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Ambient analysis by thermal desorption atmospheric pressure photoionization

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Abstract Ambient mass spectrometry has attracted substantial attention in recent years. Among ambient ionization methods, thermal desorption ionization stands out because of two attributes: (1) simplicity, rendering the technique suitable for in-field applications, and (2) ability to couple with a variety of gas-phase ionization methods thereby broadening the range of molecules that can be analyzed with this method. Here, we report on improving the performance of a direct analysis in real time (DART) source by implementing atmospheric pressure photoionization (APPI) downstream of the desorption region. At identical desorption and ion sampling conditions, APPI leads to detection of radical molecular ions from non-polar compounds that are absent from the spectra generated by DART alone. Moreover, a factor of 3–5 improvement in sensitivity is observed using APPI for positive ions commonly detected by DART and DART-APPI. Using helium and nitrogen as desorption gases, APPI shows identical performance regardless of desorption gas type. In contrast, a dramatic decrease in sensitivity is observed for DART operated with nitrogen compared to DART with helium. Comparable performance for DART and DART-APPI are observed in negative ion mode, although both show a drastic improvement in the absence of the Vapur interface. This interface creates a differentially pumped chamber prior to inlet of the mass spectrometer and reduces the mass spectrometer gas load when helium is used as desorption gas.

Keywords Ambient mass spectrometry · Photoionization · Direct analysis in real time

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Introduction

Ambient mass spectrometry was introduced into the mainstream with the development of desorption electrospray ionization (DESI) [1] and direct analysis in real time (DART) [2], aiming at fast analysis with minimal sample preparation. Many variations have been introduced since then with multiple reviews documenting the progress in the field [3–7]. However, DART and DESI are still the most used techniques, partly due to their commercial availability. The ambient ion sources can be categorized based on desorption and ionization mechanisms. Here, we focus on thermal desorption followed by gas-phase ionization. The simplicity of thermal desorption lends this approach well 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 [8]. However, a limitation of thermal desorption is in the analysis of large molecules (e.g., proteins) because these analytes do not vaporize. On the other hand, this attribute can be beneficial when small molecules are of interest as the large molecules will not interfere with the ionization.

In plasma-based thermal desorption ionization sources, reactive species are generated by a discharge and become

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entrained in the gas flow prior to interaction with the sample. For example, helium metastable atoms in DART [9] and helium ions and metastable atoms in flowing atmospheric pressure after glow [10, 11] 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 [12]. These reactions generally produce protonation reagents, giving rise to protonated analyte ions.

For non-polar 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) [9]. 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.

A more efficient method for generating charge transfer reagents for ambient analysis is photoionization as demonstrated using the recently developed desorption atmospheric pressure photoionization source [13, 14]. Generally, dopants are infused into the desorption gas, leading to generation of reagent ions via photoionization of the dopant. Importantly, the ionization potential for the dopants is below that of solvent and atmospheric gases, prolonging the life time of the reagent ions in the ionization region and improving efficiency of charge transfer mechanism. However, easily ionizable matrix can still quench the reagent ions, altering the ionization chemistry [15].

A notable feature of photoionization is that reagent ion generation can occur after desorption. In other words, a photoionization lamp can be placed downstream of the sample, making photoionization a relatively straightforward addition to plasma-based desorption ionization techniques. Here, we report on augmenting capabilities of DART via coupling with atmospheric pressure photoionization (APPI). Ion types and sensitivities are compared for positive and negative ion modes, demonstrating advantages of such combination for ambient analysis. Desorption parameters are kept constant for the two ionization methods, providing a platform for side-by-side comparison of ionization capabilities.

Experimental

A single-quadrupole mass spectrometer (6130, Agilent, Santa Clara, CA) was used for the studies. Source configuration is shown in Fig. 1. A DART-100 ion source (IonSense, Saugus, MA) was mounted on the mass spectrometer using an aluminum bracket (IonSense, Saugus, MA) that closed the mass spectrometer source interlocks. Also a Vapur interface [16] (IonSense, Saugus, MA) with a ceramic tube was used to extend sampling inlet of the mass spectrometer to the ionization region. The Vapur interface replaced the spray shield and provided 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. With this configuration, the Vapur interface is connected to the high-voltage power supply of the spray shield and extreme care must be taken to avoid contact with the interface during analysis. For sample introduction, a 1-μL aliquot of the analyte mix solution was deposited at the closed end of a glass melting tube (Fisher Scientific, Pittsburgh, PA) and pushed into the ionization region using a home-made rail ~3 mm downstream of the DART outlet.

Photoionization capability was added to the DART unit by placing an RF-excited krypton lamp (Syagen Technology Inc. Tustin, CA) downstream of the desorption region as depicted in Fig. 1. Dopant was supplied at flow rates of 1–5 μL/min using a syringe pump (Harvard Apparatus,

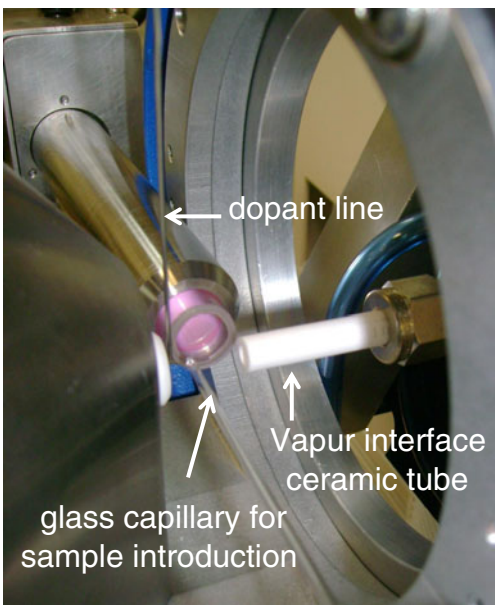

Fig. 1 DART-APPI experimental setup

Holliston, MA) connected to a 1/32″ o.d., 100 μm i.d. stainless steel tube (Idex Health and Scieces, Oak Harbor, WA) placed ~ 1 mm downstream the outlet of the DART ion source. The heated gas from DART vaporized the dopant.

The operating parameters were optimized by monitoring the analyte signals. For both helium and nitrogen gases, the DART discharge was operated with the following parameters: discharge needle voltage 3500 V, discharge electrode 150 V, grid electrode 250 V in positive mode and 0 in negative mode. For operation using helium, the gas flow was 2.8 L/min and the heater was set to 280 C. Operation using nitrogen required a flow rate of 8 L/min 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. 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. Simultaneous operation of DART discharge and APPI lamp did not show any difference compared to discharge off/lamp on for the analytes studied. Therefore, the results for this configuration are not presented.

Sample preparation

Verapamil, cortisol, 17-α-estradiol, 2-nitophenol, benzilic acid, anthracene, and 2,5-dinitrobenzotrifluoride were purchased from Sigma-Aldrich. Aldicarb sulfone was donated by California Department of Agriculture. The analytes were selected to cover a wide range of polarities and melting points encountered in environmental, biological, and homeland security applications. Stock solutions of analytes were prepared in methanol. The working solutions were dilutions of the stock solutions using 1:1 water/methanol solvent. HPLC-grade methanol and water were used throughout the experiments. Photoionization dopants were toluene in positive mode and acetone in negative mode.

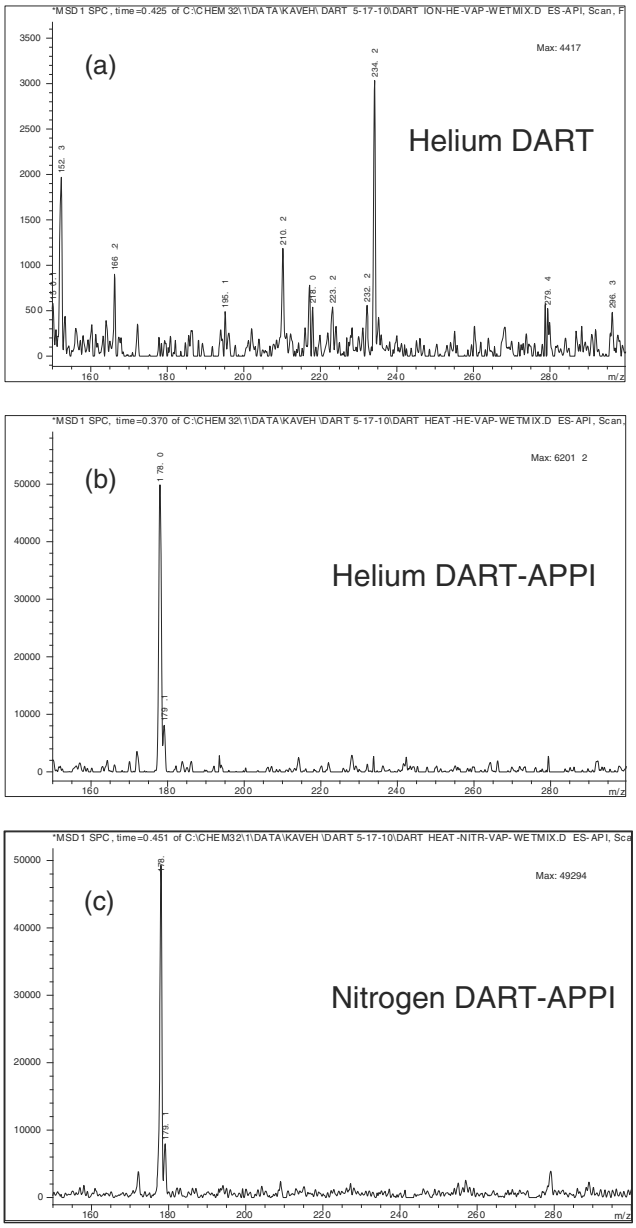

Fig. 2 Mass spectra obtained from introduction of 6 ng anthracene in 1:1 water/methanol solvent using **a** DART with helium gas, **b** DART-APPI with helium gas, and **c** DART-APPI with nitrogen gas. Anthracene molecular ion appears at *m/z* 178

Results and discussion

Ion types in positive mode

As noted above, an advantage of photoionization is a more robust charge transfer ionization pathway. This characteristic is highlighted in Fig. 2 where blank-subtracted mass spectra obtained by desorption/ionization of 6 ng anthracene in 1:1 water/methanol solvent are compared for DART and DART-APPI. Note that anthracene desorption occurs simultaneously with the solvent evaporation. Therefore, ionization takes effect 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 APPI lamp is on. In DART-APPI configuration, gas flow mainly provides the heat for desorption. Therefore, ionization mechanism can be tuned by the choice of dopant independent of the gas. This is shown in Fig. 2c 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 3 compares the ion types in positive mode for verapamil (1.8 ng), cortisol (6 ng), aldicarb sulfone (5 ng),

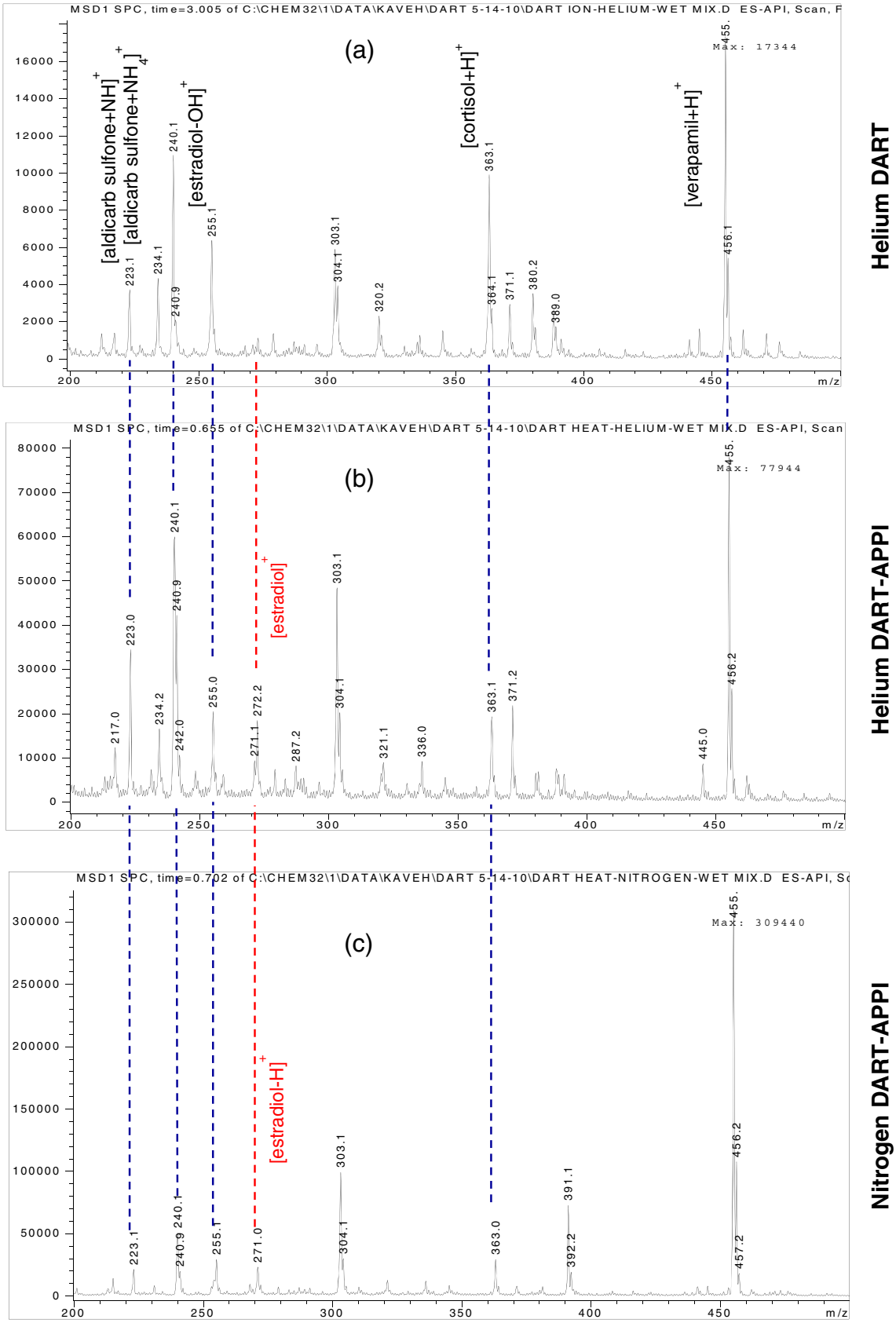

Fig. 3 Comparison of ion types generated by **a** DART using helium gas, **b** DART-APPI using helium gas, and **c** DART-APPI using nitrogen gas. *Red dashed lines* show unique ions for each ionization configuration. *Blue dashed lines* show the common ion types

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 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 [17].

Formation of ammonium adduct by aldicarb sulfone 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 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 was observed in the case of 17-α-estradiol. Helium DART alone promoted the formation of $[M\text{-}OH]^+$ for this analyte which 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 gave rise to formation of $M^{+\cdot}$, an indication of charge transfer mechanism promoted by dopant-assisted photoionization. Note that $[M\text{-}OH]^+$ for 17-α-estradiol was also observed using APPI, suggesting formation of protonated ions by photoionization via the mechanisms discussed above.

Yet another unique feature of DART-APPI is formation of $[M\text{-}H]^+$ ion observed at *m*/*z* 271 for 17-α-estradiol (Fig. 3c). Loss of hydrogen from radical cation can result from transfer of a hydrogen atom to background gas (e.g., oxygen) present in ambient ionization conditions. 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 kinetics of hydrogen loss.

Sensitivities in positive mode

Thermal desorption vaporizes the analytes in the order of their vapor pressure. Accordingly, separation of ions over time is observed [8]. To account for this effect, we used the average area under extracted ion chromatogram for each ion from three trials for sensitivity comparison between the desorption/ionization methods. The data are summarized in Fig. 4 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. 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.

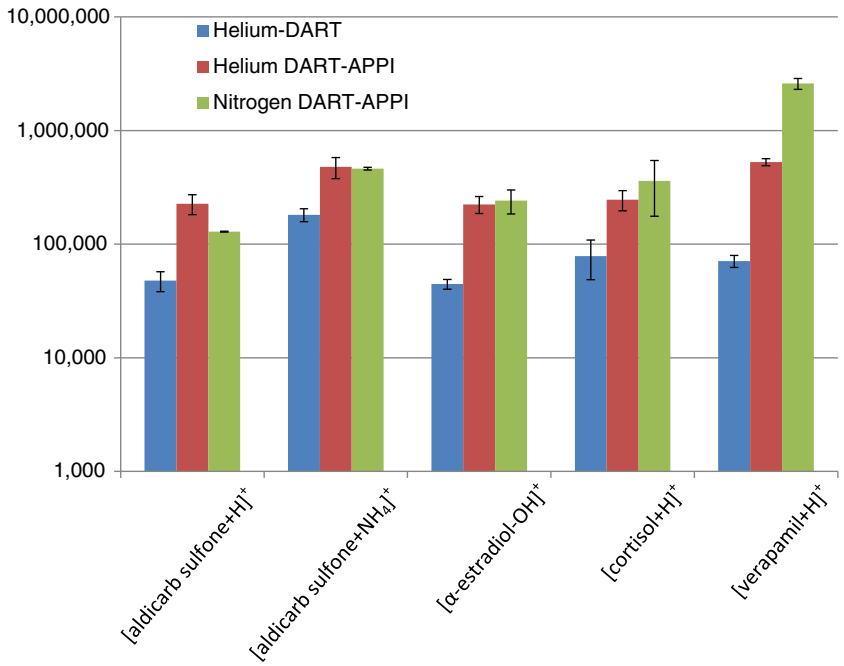

Fig. 4 Comparison of sensitivities for common ion types using DART and DART-APPI

Negative ion mode

Figure 5 compares the performance of helium DART alone with that of helium DART-APPI in negative mode. 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 were observed for helium DART alone and helium DART-APPI, suggesting electron capture and dissociative 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 [18]. However, the chemical noise in the case of DART-APPI

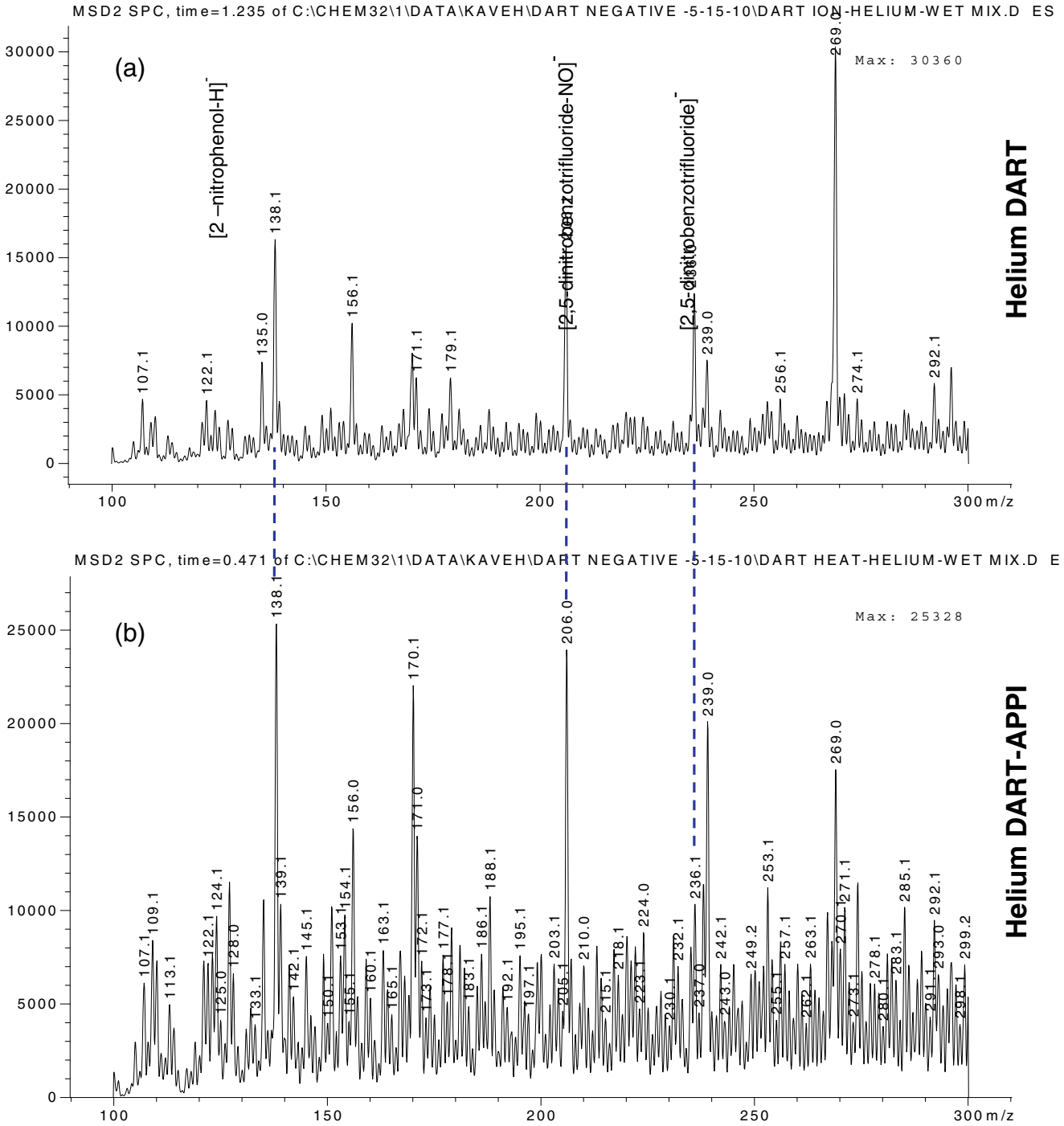

Fig. 5 Negative ion types generated by **a** DART using helium gas, and **b** DART-APPI using helium gas. *Dashed blue lines* show the common ion types from the analytes

was higher which may be attributed to survival of toluene related clusters in the absence of counterflow gas (see below for more discussion on counterflow gas effect). Importantly, benzilic acid was 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 neutral or ions) during the transit in the hotter nitrogen gas.

An interesting trend was observed for negative ions by removing the Vapur interface. For this experiment the spray shield was mounted back on the MS interface. The counterflow gas was increased to 5 L/min to avoid pressure hike in the mass spectrometer due to the use of helium gas in DART. Note that the DART nozzle was ~15 cm from the spray shield in this configuration. As depicted in Fig. 6, the sensitivities for negative ions improved drastically for both DART and DART-APPI. Such a drastic change was not

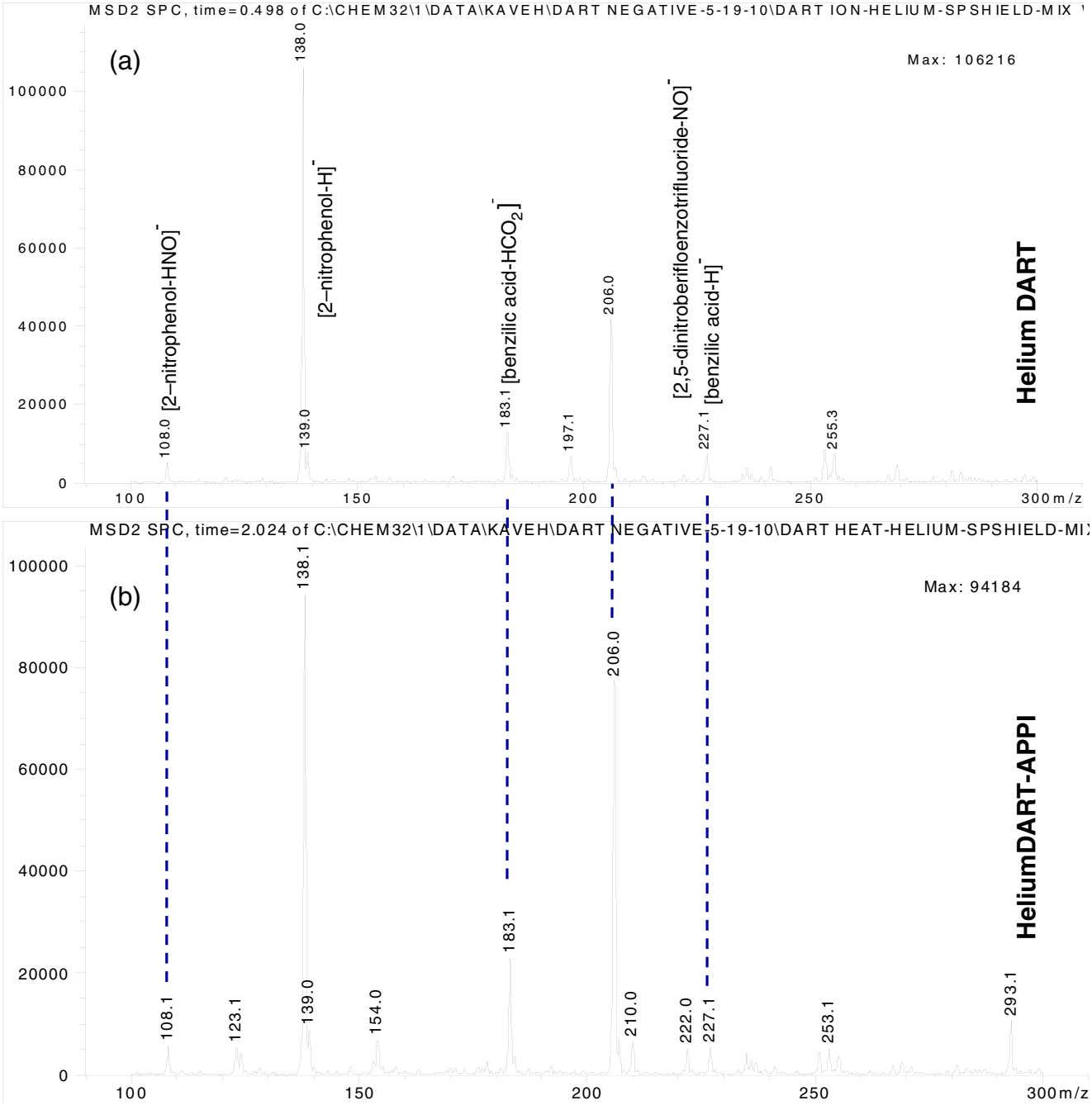

Fig. 6 Negative ion types in the absence of Vapur interface from **a** DART using helium gas, and **b** DART-APPI using helium gas. *Dashed blue lines* show the common ion types from the analytes

observed for positive ions. We attribute this improvement in negative ion mode to rapid cooling of desorption gas via mixing with the counterflow gas. In addition, solvent clusters are removed with the use of counterflow gas, reducing the noise levels.

Conclusions

The results above underline 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. We have also demonstrated that the Vapur interface for DART can adversely affect sensitivity, particularly for negative ions. This effect may be attributed to longer reaction times for ions with matrix and solvent during the transit through the interface. It is shown that rapid dilution of the desorption gas by the counterflow gas improves sensitivity.

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.

Note that dopants are needed for optimum operation of APPI. Although used at very small quantities (1 μL/min in this study), one has to consider safety issues as well as 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.

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