A Combination Atmospheric Pressure LC/MS:GC/MS Ion Source: Advantages of Dual AP-LC/MS:GC/MS Instrumentation

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Modification of commercial LC/MS instrumentation to allow both atmospheric pressure (AP) LC/MS and GC/MS is described. Advantages of this additional capability versus LC/MS alone include higher chromatographic resolution in the GC versus LC mode, greater peak capacity for complex mixture analysis, higher sensitivity for a variety of volatile compounds, and the ability to observe compounds of low polarity that are not readily observed in LC/MS. Advantages over conventional GC/MS include the ability to use higher carrier gas flow and shorter columns for passing less volatile materials through the gas chromatograph, selective ionization, and rapid switching between positive and negative ion modes. Other advantages include application of the enhanced capabilities of LC/MS instrumentation to GC/MS analyses such as cone voltage fragmentation, MS^n, high mass resolution, and accurate mass measurement. Limitations of APGC/MS include the inability to observe saturated hydrocarbon and certain other highly nonpolar compounds and less odd-electron fragmentation for computer aided library searching. For some analyses, the limitation related to ionization of highly nonpolar compounds is advantageous, as is the simplified mass spectrum and easy molecular weight identification that results from less fragmentation observed in the AP ionization mode. (J Am Soc Mass Spectrom 2005, 16, 1730–1738) © 2005 American Society for Mass Spectrometry

Gas chromatography interfaced to mass spectrometry (GC/MS) is a well established and powerful method for the analysis of volatile and semi-volatile materials [1]. In comparison to liquid chromatography interfaced to mass spectrometry (LC/MS), GC/MS has the advantages of higher chromatographic resolution and higher peak capacity, easier quantitation with flame-ionization detection, a single mobile phase (helium), fewer issues with solubility, and separations that can be adjusted by electronic controls such as temperature programming [2]. These advantages are especially important in the study of complex mixtures. A timely example is metabolomics analysis [3].

The effluent from the GC is introduced into the vacuum of the mass spectrometer either directly from capillary fused silica columns or after a differential pumping stage for higher gas load columns. Ionization occurs under vacuum conditions either by electron ionization or by chemical ionization [1]. On the other hand, ionization in LC/MS typically occurs at atmospheric pressure and the ions are swept into the vacuum system through differentially pumped regions

separated by apertures or capillaries [4]. Ionization in atmospheric pressure LC/MS is by electrospray ionization (ESI) [5], corona discharge ionization [atmospheric pressure chemical ionization (APCI)] [6], photo ionization [7], or surface ionization [8]. Because ionization in GC/MS occurs under vacuum conditions and in LC/MS occurs at atmospheric pressure, the two separation methods require entirely different interfaces to the mass spectrometer and are thus usually performed on instruments dedicated to the particular chromatography method.

However, GC/MS can also be achieved under atmospheric pressure ionization conditions. APCI was initially developed by Horning et al. using ^{63}Ni β decay for ionization [9]. A corona discharge ion source later replaced the ^{63}Ni as the source of ionization [6]. Horning et al. were the first to interface a GC instrument to an APCI ion source [10, 11]. Since these initial publications, a series of papers originating at the National Center for Toxicological Research in Jefferson, Arkansas, have been published in which the effluent from a gas chromatograph is ionized at atmospheric pressure [12–21]. The interface used in these experiments couple the GC to a ^{63}Ni ion source of a mass spectrometer built for APCI gas-phase studies. In particular, GC/APMS operated in the negative ion mode was demonstrated to be a highly sensitive method for detecting a number of environmentally important compounds. APCI ion
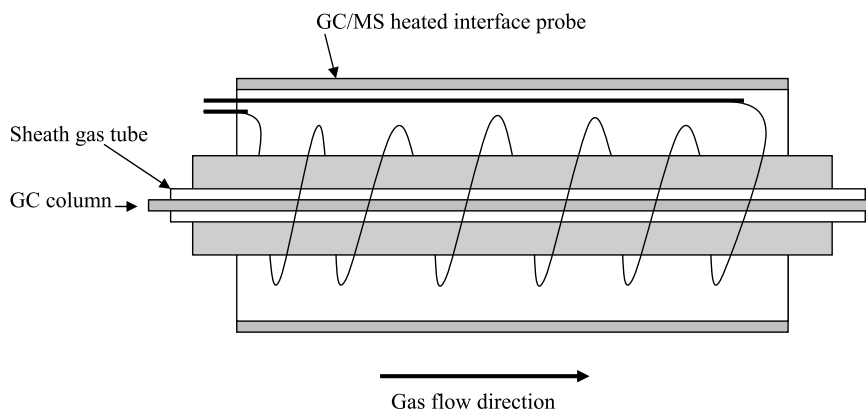
Figure 1. Diagram of the exit end of the GC/APMS interface showing the GC column extending through a heated sheath tube. Nitrogen gas flowing through the sheath tube and over the GC column heats the column uniformly to the exit tip.

sources for gas analysis have been interfaced to commercial instruments (Extranuclear Laboratories, Inc., now ABB, Inc., Norwalk, CT, [22] MDS Sciex, Concord, ON, Canada, [23, 24] and Finnigan-Mat, now ThermoFinnigan, Inc., San Jose, CA [21]). Even so, GC/APMS never became popular, probably because of the high costs of the specialized instrumentation needed for these analyses.

APCI sources attached to mass spectrometers have also been used for gas analysis such as the determination of volatiles in breath and fragrances emulating from skin and clothing [25, 26]. Pyrolysis with ionization of the gaseous pyrolysate has also been reported, [27] as has APCI of warfare agent simulants, [28] and organic compounds at the parts per trillion level [29]. Supercritical fluid chromatography has also been interfaced to APCI-MS [30–32]. However, the primary use of this ionization method has been as an ionization interface between liquid chromatography and mass spectrometry [11].

In recent years, atmospheric pressure mass spectrometers have proliferated, primarily because of electrospray ionization and the ease of interfacing this atmospheric pressure ionization method to liquid chromatographs [5]. In addition, many of the mass spectrometers currently used for LC/MS have capability for MS^n studies and/or accurate mass measurement, capabilities that are more rare for GC/MS instrumentation.

In this paper, we introduce a simple modification of the atmospheric pressure ion sources used in LC/MS instrumentation that converts the source into a more universal ion source able to perform GC/APMS in addition to APCI, ESI, or PI LC/MS. The combination ion source can be readily adapted to most LC/MS instruments without reduction of LC/MS sensitivity. Both positive and negative ion GC/APMS spectra can be obtained with high sensitivity. In addition, all of the capabilities common with LC/MS instruments such as high-resolution and accurate mass measurement, cone voltage fragmentation, MS^n, and multiple reaction monitoring can be applied to GC/APMS.

Experimental

For these studies, either a Micromass LCT or QTOF I mass spectrometer (Waters Corporation, Beverly, MA) with Z-Spray ion sources were modified for dual LC/MS:AP-GC/MS operation. For the GC/APMS studies, the GC with attached heated interface probe was aligned so that the interface probe inserted into the ion source region of a Micromass LCT or QTOF I mass spectrometers. For most experiments, the interface probe (see Figure 1) inserted into the atmospheric pressure ion source volume in the position normally occupied by the ESI or APCI probe (see Figure 2). This was done by simply replacing the source cover flange
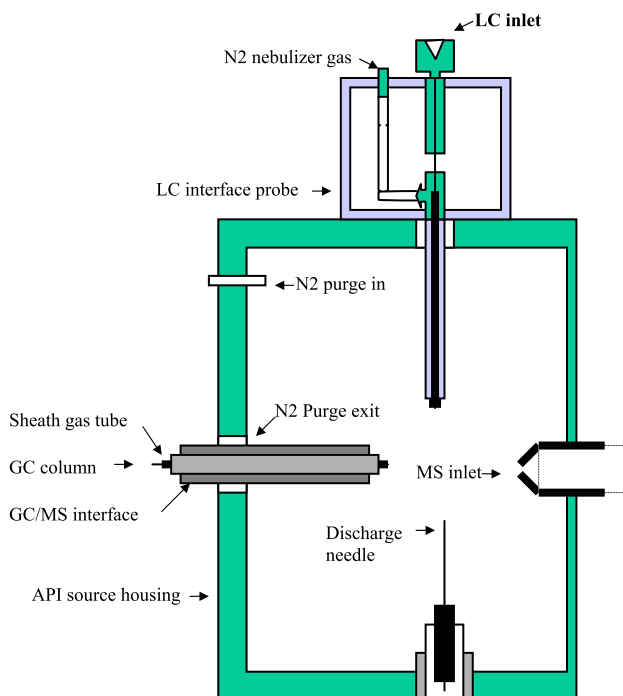

Figure 2. Diagram of an atmospheric pressure ion source designed to interface to both an LC and a GC.
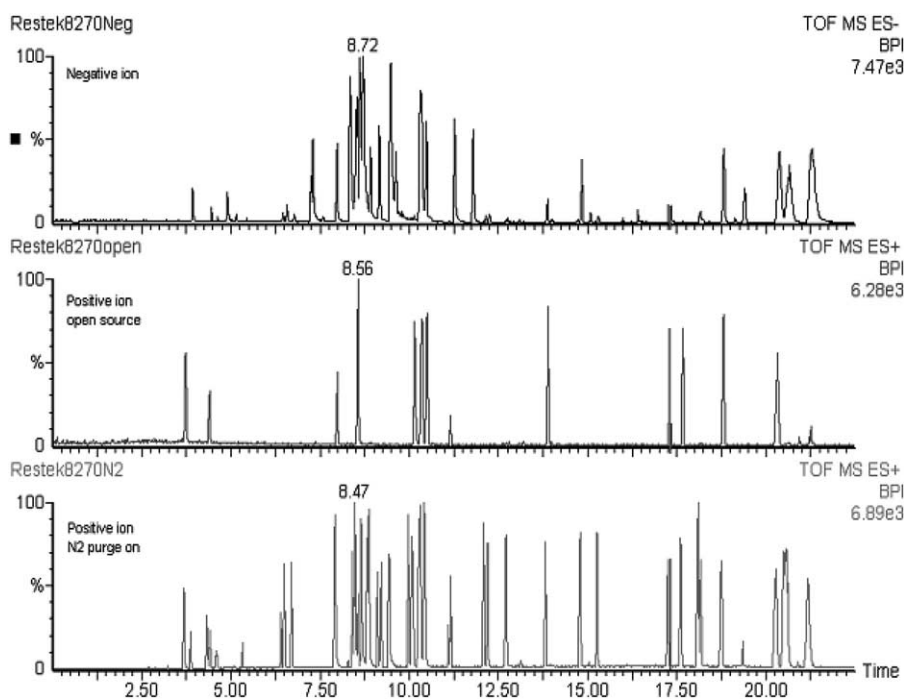
Figure 3. Base peak positive ion mass chromatograms of a Restek 8270 mixture using a dual GC/APMS:LC/MS ion source operated in the GC/MS mode. A list of the components in the mixture can be found at *www.restek.com/fantasia/pdfcache/pres-2001-1037.pdf*. Top: Negative ion base peak chromatogram obtained with the ion source open to the room air. Middle: Positive ion base peak chromatogram obtained with an open source and no purge gas. Bottom: Positive ion base peak chromatogram obtained with the source area sealed from the surrounding air and purged with a flow of dry nitrogen gas.

and associated ESI/APCI probe with a metal flange having ports for the GC interface probe insertion and purge gas entrance. The exit end of the GC interface probe (Figure 1) was placed at about the position that the exit end of the ESI/APCI probe normally occupies. Because the GC was situated on an adjustable cart with wheels, it was possible to adjust the probe somewhat and easily remove it for rapid switching back to the LC/MS mode. The cart also allowed the GC to be easily moved between mass spectrometers. Figure 2 shows a diagram of an alternate source design used in some experiments where both the ESI/APCI LC interface probe and the GC interface probe were inserted in the ion source. This configuration provided equivalent data to the above described arrangement when the GC interface probe was adjusted for maximum sensitivity (about 1 cm from the entrance aperture of the mass spectrometer).

Ionization in the atmospheric pressure ion source was produced by applying a voltage to either a Picotip emitter from New Objective, Woburn, MA, without liquid or to the standard APCI needle used in the Micromass Z-Spray APCI ion source. The Picotip was used for the arrangement in which both the LC and GC interface probes were in the ion source simultaneously (Figure 2) and was used as a convenient means of producing a corona discharge. In this arrangement, the Picotip was held in place using the Micromass nano-

flow interface and the discharge voltage was applied to the nanospray source as if it were operating in the electrospray mode. The standard APCI needle was used in the ion source, described above, in which the GC interface probe replaced the LC probe and was operated as if it were in the APCI mode. A voltage of between 2000 and 3500 V was used to generate discharge conditions.

The gas chromatograph used in these studies was a Hewlett Packard 5890 Series II (Agilent Corporation, Wilmington, DE) fitted with a ThermoFinnigan (Thermo Corporation) heated interface probe. The GC was originally interfaced to a Thermo model SSQ 7000 GC/MS instrument. The exit tip of the interface probe was modified as shown in Figure 1 using ceramic tubing and Sauereisen no. 1 cement (Sauereisen Cements Company, Pittsburgh, PA). The capillary GC column was inserted through a Swagelok tee fitting (Swagelok Corporation, Solon, OH) and through the interface probe and the heated sheath tube shown in Figure 1. Nitrogen gas from a liquid nitrogen dewar refrigerated container was fed through 1/16 inch o.d. stainless steel tubing that coiled inside the GC oven and was connected to the center position of the Swagelok tee. Because the GC column was connected to the oven side of the tee with a gas-tight fitting, nitrogen gas from the Micromass nanoflow regulator was forced through the stainless steel tubing into the heated interface and
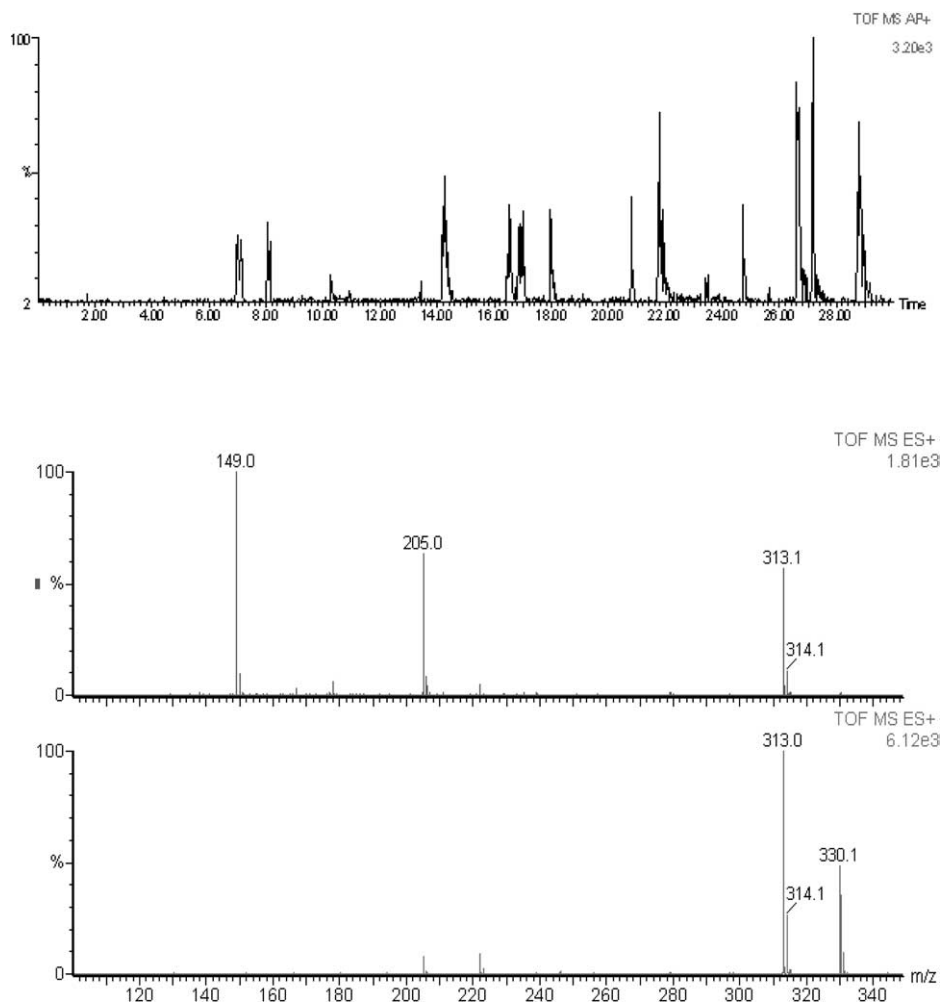
Figure 4. Top: Base peak positive ion mass chromatogram under conditions described in Figure 3 (top) except a vial containing a saturated aqueous solution of NH₃ is open in the ion source volume. Middle: Positive ion mass spectrum of benzylbutylphthalate with the cone voltage set at 50 V. Bottom: Cone voltage set at 20 V.

through the sheath tubing shown in Figure 1. In this way, the heated nitrogen gas (ca. 300 °C) maintained the GC column hot to the exit tip.

It was important to condition new GC columns before initial use by heating to 300 °C with a 5 min hold several times before initial operation. Background ions could also be significantly reduced by heating the GC to MS interface to 325 °C overnight while passing nitrogen gas through the interface. This resulted in a reduction in off-gasses from the column polyimide coating and any contaminants in the interface.

The GC was operated at a split ratio of 10:1 unless otherwise noted. One microliter of a solution of Restek 8270 Matrix spike mix [for a list of components go to *www.restek.com/fantasia/pdfcache/pres-2001-1037.pdf*] (Restek Corporation, Bellefonte, PA) diluted with methylene chloride was injected for each run. The GC column used in all experiments was a Restek RTX-5 (15 m × 0.25 mm × 0.25 um). The injector was set at 250 °C and the oven was maintained at 50 °C for 1 min after injection before temperature programmed

heating at 7 °C/min. for 32 min. The interface temperature was maintained at 300 °C and the entrance aperture of the Z-Spray source was heated to 150 °C. In some experiments the ion source region was enclosed except for an entrance and exit aperture for nitrogen purge gas. The nitrogen purge gas was taken from the Micromass cone gas regulator on the LCT or QTOF mass spectrometers at a flow rate of ~10 L/h. In open source experiments, the glass enclosure has an opening to the room air and no purge gas was used.

For comparison with LC/APMS, the mass spectrometer was operated under the standard conditions used for LC/MS analysis in our laboratory. No attempt was made to optimize the LC conditions for the Restek 8270 analysis. For the LC, mobile phase A was 98:2:0.005 parts water:acetonitrile:formic acid and mobile phase B was 98:2:0.005 parts acetonitrile:water:formic acid. The LC column was an Agilent Zorbax SB-C18 (5 um, 2.1 × 150 mm). A linear gradient elution using a flow rate of 250 ul/min was run from 25% B to 100% B in 25 min.

gcapms methylbenzophenone 50ppb MSMS 197
APGCMSMEBZPHONE50PPBMSMS 388 (7.569) Cm (387:391)
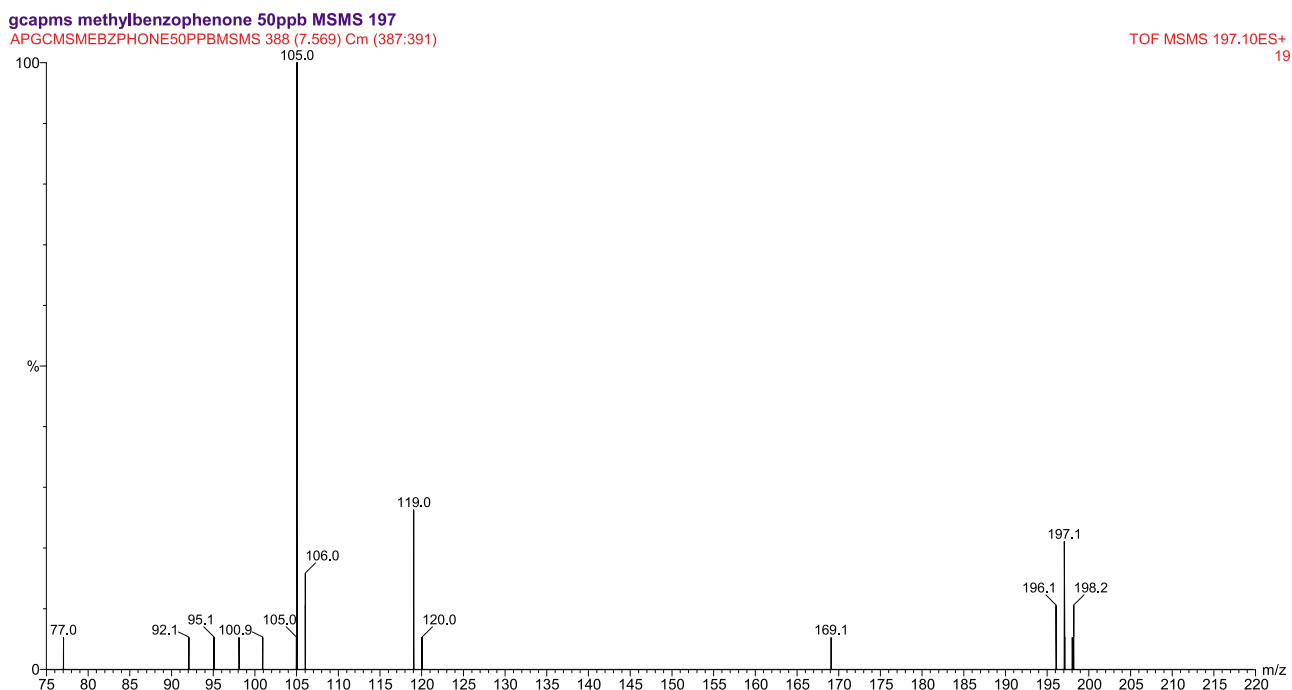
TOF MSMS 197.10ES+
19

Figure 5. Positive ion GC/APMS/MS spectrum of the MH$^+$ ion of 50 pg injection of 2-methylbenzophenone using a collision energy of 24 V obtained on a micromass QTOF I mass spectrometer.

The mass spectrometry conditions were optimized on the m/z 354 ion from tri-n-octylamine (TOA) using 50% B isocratic conditions with a flow rate of 250 ul/min from the LC with infusion of TOA into the LC flow before the ion source.

Accurate mass measurement data were acquired on a Micromass LCT using a data acquisition time of 0.45 s and a reset time of 0.05 s per spectra. Before AP-GC/MS analysis, the instrument was calibrated using a polyalanine methanol solution. The polyalanine solution was infused into the ion source under electrospray ionization conditions to generate reference ions over the mass range of 70 to 1000 Da. A single reference ion (m/z 354.4100) from TOA was used to adjust the mass scale during AP-GC/MS acquisitions. To generate steady ion abundance for the m/z 354 reference ion, a vial containing TOA and having an adjustable wick was placed into the ion source region to allow controlled evaporation of the TOA. The volume of wick exposed to the nitrogen atmosphere was roughly adjusted to achieve the desired ion abundance.

MS/MS spectra were obtained on the Micromass QTOF I instrument using a data acquisition time of 0.7 s per spectra. Reproducible MS/MS spectra were obtained injecting 1 ul of a 50 ppb solution of 2-methylbenzophenone in acetonitrile using a 5:1 split ratio and a GC carrier gas flow of 5 ml/min.
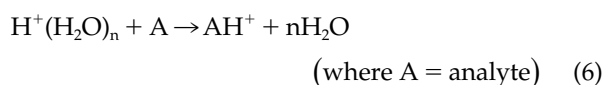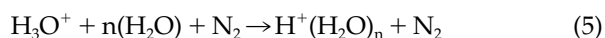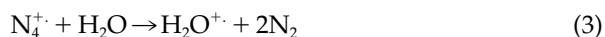
Results and Discussion

In a study designed to determine the capabilities of electrospray ionization for ionizing substances in air, we rediscovered APCI for ionization of volatile materials. Using a Picotip emitter containing a water/methanol solution, molecular ions were observed for certain volatile components that had been introduced into the air near the ion source. However, when the capillary became dry, the kinds of compounds that could be observed and the sensitivity with which they could be observed increased. It occurred to us that an LC/MS instrument could easily be converted to a combination GC/APMS-LC/APMS instrument.

Interfacing a GC to an atmospheric pressure ionization source requires that the exit of a capillary GC column be near the atmospheric pressure aperture inlet to the mass spectrometer without cold spots along the entire length of the GC column. It is especially important for less volatile compounds that the exit tip of the column be at a high enough temperature to prevent compound condensation. This is achieved by using a modified GC to MS heated transfer line shown in Figure 1. The nitrogen gas used to heat the column to the exit tip is taken from the nanoflow controller used for ESI operation and is heated by the GC oven and interface transfer line before flowing through the sheath tube and thus over the GC column. It was also important for less volatile compounds that the source block area be heated. With the MicroMass LCT and QTOF mass spectrometers (Waters Corporation), the maximum source temperature of 150 °C was used. With this setup, even relatively nonvolatile compounds could be ionized without loss of chromatographic resolution.

Discharge ionization was found to be effective in either the positive or negative ion modes. A Townsend/

corona discharge could be generated by applying a voltage to the APCI needle or a dry Picoflow tip to generate a discharge. Trace levels of water vapor present in the atmosphere are sufficient to prevent compounds less basic than H_2O, or more properly, water clusters, from being ionized. The responsible ion molecule reactions are

$$N_2 + e \rightarrow N_2^{+\cdot} + 2e \tag{1}$$

$$N_2^{+\cdot} + 2N_2 \rightarrow N_4^{+\cdot} + N_2 \tag{2}$$

$$N_4^{+\cdot} + H_2O \rightarrow H_2O^{+\cdot} + 2N_2 \tag{3}$$

$$H_2O^{+\cdot} + H_2O \rightarrow H_3O^+ + \cdot OH \tag{4}$$

$$H_3O^+ + n(H_2O) + N_2 \rightarrow H^+(H_2O)_n + N_2 \tag{5}$$

$$H^+(H_2O)_n + A \rightarrow AH^+ + nH_2O$$
$$(\text{where } A = \text{analyte}) \tag{6}$$

Less polar compounds are ionized in the APCI ion source with increased sensitivity by purging the ion source region with a dry inert gas such as nitrogen, presumably because the water vapor and contaminants present in the ionization region are swept from the source by the flow of dry purge gas.

The base mass peak chromatograms generated from GC/APMS of a Restek 8270 mixture in the negative and positive ion modes is shown in Figure 3. No effort was made to optimize the chromatographic conditions in these experiments. The negative ion mass spectrum obtained with the ion source open to lab air and without a nitrogen gas purge is shown in Figure 3 (top). The positive ion mass spectrum obtained under the same conditions is shown in Figure 3 (middle). In this configuration, ionization is primarily by ion-molecule proton transfer reactions between protonated water clusters and the analyte molecules (eq 6). As noted above, only compounds sufficiently basic for exothermic proton transfer from protonated water clusters are observed. Figure 3 (bottom) shows the mass chromatogram obtained when the source is enclosed except for an entrance and exit port for introduction and escape of dry nitrogen purge gas. More compounds in the Restek 8270 mixture are observed when the enclosed ion source region is purged with dry nitrogen gas (Figure 3, bottom) than is obtained when the source is open to room air (Figure 3, middle). It is believed that a dry purge gas reduces the amount of contaminants and water vapor so that ionization is primarily by H_3O^+ proton transfer and N_2^+/N_4^+ charge-transfer reactions. Compounds such as naphthalene, acenaphthylene, dimethylphenol, dinitrophenol, and chloromethylphenol are ionized with good sensitivity using the nitrogen purge gas but are poorly ionized in the source that is open to air and moisture. With the nitrogen purge on, 73 of the 76 compounds listed for Restek 8270 were

observed with good sensitivity in the positive ion mode. Compounds reported to be in the mixture but not observed by positive ionization are azobenzene, bis-(chloroethoxy)methane, and bis(chloroisopropyl)ether. More compounds were observed in the positive ion mode than were observed under negative ion conditions, but for those compounds with a large cross section for electron capture, the negative ion sensitivity could exceed that obtained under positive ion conditions.

Contaminants can also interfere with the sensitivity and reduce the number of compounds observed. Two such sources of contaminants are the GC column bleed and the polyimide coating on the section of the GC capillary column over which the heated sheath gas passes. Conditioning the column and especially conditioning the section of column over which hot nitrogen gas passes significantly reduces background ions.

Purging the source region with dry and clean nitrogen gas increases the sensitivity for observing low polarity compounds, but adding ammonia gas by, for example, evaporation of an ammonium hydroxide solution in the source region increases the selectivity of the ionization. Only compounds more basic than ammonia or compounds capable of stable gas-phase attachment of NH_4^+ are observed. Figure 4 (top) shows a base peak mass chromatogram of a GC injection of the Restek 8270 mixture under conditions in which $NH_4(NH_3)_n^+$ are the dominant reagent ions. The mass spectra of one of the compounds observed in the base peak chromatogram is shown using a high cone voltage to enhance fragmentation (Figure 4, middle) and lower cone voltage to minimize fragmentation (Figure 4, bottom). The ion at m/z 330 is the $[M + NH_4]^+$ ion of benzylbutylphthalate. Thus, using GC/APMS, molecular ions are readily identified. By adjusting the voltage between the first and second pumping stages of the AP source (cone voltage), it is possible to generate fragment ions.

The sensitivity of GC/APMS in the negative ion mode has been well demonstrated for compounds that efficiently capture electrons. For example, the detection limit for 1-nitronaphthalene was reported to be 0.3 pg using selected ion monitoring [15]. However, the positive ion mode of GC/APMS has been neglected and sensitivity information is not available. Using the QTOF I mass spectrometer and full scan acquisition, it was possible to construct a linear calibration curve for injections ranging from 5 to 1000 pg of 2-methylbenzophenone injected using a split ratio of 5:1. The sensitivity of GC/APMSMS can also be demonstrated. Figure 5 shows the MS/MS CID mass spectrum of the 197 MH^+ ion for 1 ul of a 50 ppb solution of 2-methylbenzophenone injected using a 10:1 split ratio. GC/APMS can be compared to LC/MS for the Restek 8270 mixture by comparison of Figure 1 with Figure 6. Figure 6 (top) shows the LC base peak chromatogram for 5× the amount of sample injected to produce Figure 1 and Figure 6 (bottom) shows the diode array UV spectrum
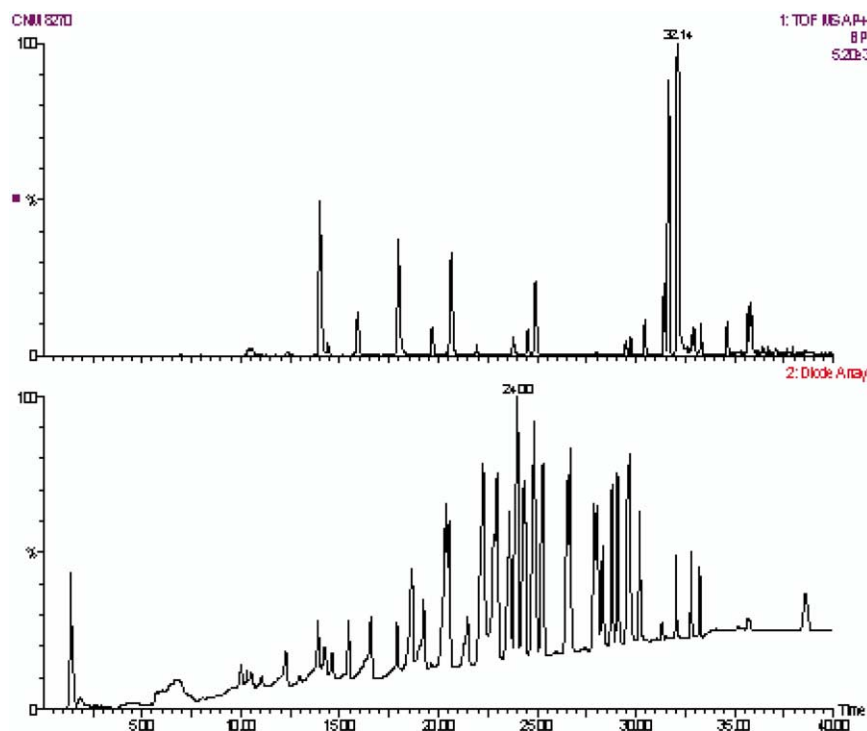
Figure 6. Base peak positive ion APCI LC/MS mass chromatogram using 5× the amount of Restek 8270 mixture injected for the spectra shown in Figure 1. LC conditions were 200 ul/min water/acetonitrile gradient using a 2.1 mm × 150 mm [18]C column. Top: LC base peak chromatogram of Restek 8270 mixture. Bottom: Diode array chromatogram.

for this sample. Clearly, for most of the compounds in the 8270 mixture, GC/APMS is more sensitive than LC/APMS under the conditions of these experiments. With this mixture, the same is true for electrospray LC/MS. This work demonstrates a clear advantage of having GC/APMS in addition to LC/MS capabilities.

Time-of-flight mass spectrometers are well suited for GC/APMS because of the fast data acquisition and the ability to obtain accurate mass measurement. With the Micromass QTOF and LCT mass spectrometers, after an initial calibration, a single reference ion can be used to adjust the mass scale and obtain good mass accuracy of all peaks in the spectrum. A reference standard can be constantly added to the ion source by allowing evaporation of a suitable compound to occur at a suitable rate. Tri-*n*-octylamine was allowed to evaporate from a partially enclosed vial placed in the ion source enclosure and the MH$^+$ ion at m/z 354.4100 was used as a single reference ion to adjust the pre-calibrated mass scale. Representative accurate mass measurement data using

this method are shown in Table 1. Because of the sharpness of the GC peaks, the measurements are of a single 0.5 s acquisition on a Micromass LCT. Mass accuracy is consistently within the instrument specifications for low-mass ions.

Conclusions

GC/APMS is best compared to chemical ionization GC/MS, and in the positive ion mode is shown to have comparable sensitivity. Superior negative ion sensitivity has previously been demonstrated in a series of papers dealing primarily with halogenated aromatic compounds using a dedicated GC/APMS instrument [14, 16, 18, 33]. One clear advantage of interfacing a GC to an atmospheric pressure ion source is the ease of interconversion between GC/MS and LC/MS. Other advantages are a wide range of carrier gas flow rates without affecting the atmospheric pressure ionization process. Higher carrier gas flow rates increase the speed

Table 1. Accurate mass measurement of GC/APMS eluted compounds using the MH$^+$ ion of trioctylamine (354.4100) as a reference standard.

Compound	Elemental composition	Meas mass	Calc mass	MDa error
Methyl cyclohexanone	C7H13O	113.0928	113.0966	−3.8
Benzamide	C7H8NO	122.0593	122.0606	−1.2
2-Chlorophenol	C6H5OCl	128.0023	128.0029	−0.6
Dioctylamine	C16H36N	242.2821	242.2848	−2.6
Polypropylene glycol (8-mer)	C16H35O8	371.2250	371.2281	−3.1

of analysis or, by using shorter columns of wide bore, less volatile compounds can be made to pass through the GC and be analyzed. In addition, all of the capabilities common with LC/MS instruments such as high-resolution and accurate mass measurement, cone voltage fragmentation, MS^n, and reaction ion monitoring can be applied to GC/APMS. Disadvantages of GC/APMS include the low abundance of odd-electron fragmentation for computer aided compound identification and poor ionization efficiency for nonpolar compounds having little or no functionality such as saturated hydrocarbons.

GC/APMS combined with LC/MS also has a number of advantages relative to dedicated LC/APMS instrumentation. Advantages include efficient ionization of volatile low polarity compounds and higher chromatographic resolution. Over 300 compounds can be determined from a single sample using GC/MS [34]. These advantages are especially important for complex mixtures such as those encountered in environmental and metabolomic analyses. Other advantages of GC/APMS versus LC/MS include few solubility issues and the simplicity of method development. It is now possible to have a mass spectrometer capable of LC/APMS, GC/APMS, and AP-MALDI.

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