

Direct Mass Spectrometric Analysis of Semivolatiles Derived from Real Samples at Atmospheric Pressure

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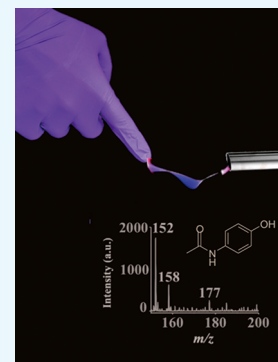


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Supporting Information

ABSTRACT: This study demonstrated a facile ionization method with the use of real samples for the ionization of their main compositions at ambient conditions for mass spectrometric analysis. Analyte ions derived from the real samples were readily observed in the mass spectrum when placing the samples close (≤ 1 mm) to the inlet of the mass spectrometer applied with a high voltage. No additional accessories such as an ionization emitter, a plasma generator, or a high voltage power supply were required for this approach. Ionization of semivolatiles derived from the samples occurred between the samples and the inlet of the mass spectrometer presumably owing to the dielectric breakdown induced by the electric field provided by the mass spectrometer. Real samples including plants, medicine tablets, and gloves with contaminants were used as the model samples. The putative ionization mechanisms are also discussed in this study.



INTRODUCTION

Natural products contain complex compositions. Thus, sample pretreatment is usually required for real samples such as natural products prior to mass spectrometric analysis. Nevertheless, the emergence of ambient ionization mass spectrometry (MS)¹ has eliminated or minimized the pretreatment steps when analyzing real samples. For example, desorption electrospray ionization¹ and direct analysis in real time² can detect the main compositions of real samples in their native environments. Moreover, paper spray ionization (PSI) has attracted considerable attention because ESI can readily occur from a piece of paper with a sharp end deposited with the sample solution.³ Nevertheless, a high voltage power supply¹ or a plasma generator² is usually required to carry out the ionization of analytes. High voltage and plasma are used to generate ionic species for the subsequent analysis of analytes. The development of ambient ionization techniques for MS analysis aims to simplify the ionization setup. Thus, zero voltage PSI⁴ has been developed to eliminate the requirement for applying a high voltage on the paper emitter. Fine droplets from the sample solution on the paper emitter were generated owing to the pneumatic force derived from the mass spectrometer when the paper emitter was put very close (0.3–0.5 mm) to the inlet of the mass spectrometer with zero voltage.⁴ Followed by solvent evaporation, ions were formed for MS analysis. Nevertheless, considering that most mass spectrometers are usually equipped with a high electric field, ionization might occur on the basis of induction by the electric field provided by the mass spectrometer. Thus, field-induced electrospray ionization (ESI)^{5–12} and field-induced atmospheric pressure chemical ionization^{13–16} have been explored.

No additional electric voltage or contact was made on the ionization emitter. Unlike field-induced ionization, matrix-assisted ionization (MAI)¹⁷ requires a matrix to initialize ionization in the subatmospheric pressure region of the heated inlet tube that is coupled to the mass spectrometer. No additional voltages were required for MAI to occur. Most of these existing ionization techniques still need small accessories such as capillaries,^{4,6,10,11} carbon fibers,^{7,12–15} or a matrix¹⁷ for the facilitation of ionization of analytes. The elimination of these small accessories can further simplify ionization methods. The ideal condition is that analytes derived from real samples can be readily ionized for MS analysis by simply placing real samples in front of the mass spectrometer without requiring any additional accessories or matrices.

One may wonder the reasoning to explore such a simple ionization technique. By considering the mechanism for the generation of plasmas for the ionization of analytes from plasma-based ionization technique, the development of such an ionization technique is possible. For example, plasmas can be readily generated in a glass container filled with noble gases with a high-voltage electrode at the center of the container, i.e., a plasma ball.¹⁸ Thus, the high voltage applied on the inlet of the mass spectrometer is similar to the high voltage applied at the center of the plasma ball, whereas the air between a real

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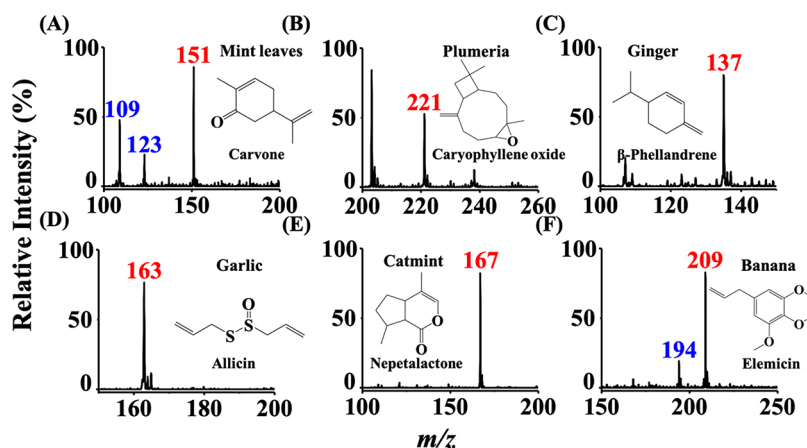


Figure 1. Mass spectra of the samples obtained by directly placing a piece of (A) mint leaf, (B) plumeria, (C) ginger, (D) garlic, (E) catmint, and (F) banana close (≤ 1 mm) to the inlet of the mass spectrometer.

sample and the inlet might work as the medium for the generation of plasma. Accordingly, we examined several real samples, including plants, drug tablets, and gloves with contaminants, to demonstrate our idea for establishing a facile ionization method relying on samples themselves.

EXPERIMENTAL SECTION

Reagents and Materials. Ametryn and atrazine were acquired from Riedel de Haën (Seelze, Germany). Isoprocab was purchased from Chem Service (West Chester, PA). Methylamine was purchased from Alfa Aesar (Ward Hill, MA). Acetonitrile, acetone, methanol, and toluene were obtained from Merck (Darmstadt, Germany), Macron Fine Chemicals (Center Valley, PA), Echo Chemical, and Avantor Performance Materials (Corporate Parkway, PA), respectively. Ultrapure water (18.2Ω) was obtained from a Merck Millipore water purification system (Billerica, MA). Mint, ginger, garlic, catmint, banana, tomato, coffee beans, mothballs, plumeria, Inderal, and Panadol tablets were purchased from local shops.

Instrumentation. A Bruker Daltonics AmaZon SL mass spectrometer (Bremen, Germany) was used to obtain the mass spectra. The voltages set on the orifice of the mass spectrometer were -4500 and $+4500$ V when the mass spectrometer was operated at the positive- and negative-ion modes, respectively. The nebulizer was switched off during the MS analysis, whereas the temperature of the ion transfer capillary was set to 200°C . The number of ions set at the ion charge control was 100000, whereas the maximum acquisition time was set to 100 ms. The length of the metal extension tube (inner diameter: ~ 1.2 mm; outer diameter: ~ 1.5 mm) adapted to the orifice of the mass spectrometer was ~ 4 cm. A camera (SG-210X) from Sage Vision (New Taipei City, Taiwan) was used for recording videos and taking images.

Setup of the Ionization Method. Figure S1 shows a representative photograph of the setup using garlic as the model sample. The sample held by either a three-prong extension clamp or a pair of wooden tweezers was placed in front of the mass spectrometer with a distance of ≤ 1 mm. Mass spectra were immediately acquired once the mass spectrometer was switched on. Protective gloves, e.g., nitrile gloves, should be worn when operating the MS experiments to prevent any accidental touch on the inlet of the mass spectrometer, although the current on the inlet was only few nA (Table S1).

RESULTS AND DISCUSSION

Given that the dielectric breakdown may occur between a dielectric sample and the inlet of the mass spectrometer applied with a high voltage (e.g., -4.5 kV), ion species could be generated during the breakdown to initialize the plasma-like ionization processes. Thus, mint leaves, plumeria, ginger, garlic, catmint, and banana were initially selected as the model samples because these real samples possess unique aroma molecules. Moreover, they contain a certain amount of water, leading them to have good dielectric properties. Namely, if ion species were generated between the samples and the inlet of the mass spectrometer, the aroma molecules derived from these samples could be readily ionized and detected by the mass spectrometer. Thus, we directly placed a piece of these samples close to the inlet of the mass spectrometer to examine whether the main aroma molecular ions derived from these samples could be detected by the mass spectrometer. Figure 1 shows the resultant mass spectra. The ions at m/z 151, 221, 137, 163, 167, and 209 derived from mint leaves,¹⁹ plumeria,⁹ ginger,¹⁵ garlic,¹⁵ catmint,^{19,20} and banana,¹⁵ corresponding to carvone (MW = 150.22 Da), caryophyllene oxide (MW = 220.35 Da), β -phellandrene (MW = 136.23 Da), allicin (MW = 162.30 Da), nepetalactone (MW = 166.22 Da), and elemicin (MW = 208.25 Da), respectively, dominated the resultant mass spectra. Fragments (marked with blue) derived from the aroma molecules were also observed in some mass spectra. We also observed that the sample should not completely attach to the inlet of the mass spectrometer. A small gap (≤ 1 mm) between the sample and the inlet of the mass spectrometer was required to initialize ionization of the main aroma molecules from these samples. These results indicated that detection of the main aroma molecules from these real samples was possible by simply placing the samples in front of the mass spectrometer. Additional electric contact or an ionization emitter to facilitate the generation of ion species-containing plasma was not required. We also noticed if the samples were too dry, such as dry coffee beans, ions derived from aroma molecules were barely observed using this approach. However, adding trace solvent such as water or alcohol on the surface of real samples could help in obtaining the mass spectra. Further discussion is provided later.

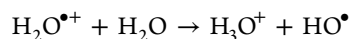
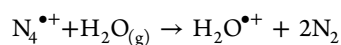
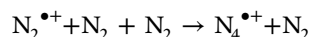
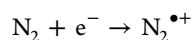
To further demonstrate that a plasma was generated during ionization, we examined the ionization region by placing samples in front of the mass spectrometer with a camera during

MS ionization. We found that a tiny plasma could be observed when we held a piece of banana or onion close to the inlet of the mass spectrometer applied with -4.5 kV. Figure 2 shows



Figure 2. Photograph of a banana placed in front of the mass spectrometer applied with -4.5 kV during MS ionization.

the photograph extracted from the video obtained during MS analysis (Supporting Information video 1). A purplish plasma was clearly observed. This is understandable because gas molecules in the air can produce plasma when discharges occur.¹⁸ Thus, the ionization mechanism should be similar to what has been proposed previously^{21,22} as listed below, although the real conditions must be much more complicated than the possible reactions shown below by considering O_2 and water can be excited first and plasma is a really complicated environment. Nevertheless, to make the possible ionization mechanism easily understood, we only showed the putative ionization mechanism initialized from N_2 .



Cationic nitrogen ions were formed initially followed by ionization of trace water molecules in the air to generate protons for ionization of analytes in gas phase. The results indicated that plasma occurred during MS analysis. This is why the aroma molecules demonstrated above were ionized with this simple approach. In addition, it is worth mentioning that the plasma was not easily observed from other than high water-containing samples such as banana or onion, although the major semivolatiles derived from other samples could be easily observed. The plasma images were observed when a camera with magnification was used. Nevertheless, we believed that an invisible plasma was generated during MS analysis. Additional discussion and results are provided later.

Not all of the samples containing semivolatiles like those aroma molecules demonstrated above were able to be directly analyzed using our approach. For example, it was difficult to see the main compositions of medicine tablets. However, adding a bit solvent such as methanol on the tablets prior to

MS analysis was helpful. Two tablets containing propranolol and acetaminophen were selected as the model samples. No peaks were observed when the tablets were placed directly in front of the mass spectrometer. Methanol ($10 \mu\text{L}$) was then added to the surface of each tablet. After solvent evaporation, individual tablets were directly placed in front of the mass spectrometer for MS analysis. Figure 3 shows the resultant

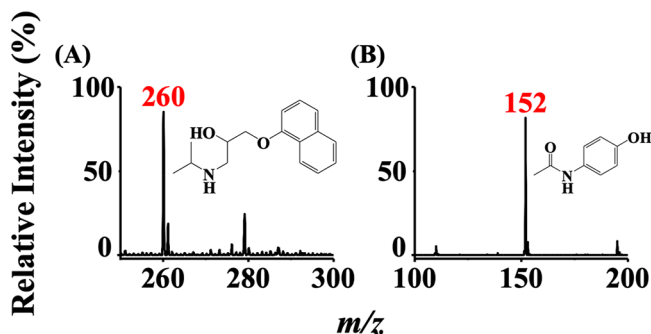


Figure 3. Mass spectra of the samples obtained by placing (A) an Inderal tablet and (B) a Panadol tablet in front of mass spectrometer. $10 \mu\text{L}$ of methanol was added on the surface of the tablets. After solvent evaporation, the tablets were ready for MS analysis.

mass spectra. The ion peaks at m/z 260 and 152 derived from protonated propranolol and acetaminophen, respectively, dominated the mass spectra in Figure 3A,B. The results showed that adding trace solvent such as methanol on the tablet was helpful to facilitate MS analysis of the composition from these tablet samples. Presumably, the presence of the solvent on the tablet helped to extract main compounds to the surface of the tablets and bring the semivolatiles to the gas phase. Although the tablet looked dried after solvent evaporation, trace solvent probably remained on the tablet to facilitate the ionization processes.

To further examine the solvent effect, we used a coffee bean as the model sample. When placing a coffee bean in front of the mass spectrometer for MS analysis, the ion at m/z 195 corresponding to protonated caffeine was observed with a very low intensity (Figure S2A). The inset photograph showed how the coffee bean was placed in front of the mass spectrometer. To determine the solvent effect against the ionization efficiency in our setup, we placed a sample vial containing different solvents below the coffee bean (inset in Figure S2B). Figure S2B–F shows the resultant mass spectra of the coffee beans obtained after the solvents, including water, methanol, acetonitrile, acetone, and toluene, respectively, were placed underneath the coffee bean during the MS analysis. The corresponding ionization energy and vapor pressure of these solvents^{23,24} are listed in Table S2. The ion at m/z 195 became intensive after placement of the solvent. A mothball, a common pesticide, contains naphthalene,²⁵ which is a sublimation compound. The ionization energy of naphthalene is the lowest compared with those solvents used above (Table S2). Thus, we also placed a mothball underneath the coffee bean (inset in Figure S2G) during the MS analysis. Figure S2G shows the resultant mass spectrum of a coffee bean obtained with a mothball placed underneath. The intensity of the ion at m/z 195 looked slightly higher than those shown in Figure S2C–F. To further demonstrate that the intensity enhancement of the ion peak at m/z 195 was due to the naphthalene sublimation, we also placed a piece of naphthalene powder underneath the

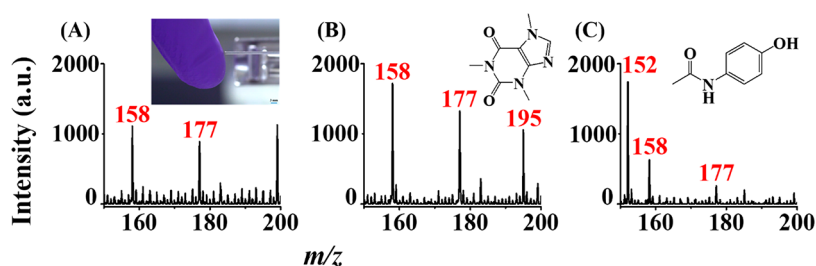


Figure 4. Detection of trace residues from a glove. Mass spectra obtained from a glove (A) without and with contact of (B) a coffee bean and (C) a Panadol tablet.

coffee bean (Figure S2H). The ion intensity at m/z 195 looked similar to that shown in Figure S2G. These results indicated that the presence of the vapor molecules derived from these solvents and mothballs can facilitate the ionization of semivolatiles to further increase the ion intensity of analytes.

The main advantage of using this approach for analysis of main components is its simplicity since no additional ionization emitters or accessories are required. By simply placing a sample in front of the inlet of the mass spectrometer, volatiles or semivolatiles can be readily detected by the mass spectrometer. Such features are suitable for screening of the presence of target semivolatiles from intact samples without any pretreatment. High-throughput analysis can be conducted easily this way. For example, pesticide residues remaining on intact fruits can be rapidly screened using the current method. To simulate real world samples, cherry tomatoes were sprayed with trace pesticides. After the spray dried, the individual cherry tomatoes were directly placed in front of the mass spectrometer for MS analysis. Multiple reaction monitoring (MRM) mode was used without applying additional collision energy. Figure S3A–C shows the resultant mass spectra of the cherry tomatoes sprayed with atrazine (10^{-7} M, $MH^+ = 216$), isoprocarb (10^{-8} M, $MH^+ = 194$), and ametryn (10^{-8} M, $MH^+ = 228$), respectively. Figure S3A–C was obtained by monitoring the ions at m/z 216, 194, and 228, respectively. Protonated pesticide ions dominated the resultant mass spectra. The analysis of one sample only took a few seconds. The corresponding MS/MS spectra of the target ions could also be obtained during the MS analysis. Figure S3D–F shows the resultant MS/MS spectra by selecting the ions at m/z 216, 194, and 228, respectively, as the parent ions from the same samples as used to obtain the results in Figure S3A–C. The fragment ions were marked with blue, and their corresponding fragments are shown on the inset in the mass spectra. The lowest detectable concentration when using our approach for analysis of isoprocarb and ametryn on the as-prepared tomatoes was as low as 10 nM. One may wonder whether the ion intensity of target analytes increases as the voltage applied on the orifice of the mass spectrometer increases. Thus, SI Figure S4 shows the total ion chromatogram (TIC) versus the changes of the voltage (–2000 to –6000 V) applied on the orifice of the mass spectrometer when using a tomato sprayed with ametryn as the sample. Apparently, the total ion intensity was increased with the increase of the applied voltage. The ion intensity looked similar when the applied absolute voltage value was set to higher than 4500.

To demonstrate the feasibility of using our approach for high-throughput analysis of residues from intact samples without requiring any sample pretreatment, a cherry tomato sprayed with the mixture of atrazine, isoprocarb, and ametryn

was further used as the model sample. The MRM mode was still used by monitoring the protonated molecular ions of these pesticides at m/z 216, 194, and 228. Figure S5 shows the resultant mass spectra. The ion peaks at m/z 194, 216, and 228 were observed in the same mass spectrum, indicating the possibility of using the current approach for high-throughput analysis.

In addition, this current approach should also be very useful for analysis of trace evidence for forensic applications. Figure 4A shows the mass spectrum obtained by placing a glove in front of the mass spectrometer. The inset in Figure 4A shows how the nitrile glove was placed in front of the mass spectrometer. Some common background ions at m/z 158²⁶ and 177²⁷ derived from the glove appeared in the mass spectrum. As mentioned in the discussion for the results of Figures 1 and 3, trace solvents such as water or alcohol were helpful for enhancement of the ion intensity of the main semivolatiles derived from the samples. Although no additional solvent was added to the glove, trace water must have retained on the surface of the glove considering the 40–55% humidity maintained in our laboratory, leading to the ionization of the background species derived from the glove. This was further demonstrated when a glove was used to pick up the sample from a dry coffee bean followed by putting the glove close to the inlet of the mass spectrometer for MS analysis. The peak at m/z 195 derived from caffeine was observed in the mass spectrum. The ion intensity at m/z 195 was apparently higher than that shown in Figure S2A. The enhancement effect toward ion intensity was similar to the results shown in Figure S2B–H when highly volatile solvents/chemicals were placed underneath a coffee bean. Presumably, the appearance of background ions at m/z 158 and 177 was also due to the presence of trace water moisture on the glove. Namely, trace water on the glove also facilitated the ionization of caffeine derived from the coffee bean. In addition, we also used a glove to touch the surface of a Panadol tablet and analyzed it by placing the glove in front of the inlet of the mass spectrometer applied with –4.5 kV. Figure 4C shows the resultant mass spectrum. An ion peak at m/z 152 derived from protonated acetaminophen dominated the mass spectrum, whereas the background ions at m/z 158 and 177 were still observed in the same mass spectrum. The main composition, i.e., acetaminophen, derived from the tablet was observed in the mass spectrum (cf. Figure 3B). The results demonstrated that it was possible to detect trace analytes directly from a glove without additional accessories. Moreover, the results implied that the presence of trace water molecules on the gloves could even enhance the ionization efficiency of trace analytes on the glove. Gloves that can protect researchers from potential risks are commonly used in the laboratory. Using a glove to pick up

samples from the surface of any objectives is ideal. The glove can then be directly analyzed by MS. The approach should be potentially useful for forensic analysis.

As mentioned previously, plasmas were not easily observed in most of the samples during MS analysis even though the ions derived from the major semivolatiles could be observed in the mass spectra (e.g., Figure S3 and Figure 4) using our approach. Although no plasma was observed when obtaining the mass spectra in Figure S3, we believe that an invisible plasma must have been generated since the protonated molecular ions derived from pesticides were also observed in the mass spectra. To make the plasma visible during MS analysis, we alternatively used a three-prong extension clamp without the insulating protection-cover to hold the samples (Figure S6A), including a cherry tomato and a grape, close to the inlet of the mass spectrometer. Because no apparent semivolatiles were derived from tomatoes and grapes we sprayed ametryn on the fruits followed by drying prior to our experiments. It should be cautioned that a pair of gloves, e.g., nitrile gloves, should always be worn when operating such experiments. Similar to the image shown in Figure 2, a purplish plasma was observed from the sample placed close to the inlet of the mass spectrometer (Figure S6B,C). Figure S6D,E shows the corresponding mass spectra when the plasma on the fruit sample was observed. The ion at m/z 228 derived from the protonated ametryn dominated both mass spectra. The results demonstrated again that a tiny plasma was generated during MS analysis.

To further clarify the correlation between the plasma and ionization of analytes, we conducted the other experiment by moving a cherry tomato sprayed with ametryn close and away the inlet of the mass spectrometer applied with -4500 V for MS analysis using our approach. When the tomato was placed close to the inlet of the mass spectrometer, a purplish plasma similar to that shown in Figure S6B was observed. The plasma immediately vanished when the tomato was moved away. Figure S7A shows the corresponding TIC obtained by moving the as-prepared tomato close, away, and close to the inlet of the mass spectrometer. The ion intensity derived from the sample was high when the cherry tomato was moved close to the inlet of the mass spectrometer, while the ion intensity became zero when the tomato was moved away. Figure S7B–D shows the corresponding mass spectra obtained from the tomato by moving the cherry tomato close, away, and close, respectively, to the inlet of the mass spectrometer. The protonated ametryn ion peak at m/z 228 dominated the mass spectra in Figure S7B,D, while no ions were observed in the mass spectrum in Figure S7C. The results demonstrated again that the generation of plasma was the main ionization source for the analytes derived from the samples in our approach.

In addition, we believed that the ionization of our approach was initialized by dielectric breakdown. Thus, we prepared a sample by spraying ametryn on a glove in which one glove finger was filled with nitrogen and the other glove finger was filled with water. After solvent evaporation, the as-prepared samples were placed close to the inlet of the mass spectrometer applied with -4500 V one by one for MS analysis. Figure S8A shows the image of the glove finger filled with nitrogen, whereas Figure S8B shows the corresponding mass spectrum. It was hard to see any plasma in Figure S8A. Nevertheless, the ion peak at m/z 228 derived from protonated ametryn molecular ions dominated the mass spectrum (Figure S8B), indicating ionization of ametryn on the glove finger still

occurred. Figure S8C shows the image of the glove finger filled with water. A very tiny plasm (white circle) was observed in Figure S8C. Figure S8D shows the resultant mass spectrum derived from the glove finger, which was dominated by the ion peak at m/z 228 derived from the protonated ametryn molecular ion. The ion intensity of the peak at m/z 228 in Figure S8D was ~ 7 -fold higher than that obtained in Figure S8B. The results demonstrated that observing a plasma generated from the glove finger filled with water was much easier than the glove finger filled with nitrogen. It was understandable since the dielectric breakdown of the glove finger filled with water was easier to be overcome than that of the glove finger filled with nitrogen. Moreover, the ionization efficiency assisted by the glove finger filled with water was much higher than by the glove finger filled with nitrogen. These results suggested that it was highly possible that dielectric breakdown was involved in the initialization of ionization in our approach.

Moreover, the current approach was also suitable for conducting reactive MS²⁸ to selectively react with target analyte by a reagent during MS analysis. Reactive MS has been used to improve the detection of target analytes by using amine-containing derivatized reagent to react with target analytes during MS analysis.^{15,29} We selected garlic, plumeria, and catmint as the model samples. Figure S9A shows the photograph of the setup. Figure S9B–D shows the resultant mass spectra of the samples including garlic, plumeria, and catmint, respectively, with methylamine (0.1 mM, 2 mL) underneath the inlet. Apparently, the target analyte ions shifted 31 amu (marked with purple) (cf. Figure 1B,D,E), indicating the derivatization occurred in situ during MS analysis. The results indicated our approach can work quite fine for application of reactive MS to further confirm the presence of target analytes and to enhance the ion intensity of target analytes.

CONCLUSIONS

We have successfully demonstrated a new and facile ionization method that can be used to detect semivolatiles directly derived from real samples. The ionization mechanism is presumably based on generation of ion species via dielectric breakdown occurring between the dielectric sample and the MS inlet applied with a high voltage. Without the requirement of any additional accessories, this method can be easily operated. Gas and water molecules in the air are involved in the ionization processes. Thus, protonated analytes derived from semivolatiles are commonly observed in the resultant mass spectra. Given that MS analysis can be carried out by simply placing real samples close to the inlet of the mass spectrometer, this approach can be used for high-throughput analysis for detection of main compositions from real samples. Our results suggested that the current method should be potentially useful for forensics analysis since a glove can be used to pick up the sample followed by direct MS analysis. For example, people can wear gloves and pick up a sample directly from crime scenes. The glove can then be directly analyzed by MS without any sample pretreatment. The main advantage of our approach is its simplicity since additional accessories are not required. Moreover, although the current method emphasizes detection of semivolatiles, it should be possible to detect polar analytes using field-induced ESI approaches. Nevertheless, further investigations should be conducted to realize the possibility. Moreover, the ionization mechanism

occurring in the current approach must be much more complicated than we estimated. Thus, design of proper experiments to further clarify the ionization mechanisms is underway in our laboratory.

■ ASSOCIATED CONTENT

SI Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acsomega.1c06869>.

List of the ion current correlated with the voltage on the MS orifice (Table S1); list of the ionization energy and vapor pressure of solvents and chemicals (Table S2); photograph of the sample-based ionization setup (Figure S1); mass spectra of coffee beans (Figure S2); mass spectra of three cherry tomatoes sprayed with three pesticide samples (Figure S3); TIC and the voltage on the orifice of the mass spectrometer (Figure S4); mass spectra of a cherry tomato sprayed with a pesticide mixture (Figure S5); plasma and mass spectra obtained from fruits (Figure S6); TIC and distance effects (Figure S7); images and mass spectra obtained from glove fingers (Figure S8); reactive MS analysis (Figure S9) (PDF)

MS analysis of a banana (AVI)

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Notes

The authors declare no competing financial interest.

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