Ambient Ionization Mass Spectrometry

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Key Words

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Abstract

Mass spectrometric ionization methods that operate under ambient conditions and require minimal or no sample pretreatment have attracted much attention in such fields as biomedicine, food safety, antiterrorism, pharmaceuticals, and environmental pollution. These technologies usually involve separate ionization and sample-introduction events, allowing independent control over each set of conditions. Ionization is typically performed under ambient conditions through use of existing electrospray ionization (ESI) or atmospheric pressure chemical ionization (APCI) techniques. Rapid analyses of gas, liquid, and solid samples are possible with the adoption of various sample-introduction methods. This review sorts different ambient ionization techniques into two main subcategories, primarily on the basis of the ionization processes, that are further differentiated in terms of the approach used for sampling.

1. INTRODUCTION

The ionization of analytes in different states under ambient conditions, known as ambient ionization mass spectrometry, is currently a fruitful research area in mass spectrometry. To distinguish the ambient ionization approaches from preexisting atmospheric pressure ionization methods, the former are commonly defined as those mass spectrometric ionization methods that operate under ambient conditions and require minimal or no sample pretreatment (1–3). A characteristic of this technology is that sample introduction and ionization are usually separate events, thereby allowing independent control of each set of conditions. Through variation of the methods used to introduce the sample, unique applications for the analyses of liquid, gas, and solid samples have been demonstrated. Furthermore, a wide variety of mass spectrometers can be easily attached to the source to detect the ions generated through ambient ionization. It is not necessary to introduce additional lens or electrode systems to focus the ions prior to mass spectrometric detection. In general, mass spectrometers equipped with an electrospray ionization (ESI), atmospheric pressure chemical ionization (APCI), or atmospheric pressure photoionization (APPI) source can be connected to the existing ambient ionization sources. Because most ambient ionization techniques are essentially noninvasive in sampling, they are ideal tools for investigations of the surface composition of different solids.

Ambient ionization techniques can be distinguished on the basis of differences in analytical processes. The analyte is ionized in one of two ways: (*a*) Either the analyte molecules are formed and brought to the ambient ionization source for postionization, or (*b*) charged reactive species (e.g., ions, charged/neutral solvent droplets) or metastable atoms generated by an ambient ionization source are brought to the sample surface for desorption and ionization. **Figure 1** provides

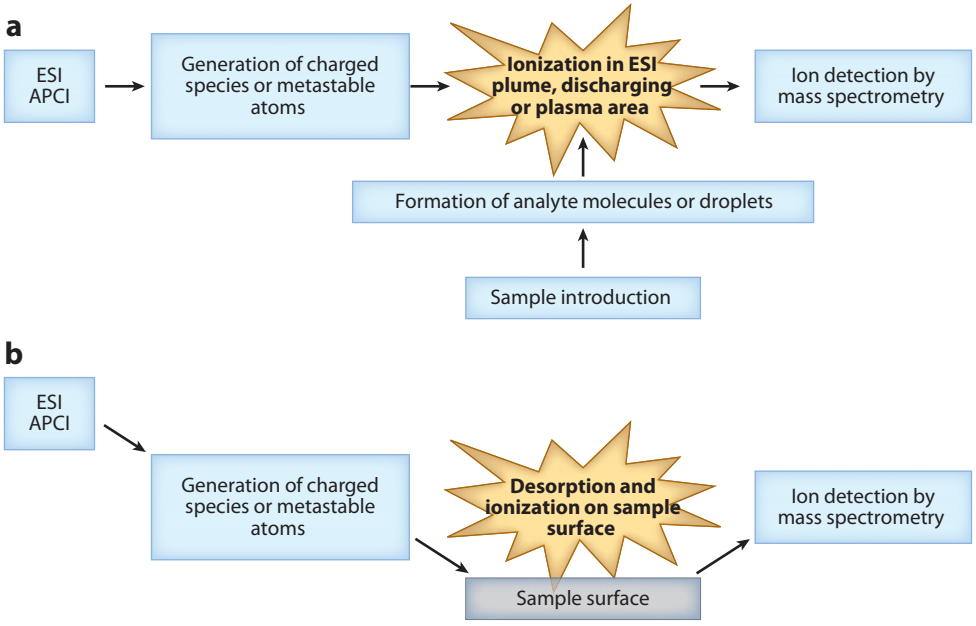

Figure 1

General analytical schemes involved in ambient ionization mass spectrometry in which (*a*) the analyte molecules are brought to the charged species and (*b*) the charged species are brought to the sample surface. Abbreviations: APCI, atmospheric pressure chemical ionization; ESI, electrospray ionization.

schematic representations of both ambient ionization methods when ESI and APCI are used. In the first case, except for the fact that the ionization is performed under ambient conditions, the analytical processes are similar to those used in gas chromatography mass spectrometry (GC-MS), in which the analyte molecules are separated in the GC column and transferred to the ion source for postionization (4). In the second case, except for the fact that the desorption and ionization events are performed under ambient conditions, the analytical procedures are similar to those used in fast atom bombardment (FAB) or secondary ion mass spectrometry (SIMS) (5, 6). Both approaches differ from those used in conventional atmospheric pressure ionization methods such as ESI, in which the analytes are generated and ionized directly from the sample solution.

In addition, conventional liquid-based atmospheric pressure ionization techniques, including ESI, APCI, and APPI, usually require tedious sample-pretreatment processes (7–9). For example, because these systems are commonly used as detectors for compounds separated through liquid chromatography (LC) or capillary electrophoresis (CE), the solution composition must be adjusted to fulfill the requirements of LC and CE during separation (10, 11). Although the sample solutions can be introduced into these sources through direct infusion, sample pretreatment is still required because the ionization efficiency relies heavily on the composition of the sample solution.

The postionization methods used in the ambient ionization source are usually not new. Two conventional atmospheric pressure ionization methods, ESI and APCI, are the ones most commonly adapted to the ambient ionization sources. Multiply charged solvent droplets and ions are generated during ESI (12); protons, reagent ions, electrons, and metastable atoms are generated through corona discharge or plasma formation during APCI (13, 14). Ion formation occurs through ESI or molecular interaction/charge-transfer processes between analyte molecules and reagent species.

Other than direct impinging of the sample surface with reagent species for sampling, there are many other ways to produce analyte molecules from liquid and solid sample surfaces, for example, laser desorption, laser ablation, shock waves created by laser irradiation or radio frequency waves, pneumatic or ultrasonic nebulization, thermal evaporation, and pyrolysis. Different terminologies are employed for technologies that are based on the same ionization principle but that use different methods to generate the analyte molecules/ions or to introduce the sample into the source. As a result, this field of research can appear complicated and confusing. Indeed, more than 25 different ambient ionization techniques have been described in the literature, each adopting different terminologies and acronyms. Several review articles have attempted to classify or categorize the existing ambient ionization sources to simplify the field (1–3, 15–17). In this review, we classify the various ambient ionization sources on the basis of the chosen ionization methods (ESI versus APCI) and sampling methods. We hope that this classification clearly and simply explains the ambient ionization techniques in terms of the instrumentation, sampling procedures, and ionization principles used.

2. ELECTROSPRAY IONIZATION–BASED AMBIENT IONIZATION TECHNIQUES

The ionization processes involved in ESI-based ambient ionization techniques resemble ESI mechanisms in that they provide ESI-like mass spectra. The sample can be gas, liquid, or solid. For gaseous or volatile samples, the analyte molecules are directly conducted into the ESI plume for ionization. For liquid samples, the solutions are either nebulized or desorbed to form mists, which are subsequently joined with the ESI plume for further ionization. For solid samples, the analyte molecules on the sample surface are first desorbed, then postionized upon entering the ESI plume. Several methods, including laser desorption, matrix-assisted laser desorption, and laser-induced

acoustic desorption, have been used to desorb the analyte molecules from the sample surface. One of the distinguishing advantages of using ESI for the postionization of airborne gases, droplets, and particles is its capability to form singly and multiply charged species, which allows the analysis of both small and macromolecular species. Because the postionization processes that use APCI are limited to the formation of singly charged ions, they are suitable only for analyses of small molecules.

Other than by introducing the analyte molecules into the ESI plume, the solid sample can also be analyzed by directly impinging the sample surface with charged solvent droplets generated through ESI, then desorbing and ionizing the analyte molecules from the surface. Although the ionization mechanisms of these techniques differ from those in which the analyte molecules are introduced directly into an ESI plume, ionization of the analyte molecules from the sample surfaces still occurs through ESI-generated species; therefore, these approaches are considered to be ESI-related ambient ionization techniques.

One of the advantages of postionizing the analyte molecules in an ESI plume is that a large quantity of charged species is produced and available for interaction with the analyte molecules or analyte-containing droplets introduced into the plume, which leads to higher ionization efficiency. In addition, the configuration of the source in the ionization part is extremely simple; no additional ion-focusing lenses are needed. Although the ion intensity is influenced by the spatial relationships among the electrosprayer, sample plate, and MS inlet, a stable ESI plume is the foundation for obtaining a stable analyte ion signal in these techniques. Therefore, after the optimal ESI signal is obtained from the solvent, the positions of the ESI capillary and the mass spectrometer inlet are usually fixed during analysis. The categorization of techniques employing ESI-related ambient ionization sources is basically defined by how the sample is introduced into the system and how the ions are generated.

2.1. Techniques That Use Electrospray Ionization for Postionization

In these techniques, the analyte molecules generated by thermal evaporation, pyrolysis, pneumatic or ultrasonic nebulization, laser desorption, or laser-induced acoustic desorption are delivered and introduced in an ESI plume for postionization.

2.1.1. Gas chromatography ESI, secondary ESI, multiple-channel ESI, and pyrolysis ESI.

The use of ESI to postionize analyte molecules can be traced back to the GC-ESI technique reported in 1998 (18). Conventionally, analyte molecules exiting a GC or a direct insertion probe are ionized in the electron impact (EI) or chemical ionization (CI) source in a vacuum (8, 19, 20). When the EI or CI source is replaced by an ESI source, all of the analytical processes are conducted under ambient conditions (18, 21). The analytical processes in GC-ESI involve the analyte molecules exiting the GC column, entering the ESI plume generated from an acidic methanol solution, and then reacting with the charged solvent species through ion-molecule reactions to form analyte ions. The analyte molecules can also fuse with the charged solvent droplets in the plume; in this case, ESI proceeds continuously from the analyte-containing droplets to form analyte ions. An ESI-like mass spectrum is, therefore, obtained through use of GC-ESI (18). The schematic representation in **Figure 2** displays the analytical mechanisms of GC-ESI. An analyte suitable for GC-ESI-MS analysis must be able to carry a charge generated through ion-molecule reactions or ESI processes. For example, a mixture of fatty acid methyl esters differing only in alkyl chain length has been successfully separated and detected by use of GC-ESI-MS (18). A similar principle has been applied to secondary ESI to characterize volatile compounds eluting from LC or GC columns (22, 23).

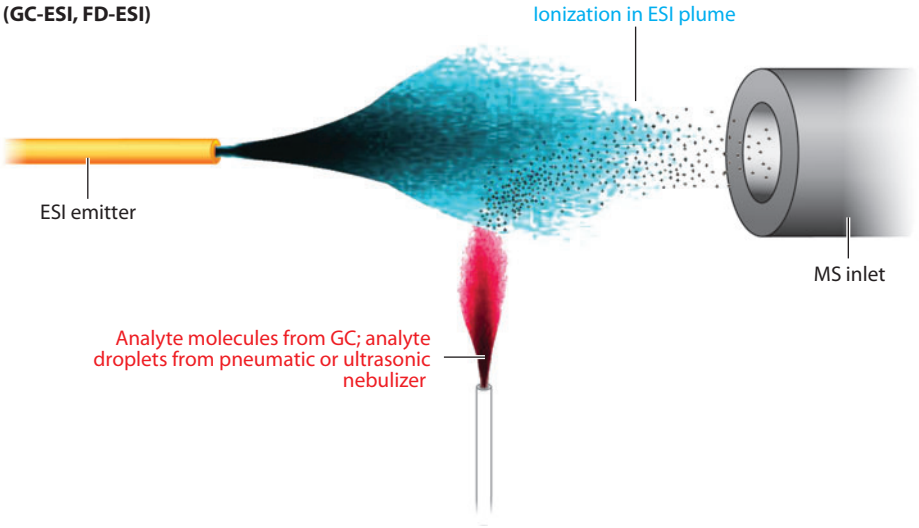

Figure 2

Schematic representation of gas chromatography electrospray ionization (GC-ESI) and fused-droplet (FD)-ESI analyses of sample molecules and analyte-containing droplets. Abbreviation: MS, mass spectrometer.

Modifications of the ESI source can enhance the ionization efficiency of the analyte molecules exiting from the GC column. Higher ionization efficiencies are obtained when the analyte molecules are introduced closer to the Taylor cone, where larger-sized charged droplets are generated. It appears that analyte-droplet fusion processes are more efficient when larger droplets are involved (18). To prevent any rapid decrease in the solvent droplet size, the nebulizing gases commonly used in conventional ESI sources are not used in GC-ESI-MS. To further increase the ionization efficiency, the GC-ESI system is equipped with six electrosprayers surrounding the central GC column. The high voltage required to generate electrospray plumes is introduced into each electrosprayer by liquid conduction through a metallic connector, which electrically contacts the solution flowing in each electrosprayer. The idea behind this multiple-channel ESI system has also been used to directly interface conventional high-performance liquid chromatography (HPLC) with the ESI source (24). Such a source featuring 16 ESI emitters can tolerate HPLC flow rates of up to 0.5 ml min^{-1} and still provide reasonably good mass spectral quality. The concept behind GC-ESI has also been applied to connect a Curie-point pyrolytic probe or a thermally pyrolytic oven with an ESI ion source to ionize polar pyrolytic products originating from macromolecules, tire rubbers, ambers, and synthetic mixed polymers (25–27).

2.1.2. Fused-droplet ESI, extractive ESI, and neutral desorption extractive ESI. The fused-droplet electrospray ionization (FD-ESI) technique was developed to characterize large analytes, such as peptides and proteins, dissolved in aqueous solutions through a two-step ESI process (**Figure 2**) (28). A probe nebulizes the aqueous sample solution ultrasonically (or pneumatically in the absence of high voltage) to form fine mists, which are then conducted into an ESI plume (**Figure 3*d***). Because multiply charged protein ions are generated in this manner, it has been suggested that the formation of the protein ions occurs as a result of fusion of the analyte mists with the solvent droplets in the ESI plume and that ESI then proceeds from the fused droplets to produce the protein ions. The polarities of the solutions used to produce the sample mists

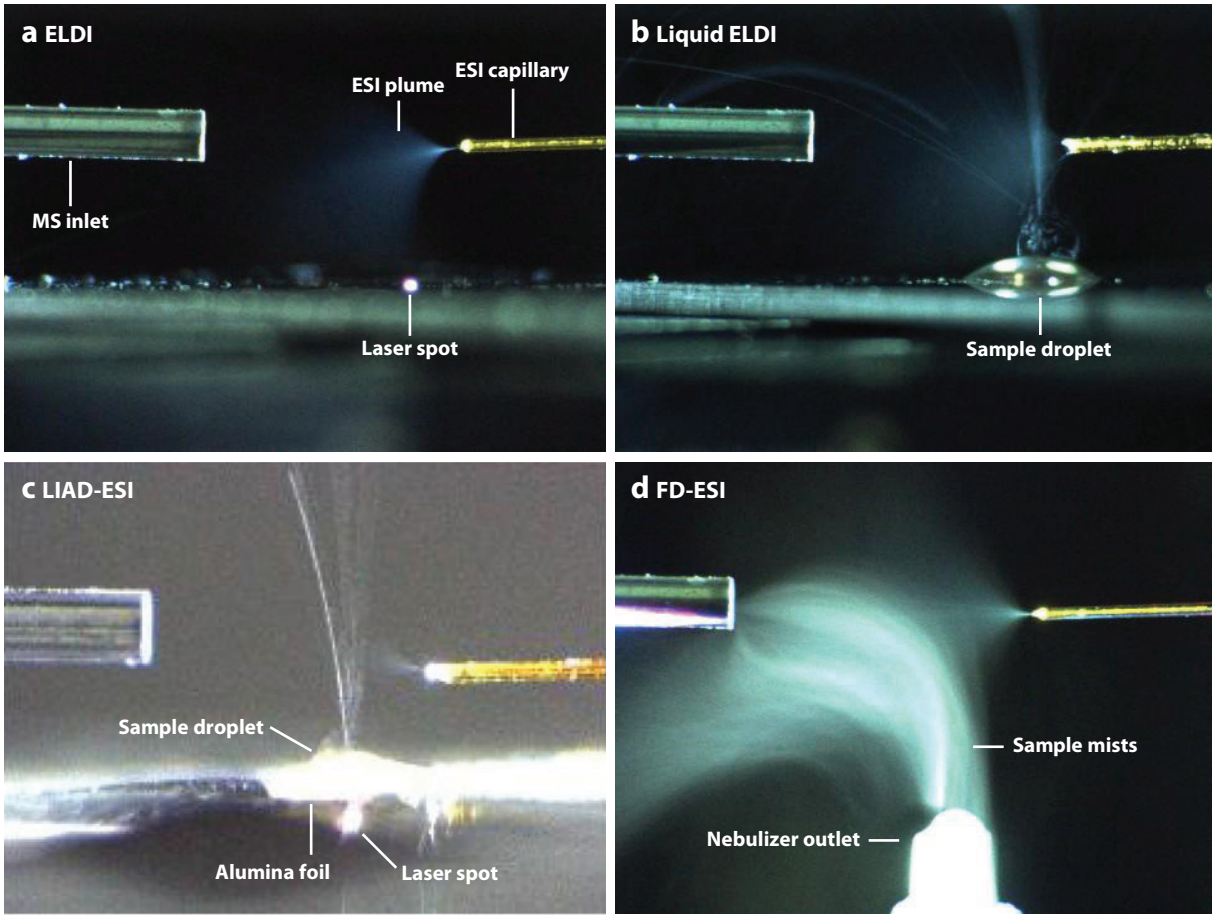

Figure 3

Photographs of analyte molecules and droplets joining electrospray ionization (ESI) plumes for (*a*) electrospray laser desorption ionization (ELDI) with a solid sample, (*b*) ELDI with a liquid sample, (*c*) laser-induced acoustic desorption (LIAD)-ESI with a liquid sample, and (*d*) fused-droplet (FD)-ESI with a liquid sample. Abbreviation: MS, mass spectrometer.

and the ESI droplets should be close so that they can fuse together. Methanol containing a small amount of acetic acid (0.1%–1% by volume) is the most common solution used to generate electrospray plumes in an FD-ESI source (28, 29). The salt tolerance of FD-ESI is much higher than in conventional ESI analysis (30). Indeed, protein ions have been detected from the solutions saturated with NaCl or sodium phosphate, presumably because the solubility of inorganic salts in methanol is low; that is, the salts within the sample mists are excluded upon fusing with the methanol droplets. It is also possible that the less polar analyte molecules are positioned at the surfaces of the neutral sample droplets, whereas the salts are stabilized through increased solvation at the droplet centers; the analyte molecules can then be extracted into the charged droplets during droplet fusion (30, 31).

Because the composition of the ESI solution in FD-ESI can be changed, analytes of various polarities can be characterized selectively by use of ESI solvents of different compositions. The technique, termed extractive ESI, is useful for characterizing both volatile and nonvolatile

compounds (31–36). One recent application has been the rapid characterization of melamine in milk (37). Analyte molecules can also be generated by blowing the solid sample surface with a heated gas stream, with the molecules subsequently ionized in the ESI plume; this technique is known as neutral desorption extractive ESI (38, 39). Through use of this approach, analyte molecules have been transported efficiently over distances greater than 1 m for remote analysis. Volatile components have been detected from human breath and other biological samples (e.g., skin, frozen meat, and plant tissue) (40–42).

2.1.3. ELDI, liquid ELDI, MALDESI, LA-ESI, and LIAD-ESI. A two-step ESI technique, named electrospray laser desorption ionization (ELDI)-MS, has been developed to characterize nonvolatile analyte molecules directly from the surfaces of solid samples (43). The analyte molecules are produced by irradiating the sample surface with the pulsed nitrogen laser, and they are then postionized in an ESI plume (**Figure 4**). Because the pulse of laser irradiation provides high energy, the chemical compounds in samples with very hard surfaces are detectable through ELDI-MS. Although no organic matrix is used, fragile biological compounds such as peptides and proteins can survive the laser irradiation to be detected as intact molecular ions (44). In contrast, an organic matrix is necessary for generating protein ions in matrix-assisted laser desorption/ionization (MALDI); for ELDI, however, the analyte molecules are ionized during the ESI processes, making it unnecessary to use a matrix for ionization. As a result, sample preparation becomes extremely simple; because interference from matrix ions is not encountered, ELDI can be used to characterize small molecules (45, 46).

The instrumentation of ELDI-MS comprises an electrosprayer without a nebulizing gas stream (an acidic methanol solution is commonly used to produce a stable ESI plume) and a metallic sample plate set on a moving stage with a pulse from an ultraviolet (UV) or infrared (IR) laser. The sample is prepared by depositing a drop of the sample solution onto the metallic sample

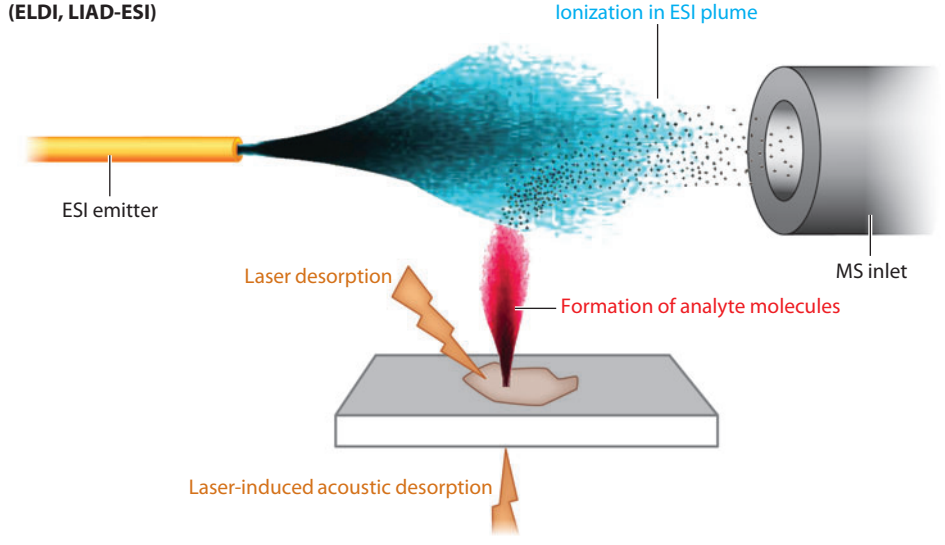

Figure 4

Schematic representation of the electrospray laser desorption ionization (ELDI) and laser-induced acoustic desorption electrospray ionization (LIAD-ESI) analyses of sample molecules on surfaces. Abbreviation: MS, mass spectrometer.

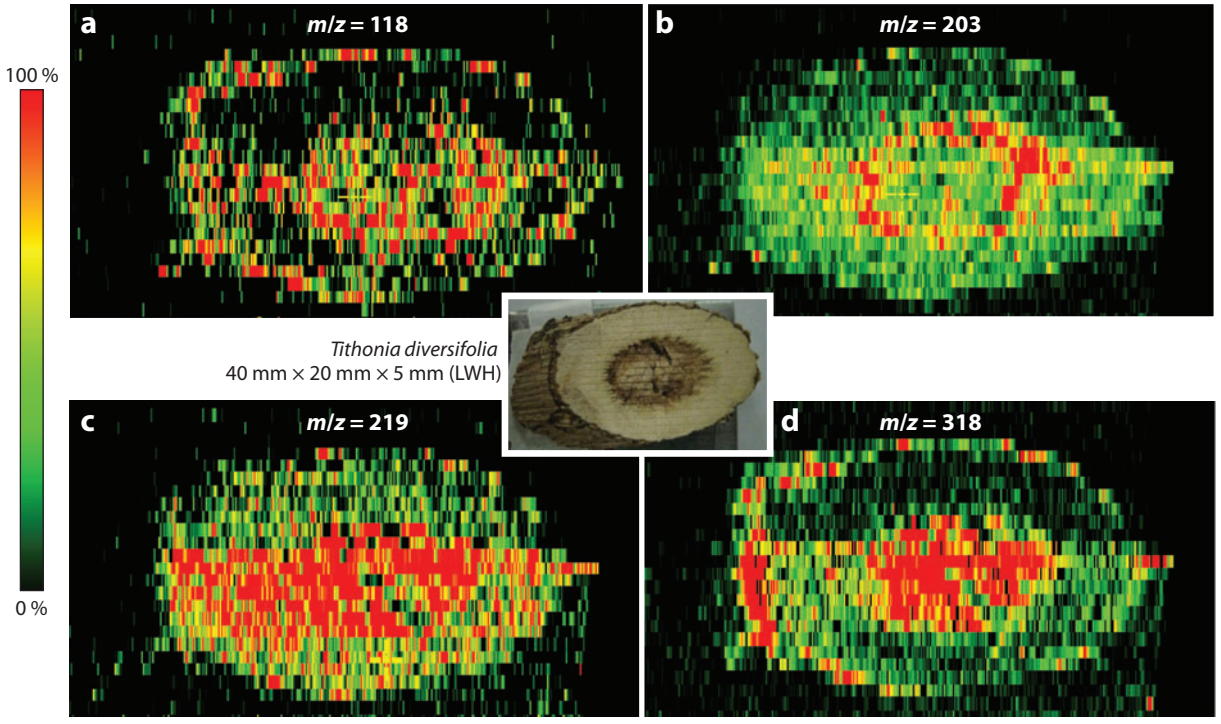

Figure 5

(*Center*) Photograph of a *Tithonia diversifolia* slice. (*a–d*) Molecular images obtained from the slice at *m/z* 118, 203, 219, and 318. Images were recorded with electrospray laser desorption ionization mass spectrometry.

plate; after air-drying, a thin sample layer is formed (**Figure 3*a***). Because the sample molecules are completely removed from the sample spot after laser irradiation, the sample plate must move continuously during ELDI analysis to continuously provide a fresh sample area for laser irradiation (43–45). The sample stage in an ELDI analysis is typically moved at a rate of 0.2 mm s^{-1}. With the assistance of the precision movement of a stepper motor and the use of laser desorption for sampling at a high spatial resolution, molecular profiling and imaging of plant slices have been demonstrated (**Figure 5**) (47, 48).

Analytes dissolved in liquids have been detected through ELDI-MS after small amounts of fine carbon powders had been added to the solution (49). The UV laser energy is adsorbed by the carbon powder and transferred to the surrounding solvent and analyte molecules, leading to their desorption; the liquid that dissolves the analyte appears to play no role during desorption, except as an energy-transfer medium (**Figure 3*b***) (50). Therefore, all the chemical compounds dissolved in the liquid medium—which may be viscous (whole blood), hydrophilic, or hydrophobic and may consist of strongly acidic and basic species, inorganic salts, and volatile and nonvolatile organic solvents—can be characterized directly from solution by liquid ELDI–MS (**Figure 6**). The status of ongoing chemical and biochemical reactions occurring in the solution can also be continuously monitored (50). The ionization event in the liquid ELDI technique is a very soft process, as evidenced by the fact that signals in mass spectra of myoglobin ions detected from acid-free aqueous solutions are nearly all in the native conformation (49).

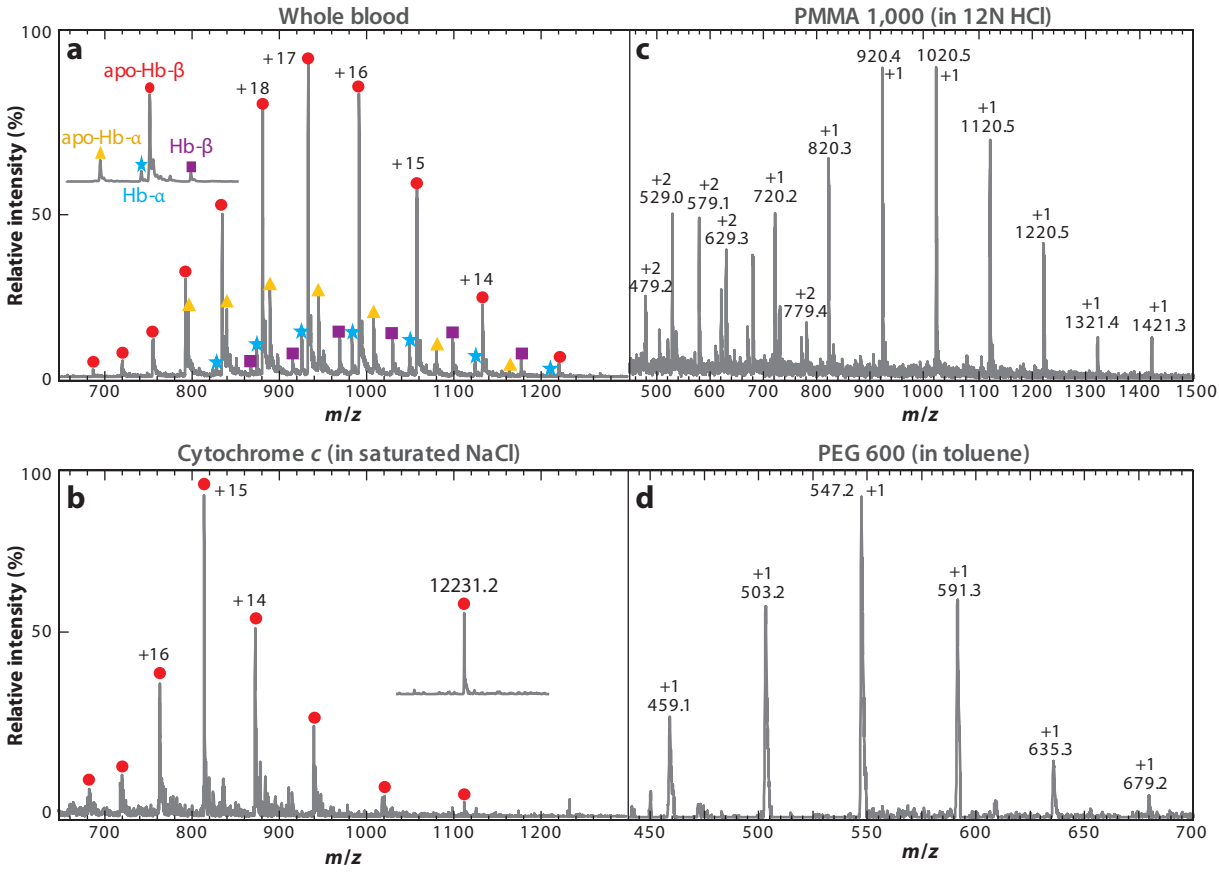

Figure 6

Electrospray laser desorption ionization (ELDI) mass spectra of (*a*) whole blood, (*b*) cytochrome *c* in saturated NaCl, (*c*) PMMA 1000 in 12N HCl, and (*d*) PEG 600 in toluene. Abbreviations: PEG, poly(ethylene glycol); PMMA, poly(methyl methacrylate).

The development of reactive ELDI provides additional analytical capabilities through the incorporation of gas-phase reactions prior to ELDI-MS measurement (51). Unique reactions can occur between the chemicals added in the ESI solution and the analyte molecules desorbed by laser desorption. For example, biochemical reactions (e.g., disulfide bond reduction achieved by addition of dithiothreitol, a disulfide bond cleavage reagent) and changes in protein conformation (obtained by mixing in an organic solvent) can be performed during the ELDI ionization process (51).

Several other ionization methods that use desorption and ionization principles similar to those for ELDI, including matrix-assisted laser desorption electrospray ionization (MALDESI) and laser ablation electrospray ionization (LA-ESI), were subsequently developed (52–57). In MALDESI, a conventional organic matrix is mixed with the analyte (e.g., a protein) in the solid or liquid state prior to desorption of the analyte upon laser irradiation. For LA-ESI, an IR laser is used to desorb the protein dissolved in an aqueous solution or as a solid. Similar principles have also been used for the analysis of volatile and semivolatile compounds by impinging the sample surfaces with a heated stream of high-velocity N_2 gas; the thermally evaporated analyte molecules were then transferred into the ESI plume for further ionization (58).

Recently, ESI was combined with laser-induced acoustic desorption electrospray ionization (LIAD-ESI) under atmospheric pressure to characterize small organic and large biological compounds as solids and in solution (**Figure 3*c***) (59). The acoustic and shock waves are generated by UV or IR laser irradiation on the rear side of a metal foil bearing the predeposited dry sample. The analyte molecules are generated through the mechanical action of the acoustic and shock waves and heating; they are then postionized in an ESI plume (**Figure 4**). Because the technique does not require direct exposure of the sample to laser light, it is particularly useful when the sample is sensitive to the laser wavelength used. In addition, because all the parts and the laser beam are located on the rear side of the sample foil, much more working space is available on the sample side for the LIAD source than for an ELDI source. Direct LIAD-MS analyses of chemical compounds separated on thin-layer chromatography (TLC) plates were recently demonstrated (60).

2.2. Techniques That Use Electrospray Ionization Droplets for Desorption and Ionization

Desorption electrospray ionization (DESI) is performed by bringing the charged species to the sample surface for desorption and ionization (61). A high-speed jet of charged ESI droplets is directed onto the sample surface; the secondary ions generated by the interaction of the charged microdroplets with the analyte molecules on the sample surface are collected. **Figure 7** presents a conceptual diagram of a DESI system used for surface analysis. The ionization mechanisms and operative processes of the DESI source are different from those described above; in this case, the ionization agents (charged solvent droplets) generated by the electrospray collide with the sample surface with the assistance of a high-pressure sheath gas. Droplet collisions on the surfaces cause a large number of new progeny droplets to be expelled from the surface at various sizes, velocities, and angles. It has been suggested that during DESI a two-step analyte-pickup mechanism is involved whereby an initial surface film comprising solvent and analyte is laid down by the sprayer and the analyte of interest is contained within the wetted surface (62–64). The

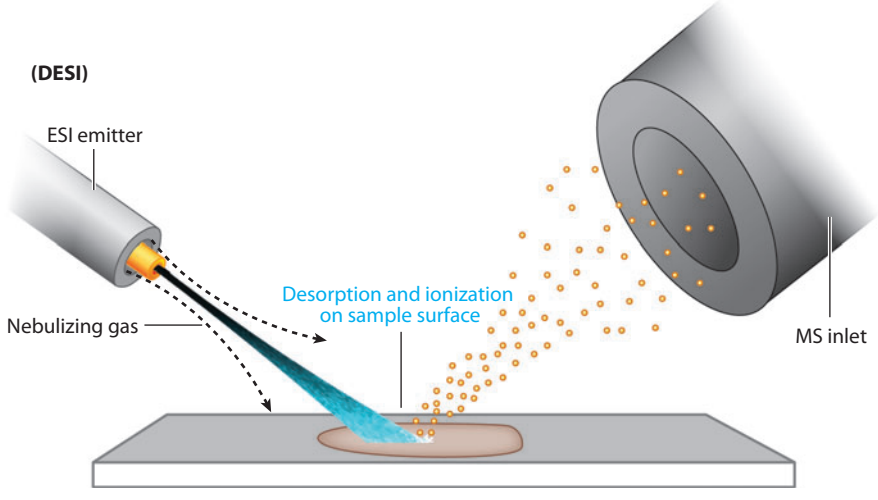

Figure 7

Schematic representation of a desorption electrospray ionization (DESI) analysis of molecules on a sample surface. Abbreviation: MS, mass spectrometer.

so-called droplet-pickup mechanism involves an incident droplet collision desorbing the surface liquid and transporting it into the mass spectrometer.

Desorption/ionization of chemical compounds achieved by impinging the sample surface with an object has been an active research area ever since the development of SIMS, FAB, and plasma desorption techniques. The experimental procedures for DESI are similar to those used for SIMS and other related desorption/ionization methods, except that DESI analysis is performed under atmospheric pressure and the impact objects possess a larger size and higher charge number. A DESI source can be as simple as a conventional electrospray emitter aimed at an angle relative to the sample surface and the mass spectrometer inlet. Again, as in ELDI, the stability and intensity of the analyte ion signals in DESI depend strongly on the spatial relationship among the electrospray emitter, sample surface, and mass spectrometer inlet (65, 66).

Because in DESI sample pretreatment is unnecessary in principle, the emergence of this technique in 2004 attracted many users—particularly those interested in surface analysis (61). Many applications of DESI have been reported, including (*a*) characterization of the active ingredients in pharmaceutical or illicit Ecstasy tablets, industrial polymers in solid and solution phase, peroxide-based explosive chemicals and warfare agents, untreated bacteria cultures, alkaloids in plant tissue, and chemical compounds separated on TLC plates and (*b*) the imaging and profiling of intact biological tissues (67–77). The so-called reactive DESI technique has been used to enhance the detection sensitivity of certain chemicals by doping the ESI solution with selective chemical reagents (e.g., alkali halides and alkylamines) (78, 79). The reactions induced by the addition of chemical reagents in reactive DESI include ion-transfer reactions and adduct formation.

Desorption sonic spray ionization (DeSSI) is performed in the same manner as DESI, except that the impact droplets are generated through sonic spray ionization (SSI; a high-voltage free-spray method) (80). In SSI, the analyte solution is sprayed from a fused-silica capillary with a supersonic nebulizing gas flow coaxial to the capillary. Charged droplets are produced as a result of unbalanced charge distribution during droplet formation in the supersonic pneumatic spray. SSI usually produces droplets that have much lower charge numbers than those produced through ESI. The so-called easy ambient SSI is a modified DeSSI source; the analytes are selectively permeated on a cellulose dialysis membrane (a solid but permeable and flexible membrane) and are then desorbed and ionized through DeSSI processes (81–84).

2.3. Techniques That Generate Electrospray Ionization from Probe

The ambient ionization techniques described above differ from one another in terms of the ways in which the analyte molecules are formed, the ions are generated, and the samples are introduced. Several other ESI-related techniques differ in terms of the way in which the sample solution is introduced into the ESI source. The direct electrospray probe (DEP) method is one such technique (85–87). Instead of being generated at the tip of the capillary, ESI is generated from a sample droplet predeposited on a small metal ring subjected to a high voltage. The sample solution (submicroliter volume) is deposited on the metal ring through a micropipette. The sample-introduction systems required for conventional ESI (e.g., fused-silica capillary, syringe pump, and nebulizing gas) are unnecessary. DEP is particularly useful for rapid analysis of dirty samples or of samples only available in extremely small volume. A similar sampling strategy is also used in probe ESI, a modified DEP technique for rapid sample analysis in which a needle is used to provide a very small sample droplet by being dipped and lifted from the sample solution (88–90).

Under a high electric field, a solvent flow can be induced through the channels created between two bound solid-phase microextraction graphite fibers presenting adsorbed analyte molecules (91). The analyte molecules dissolve in the solvent as it flows through and are then carried to the tip of

the fibers for ESI. In another design, laser desorption from the surfaces of solids and liquids has been used to generate analyte molecules, which were then saved in a solvent reservoir connected to a capillary and syringe pump for subsequent ESI processing (92).

TLC is one of the most frequently used chromatographic methods for separating chemical compounds. Several ESI-related ambient ionization methods have been used to efficiently and rapidly characterize chemical compounds separated on TLC plates. For example, a liquid junction has been created between a surface-sampling probe (SSP) and a solid surface (e.g., a TLC bed); soluble compounds were collected by a solvent flow, which were subsequently delivered into an ESI emitter (93). A similar design has also been used in a plunger-based extractor to remove the analyte from the TLC bed for ESI-MS analysis (94). Direct characterization of chemical compounds separated on TLC plates has also been demonstrated through use of ELDI, LIAD-ESI, and DESI systems (60, 95–98).

3. ATMOSPHERIC PRESSURE CHEMICAL IONIZATION–BASED AMBIENT IONIZATION TECHNIQUES

Whereas ESI is widely used to characterize polar compounds, APCI is a more sensitive technique used for analyzing less polar and more volatile compounds. As for ESI-based ambient ionization techniques, the analytical procedures for APCI-based ambient ionization techniques can involve (*a*) bringing the analyte molecules to the charged or metastable species generated by APCI for ionization or (*b*) directly impinging the sample surface with the charged or metastable species for desorption and ionization (**Figure 1**).

Although there are a number of different methods for performing APCI, a high electric field is used to produce ions or excited-state atoms from different types of reagents (e.g., He, air, water, and organic solvent). The techniques can be divided into two subcategories on the basis of the different methods used to generate the reagent species: corona discharge–based APCI methods and plasma-based APCI methods. In corona discharge–based APCI, the analyte ions are formed through a series of ion-molecule reactions between the reagent species and the analyte molecules. Some of the ionization processes in the plasma-based APCI methods resemble the ion-molecule reactions involved in the conventional corona discharge–based APCI mechanisms, except that energy-transfer reactions between the activated reagent species (e.g., metastable He, N_2, or air) and the analyte molecules are also involved. All of the APCI-related ambient ionization techniques are commonly used for small-molecule analysis because they allow singly charged analyte ions to form.

Because different APCI sources and sample-introduction systems can be combined to generate analyte ions under ambient conditions, several APCI-related ambient ionization techniques have evolved. The schematic representation in **Figure 1** reveals the analytical procedures of the ambient ionization methods based on APCI. For the analysis of gaseous samples, the analyte molecules are conducted to interact with the reagent species for ionization. For liquid-sample analysis, the sample solution is either nebulized or desorbed to form mists, which are carried downstream by heated gas. The analyte molecules are formed through the rapid evaporation of the mists in the open air; these molecules subsequently enter the discharging or plasma area for ionization. For solid-sample analysis, the analyte molecules are formed, then delivered and postionized in the discharging area. Methods for generating analyte molecules from solid surfaces include thermal evaporation and laser ablation or desorption. Solid samples can also be analyzed by directly impinging the sample surface with charged species or metastable atoms; desorption and ionization of the analyte molecules from the sample surfaces then occur.

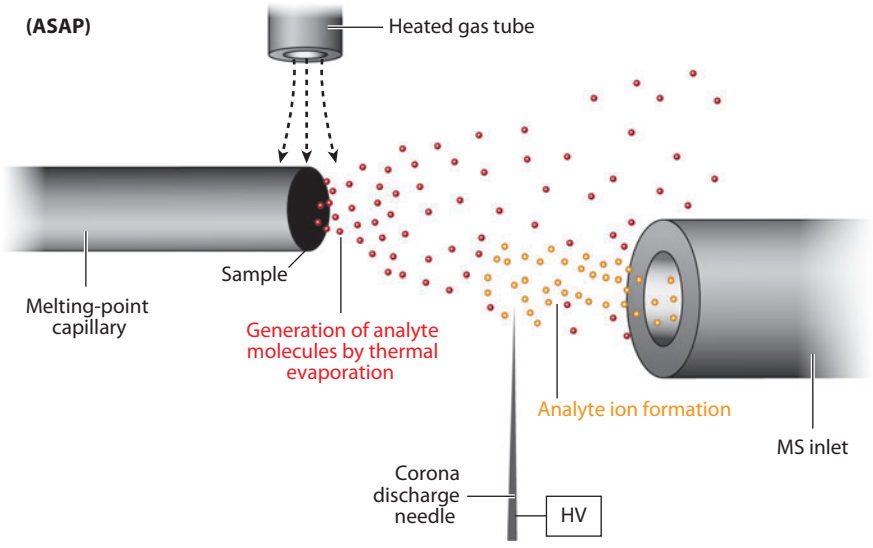

Figure 8

Schematic representation of an atmospheric pressure solids analysis probe (ASAP) analysis of sample molecules. Abbreviations: HV, high voltage; MS, mass spectrometer.

3.1. Corona Discharge–Based Atmospheric Pressure Chemical Ionization Techniques

The so-called atmospheric pressure solids analysis probe (ASAP) technique uses a hot stream of N_2 gas to impinge the solid-sample surface; the resulting analyte molecules are brought close to the APCI needle tip by the N_2 stream, where they are ionized under corona discharge–based APCI conditions (**Figure 8**) (99). Compounds such as lipids, capsaicins, and carotenoids within fresh biological tissues have been rapidly detected via such technology (99, 100). A similar design, so-called laser diode/thermal desorption, uses laser energy to evaporate the sample (101). The analyte molecules are formed through indirect heating of the rear side of a sample plate by a continuous IR diode laser beam. The analyte molecules formed are carried by a stream of preheated N_2 along the transfer tube to the corona discharge APCI needle for ionization.

Desorption atmospheric pressure chemical ionization (DAPCI) differs from ASAP in that it impinges the sample surface with the charged species generated by an APCI probe (**Figure 9**) (102). The charged species (e.g., electrons, protons, metastable atoms, N_2, O_2, solvent, or water ions) used to desorb and ionize the analyte molecules are generated by the corona discharge. Because the reaction products observed in normal APCI processes are also observable in DAPCI spectra, DAPCI may allow the implementation of characteristic ion-molecule reactions while maintaining the capability of ambient pressure desorption ionization/sampling (102). DAPCI provides increased sensitivity to the analysis of compounds of moderate polarity (103–105). Without the need to perform tedious sample pretreatment, investigators have detected trace amounts of melamine in various milk products through DAPCI, with water vapor as the reagent (106).

In corona discharge–based APCI techniques, analyte molecules of lower polarity are usually ionized with lower efficiency. Desorption atmospheric pressure photoionization (DAPPI) allows the efficient ionization of such compounds directly from sample surfaces (107). The source comprises a heated jet of vaporized solvent from a nebulizer, photons emitted from a photoionization

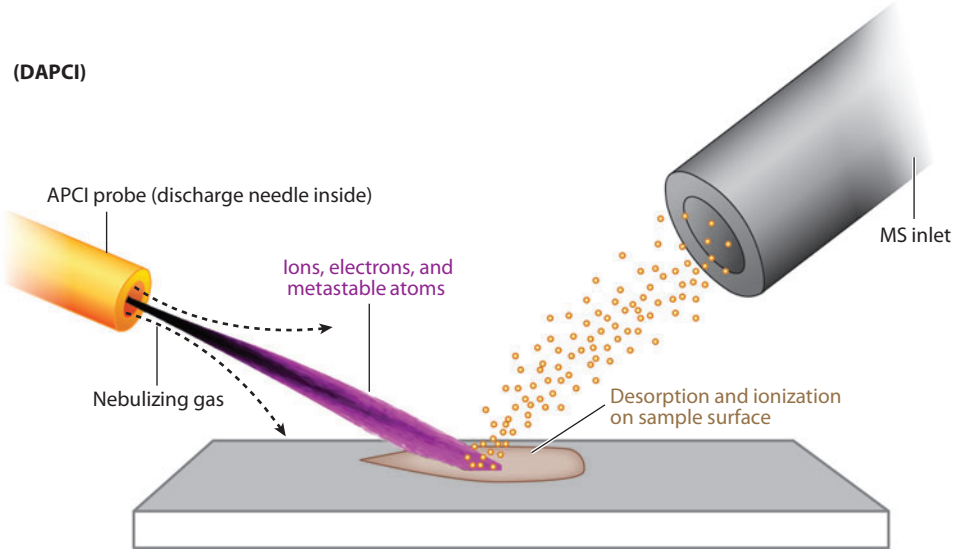

Figure 9

Schematic representation of a desorption atmospheric pressure chemical ionization (DAPCI) analysis of molecules on a sample surface. Abbreviations: APCI, atmospheric pressure chemical ionization; MS, mass spectrometer.

lamp, and a sample plate. The desorption/ionization mechanism of DAPPI has been proposed to occur through (*a*) thermal desorption of the analytes from the sample surface impinged with the heated solvent jet and (*b*) their subsequent ionization in the gas phase through reactions similar to those in conventional APPI (i.e., photoionization and gas-phase ion-molecule reactions) (108). Analytes of low polarity and proton affinity are ionized through charge exchange; analytes of high polarity and proton affinity are ionized through proton transfer (109).

Ambient ionization of analytes in a droplet suspended in air can be achieved through charge-assisted laser desorption/ionization, which is performed simply by directing the charged solvent species (from an APCI probe) toward the air-suspended sample droplet through acoustic levitation (110, 111). The sample droplet contains the analyte molecules and the organic MALDI matrix. Following charging, one side of the sample droplet is irradiated with a pulse laser beam to disintegrate the droplet surface and produce analyte ions. APCI-like mass spectra are produced; these spectra contain singly charged analyte ions. The ionization mechanism presumably involves MALDI-related phenomena, and the excess charge on the sample droplet serves to prevent ion recombination.

3.2. Plasma-Based Atmospheric Pressure Chemical Ionization Techniques

The ionization of analyte molecules in a direct analysis in real time (DART) source occurs when the sample is exposed to a stream of electronic excited-state gas species that are typically derived from He (**Figure 10**) (14). An electrical charge produces ions, electrons, and metastable neutral species. Several ionization mechanisms have been postulated; one such mechanism is Penning ionization, in which ionization of the sample occurs through energy transfer from an excited atom or molecule that has energy greater than the ionization energy of the sample (112, 113). These

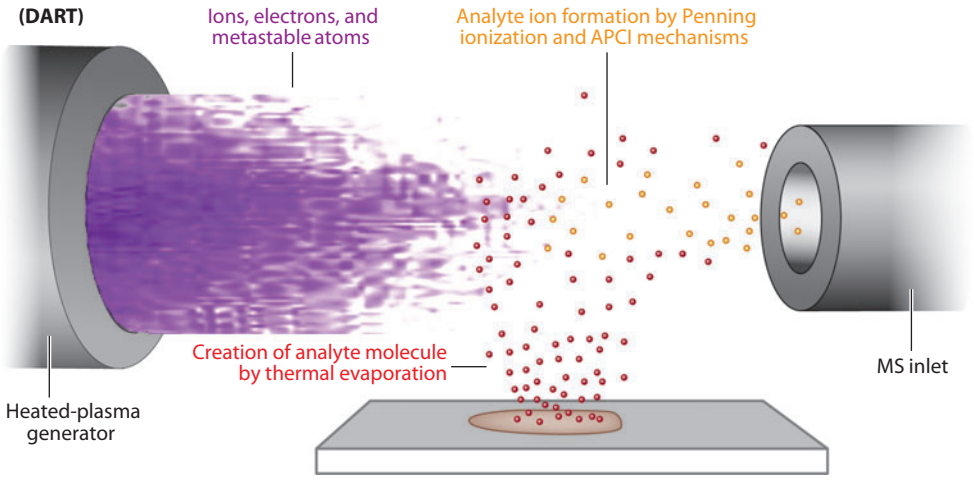

Figure 10

Schematic representation of a direct analysis in real time (DART) analysis of sample molecules. Abbreviations: APCI, atmospheric pressure chemical ionization; MS, mass spectrometer.

mechanisms involve the formation of ionized water and cluster ions, and proton-transfer reactions between the protonated water ion species and analyte molecules have also been reported.

The formation of the electronic excited-state He gas in DART occurs through direct current discharging of the heated He flowing through the cathode and anode in a chamber (114). Following the removal of the charged species via filter electrodes, the heated gas is directed toward the surface of the liquid or solid sample; it can also be used to directly interact with gaseous samples. An insulating cap protects the sample and operator from exposure to the electrodes, heater, and grid. For safety, during analysis it is necessary to shield the operator from the high voltage arising from the ESI capillary, the APCI needle array, and the sample plate. In DART, however, the sample is exposed to a stream of excited gas, and additional shielding of the source is not required. As a result, sample switching becomes extremely rapid, and no memory effects or sample carryover problems have been observed. DART has been applied to the analyses of small polar and nonpolar species in gas, solid, and liquid states, including explosives, active ingredients in pharmaceutical tablets and capsules, metabolites in urine, fatty acid methyl esters in bacterial cells, and chemical warfare agents (114–120). DART has also been used to directly characterize the compounds separated on TLC plates (121). The combination of laser desorption and DART has been used to characterize nonvolatile organic compounds directly from the surface of solid and liquid samples (122–124).

Similar techniques, including liquid-surface Penning ionization (LPI), atmospheric pressure Penning ionization (APPeI), atmospheric pressure glow discharge ionization (APGD), and laser ablation/flowing atmospheric pressure afterglow (LA-FAPA), have also been reported. LPI uses an atmospheric pressure beam of metastable argon atoms to impinge the sample solution, which is prepared by mixing the sample with a matrix (e.g., glycerol or organic solvent) and placing it on a needle tip (125). The needle is heated and applied at kilovolt potential. Ionization of the analytes occurs through Penning ionization or ion-molecule reactions among metastable argon, the solvent/matrix ions, and the analyte molecules. For the ionization of gaseous samples, the APPeI source uses a circular array of corona discharge needles in an argon atmosphere to create the metastable argon (126). Ionization in the APGD system occurs through the introduction of sample vapor through an orifice into the glow discharge region (127, 128). Much like the corona

discharge process, glow discharge is based on electrons ionizing the buffer gas. The operating currents of a glow discharge system are, however, typically several orders of magnitude higher than those in a corona discharge system. The higher current results in the generation of a much larger number and wider variety of reagent ions. The sample must be volatile so that it can be introduced into the glow discharge chamber for ionization. To avoid the problem of carryover in the APGD source, investigators developed a flowing afterglow mode (129, 130). In this mode the ions and excited species generated through APGD are transported outside the discharge chamber, where they react with atmospheric constituents. These reactions lead to the production of reagent ions, so the sample need not be introduced into the discharge chamber. In LA-FAPA, analyte molecules are generated through laser ablation and are subsequently introduced at the exit of a flowing glow discharge unit for ionization (131).

3.3. Dielectric Barrier Discharge, Low-Temperature Plasma, and Plasma-Assisted Desorption/Ionization

The dielectric barrier discharge technique involves a specific type of gas discharging in which the electrodes are isolated from each other by a layer of isolating medium (132). Dielectric barrier discharge ionization (DBDI) is performed at atmospheric pressure by placing a dielectric layer (glass slide) between two electrodes and applying an alternating potential of 3.5 to 4.5 kV at a frequency of 18 to 25 kHz (133–135). Unlike a glow discharge ion source, reduced pressure is not required in order to maintain a stable discharge for DBDI. The dielectric layer limits the average current density in the gas, forming a stable low-temperature plasma (LTP) featuring a large number of high-energy electrons. During sample analysis, the analytes deposited on the glass-slide surface move to the field of the plasma discharge for desorption and ionization. Various gases (e.g., He, N_2, Ar, air) can be used to generate plasma in a DBDI source. As for DART, the mechanism of ionization of the analytes in the plasma generated in a DBDI source may involve several processes, such as Penning ionization and ion-molecule reactions.

An LTP probe is a modified DBDI source (136, 137). The analytical procedure for use of an LTP probe is similar to that of DAPCI in that the plasma generated by the LTP probe impinges the sample surface. The LTP probe uses dielectric barrier discharge to generate the LTP. It differs from DBDI in the way in which the counter electrodes are placed within the probe: The LTP probe allows analysis of the object without the requirement of placing the sample between two counter electrodes. The LTP probe allows direct interaction of the LTP with the solid- or liquid-sample surface. The ability to extract analytes from the sample surface without heating makes LTP a good candidate for use as the ionization source in portable mass spectrometers.

Plasma-assisted desorption/ionization (PADI) is similar to DART and DBDI in that it uses plasma for ionization, except that a radio frequency (13.56 MHz, 200–500 peak-to-peak voltage) is applied to the unsharpened end of the needle to create low-power plasma from He to ionize the volatile analytes under ambient conditions (138). The ionization processes presumably involve a combination of direct EI ionization, metastable Penning ionization, and ion-molecule reactions. Similar to that of LTP, the plasma of PADI is relatively cold to the touch and does not heat the sample. This phenomenon, in turn, allows analysis of thermally unstable samples. Also, it does not require the removal of highly energetic species, as is the case in DART.

4. CONCLUSION

The recent development of ambient ionization techniques has created a new subfield in MS. These developments have simplified analyses, increased ease of use, shortened analytical time,

and extended the types of samples that can be analyzed by mass spectrometers. Moreover, many ambient ionization techniques have been used to perform surface analyses of solid and liquid samples without the need for pretreatment. Although most of these developments have focused on systems in which the analyte molecules are produced and introduced, the principles of ionization have not substantially changed. Fundamentally, the ionization concepts of the techniques can be viewed as variations on the original ESI and APCI themes.

In this review, we have sorted the existing ambient ionization techniques into two main subcategories, primarily on the basis of their ionization processes (ESI and APCI mechanisms), that we further differentiated in terms of the approach used for sampling (thermal evaporation and desorption, pyrolysis, laser ablation and desorption, shock waves, pneumatic and ultrasonic nebulization, and direct impinging of sample surfaces with charged and metastable species). No matter how the analyte molecules are produced and introduced in the source, either they are coupled with an ionization process or ionization occurs as a discrete process subsequent to sampling. ESI-related ambient ionization techniques are suitable for analysis of molecules possessing high masses, but they are limited to moderately to highly polar compounds. Spectra are often complex because of the formation of adduct or multiply charged ions during ionization. These techniques have obvious biochemical applications. APCI-related ambient ionization techniques are suitable for analysis of less polar or nonpolar compounds with simple mass spectra (no solvent clusters or multiply charged or alkali metal adducts), but they have a more limited mass range.

There is considerable overlap between various ambient ionization techniques because most of the techniques combine a limited number of sample-introduction, desorption, and ionization processes. Although it may be a challenge for scientists to realize the differences among all these techniques, a better appreciation of the existing ambient ionization techniques for their analytical potential in different areas will allow future modifications and development of alternative protocols to advance this field. Ambient ionization has already been an important part of modern MS; it will continue to be an active area of research.

DISCLOSURE STATEMENT

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

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