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Low-Temperature Plasma Probe for Ambient Desorption Ionization

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A low-temperature plasma (LTP) probe has been developed for ambient desorption ionization. An ac electric field is used to induce a dielectric barrier discharge through use of a specially designed electrode configuration. The low-temperature plasma is extracted from the probe where it interacts directly with the sample being analyzed, desorbing and ionizing surface molecules in the ambient environment. This allows experiments to be performed without damage to the sample or underlying substrate and, in the case of biological analysis on skin surfaces, without electrical shock or perceptible heating. Positive or negative ions are produced from a wide range of chemical compounds in the pure state and as mixtures in the gaseous, solution, or condensed phases, using He, Ar, N_2, or ambient air as the discharge gas. Limited fragmentation occurs, although it is greater in the cases of the molecular than the atomic discharge gases. The effectiveness of the LTP probe has been demonstrated by recording characteristic mass spectra and tandem mass spectra of samples containing hexahydro-1,3,5-trinitro-1,3,5-triazine (RDX) and 2,4,6-trinitrotoluene (TNT) from poly(tetrafluoroethylene) (PTFE) surfaces where limits of detection are as low as 5 pg. Other performance characteristics, when using a commercial ion trap mass spectrometer, include 3−4 orders of magnitude linear dynamic range in favorable cases. Demonstration applications include direct analysis of cocaine from human skin, determination of active ingredients directly in drug tablets, and analysis of toxic and therapeutic compounds in complex biological samples. Ionization of chemicals directly from bulk aqueous solution has been demonstrated, where limits of detection are as low as 1 ppb. Large surface area sampling and control of fragmentation by a simple adjustment of the electrode configuration during operation are other demonstrated characteristics of the method.

Mass spectrometry (MS) is recognized as among the most sensitive general purpose analytical methods. Ambient ionization of samples lifts the sample preparation/preseparation requirement of mass spectrometry,[1,2] so providing a significant advantage for real-time and in situ chemical analysis. In the few years since direct ambient ionization was first demonstrated with desorption electrospray ionization (DESI)[3] and direct analysis in real time (DART),[4] more than a dozen ambient desorption ionization methods have been reported.[2] Various chemical and physical agents and processes are used for desorbing and ionizing analytes from mixtures in the condensed phase, including charged droplets, plasmas, photons, and heated gas. The desorption ionization process can be implemented in a single step using a single agent, such as the charged droplets from an electrospray source as in DESI[3] or the metastable atoms from a discharge as in DART.[4] Alternatively, the experiment can be performed in two steps, with desorption caused by one agent, such as a laser beam[5,6] or a hot gas,[7] followed by ionization using a different agent or method, such as ESI, as is the case for electrospray laser desorption ionization (ELDI),[5−7] matrix-assisted laser desorption electrospray ionization (MALDESI),[8] and laser ablation electrospray ionization (LAESI).[6]

Among the set of ambient ionization methods are several which employ atmospheric pressure plasmas including DART,[4] desorption atmospheric pressure chemical ionization (DAPCI),[9] flowing afterglow atmospheric pressure glow discharge (FA-APGD),[10] plasma-assisted desorption ionization (PADI),[11] and dielectric barrier discharge ionization (DBDI).[12] All these desorption ioniza-

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Table 1. Ambient Ionization Sources Using Low-Temperature Plasmas

source	discharge type	sample exposed to discharge?	temperature at sample surface (°C)	discharge gas	gas flow rate (L/min)	voltage and power (used in demonstration)
LTP probe	ac DBD[a]	N	30	He, Ar, N_2, air	<0.4	ac, 2−5 kHz, 2.5−5 kV_{pp}, <3 W
DBDI[b]	ac DBD	Y	N/A	He, Air	<0.2	ac, 20.3 kHz, 3.5−4.5 kV_{pp}, 5−30 W
PADI[c]	rf discharge	Y	N/A	He	>0.7	rf, 13.56 MHz, 0.3 kV_{pp}, <5 W
DART[d]	dc discharge	N	250−350	He, N_2	1	dc, +1−5 kV[e]
FA-APGD[f]	dc discharge	N	200	He	0.9−1.5	dc, −500 to −700 V, 3−20 W

[a] DBD: dielectric barrier discharge. [b] Refs 12 and 14. [c] Ref 11. [d] Refs 4, 15, and 16. [e] Additional heating is applied. [f] Refs 10 and 17.

tion sources are significantly different from traditional plasma ion sources used for inductively coupled plasma mass spectrometry (ICPMS), where high-temperature plasmas are used and molecular structures are not represented in the resulting ions. Nonequilibrium, low-temperature plasmas (LTP) can be generated at atmospheric pressure, instead of using decreased pressure as in glow discharge (GD) ionization.[13] Differences with DAPCI center on the nature of the discharge and support gas, whereas there are major differences in device configuration, discharge, and temperatures from those used in DART, PADI, and the FA-APGD sources. The method is most closely related to the previously reported dielectric barrier method, but the use of a probe configuration which allows direct interaction of the plasma with the sample is the distinguishing feature of the LTP probe. Thus, although the LTP probe utilizes dielectric barrier discharge to create the LTP, it is different from DBDI in the way the counter electrodes are placed within the probe allowing the analysis of any type of object (fixed, small, large, etc.) without having to place the sample between two counter electrodes. Table 1 summarizes the features of the ambient sampling ionization methods utilizing plasmas.

Nonequilibrium, low-temperature plasmas operate through numerous microdischarges which generate such chemically active species as high-energy electrons, metastable neutrals, and radical ions.[18] In addition to their applications for mass spectrometry, atmospheric pressure LTP devices have also been designed in the past for spectrochemical analysis and for modification of biological and biocompatible surfaces.[19−22]

In this work, an LTP probe of unique configuration has been developed for rapid and easy sampling of surfaces for mass spectrometry. The dielectric barrier discharge mechanism is used to generate and maintain a stable low current (microamps), low-temperature plasma at atmospheric pressure. Special consideration has been taken to extract the plasma generated species from the discharge region between the counter electrodes to allow easy scanning of surfaces. There are many similarities and differences between the LTP probe and other plasma-based ambient desorption ionization sources. We report unique capabilities of the LTP probe as an ion source for mass spectrometry. These capabilities include the use of air as the discharge gas, the ability to control fragmentation by a simple adjustment of the electrode configuration, the ability to directly analyze bulk aqueous solutions with no sample preparation, and the ability to analyze large surface areas.

CONFIGURATION OF THE LOW-TEMPERATURE PLASMA PROBE

The LTP probe consists of a glass tube (o.d. 6.35 mm and i.d. 3.75 mm) with an internal grounded electrode (stainless steel; diameter, 1.57 mm) centered axially and an outer electrode (copper tape) surrounding the outside of the tube, as shown in Figure 1a. The wall of the glass tube serves as the dielectric barrier. An alternating high voltage, 2.5−5 kV at a frequency between 2−5 kHz, is applied to the outer electrode with the center electrode grounded to generate the dielectric barrier discharge. The discharge ac voltage was provided by a custom-built power supply with total power consumption below 3 W. In the power supply, a square waveform with adjustable frequency and amplitude was generated by a digital circuit. The square waveform was then amplified using a power amplifier and an automobile engine ignition coil to provide an ac with an amplitude as high as 5 kV. A discharge gas, either He, Ar, N_2, or air, is fed through the glass tube to facilitate the discharge and to transport analyte ions to the mass spectrometer. The flow rate of the discharge gas can be lower than 0.4 L/min, which is the lowest flow rate measurable with a FR2A14SVVT variable flow meter (Key Instruments, Trevose, PA) used in the study.

Instead of placing the sample close to or within the discharging area for ionization, as in most cases where plasma ionization is performed, the design of the LTP probe allows the plasma species to be extracted by the combined action of the gas flow and the electric field, with a torch (visible when He or Ar is used as discharge gas) extending beyond the glass tube and suitable for direct surface sampling. The temperature of the surface area in contact with the sampling plasma torch was measured, using a Fluke 62 mini IR thermometer (Fluke Corporation, Everett, WA), to be approximately 30 °C, so there is no damage to the surface due to heating. Since the high-voltage electrode is electrically isolated from the direct discharge region, the sample is not subjected to the possibility of electric shock. These features mean that even chemicals on a human finger can be directly analyzed

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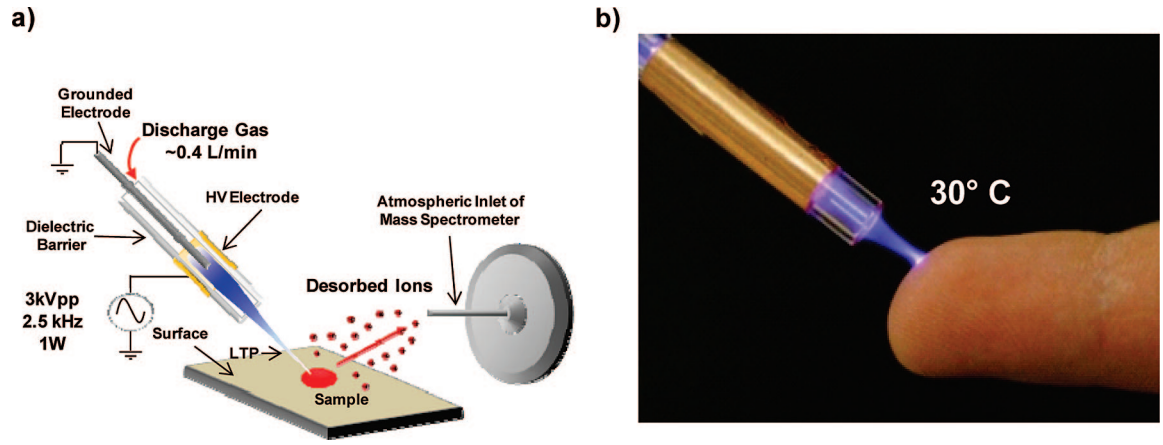

Figure 1. LTP probe for ambient ionization MS: (a) schematic of the configuration and (b) photo of the extracted plasma being used to sample compounds on a human finger. Insulation has been removed from the HV electrode to show placement of the probe; all experiments performed included HV insulation on the probe for safety.

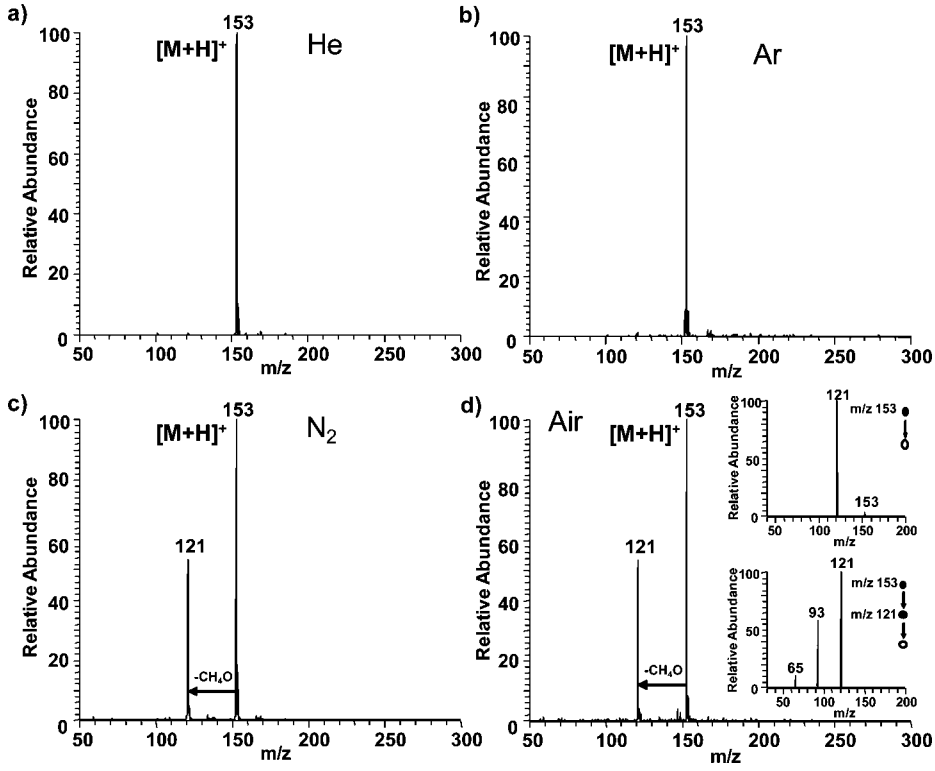

Figure 2. Mass spectra of methyl salicylate vapor in air acquired in the positive ion mode using the LTP probe with (a) helium, (b) argon, (c) nitrogen, and (d) air as discharge gas.

using the LTP probe (as shown in Figure 1b and discussed in detail later). The extent of the plasma torch from the probe can be controlled by adjusting the center electrode position to decrease its overlap with the outer electrode so that the electric field along the tube axis is enhanced.

Characterization of the LTP probe was performed using a Thermo Fisher LTQ mass spectrometer (Thermo Fisher, San Jose, CA). A DESI 2D imaging stage[23] was modified to mount the LTP probe instead of a DESI source. For ambient ionization sources like DESI, which use relatively high gas flow rates, a narrow range of angles for the sprayer−surface−inlet configuration is usually required to obtain optimum efficiency.[24] The performance of the LTP probe was found to be minimally sensitive to the distances and angles of the probe−sample−MS inlet geometry. The samples were placed on the sample plate of the imaging stage, typically 1−3 cm away from the LTQ inlet. The LTP probe was usually placed with its end 1 mm to 2 cm away from the surface with an angle between 5° and 60° from the sample surface. The effects of these variables are discussed below.

CHARACTERIZATION OF THE LTP PROBE

Discharge Gas. To demonstrate that the LTP probe can be used to ionize gas-phase molecules, a vial containing 1 mL of

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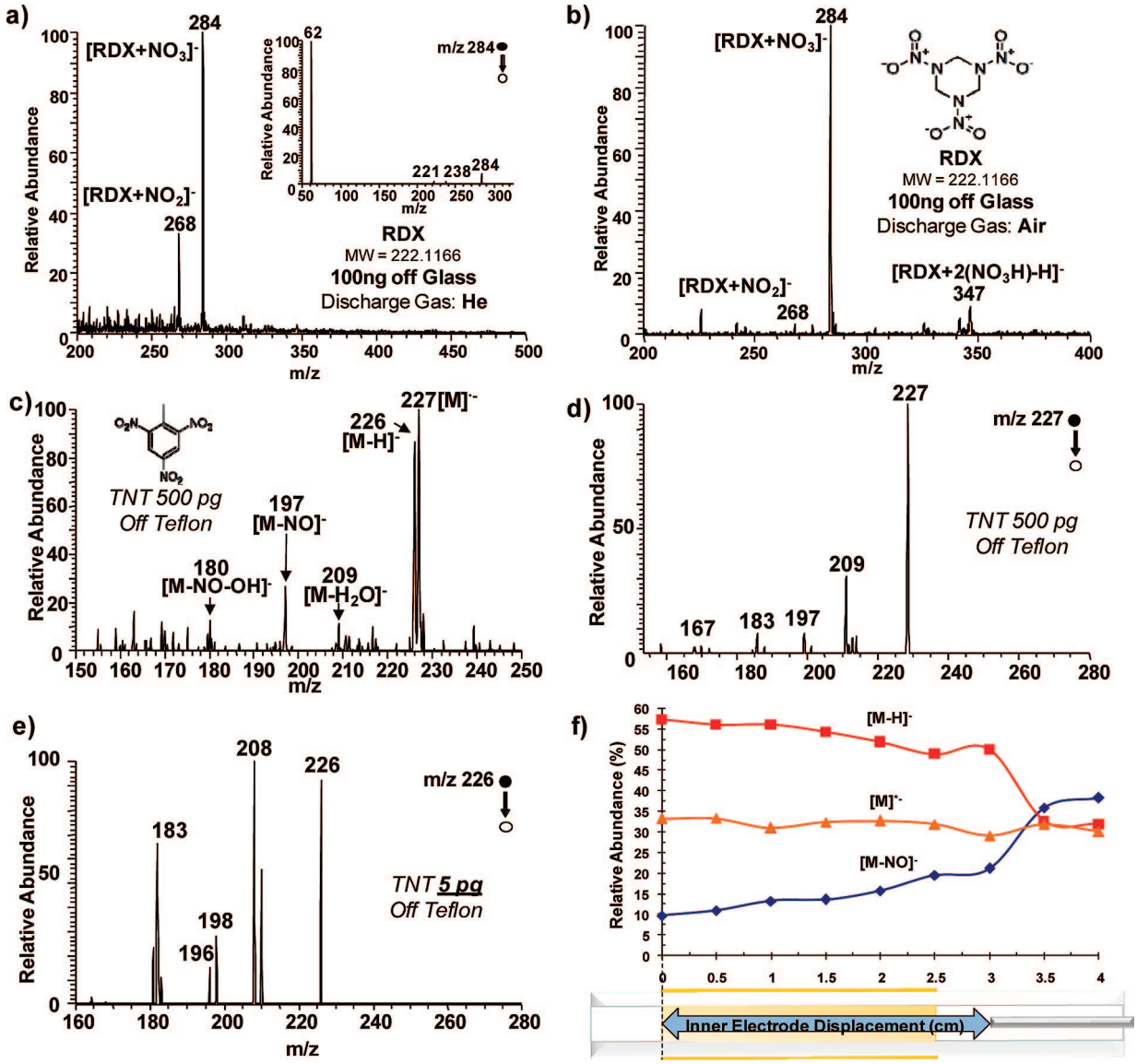

Figure 3. Mass spectra of explosive RDX with (a) He as discharge gas (inset MS^2 data) and (b) air as discharge gas when desorbing 100 ng of RDX from glass surfaces. (c) MS spectra for 500 pg of TNT on a PTFE surface, (d) product ion MS^2 of *m/z* 227 at 500 pg concentration, (e) product ion MS^2 of *m/z* 226 at 5 pg concentration (limit of detection, LOD), and (f) adjustment of degree of fragmentation by varying the center electrode position.

methyl salicylate ($C_8H_8O_3$), a common chemical warfare agent simulant, was held 1 m away from the LTP probe; the vial was opened for 1 s to allow headspace vapor to escape for analysis. After a delay of ~5 s to allow diffusion of the vapor to the LTP probe, mass spectra with good signal-to-noise ratios were recorded in the positive mode with He, Ar, N_2, or air as the discharge gas (Figure 2). MS^2 spectra using collision-induced dissociation (CID) to activate the mass-selected precursor ion were also acquired with air as the discharge gas as shown in Figure 2d, inset. Interestingly, an abundant fragment ion *m/z* 121 (loss of CH_4O from molecular ion) was observed in the MS spectra recorded with N_2 and air, but not with He or Ar, as the discharge gas. The metastable He atom has an internal energy as high as 19.8 eV (2S3 state), sufficient to fragment most organic molecules. The lack of fragmentation with He indicates that mechanisms other than direct penning ionization must be responsible. The fragment ions observed are likely due to the gas-phase charge-transfer reactions initially involving $N_2^{+\bullet}$ or $O_2^{+\bullet}$.[25,26] As is the case in DART, energetic species such as metastable He atoms are likely to rapidly generate secondary ions such as the observed protonated water clusters[4] among which $(H_2O)_2H^+$ and $(H_2O)_3H^+$ as the most abundant.

Explosives Analysis. Trace analysis of explosives is important to public safety[27] and is challenging in that trace in situ analysis is required. Direct detection of solid explosives from surfaces using the LTP probe was demonstrated in the cases of hexahydro-1,3,5-trinitro-1,3,5-triazine (RDX) and 2,4,6-trinitrotoluene (TNT) on poly(tetrafluoroethylene) (PTFE) and glass surfaces with mass analysis in the negative ion mode. The RDX sample surface was prepared by spotting a 5 μL methanol solution containing 100 ng of RDX onto a 12 mm^2 area of a glass microscope slide and

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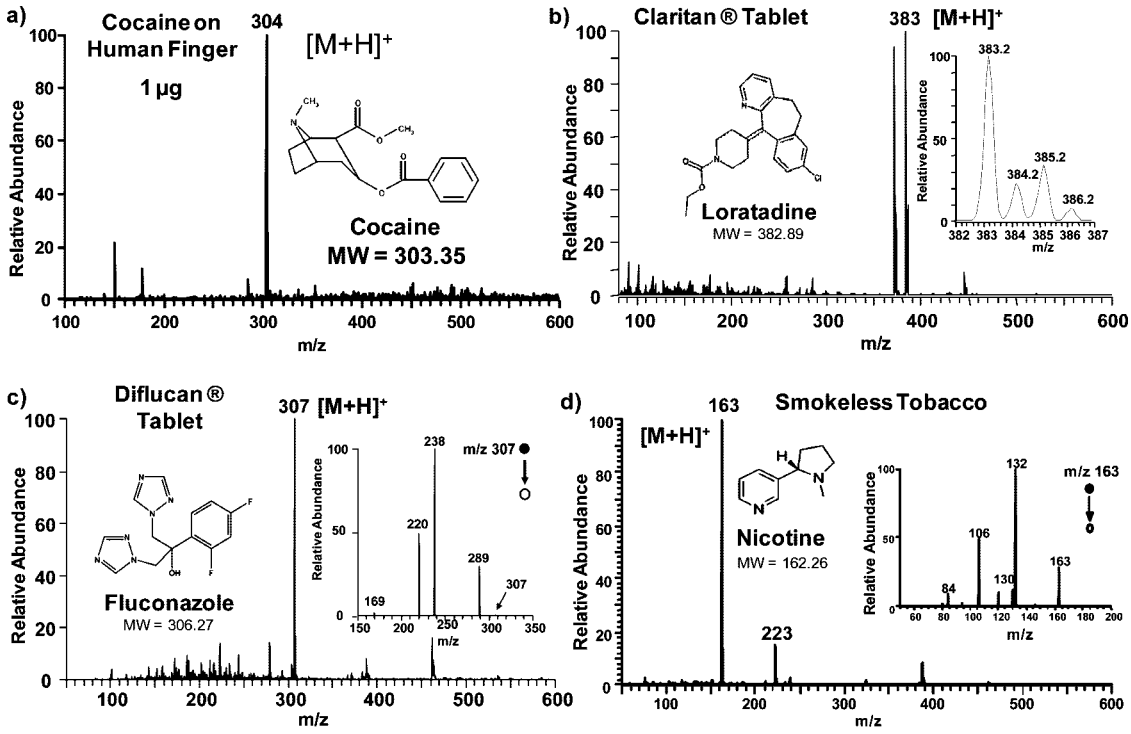

Figure 4. Analysis of chemicals from various substrates and matrixes using the LTP probe: (a) 1 μg of cocaine on a human finger, (b) a 10 mg Claritin tablet containing loratadine, (c) a 100 mg Diflucan tablet containing fluconazole, and (d) about 250 mg of smokeless chewing tobacco. Insets are (b) molecular ion region and (d and c) product ion MS/MS spectrum.

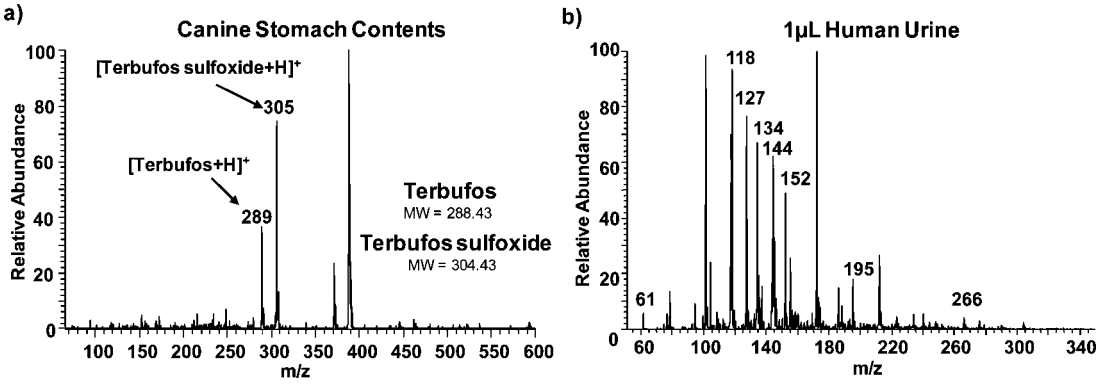

Figure 5. Analysis of complex mixtures: (a) stomach content of a deceased canine and (b) 1 μL of raw urine dried on a PTFE surface.

allowing it to dry. The mass spectra recorded in the negative ion mode using the LTP probe with He and air as the discharge gas are shown in Figure 3, parts a and b, respectively. Adduct ions $[M + NO_3]^-$ (m/z 284) and $[M + NO_2]^-$ (m/z 268) were observed with He as the discharge gas, whereas both adduct ions with NO_3 and NO_2 were observed with air as well as adduct ion $[M + 2(NO_3H) - H]^-$ (m/z 347). The TNT sample was prepared by spotting a 0.5 μL MeOH solution containing 500 pg of TNT onto a PTFE surface, so as to cover an area of about 2 mm^2 after drying. MS spectra with good signal-to-noise ratios were recorded for the negatively charged ions desorbed using the LTP probe (Figure 3c). Both the radical ion (m/z 227) and the deprotonated (m/z 226) molecule were present along with fragment ions $[M - H_2O]^-$ (m/z 209), $[M - NO]^-$ (m/z 197), and $[M - NO - OH]^-$ (m/z 180). The MS^2 spectrum was recorded for the radical ion m/z 227 to confirm the assigned chemical structure (Figure 3d). Limits of detection for TNT were determined to be as low as 5 pg on glass or PTFE surfaces in the MS^2 mode (inset Figure 3e), which is comparable to the value achieved in DESI experiments.[9]

Fragmentation Control. In comparison with desorption methods using sprayed charged droplets,[3] significant fragmentation is often observed for desorption using methods involving gaseous discharges.[4,10,11,14] In some of these methods this is because the sample is routinely heated to enhance ionization. Fragmentation complicates the mass spectra of mixtures so is generally undesirable; however, it can be produced as needed by using tandem mass spectrometry. With the use of the LTP probe, fragmentation is normally minimal, as discussed further below. It was found that the extent of the fragmentation could be adjusted effectively by adjusting the electric field along the tube axis. A series of spectra was recorded for TNT while the center electrode was moved along the tube axis. The intensities of the radical molecular ion M^{*-} (m/z 227), the deprotonated molecule $[M - H]^-$ (m/z 226), and the fragment ion $[M - NO]^-$ (m/z 197),

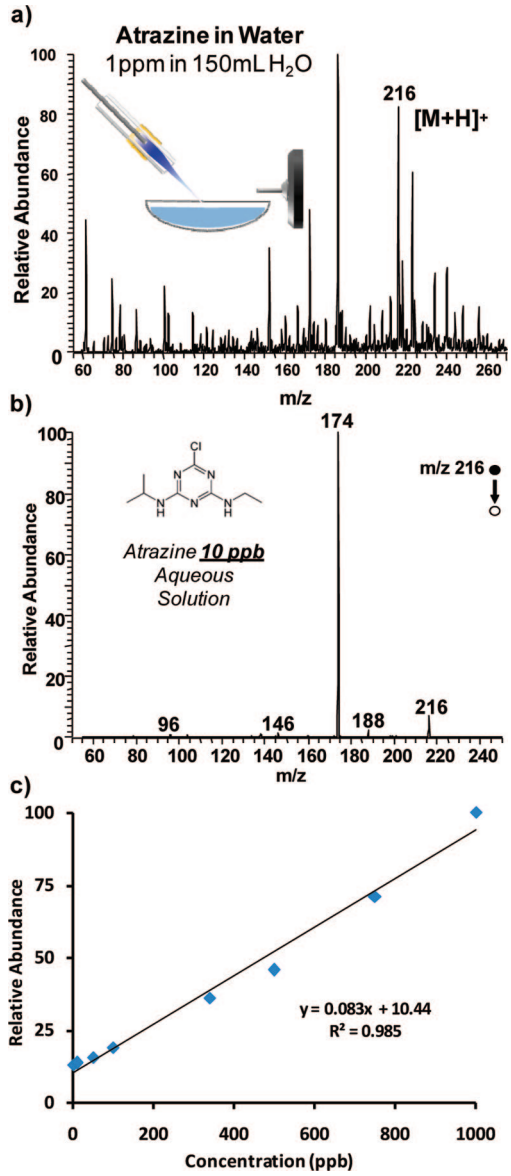

Figure 6. LTP desorption ionization of atrazine directly from an aqueous solution: (a) MS of 1 ppm solution and (b) product ion MS^2 spectrum of *m/z* 216 10 ppb solution. (c) Plot of relative abundance of atrazine vs concentration showing the linear dynamic range between 1 ppb and 1 ppm.

plotted as a function of displacement with respect to the center electrode, are shown in Figure 3f. As the distance between the front ends of the central and high-voltage electrodes increases, the intensity of the deprotonated molecule $[M - H]^-$ (m/z 226) decreases while the intensity of the fragment ion $[M - NO]^-$ (m/z 197) increases. As the center electrode is displaced farther from the high-voltage electrode, the electric field component along the tube axis increases, which results in an increase in the maximum accelerating field for the ionic species in the plasma and hence to more energetic fragmentation of the analyte molecules during desorption. The ease of adjustment of the fragmentation during desorption ionization is an advantage for identifying unknown analytes by chemical structure confirmation, especially when mass spectrometers without tandem mass spectrometry capability are used. With tandem mass spectrometers, it is convenient to ionize gently and to use tandem mass spectrometry to produce fragmentation to the extent needed.

Analysis of Chemical on Human Skin. As discussed earlier, the design of the LTP probe allows the use of the extracted plasma to be scanned across a surface so that the surface is not affected by the electric potential or by heat. Direct analysis of chemicals from human skin was demonstrated by desorbing cocaine ($C_{17}H_{21}NO_4$) from a human finger using the LTP probe. A 1 μL MeOH solution containing 1 μg of cocaine was spotted on a 4 mm^2 area of skin and allowed to dry. The LTP probe, with air as the discharge gas, was used to analyze the sample area on the finger, and a spectrum was recorded in the positive ion mode. Figure 4a shows that the protonated molecule m/z 304 is observed.

Complex Matrixes Analysis. The convenience of using the LTP probe for ambient sampling with little or no sample preparation is demonstrated by direct analysis of the chemicals in such complex matrixes including drug tablets and smokeless tobacco. Tablets of the antihistamine Claritin (Schering-Plough, Kenilworth, NJ) and the prescription antifungal agent Diflucan (Pfizer, New York, NY) were analyzed using the LTP probe (He discharge gas) with no pretreatment besides removing a thin layer of the tablet to expose the subsurface region. The spectra recorded show the protonated molecule of the active ingredient loratadine in Claritin (Figure 4b) and fluconazole in Diflucan (Figure 4c). The inset to Figure 4b shows the characteristic chlorine isotopic signature of Claritin matching DESI-MS data obtained for Claritin using an Orbitrap mass spectrometer.[28] Tandem mass spectrum acquired for the molecular ion m/z 307 ($[M + H]^+$) via CID (Figure 4c, inset) confirms the identity of this signal as corresponding to fluconazole; the fragmentation pattern is very similar to that previously reported using electrospray ionization.[29] A small pinch (about 250 mg) of the Copenhagen smokeless tobacco (U.S. Smokeless Tobacco Co., Stamford, CT) was also exposed to the plasma of the LTP probe, and the recorded spectra show a intense signal due to protonated nicotine (m/z 163) (Figure 4d). Tandem mass spectrometry experiments were performed by selecting the ion m/z 163 for dissociation, and the MS^2 spectrum shows the characteristic fragmentation pattern of nicotine (Figure 4d, inset).

It is noteworthy that fluconazole has a tertiary alcohol molecular structure, which means that protonated fluconazole is expected to fragment readily by dehydration.[29] The MS^2 spectrum of ion m/z 307 (Figure 4c, inset) shows complete dissociation of the protonated molecular ions, which confirms its relatively fragile nature. However, the observation of the fluconazole protonated molecule as the major species desorbed from the tablet and the almost complete absence of any signal due to dehydration in the mass spectrum indicates that ionization using the LTP probe is a very gentle chemical process.

The capability of the LTP probe to analyze samples in complex matrixes has been further demonstrated by examination of the stomach contents of a deceased dog, suspected to have died from ingestion of an insecticide. Without any sample workup, extraction, or separation, a small amount (about 1 g) of stomach contents

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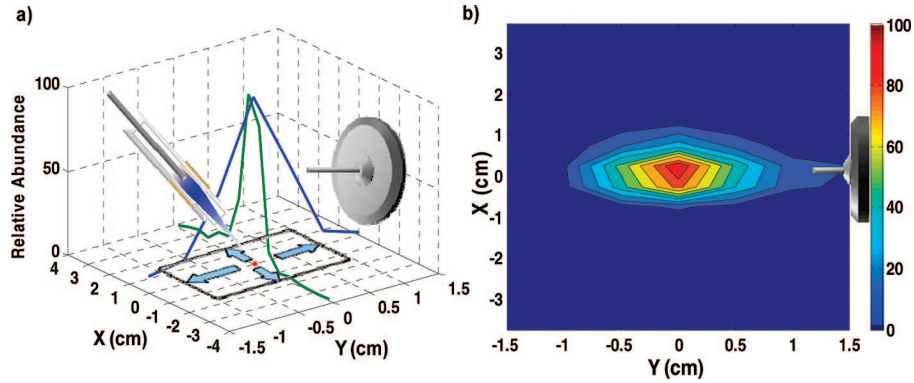

Figure 7. Characterization of the LTP probe sampling area using 1 μg of cocaine: (a) relative intensity of *m/z* 304 along the *x*- and *y*-axes; (b) extrapolated 2D distribution of the relative desorption efficiency.

was placed on a glass slide and analyzed directly via the LTP probe with N_2 as the discharge gas. Mass spectra of the stomach contents (Figure 5a) clearly show the protonated molecule Terbufos (*m/z* 289) and Terbufos sulfoxide (*m/z* 305), two active chemicals in common Terbufos-based insecticides. The spectra acquired using LTP are similar to those by DESI.[30] Urine is another complex sample; direct MS analysis of urine using ESI or APCI is usually problematic due to the high concentration of salts and matrix interferences.[31] With the use of ambient sampling by DESI, patterns of occurrence of metabolites can be quickly acquired from raw urine without pretreatment.[32] In this work, 1 μL of raw human urine was spotted on a PTFE surface, dried, and then analyzed using LTP desorption with He as the discharge gas. A spectrum was recorded in the positive ion mode as shown in Figure 5b. The peak at *m/z* 195 corresponds to protonated caffeine, which was confirmed with MS^2 spectra (data not shown). The peaks at *m/z* 61 and 144 are likely to correspond to urea and uracil, respectively.

Direct Analysis of Aqueous Solutions. A feature of the LTP probe is that it can be used to ionize analytes directly from aqueous solutions, a capability recently shown also for ELDI.[33] However, a matrix of carbon powder is necessary in the solution-phase ELDI experiments which also require a laser as well as an ESI source. In the LTP probe experiments, the simple probe itself can be used to directly desorb and ionize the analytes from aqueous solutions. To demonstrate this feature, a glass dish containing 150 mL of deionized water was spiked with atrazine (agricultural herbicide) resulting in a 1 ppm aqueous solution. The solution was placed near the MS inlet, and the LTP probe (He discharge gas) was used to direct the plasma over the liquid surface. Protonated atrazine gives a signal at *m/z* 216 which can be clearly seen in the spectrum recorded in the positive ion mode (Figure 6a). The MS^2 spectrum (Figure 6b), taken using a 10 ppb solution, sufficed to confirm the assigned structure of the ion. The linear dynamic range for this experiment varies from 1 ppb to >1 ppm for atrazine in deionized water (Figure 6c). This capability of the LTP probe has the potential for wide application involving direct analysis to bulk liquids, such as flowing streams, without sample collection, cleaning, or even drying.

Large-Area Analysis. As already described, the sampling of surfaces using LTP is minimally sensitive to the relative position of the sample and the angles used in the desorption setup, which makes it promising for large-area sampling. Although high spatial resolution with focused desorption sampling is required for imaging analysis,[34−37] sampling of chemicals simultaneously from a large area is desirable in applications such as fast screening of luggage for illicit chemicals, where scanning across the surface slowly is not tolerable. The large-area analysis capability of the LTP probe was characterized by determining the area in which a cocaine sample could be detected. A 1 μL MeOH solution containing 1 μg of cocaine was spotted on a PTFE surface resulting in a sample spot size of 3 mm^2 after drying. The LTP probe and MS inlet were held stationary relative to each other at a distance of 1.25 cm. The sample spot was then moved 3 cm in the *y*-direction (*x*-coordinate set at 0 cm) and 7.5 cm in the *x*-direction (*y*-coordinate set at 0 cm), with stops at each increment of 0.5 cm where spectra were recorded and averaged for 20 s. The peak intensity of protonated cocaine *m/z* 304, recorded at each location, was first normalized to obtain the highest intensity and then plotted against the spatial coordinates as shown in Figure 7a. Figure 7b shows a 2D distribution of the cocaine signal in the LTP desorption ionization experiment. The current configuration of the LTP probe allows sampling of an area >5 cm^2 using this simple scanning procedure.

CONCLUSION

An ambient desorption ionization source based on a discharge barrier plasma desorption and fashioned in the form of a low-temperature plasma probe has been developed for desorption ionization of samples in the solid, solution, and gas

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phases for fast mass spectrometry analysis.[38] There are both similarities and differences between the LTP probe and other plasma-based ambient desorption ionization sources. Analytical performance comparisons between the LTP probe and these sources have not been performed; however, the LTP probe has several unique capabilities which are reported. The novel design of the probe allows the low-temperature plasma to be extracted from the source and used to sample surfaces without significant heating. This makes this ionization method extremely gentle, as shown, for example, by the lack of fragmentation of protonated tertiary alcohols. The ability to perform desorption ionization using air as discharge gas makes the LTP probe a candidate as the ionization source for portable mass spectrometers, where consumables like helium might be inconvenient or disallowed. The capability of desorbing chemicals from bulk aqueous solutions without the need for a matrix or laser and the potential for large-area surface sampling should allow the LTP probe to be applied to a wide range of applications. The data also show that the method is successful in providing both positive and negative ion mass spectra from a wide range of organic compounds.

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