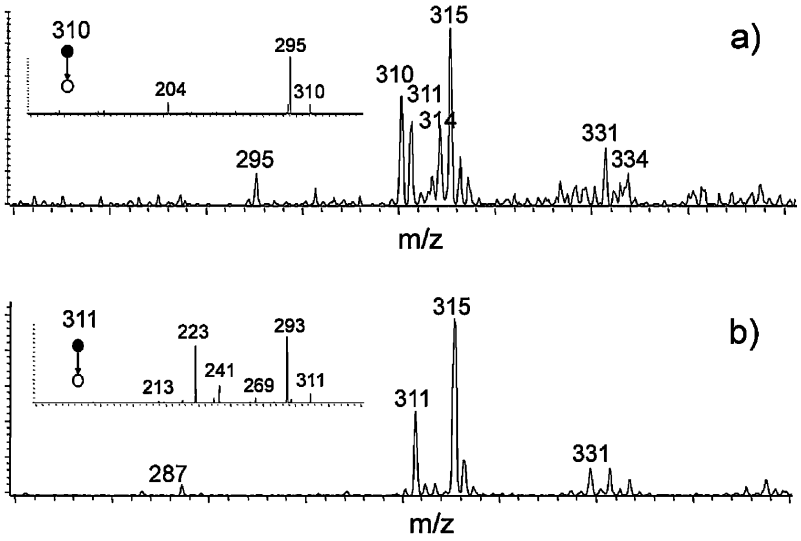

Fig. 13.12. Analysis of a hashish slab with DAPPI using toluene **(a)**and acetone **(b)** at flow rates of 2 ml min^{-1} as spray solvents. The insets show the tandem mass spectra of **(a)** the $M^{+\bullet}$ ion of cannabinol and **(b)** the $[M+H]^+$ ion of cannabinol; the ions at *m/z* 314 and 315 are attributed to the respective ionic species of tetrahydrocannabinol (THC). Reproduced from Ref. [29] with permission. © John Wiley Sons, Ltd., 2008.

13.4 Other Methods Related to DESI

Variation of the DESI theme by changing the mode of sample supply opens up a large variety of partially awe-inspiring, partially slightly odd, but always interesting analytical applications, some of which are so new that even the term is not finally coined at the time of their first publication.

13.4.1 Desorption Sonic Spray Ionization

In ESI an electrolytic solution is sprayed mainly by the action of an electric field inducing charge separation and subsequent disintegration of a bulk liquid into an electrostatically charged mist. A nebulizing gas flow at sonic speed coaxially to the liquid flow can also create a statistical imbalance of charges, i.e., a charge separation sufficient for the purpose of forming charged droplets. This is known as *sonic spray ionization* (SSI) [30-32]. The advantage of SSI is that it operates free of a high voltage and thus appears ideal for handling under ambient conditions [3]. An adaptation of SSI for ambient mass spectrometry was thus made and initially termed *desorption sonic spray ionization* (DeSSI) [3].

Note: Soon after its introduction, DeSSI was renamed *easy ambient sonic-spray ionization* (EASI) [33], the superfluous inclusion of the adjective "easy" and the generation of a rather blatant acronym (EASI) seem to have driven this change.

DeSSI (or EASI) requires unusually high backpressure of ca. 30 bar to achieve the sonic velocity of the nebulizer gas stream resulting in a flow of about 3 l min^{-1} to dissipate the liquid flow of 20 µl min^{-1} methanol/water solution. The curtain gas pressure of the API interface is also set to a rather high value of 5 bar.

The method has shown to deliver good results for the fingerprinting of biodiesel fuel [34] and perfumes [33], for the analysis of fabric softeners and surfactants [35], coupling to membrane inlet systems (MIMS-DeSSI) [4], and to analyze components separated on TLC plates [36]. However, the method appears to exhibit low inter-system compatibility; in some laboratories high voltages were needed to obtain a signal.

13.4.2 Extractive Electrospray Ionization

Analyte ions can also be efficiently generated when sample vapor or finely dispersed sample droplets transported by a carrier gas stream are admixed to the expanding electrospray plume. This technique, simple yet effective, has been introduced as *extractive electrospray ionization* (EESI) [37]. It utilizes two separate sprayers, one conventional ESI sprayer to provide the electrostatically charged mist and another to supply the sample vapor or mist (Fig. 13.13). While this approach is suggested for API interfaces with the heated transfer capillary design, the sample carrier stream may alternatively be passed into the desolvation gas of interfaces employing the heated curtain gas design (Fig. 13.14) [6,38].

Instead of a separate sample sprayer, an ultrasonic nebulizer may also deliver a sample-containing aerosol, which is transported and admixed to the electrospray mist by action of a mild stream of nitrogen. As the droplets of both origins are "fused" inside a small housing enclosing the spray, this approach has been termed *fused-droplet electrospray ionization*, and thus, led to the the somewhat confusing acronym FD-ESI [39,40].

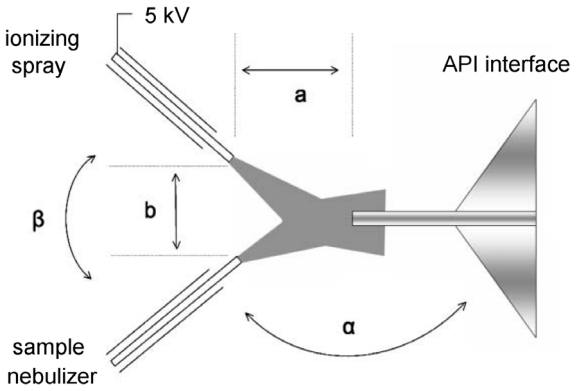

Fig. 13.13. Extractive electrospray ionization interface with two mixing sprays in front of a heated transfer capillary. The distances a and b and the angles α and β are adjusted as required for optimum signal intensity. Adapted from Ref. [37] with permission. © The Royal Society of Chemistry, 2006.

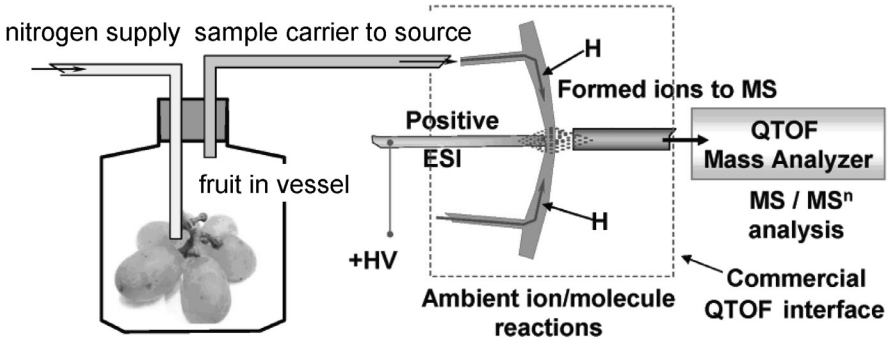

Fig. 13.14. Schematic of an EESI source where the sample carrier gas is fed into the curtain gas of the API interface. Here, the experiment is designed to determine the ripening of fruit from its headspace, i.e., odor. Adapted from Ref. [41] with permission. © The American Chemical Society, 2007.

EESI has its strengths in headspace analytical applications; it has been employed to classify authentic perfumes and to detect counterfeit products from chemical fingerprints of the fragrances after their application on paper strips as usually performed for customer's testing [42]. It may serve for the rapid determination of the ripening of fruit via headspace analysis as pointed out in Fig. 13.14 [41], or to identify spoiled food, either vegetables or meat samples, even in the frozen state, by detection of typical degradation products or metabolites from bacterial growth [5,38]. It is also possible to detect melamine in milk [43] (a sort of analysis one never would have assumed to be necessary until after the Olympic games in China in 2008). Finally, as the location of the extraction can be several

meters away from the mass spectrometer, traces of toxic chemicals, explosives, or drugs on skin can be detected by EESI without any hazard to a person [6,44].

13.4.3 Electrospray-Assisted Laser Desorption/Ionization (ELDI)

The technique of *electrospray-assisted laser desorption/ionization* (ELDI) combines two well-matured techniques of ionization for the benefit of improved analysis of samples under ambient conditions. The development of ELDI emanates from the fact that in (MA)LDI by far more neutrals than ions are released from the sample layer (Chap. 11) [45]. Consequently, post-ionization of laser-desorbed neutrals is promising and such methods have indeed been developed (cf. Refs. in [46]). The unique feature of ELDI is to laser-irradiate the sample in the ambient close to the ESI plume, wherein the neutrals are then ionized by ion–molecule reactions [46].

Standard conditions of ESI for ELDI involve a methanol : water = 1 : 1 mixture with 0.1% acetic acid sprayed at 3–5 µl min^{-1} from a grounded needle as to pass closely over an also grounded sample support. The orifice of the API interfaces acting as the counter electrode is held at 4–5 kV negative voltage. The UV nitrogen laser is adjusted to irradiate the sample sideward at an angle of about 45° while spraying (Fig. 13.15).

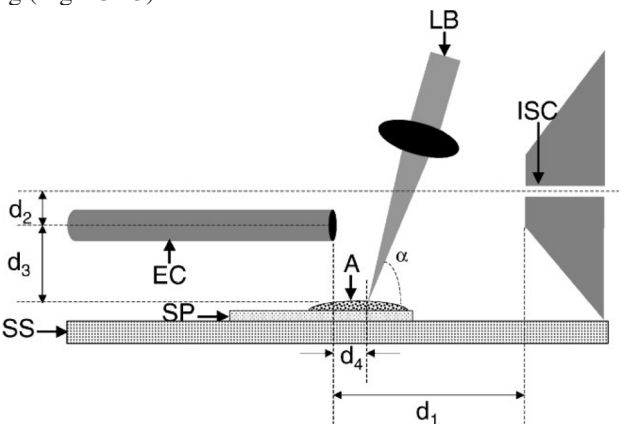

Fig. 13.15. ELDI setup. **A**: analyte, **SP**: stainless steel sample support plate, **SS**: mobile sample stage, **EC**: electrospray capillary, **LB**: UV laser beam, **ISC**: ion sampling capillary of the API interface. The distances $\mathbf{d_1}$ through $\mathbf{d_4}$ are all in the order of millimeters. Reproduced from Ref. [46] with permission. © John Wiley & Sons, Ltd., 2005.

Example: The combined use of ESI and LDI in ELDI is demonstrated for a sample of neat bovine cytochrome c on a stainless steel target (Fig. 13.16). The first spectrum (**A**), basically a blank spectrum, was obtained under pure LDI conditions. Spectrum **B** was measured with ESI on, but no laser irradiation. Finally, spectrum **C** was generated with both ESI and LDI active. It clearly shows the charge state distribution of the protein as typical for ESI spectra. The advantage of

ELDI is that samples can be presented to the inlet nozzle directly from the outside as compared to ESI or MALDI that require additional sample preparation [46]. ELDI has also been applied to the analysis of peptides and proteins [47] even from biological media [48], to detect chemicals on different surfaces [49], and of course, for compound identification on TLC plates [50]. It has been found that addition of a matrix is beneficial for the laser desorption part of the method. This gave rise to *matrix-assisted laser desorption electrospray ionization* (MALDESI) [51].

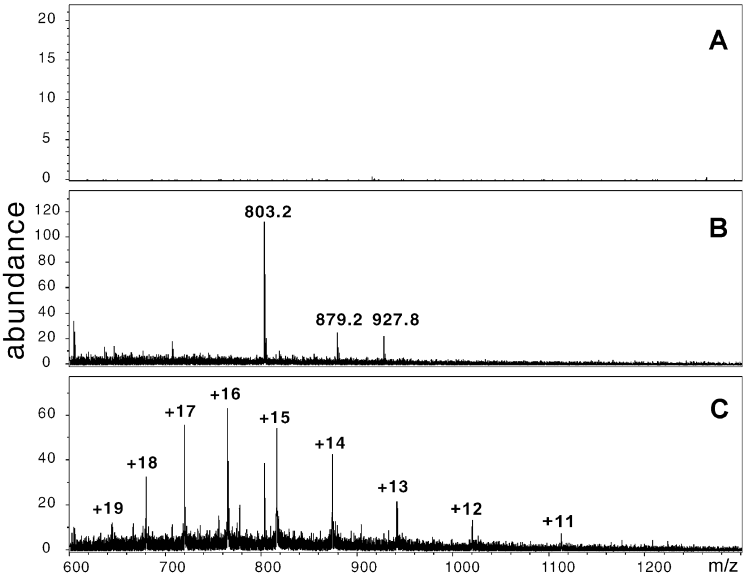

Fig. 13.16. Effect of the combined use of ESI and LDI in ELDI for a sample of neat bovine cytochrome c. Spectrum **(A)** was obtained under laser desorption only; **(B)** under ESI only; and **(C)** with both ESI and LDI active. Reproduced from Ref. [46] with permission. © John Wiley & Sons, Ltd., 2005.

13.4.4 Laser Ablation Electrospray Ionization

As just described, ELDI and MALDESI require pretreated samples, making them unfavorable for the (*in vivo*) analysis of water-rich biological samples that would preferentially be examined under ambient conditions. By replacing the UV laser with an IR laser (Er:YAG laser of 2.94 μm wavelength), the energy may directly be coupled into the OH vibrational modes of water-rich samples such as tissues. This experimental approach has been termed *laser ablation electrospray ionization* (LAESI) [52-54]. In contrast to AP-IR-MALDI, in LAESI the infrared laser only ablates neutrals from the sample, a noteworthy amount of them even in particulate state, which could be ascertained by flash shadowgraphy [52]. The laser impinging on the sample surface at 90° creates a plume that intercepts an electros-

pray operating in the cone-jet mode parallel to and at about 25 mm distance from the sample surface. The electrospray post-ionizes the neutrals and the particulate matter in that plume and transports the incipient analyte ions along the spray axis into the sampling orifice of an orthogonal acceleration time-of-flight (oa-TOF) mass spectrometer [52]. Apart from the IR laser, the experimental setup is sufficiently similar to ELDI to omit a schematic here.

Example: For LAESI, tissue samples are mounted on microscope slides, positioned 10–30 mm below the spray axis and 3–5 mm ahead of the emitter tip, and ablated using an Er:YAG laser with a pulse length of < 100 ns and 5 Hz repetition rate. The scanning electron microscope (SEM) image of the ablation crater produced by a single laser pulse on the adaxial leaf surface of a Zebra plant (*Aphelandra squarrosa*) is shown below (Fig. 13.17). The waxy cuticle and some of the upper epidermal and palisade cells were removed from a slightly elliptical area with axes of 300 and 280 µm indicating effective ablation of tissue [53]. This way, LAESI offers lateral mapping of metabolite distributions and their variations with depth on plant leaves. However, at present, LAESI cannot compete with vacuum imaging methods such as SIMS or MALDI [52].

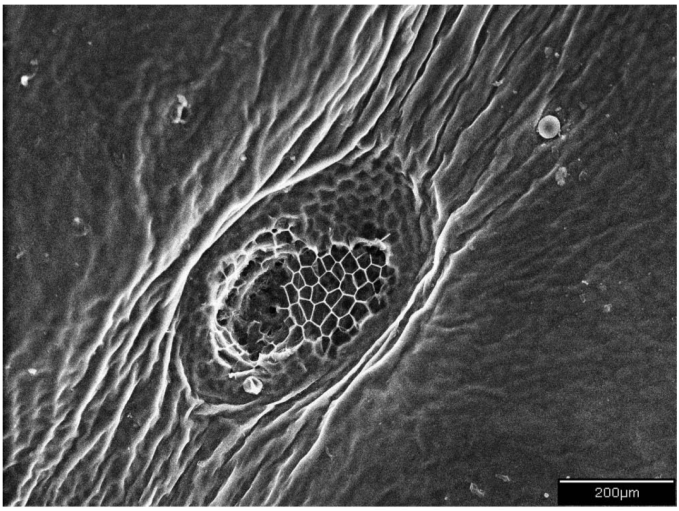

Fig. 13.17. SEM image of the ablation crater produced by a single laser pulse on the adaxial leaf surface of a Zebra plant (*Aphelandra squarrosa*). Scale bar indicates 200 µm. Multiple laser pulses penetrated deeper. The wrinkles on the cuticle were caused by the collapse of the underlying cells due to water loss in the vacuum environment during SEM imaging. Adapted from Ref. [53] with permission. © The American Chemical Society, 2008.

Note: In order to minimize the interference of external electromagnetic fields and air currents the LAESI system is shielded by a Faraday cage and a plastic enclosure, respectively. The enclosure also provides protection from potential health hazards of the fine particulates generated in the laser ablation process.

13.4.5 Atmospheric Pressure Solids Analysis Probe

The *atmospheric pressure solids analysis probe* (ASAP) [55,56] addresses a more classical field of application as it aims to offer an alternative to EI or CI using a direct insertion probe to introduce the analyte into the vacuum. By simply inserting a melting point tube into a stream of hot nitrogen gas, the solid is evaporated from the tube's surface and then ionized at atmospheric pressure by the corona discharge of an APCI source. The hot gas stream (350–500°C) may either be provided by the APCI sprayer or by an ESI sprayer. In contrast to DESI or DAPCI, no solvent is employed in ASAP. The only modification of a commercial API source is the creation of a small port in the housing around the spray region to insert the tube or to seal the hole by a plug to switch back to standard ESI operation.

13.5 Direct Analysis in Real Time

This section on *direct analysis in real time* (DART) [2] has not been placed at the end of this chapter because it would be inferior to the preceding techniques, but because DART relies on much different phenomena. In fact, DART delivers analytical results very similar to those of DESI, even more so to those of DAPCI or DAPPI, and thus presents an alternative concept of ambient MS.

13.5.1 Experimental Setup for DART

A gas flow, typically helium or nitrogen, is guided through a tube divided into three segments. In the first section, a corona discharge between a needle electrode and a first perforated disk electrode produces ions, electrons, and excited atoms (Fig. 13.18). The cold plasma passes through a second chamber where a second perforated electrode can remove cations from the gas stream that is subsequently heated and passed through a final grid electrode removing oppositely charged species. The ionizing neutral gas may either be directed towards the sampling orifice of an API interface, or analogous to DESI, may hit the sample surface at an angle suitable for its reflection into the entrance of the mass spectrometer [2].

Typical operating conditions for DART use a positive discharge needle potential of 1–5 kV while the counter electrode (first perforated disk electrode) is grounded. The potentials of the second perforated electrode and the exit grid electrode are set to positive potentials for positive-ion DART and to negative potentials in the order of a hundred volts for negative-ion mode. The insulator cap protects sample and operator from any high voltage. The gas flow is adjusted to about 1 l min^{-1} and the gas temperature may vary from room temperature up to 250°C. The DART source is adjustable over a range of angles and distances. Typically, a gap of 5–25 mm is established to insert the sample (Fig. 13.19). However, in certain circumstances ions can be detected even when the DART process occurred 1 m away from the mass spectrometer.

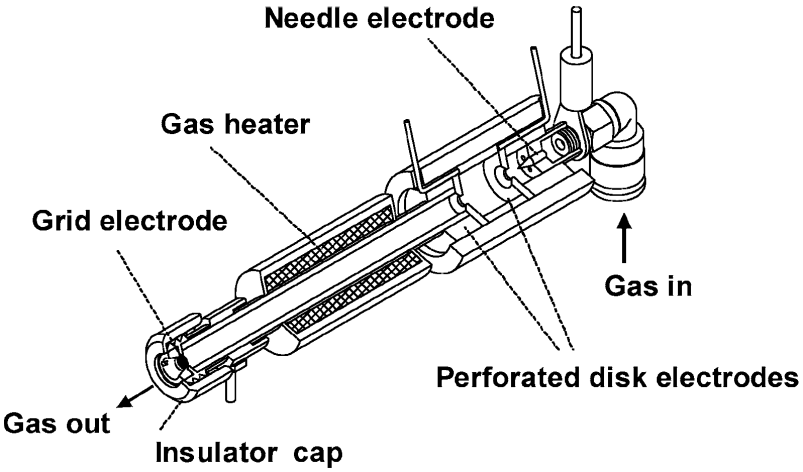

Fig. 13.18. Cutaway view of the DART source. The emanating gas effects ionization of sample independent of its state of aggregation. Reproduced from Ref. [2] with permission. © The American Chemical Society, 2005.

Fig. 13.19. Commercial DART source. Here it is used for the analysis of volatiles from a garlic clove. The sample is simply held in the open gap between the metastable atom source (*lower right part*) and the orifice of the API interface (*upper left*). Photograph by courtesy of JEOL USA.

13.5.2 Ion Formation in DART

The electrical discharge in helium produces a stream of gas-containing electronically excited atoms (metastable atoms), ions, and electrons. The cold plasma gas is then heated and fully depleted of ions by passing it through electrically charged grids. When the stream exits to the open, it may effect ionization of gases, and by direct contact also liquids and solids. It has been proposed that the metastable helium atoms (He*) induce *Penning ionization* (Chap. 2.1.3) of nitrogen and atmospheric water [2,57]:

$$He^* + N_2 \rightarrow He + N_2^{+\bullet} + e^- \quad (13.1)$$

$$He^* + H_2O \rightarrow He + H_2O^{+\bullet} + e^- \quad (13.2)$$

By ion–molecule reactions, the primary ions then deliver protonated water clusters, the most abundant being $H_5O_2^+$. These clusters act as reagent ions for analyte ion generation by chemical ionization mechanisms [58].

Note: The DART discharge belongs to the corona-to-glow (C-G) discharge type that operates with discharge currents in the order of 2 mA at a temperature of 50–60°C [59]. Recently, efforts have been made to provide a more efficient source for metastable atoms. A direct current *atmospheric pressure glow discharge* (APGD) sustained in helium and used in the *flowing afterglow* (FA) mode seems promising [57,59,60].

In negative ion mode, thermal electrons are presumed to generate mostly $O_2^{-\bullet}$ ions from air that serve as reagent ions. Of course, direct electron capture by the analyte as well as dissociative electron capture, deprotonation, or anion attachment are also feasible [58]. Thus, it has been inferred from the close similarity of the negative-ion products of DART and APPI that the same group of mechanisms of ion formation are effective.

13.5.3 Analytical Applications of DART

From the very beginning, DART has been applied variously. This includes the typical safety-related and forensic usages of ambient MS like detection of explosives, warfare agents, or pharmaceuticals and drugs of abuse from cloth, bank notes etc. [2,58,61]. DART also serves for clinical studies of compounds from plasma and urine [62,63] or for examining ballpoint-pen inks on paper, e.g., signatures in cases of check fraud [64]. At the borderline between forensic and environmental applications one finds the analysis of flavors and fragrances even including residues from cosmetic products such as from shampoo on a single hair [65]. In the life sciences, DART is applied for the rapid analysis of fatty acid methyl esters from whole cells [66] or for the recognition of different hydrocarbon profiles on living flies before and after courtship [67]. DART is sensitive enough to analyze self-assembled thiol and dithioether monolayers on gold surfaces [68].

Finally, the analysis of nonpolar compounds such as steroids and hydrocarbons makes DART a very strong competitor for DAPPI [69].

Example: Still under the impression of the 2001 terrorist attack on the World Trade Center, ambient MS initially had a strong focus on the detection of explosives. Negative-ion DART is very sensitive for the analysis of explosives exhibiting extremely low but non-zero vapor pressure [58]. Nitroglycerin has been detected on a man's necktie 8 h after exposure to the plume from blasting at a construction site (Fig. 13.20a) and various explosives present at about 3 ppm in a contaminated pond water sample have been detected; placing a small open bottle with 0.1% aqueous trifluoroacetic acid (H-TFA) in proximity to the sampling zone caused them to appear as $[M+TFA]^-$ adduct peaks in the DART spectrum (Fig. 13.20b) [2].

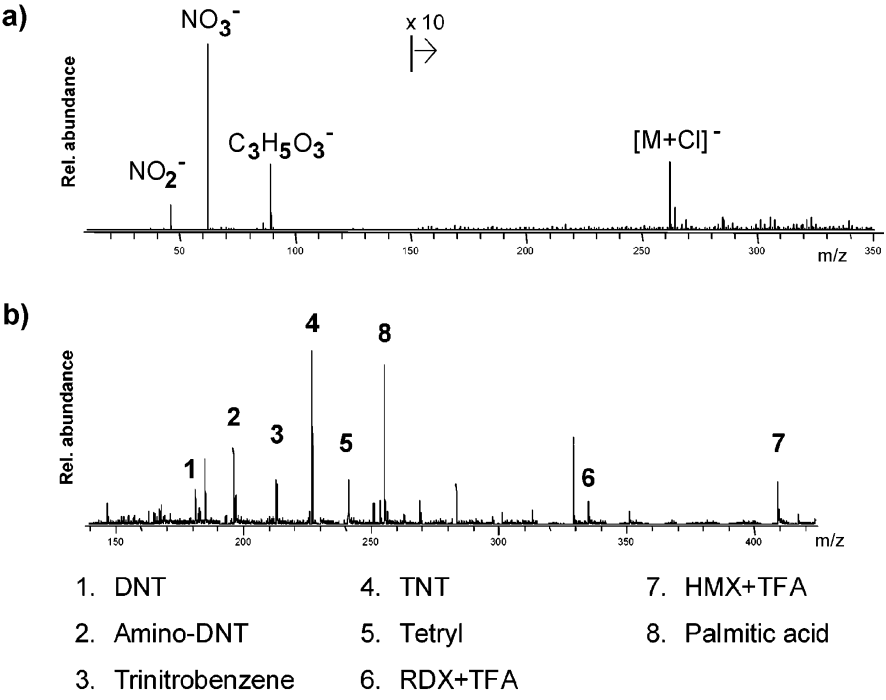

Fig. 13.20. DART spectra of explosives. Spectrum (**a**) shows nitroglycerin detected on a man's necktie 8 h after exposure to the plume from blasting at a construction site. In (**b**) a sample of contaminated pond water exhibits $[M+TFA]^-$ peaks for various explosives that are present at about 3 ppm. Reproduced from Ref. [2] with permission. © The American Chemical Society, 2005.

Example: DART allows for the cuticular hydrocarbon analysis of active fruit flies *Sophophora melanogaster (Drosophila melanogaster)*. The hydrocarbon profile as measured from the exterior of female flies comprises alkenes and alkadienes in the C_{18} to C_{29} range that are detected as $[M+H]^+$ ions. The profile has been

found to vary depending on whether the flies are observed as virgin females, 45 min or 90 min after courtship (Fig. 13.21). There is also a difference between males and females. The advantage of DART is that the fly can be exposed to the ionizing gas stream without risk of electrical shock to both fly and researcher [67].

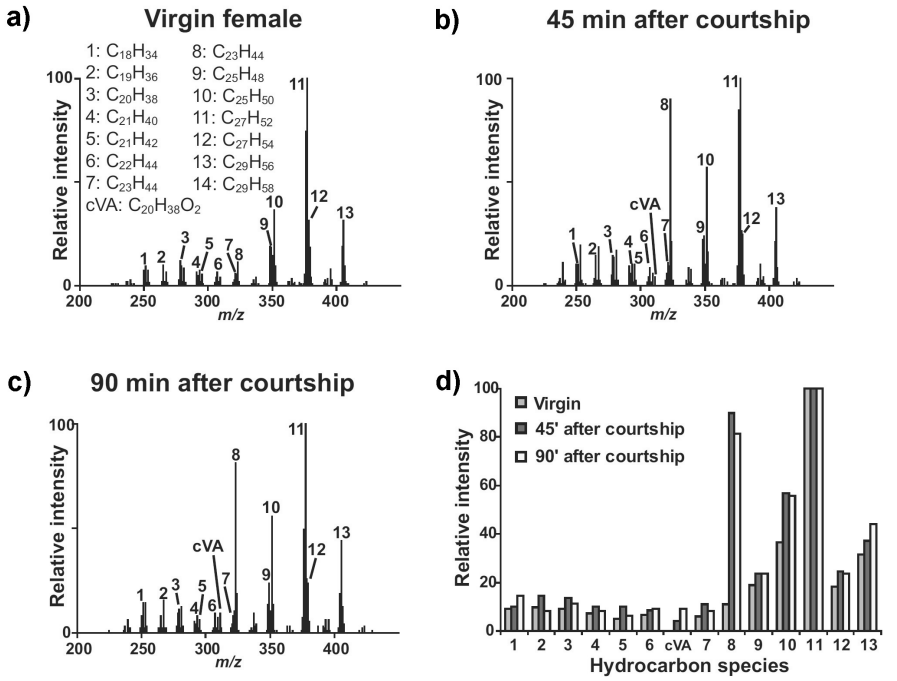

Fig. 13.21. Chemical profile changes in the same individual female fly as observed **(a)** before, **(b)** 45 min after, and **(c)** 90 min after copulation. **(d)** A histogram shows the changes in hydrocarbon concentrations, in particular, an increase in tricosene (peak 8) and pentacosene (peak 10). Reproduced from Ref. [67] with permission. © The National Academy of Sciences of the USA, 2008.

13.6 Overview of Ambient Mass Spectrometry

In closing this chapter, the below short table summarizes ambient MS methods. They are listed in alphabetical order of their acronyms together with a key reference (Table 13.2). It should be noted however, that only the truly simple-to-operate yet effective and rugged interfaces will survive over the years. Most probably, DESI and DART are the ones to persist in the long term.

Table 13.2. Methods of ambient mass spectrometry

Acronym	Full term	Basic principle and key reference
ASAP	Atmospheric pressure solids analysis probe	Evaporation of solids in hot gas stream and ionization by corona discharge [55]
DAPCI	Desorption atmospheric pressure chemical ionization	Sample surface exposed to APCI [17]
DAPPI	Desorption atmospheric pressure photoionization	Sample surface exposed to APPI [9]
DART	Direct analysis in real time	Sample surface exposed to ionizing noble gas stream [2]
DESI	Desorption electrospray ionization	Sample surface exposed to electrospray plume [1,12]
DeSSI	Desorption sonic spray ionization	Sample surface exposed to sonic spray ionization plume; equal to EASI [3]
ELDI	Electrospray-assisted laser desorption ionization	LDI with post-ionization by ESI plume [46]
EASI	Easy ambient sonic-spray ionization	Sample surface exposed to sonic spray ionization plume; equal to DeSSI [33]
EESI	Extractive electrospray ionization	Sample vapor or mist admixed to electrospray plume [6,37]
LAESI	Laser ablation electrospray ionization	IR laser ablation with postionization by ESI plume [53]
MALDESI	Matrix-assisted laser desorption electrospray ionization	Uptake of AP-MALDI plume by ESI spray and transport into API interface [51]

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