CHAPTER 5

Ambient Analysis by Thermal Desorption Atmospheric-Pressure Photoionization

JACK SYAGE*[a] AND KAVEH JORABCHI[b]

[a] Syagen Technology Inc., a subsidiary of Morpho Detection, Inc., Santa Ana, CA, USA; [b] Department of Chemistry, Georgetown University, Washington, DC 20057, USA
*Email: jsyage@morphodetection.com

5.1 Introduction

There have been many cocktail-hour discussions about whether ambient analysis began with DART (direct analysis in real time)[1] or DESI (desorption electrospray ionization)[2] or can it trace its origins to the use of direct sampling probes with MS that have been used for decades. The direct insertion probe is one example of this; solid-phase microextraction (SPME) is another. What distinguishes these methods from the current generation of ambient analysis techniques is the region of ionization. The current generation is based on atmospheric-pressure ionization (API) so that the sample can be exposed to the ionizer without inserting into a pressure differential device such as a vacuum interlock or a GC-like septum-sealing injector. However, there is yet another API ambient analysis method that has been used extensively for years, but has attracted little notice and that is the so-called swab/desorption devices used in the security and other industries to detect explosives (*e.g.*, in aviation security) and narcotics (*e.g.*, in border security).[3] Though the ion analyzers are mostly ion-mobility spectrometer (IMS)

New Developments in Mass Spectrometry No. 2
Ambient Ionization Mass Spectrometry
Edited by Marek Domin and Robert Cody

Published by the Royal Society of Chemistry, www.rsc.org

devices, the more recent generation of analyzers are based on mass spectrometry (MS).[4]

Notwithstanding the origins of ambient analysis, for this review on APPI (atmospheric-pressure photoionization) it is worth noting that there are examples of ambient analysis by APPI and other forms of photoionization (PI) that predate the current API generation of ambient analysis methods. APPI (along with other ionization sources, such as ^{63}Ni and various APCI types) has been used in IMS for many years.[5] APPI and PI with direct solid-phase sample injection has also been used for MS. Figure 5.1 shows a schematic view of a photoionization source coupled to a MS system that allows for an insertion probe. The entire assembly is heated and has been configured like a GC injector for syringe injections of liquid samples and SPME samples as well as insertion of a probe containing solid sample on the tip.[6,7] The ambient sampling probe in Figure 5.1 has been operated as an APPI source as well as a low-pressure PI source. This source offers simplicity in that no carrier gas or nebulizer/vaporizer is needed, but because of the resilience of APPI as an ionizer, room air suffices for screening operation.

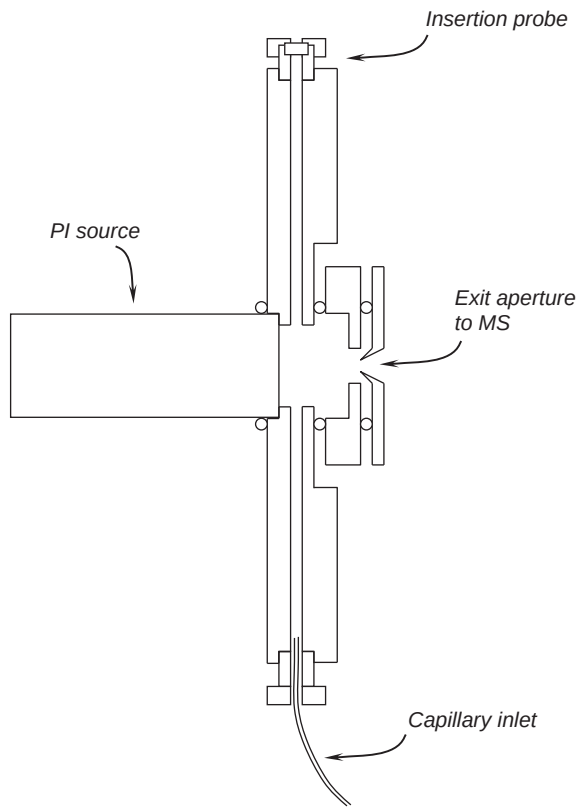


Figure 5.1 Ambient sampling photoionization source.

The source also allows for a continuous capillary flow that can serve as a calibrant, a dopant, or another sample introduction port. All flows are controlled by the pressure differential created by the vacuum behind the MS inlet.

The recent interest in ambient analysis mass spectrometry was popularized by DESI and DART. Many variations have been introduced since then with multiple reviews documenting the progress in the field.[8–12] However, DART and DESI still remain the most used techniques, partly due to their commercial availability. Ambient ion sources can be categorized based on desorption and ionization mechanisms. The APPI embodiments discussed here are based on thermal desorption followed by gas-phase ionization. The simplicity of thermal desorption is well suited for in-field analysis. Matrix effects are also less pronounced in gas-phase ionization compared to charged-droplet based methods (*e.g.* DESI), further making this approach suitable for analysis without sample preparation. Moreover, gas temperature programming may be used to effect selective desorption of analytes based on vapor pressure, creating an additional separation dimension to minimize matrix effects and to identify compounds.[13] APPI is particularly well suited to ambient analysis by thermal desorption because the heated gas can be room air rather than purified gas as is needed for other methods such as DART. Furthermore, the absence of solvent, which can absorb photons, means that the photon flux is fully available to the desorbed sample thereby enhancing sensitivity relative to its use in liquid chromatography (LC).

In plasma-based thermal desorption ionization sources, reactive species are generated by a discharge and become entrained in the gas flow prior to interaction with the sample. For example, helium metastable atoms in DART[14] and helium ions and metastable atoms in flowing atmospheric-pressure after glow[15,16] are identified as primary reactive species. These reactive species are suggested to interact with atmospheric gases (*e.g.* oxygen and water) as well as sample solvent and matrix (collectively called a microenvironment), leading to generation of ionization reagents.[17] These reactions generally produce protonation reagents, giving rise to protonated analyte ions.

For nonpolar analytes with low proton affinity, such as those encountered in the analysis of petroleum, oils, and steroid samples, the protonation mechanism is not efficient. For these compounds, charge transfer is the preferred ionization pathway. DART has been shown to generate radical molecular ions *via* reactions of analytes with helium metastable atoms and O_2^+ ions (resulting from reaction of helium metastable atoms with atmospheric oxygen).[14] However, achieving this ionization pathway requires a clean ionization region because the reactive metastable atoms and O_2^+ ions are rapidly quenched in the presence of water and trace species in air. Such conditions can be partially created by operating the DART nozzle very close to the sampling orifice of the mass spectrometer, causing the helium flow to purge the ionization region. This approach, however, reduces the residence time of neutrals in the ionization region, leading to loss of

ionization efficiency. Moreover, quenching of reactive species by sample matrix (*e.g.* solvent) cannot be avoided with this approach.

5.2 Standalone Thermal Desorption Photoionization Sources

A more efficient method for generating charge-transfer reagents in ambient analysis is photoionization. This approach was first used in desorption atmospheric-pressure photoionization source (DAPPI), where a heated spray of dopant is directed onto a surface vaporizing the analytes, followed by radiation with UV photons.[18,19] Photoionization of the vaporized dopant leads to generation of reagent ions that in turn ionize the vaporized analyte. Importantly, the ionization potential for the dopants is below that of solvent and atmospheric gases. This means the reagent ions do not react with the most-abundant species (*e.g.* air) within the ambient ionization region, making the reagent ions available for ionization of the analytes and improving efficiency of ionization. However, easily ionizable matrix can still quench the reagent ions. For example, sensitivity for detection of illicit drugs using DAPPI is reduced by a factor of 2–15 in urine matrix compared to clean solvent.[20] The same matrix, however, results in a 10-fold higher signal suppression using DESI compared to DAPPI, attesting to better matrix tolerance of desorption-APPI.[20] The type of dopant impacts the ion types, particularly in positive-ion mode. Toluene and anisole readily form positive radical molecular ions and promote charge-transfer mechanisms, leading to M^+ ions from analytes, especially in the case of nonpolar compounds such as polyaromatic hydrocarbons. Mixing these dopants with a protic solvent such as methanol as well as using dopants such as acetone, hexane, and isopropanol promote proton transfer ionization, generating $[M+H]^+$ analyte ions. For most efficient ionization, one should select the dopant with a proton affinity lower than that of the analytes of interest. In negative mode, analyte ion types are not impacted significantly with the choice of dopant, however, sensitivities show dopant dependence. Acetone is frequently used as the dopant of choice for negative mode. DAPPI has been applied to screening of confiscated drugs,[21] biomass characterization,[22] and analyses of lipids[23] and cannabis samples.[24]

5.3 ASAP Adapted for APPI

We recently reported an APPI-enabled atmospheric solid analysis probe (ASAP) as another standalone APPI-based ion source for ambient mass spectrometry. In this configuration, a commercial APPI source for LC was modified to accommodate a melting-tube capillary holder with a plunger. Samples were deposited at the tip of the melting-tube capillary and were pushed into the hot gas stream from the vaporizer of the APPI source as shown in Figure 5.2.

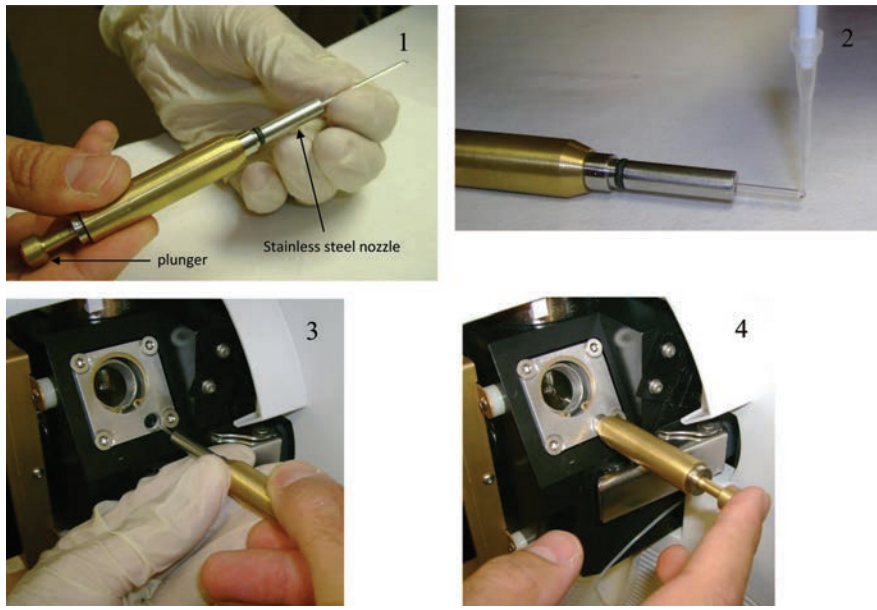


Figure 5.2 ASAP source with APPI capability. (1) The melting point capillary is installed in the probe. (2) Sample is deposited onto the capillary tip. (3) The probe is inserted into the source. (4) The capillary is pushed into the hot gas stream by the plunger.

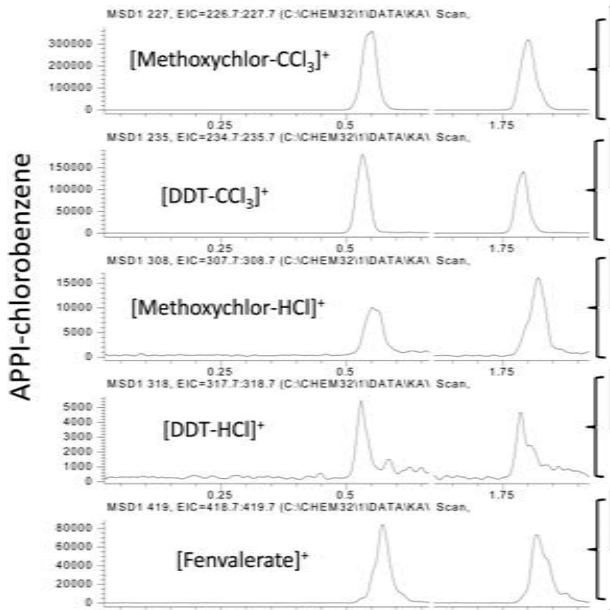
In contrast to DAPPI, the dopant was delivered to the heated area of the nebulizer gas inlet on the source and entered the nitrogen nebulizer gas stream by vaporization rather than nebulization. The heated gas desorbed the analytes and photoionization occurred downstream using a Kr RF lamp.

Figure 5.3 compares ionization of chlorinated pesticides in positive mode for ASAP-APPI and ASAP with APCI. The charge-transfer mechanism using APPI is more efficient using APPI and leads to significant sensitivity enhancement using APPI for these hard-to-ionize compounds.

Interestingly, there is a dopant enhancement for APCI. Dopants are generally not considered for APCI in LC/MS applications; however, dopant enhancement for APCI and other corona-discharge-type ionizers are routinely used in the security industry for IMS- and MS-based instruments (as discussed in Section 5.1). Still the sensitivity for dopant-assisted APPI is significantly better than any form of APCI in Figure 5.3, at least for the class of pesticide compounds.

5.4 DART-APPI

A notable feature of photoionization is that reagent ion generation can occur after analyte desorption. A photoionization lamp can, therefore, be placed downstream of the sample, making photoionization a relatively straightforward addition to plasma-based desorption ionization techniques.



	APPI-chlorobenzene	APCI-chlorobenzene	APCI
Area	7.17E+05	2.11E+04	1.05E+04
height	3.35E+05	9.90E+03	4.76E+03
Area	2.72E+05	4.07E+03	N.D.
height	1.57E+05	3.17E+03	N.D.
Area	2.88E+04	N.D.	N.D.
height	1.23E+04	N.D	N.D
Area	7.04E+03	N.D.	N.D.
height	4.48E+03	N.D.	N.D.
Area	1.76E+05	4.73E+04	1.19E+04
height	7.72E+04	1.61E+04	5.47E+03

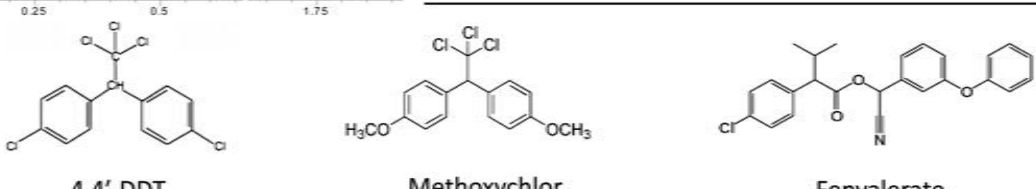


Figure 5.3 Analysis of chlorinated pesticides with ASAP-APPI and ASAP-APCI. 1 ng of each sample is deposited at the tip. The vaporizer is set to 300 °C and chlorobenzene is used as dopant at a 500 nL min^{-1} flow.

One example is combination of DART and APPI to augment the DART ionization capabilities. This configuration is discussed in detail below and has been previously published.[25]

The source configuration is shown in Figure 5.4. A DART-100 ion source is mounted on a single-quadrupole mass spectrometer modified with a Vapur interface.[26] The Vapur interface extends the sampling inlet of the mass spectrometer to the ionization region and provides a vacuum port to effect a flow towards the MS inlet, alleviating the high pressure in the MS due to the use of helium gas. For sample introduction, a 1 μL aliquot of the analyte mix solution is deposited at the closed end of a glass melting tube and pushed into the ionization region using a home-made rail ~3 mm downstream of the DART outlet.

Photoionization is added to the DART unit by placing an RF-excited krypton lamp downstream of the desorption region. Dopant is supplied at flow rates of 1–5 μL min^{-1} using a syringe pump connected to a 1/32″ o.d., 100 μm i.d. stainless steel tube (placed ~ 1 mm) downstream the outlet of the DART ion source. Toluene is used as dopant in the positive mode and acetone is used in the negative mode. The heated gas from DART vaporizes the dopant and carries the dopant molecules to the ionization region. For operation using helium, a gas flow of 2.8 L min^{-1} and a heater temperature of 280 °C are used on the DART unit. Operation using nitrogen requires a flow rate of 8 L min^{-1} and heater temperature of 450 °C. The lower thermal conductivity of nitrogen compared to helium leads to higher optimum flow rate and heater temperature for an effective heat transfer to the glass capillary.

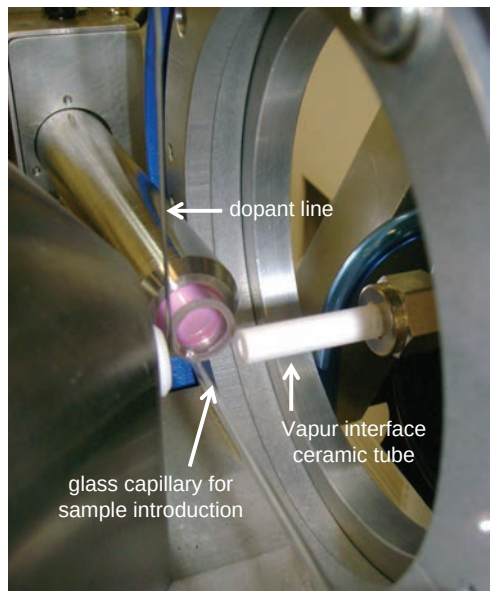


Figure 5.4 DART-APPI experimental setup.
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In the results presented below, DART alone refers to operation with the discharge on, lamp off, and no dopant, whereas DART-APPI refers to discharge off, lamp on, and dopant flow on configuration.

5.4.1 Ion Types in Positive Mode

An advantage of photoionization, as noted above, is that the charge-transfer ionization pathway can be made to dominate. This characteristic is highlighted in Figure 5.5 where blank-subtracted mass spectra obtained by desorption/ionization of 6 ng anthracene (introduced as a 5 μL droplet with 1 : 1 water : methanol solvent) are compared for DART and DART-APPI. Note that anthracene desorption occurs simultaneously with the solvent evaporation. Therefore, ionization occurs in the presence of interfering solvent molecules. The M^+ ion for anthracene is not observed using DART alone, whereas a clear signal at *m/z* 178 is detected when the APPI lamp is on. In DART-APPI configuration, gas flow mainly provides the heat for desorption. Therefore, the ionization mechanism can be tuned by the choice of dopant independent of the gas. This is shown in Figure 5.5(C) where M^+ ions for anthracene were observed with DART-APPI using nitrogen for desorption. Note that DART alone operated using nitrogen did not provide any ions from anthracene at the level used above.

Figure 5.6 compares the ion types in positive mode for verapamil (1.8 ng), cortisol (6 ng), aldicarb sulfone (5 ng), and 17-α-estradiol (2 ng) using DART and DART-APPI with helium and nitrogen gases. No analyte ions were detected using DART alone with nitrogen gas; therefore the spectrum for nitrogen DART is not included. As depicted by the blue dotted lines, analytes with high proton affinity (verapamil, aldicarb sulfone, and cortisol) show similar ion types among the three ionization conditions. Protonated molecular ions are formed by photoionization either *via* hydrogen abstraction by radical molecular ions or proton transfer from protonated dopant/solvent molecules.[27]

That aldicarb sulfone forms an ammonium adduct is an interesting observation that may be attributed to higher affinity of sulfone group to ammonium ion compared to other analytes in this study. Our investigations showed that the ammonium adduct was not observed in the absence of the Vapur interface. Therefore, we attribute the formation of ammonium adducts to the release of ammonia from the ceramic tube and adduct formation inside the Vapur interface.

The largest difference in ion type among the three conditions is observed in the case of 17-α-estradiol. Helium DART alone promotes the formation of $[M - OH]^+$ for this analyte that is similar to the ion type observed using conventional APCI, suggesting protonation followed by dehydration as ion-formation mechanism. On the other hand, helium DART-APPI gives rise to formation of $M^{+\bullet}$, an indication of the charge-transfer mechanism promoted by dopant-assisted photoionization. Note that $[M - OH]^+$ for 17-α-estradiol is also observed using APPI, suggesting formation of protonated ions by photoionization *via* the mechanisms discussed above.

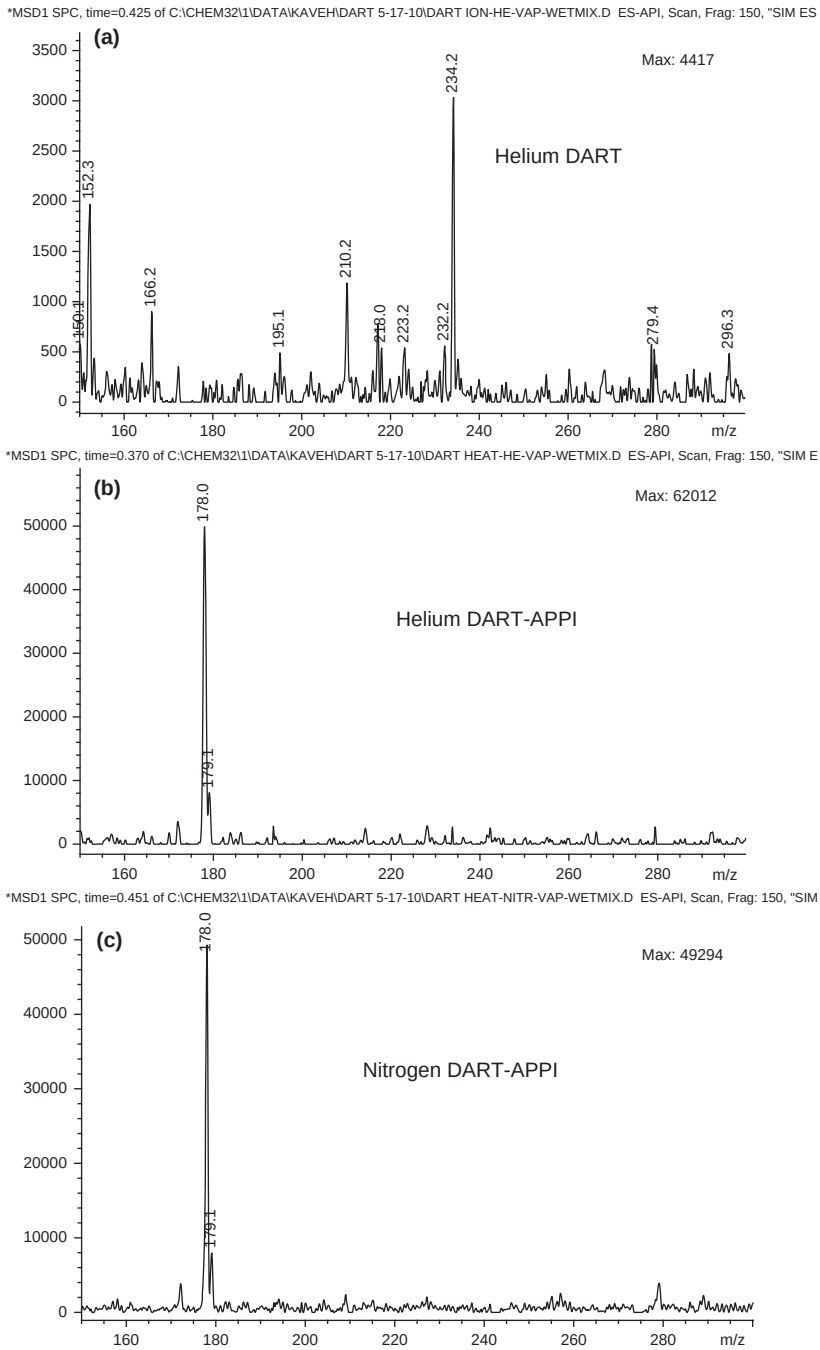

Figure 5.5 Mass spectra obtained from introduction of 6 ng anthracene in 1 : 1 water : methanol solvent using (a) DART with helium gas, (b) DART-APPI with helium gas, and (c) DART-APPI with nitrogen gas. Anthracene molecular ion appears at *m/z* 178.
Figure is reproduced from ref. 25 with permission.

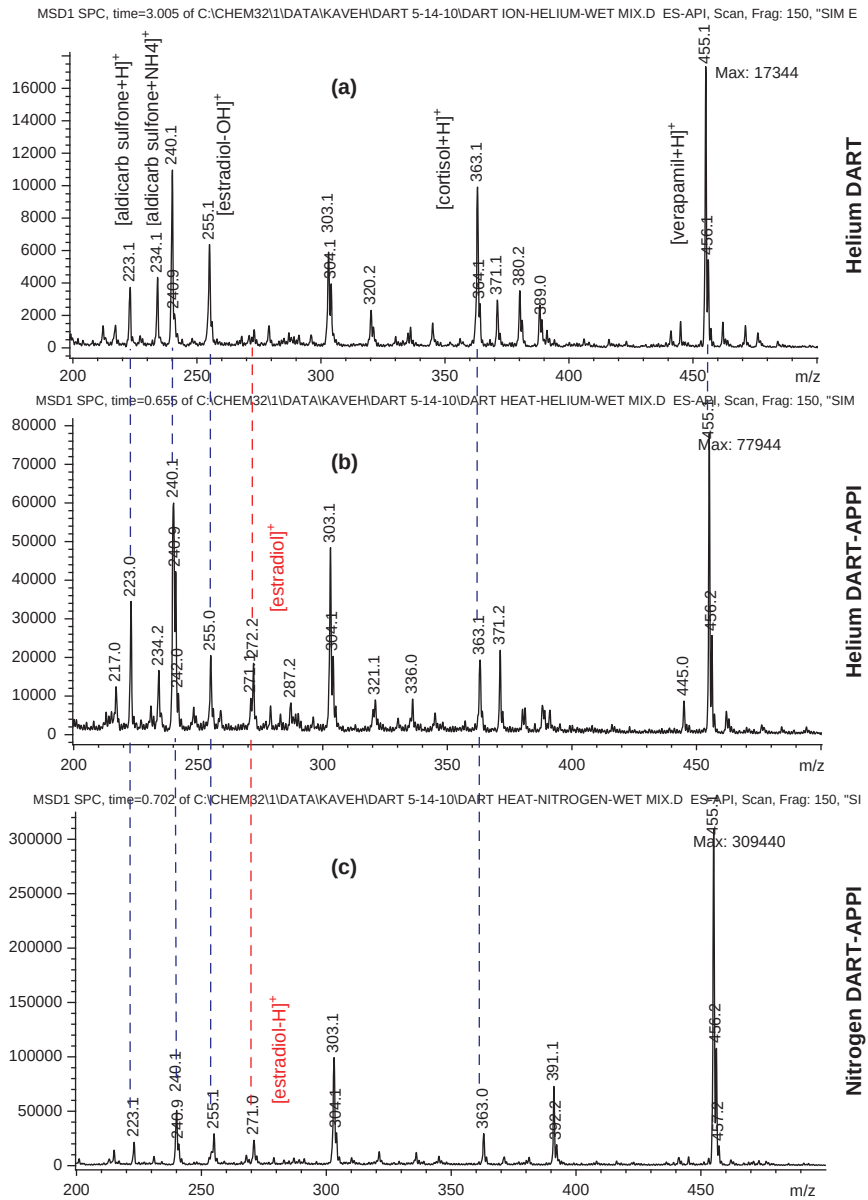

Figure 5.6 Comparison of ion types generated by (a) DART using helium gas, (b) DART-APPI using helium gas, and (c) DART-APPI using nitrogen gas. Red dashed lines show unique ions for each ionization configuration. Blue dashed lines show the common ion types.
Figure is reproduced from ref. 25 with permission.

Yet another unique feature of DART-APPI is formation of $[M-H]^+$ ion observed at *m/z* 271 for 17-α-estradiol (Figure 5.3(c)). Loss of hydrogen from radical cations can result from transfer of a hydrogen atom to background gas

(*e.g.* oxygen) present in ambient ionization conditions. The availability of benzilic or allylic hydrogens is expected to increase the efficiency of hydrogen transfer. This reaction channel, however, is not favored using helium DART-APPI as evidenced by lower intensity of *m/z* 271 compared to that of *m/z* 272 (molecular ion). But the intensity at *m/z* 271 dramatically increases compared to that of *m/z* 272 using nitrogen as desorption gas, suggesting promotion of hydrogen loss channel for 17-α-estradiol at these conditions. We attribute this change to higher temperature of nitrogen gas after desorption and through the Vapur interface, improving the kinetics of hydrogen loss.

5.4.2 Sensitivities in Positive Mode

The vaporization of the analytes by thermal desorption occurs in the order of their vapor pressures. Accordingly, separation of ions over time is observed.[13] To account for this effect, we used the average area under the extracted ion chromatogram for each ion from three trials for sensitivity comparison between the desorption/ionization methods. The data are summarized in Figure 5.7 for ions commonly observed using the three ionization conditions.

DART-APPI provides a factor of 3–5 improvement over helium DART alone for the analytes studied above. Note that the *y*-axis has a logarithmic scale.

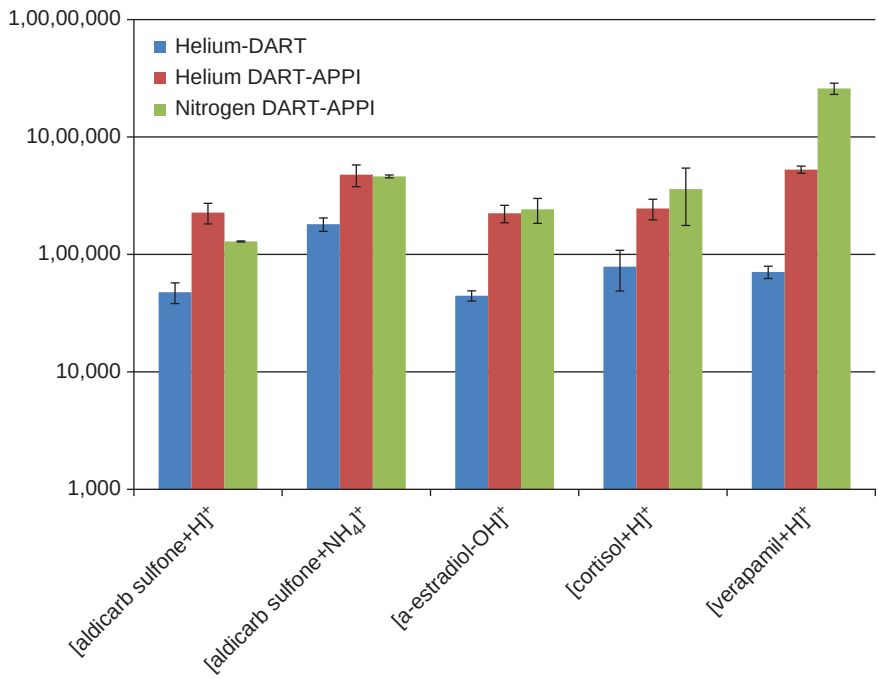

Figure 5.7 Comparison of sensitivities for common ion types using DART and DART-APPI.
Figure is reproduced from ref. 25 with permission.

More importantly, the sensitivities for helium DART-APPI and nitrogen DART-APPI are comparable. In contrast, a large loss of sensitivities is observed for nitrogen DART compared to helium DART.

5.4.3 Negative-ion Mode

The performance of helium DART alone with that of helium DART-APPI in negative mode is compared in Figure 5.8. A 1 μL sample containing 6 ng 2,5-dinitrobenzotrifluoride, 17 ng dinitrophenol, and 17 ng benzilic acid was used in these experiments. Similar ion types are observed for helium DART alone and helium DART-APPI, suggesting electron capture and dissociative

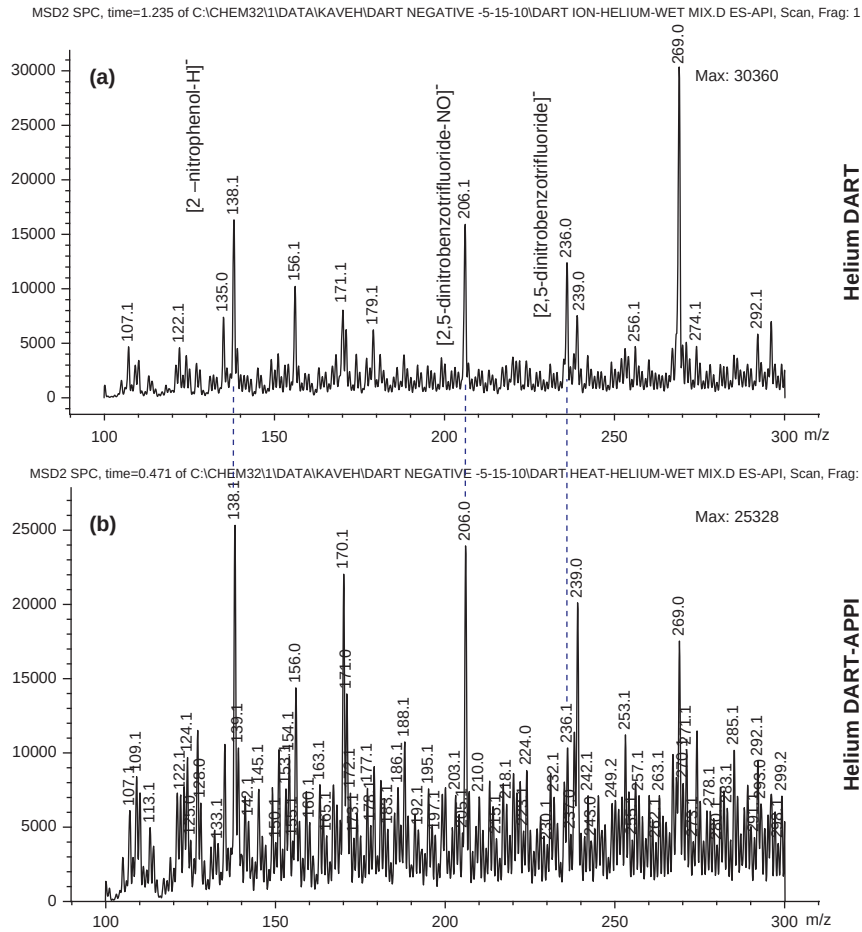

Figure 5.8 Negative-ion types generated by (a) DART using helium gas, and (b) DART-APPI using helium gas. Dashed blue lines show the common ion types from the analytes.
Figure is reproduced from ref. 25 with permission.

electron capture mechanism for 2,5-dinitrobenzotrifluoride ionization and deprotonation mechanism for 2-nitrophenol ionization. This observation is consistent with other studies reporting similar negative mode ionization mechanisms for DART and APPI.[28] However, the chemical noise in the case of DART-APPI is higher, which may be attributed to survival of toluene-related clusters in the absence of counterflow gas (see below for more discussion on the counterflow gas effect). Importantly, benzilic acid is not observed at the level introduced using either desorption/ionization conditions. We noticed a further drop in sensitivity using nitrogen DART-APPI in negative mode compared to helium DART-APPI, suggesting a faster decay of these analytes (either in the form of neutrals or ions) during the transit in the hotter nitrogen gas.

We observed an interesting trend for negative ions upon removing the Vapur interface. In this configuration, the counterflow gas is increased to 5 L min^{-1} to avoid a pressure spike in the mass spectrometer due to the use of helium gas in DART. Figure 5.9 demonstrates that the sensitivities

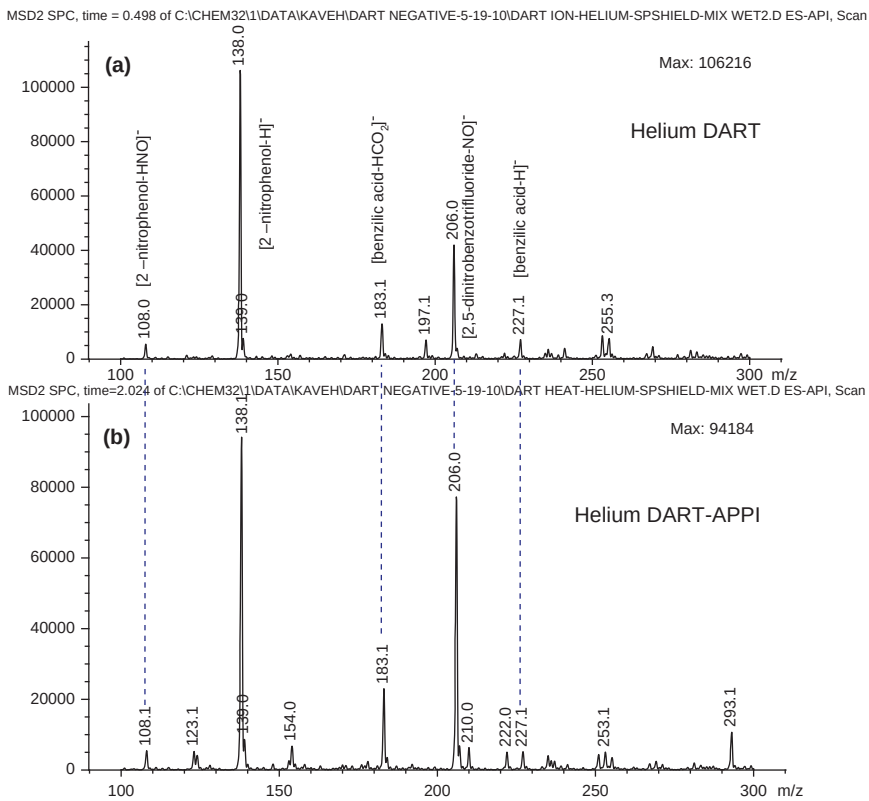

Figure 5.9 Negative-ion types in the absence of Vapur interface from (a) DART using helium gas, and (b) DART-APPI using helium gas. Dashed blue lines show the common ion types from the analytes.
Figure is reproduced from ref. 25 with permission.

for negative ions improve dramatically for both DART and DART-APPI upon removal of the Vapur interface. Such a drastic change is not observed for positive ions. We attribute this improvement in negative-ion mode to rapid cooling of the desorption gas *via* mixing with the counterflow gas. In addition, solvent clusters are removed with the use of counterflow gas, reducing the noise levels.

5.5 Conclusions

The studies above highlight the potential of photoionization as a broad-based ionization source in ambient mass spectrometry. New ion types can be generated that aid in identification of compounds. In addition, higher sensitivities are achieved with APPI. The benefits of APPI for ambient analysis are similar to those for its application for LC/MS, but with a few additional advantages:

- Wide range of ionizable compounds: Most ambient analysis methods are based on ionization sources that rely on charge (proton, cation, anion) affinity so that many compounds particularly nonpolar ones are difficult to ionize. Furthermore, the presence of high charge-affinity background compounds can steal charge and suppress the detection of analytes of interest. This problem is characteristic of ambient analysis ionization methods because the sample is generally not cleaned up or preseparated.
- Low susceptibility to ion suppression and matrix effects: This benefit of APPI is particularly important to ambient analysis because, as mentioned above, there is no clean-up or separation of the components of a sample. Photoionization relies on direct photoionization as well as dopant-assisted ionization. The latter is analogous to chemical ionization; however, the ion chemistry is much better controlled than the reliance on charge carriers in air or in solvent flows.
- High sensitivity and dynamic range: APPI is generally comparable in sensitivity to APCI for LC/MS with the edge going to APPI as the solvent flow rate decreases. Ambient analysis takes this to the limit of no flow, which greatly favors APPI over APCI for these purely thermally desorbed gas phase systems. APCI needs a charge carrier, which is usually the protic solvents used for reverse-phase LC. The solvent is generally a negative to APPI sensitivity because it can absorb photons and non-radiatively remove them from the ionization pool. APPI therefore is at its best in the absence of solvent, though very low-flow dopant introduction is still recommended. Although ambient analysis is not typically used for quantitative analysis, APPI is capable of upwards of 5 orders of linear dynamic range.
- Nitrogen (or air) can be used as desorption gas without a loss in performance when ionization is effected by APPI. This alleviates the need for additional pumping capacity required for the use of helium and

obviates the need for the Vapur interface. Moreover, this versatility makes APPI an attractive candidate for portable instruments and in-field applications where simplicity, robustness, and freedom from consumable gases are of higher importance compared to lab-based analysis.

Dopants generally improve the performance of APPI. Although used at very small quantities (1–5 μL min^{-1} in this study), one has to consider safety issues as well as the environmental impact of releasing the dopant vapor into the analysis area. Accordingly, development of safe dopants with high ionization potentials should be an area of focus to broaden the use of photoionization in ambient ionization, particularly for in-field analysis.

Acknowledgements

We thank IonSense Inc. for the loan of DART-100. We are very grateful to the California Department of Food and Agriculture for donation of pesticide standards. We also thank Sheng-Suan (Victor) Cai of Syagen for valuable discussions.

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