

# From Hydrocarbons to Highly Functionalized Molecules in a Single Measurement: Comprehensive Analysis of Complex Gas Mixtures by Multi-Pressure Chemical Ionization Mass Spectrometry

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## Abstract

Chemical Ionization Mass Spectrometry (CIMS) is a well-established analytical method in atmospheric research, process monitoring, forensics, breathomics and food science. Despite significant advancements in procedural techniques, several instrument configurations, especially operating at different ionization pressures, are typically needed to analyze the full range of compounds from non-functionalized parent compounds to their functionalized reaction products. For polar, functionalized compounds, very sensitive detection schemes are provided by high-pressure adduct-forming chemical ionization techniques, whereas for non-functionalized, non-polar compounds, low-pressure chemical ionization techniques have consistently demonstrated superior performance. Here, using a MION2 chemical ionization inlet and an Orbitrap Exploris<sup>TM</sup> 120 mass spectrometer, we present multi-pressure chemical ionization mass spectrometry (MPCIMS),

the combination of high and low pressure ionization schemes in a single instrument enabling quantification of the full distribution of precursor molecules and their oxidation reaction products from the same stream of gas without alterations. We demonstrate the performance of the new methodology in a laboratory experiment employing  $\alpha$ -pinene, a monoterpene relevant to atmospheric particle formation, where MPCIMS allows to measure the spectrum of compounds ranging from the volatile precursor hydrocarbon to highly functionalized condensable reaction products. MPCIMS carries the potential as an all-in-one method for the analysis of complex gas mixtures, reducing technical complexities and the need for multiple instruments without compromise of sensitivity.

## Introduction

The demand for rapid and direct gas-phase chemical analysis of a wide range of compounds

at low concentrations has been driving the development of direct injection mass spectrometry methods for over 50 years.<sup>1</sup> Atmospheric research has been naturally positioned at the forefront of this endeavor. Chemical Ionization Mass Spectrometry (CIMS), a leading direct injection mass spectrometry technique, was pioneered by Munson and Field.<sup>2</sup> This early work and related scientific breakthroughs stimulated a wealth of studies and the development of both mass spectrometric instrumentation as well as CI techniques, addressing the need to detect diverse compound classes at low concentrations.<sup>3,4</sup> The performance of mass spectrometers has improved dramatically regarding sensitivity, mass resolving power, and aptitude for switching between polarities. In parallel, new CI schemes have been explored to enhance the applicability of CIMS, addressing the challenge of appropriately ionizing the varied spectrum of initially neutral analyte molecules in a controlled manner, allowing subsequent quantitative detection in a suitable MS.

The ionization of a target molecule in an Ion-Molecule Reactor (IMR) occurs through a reactive interaction between the reagent ion and the analyte molecule as the result of their collision. This interaction can take place as charge transfer (electron abstraction or transfer), clustering (ion attachment), ion transfer (proton transfer or abstraction), or as dissociative mechanism.<sup>5-7</sup> The nature of this interaction determines the stability of the resulting ion and whether the analyte molecule undergoes fragmentation upon ionization. Volatile organic compounds (VOCs) such as benzene, toluene, and  $\alpha$ -pinene are only weakly polar and interact weakly with ions, necessitating harder ionization methods - such as charge or ion transfer reactions. In contrast, functionalized polar molecules like oxygenated organic molecules (OOMs) and highly oxygenated organic molecules (HOMs) often form strongly bound molecular clusters with other polar reagent ions. Thus, the analyte properties dictate the choice of reagent ions required to achieve optimal interaction.

Following initial ionization, the formed ions experience further collisions within the IMR,

which influences their stability and fate. Collisions with the bath gas are required to thermally stabilize the cluster ions. However, energetic collisions by ions accelerated in the electric fields, and collisions with other trace gases can also alter the state of the ions of interest.<sup>5,8</sup> Water is a notable reactive trace gas which, even at low humidity, is present at concentrations around  $[\text{H}_2\text{O}] \approx 10^{17} \text{ cm}^{-3}$ , vastly exceeding concentrations of other trace gases. It is well-established that water can enhance or inhibit the ionization of compounds.<sup>5,9,10</sup> After the initial ionization, collisions with water can influence the distribution of protons within the gas matrix.<sup>11</sup> In the low pressure IMRs of PTR-MS, the detection of compounds with a low gas basicity, comparable to that of water (e.g., formaldehyde, hydrogen cyanide, hydrogen sulfide, and isocyanic acid), is strongly humidity sensitive.<sup>11</sup> In high pressure IMRs, the higher frequency of collisions - analyte molecules undergo approximately  $10^4$  collisions per millisecond with water - combined with longer reaction times, enables such secondary chemistry to unfold further. Clusters of appropriately selected reagent ions with polar compounds are often sufficiently strongly bound and therefore less susceptible to subsequent reactions with water or other molecules in the sample gas, ensuring that collisions do not lead to fragmentation or loss of charge. The number of collisions in the bath gas can be effectively reduced by lowering the IMR pressure and reaction time, promoting a single-collision chemistry in regard to reactive collision partners. The resilience of ions to multiple collisions following initial ionization determines whether a low- or high-pressure IMR is required.

Low-pressure CIMS techniques have been successfully used to study VOCs. Most notable examples include proton transfer reaction mass spectrometers (PTR-MS)<sup>11,12</sup> and Selected-ion flow tube Mass Spectrometers (SIFT-MS).<sup>13</sup> In both systems the hydronium ion ( $\text{H}_3\text{O}^+$ ) is predominantly used for proton transfer. Recognizing that a single ionization scheme can not satisfy the needs of comprehensive chemical analysis, multiple low-pressure switching reagent schemes were introduced, first with

SIFT MS,<sup>14</sup> later with SRI PTR MS (Switchable Reagent Ion Proton Transfer Reaction Mass Spectrometry).<sup>15</sup> Here, the reagent ion within the low-pressure IMR can be exchanged, increasing the number of detectable compounds greatly. However, the inherent limitations of low-pressure ionization remained unchanged: While still considered soft, low-pressure chemical ionization often results in fragmentation of more complex compounds due to a relatively high collision energy in presence of high electric fields.<sup>11,16</sup> In addition, introducing sample from ambient conditions into reduced pressure results in a substantial reduction of the analyte concentration proportional to the reduction of pressure, which renders the detection of more functionalized and less volatile compounds virtually impossible.

High-pressure ion attachment techniques have been developed to overcome these limitations. Most notably, Eisele and Tanner pioneered  $\text{NO}_3^-$ -ionization at ambient pressure for the detection of sulfuric acid and methane sulfonic acid.<sup>17</sup> This technique has proven instrumental in atmospheric measurements of strong acids and HOMs that play a critical role in secondary organic aerosol formation.<sup>18</sup> While being selective and sensitive to strong acids and polar functionalized compounds, however,  $\text{NO}_3^-$ -CIMS has a very limited sensitivity to VOCs and compounds with low oxygen content. To overcome this issue, many more high-pressure chemical ionization systems have been explored.<sup>4,7,19</sup> Some of the reagent ions are typically employed at a reduced pressure of few tens to hundreds of mbar, to reduce the number of reactive collisions and thereby reducing matrix effects from a multi-collision chemistry. Meanwhile, the IMR pressures are held as high as possible to maximize the detection efficiency and create best limits of detection.

To take advantage of the diverse reagent ion properties reagent switching multi-scheme ionization techniques at high IMR pressure have been developed<sup>10,20</sup> and taken even further with fast polarity switching mass spectrometers.<sup>21</sup> However, reagent switching at constant IMR pressure does not allow to combine the advantages of low-pressure ionization

(single-collision chemistry and sensitivity to non-polar compounds) and high-pressure ionization (enhanced sensitivity for functionalized compounds). Non-selective reagent ions typically used at low IMR pressures (e.g.,  $\text{H}_3\text{O}^+$ ) are often not applicable in high-pressure IMRs, as they are prone to depletion. Therefore, the measurement of the entire spectrum of compounds has required using two dedicated instruments with low- and high-pressure ionization, respectively.

In this study we introduce the concept of multi pressure chemical ionization mass spectrometry (MPCIMS, Figure 1). We demonstrate MPCIMS with a system that combines a MION2 atmospheric-pressure chemical ionization inlet, selectively introducing reagent ions into the sample flow without other alterations of the sample composition, with a low-pressure ion source within an Orbitrap Exploris 120 mass spectrometer. We assess the performance of the Orbitrap Exploris 120 internal ion source as a low-pressure ionization source regarding VOC detection in a calibration experiment in dry and wet conditions. We further demonstrate the comprehensive sensitivity attainable with a single instrument using MPCIMS by characterizing the spectrum of more and less oxygenated organic compounds from a monoterpene oxidation system highly relevant to atmospheric sciences.

## Methods

### Instrumentation

Figure 2 shows the MPCIMS setup of this study, the combination of a multi ion MION2 high-pressure CI inlet and Orbitrap Exploris 120, featuring an EASY IC internal calibration source which we used as a low-pressure ionization source in this study. The reagent ions used in this study are bromide ( $\text{Br}^-$ ) and protonated diethylamine ( $\text{C}_4\text{H}_{12}\text{N}^+$ , generated from  $\text{CH}_2\text{Br}_2$ , and  $\text{C}_4\text{H}_{11}\text{N}$ , respectively) at ambient pressure, and positively charged fluoranthene ( $\text{C}_{16}\text{H}_{10}^+$ , generated from  $\text{C}_{16}\text{H}_{10}$ ) at low pressure.

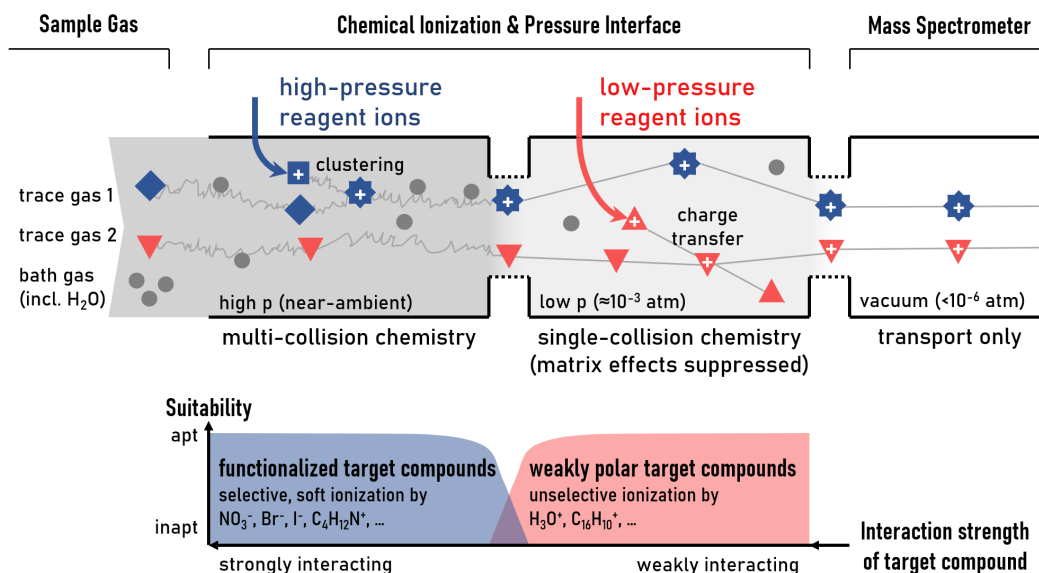


Figure 1: Principle of multi-pressure chemical ionization. Along the transfer from the source to the detector (high pressure to vacuum), ionization schemes robust against collisions with the bath gas (high-pressure ionization, here: clustering reaction, blue) or requiring single collisions between the reagent gas and the analyte (low-pressure ionization, here: charge transfer, red) are used simultaneously or sequentially. The combination of high- and low-pressure ionization creates sensitivity to compounds that require different types of ionization, i.e., functionalized and weakly polar target compounds.

### MION2 high-pressure CI inlet

MION2 is an established atmospheric pressure interface for chemical ionization.<sup>22</sup> In brief, a reagent gas is ionized by x-ray irradiation in a volume lateral to the sample flow. A series of electrodes transports the resulting reagent ion through a buffer volume that prevents cross-contamination between the reagent gas and sample gas into the sample flow. The high pressure ionization occurs at ambient pressure and a reaction time of  $\approx 23$  ms.<sup>22</sup> The ion introduction from sources into the IMR can be rapidly enabled or turned off by energizing or grounding the electrodes, allowing to select ions from multiple reagent sources (Fig. 2).

The Orbitrap capillary (inner diameter 0.58 mm, length 58 mm) transfers gas from the high pressure IMR to the S-lens, a series of annular ion optics. While the S-lens can be used as an ion funnel, the gas and ion transport is predominately advective.

### Low-pressure chemical ionization source

Figure 2 shows the low-pressure chemical ionization source, located inside the injection filter region with a local pressure below 1 mbar. The system was originally intended to provide a chemically inert ion as internal mass calibration standard (EASY-IC), not as a chemical ionization source. Crystalline fluoranthene ( $C_{16}H_{10}$ ) is evaporated from a temperature-controlled oven with a reservoir sufficient for approximately one year of continuous operation. A small nitrogen carrier flow transports the vapor into the ionization volume, where it is ionized by free electrons. The free electrons are generated by a DC plasma electron source. The dominant cation produced from the ionization is  $C_{16}H_{10}^+$ , with  $C_{16}H_9^+$  and  $C_{16}H_{11}^+$  relative abundances of less than  $10^{-3}$ .  $N_2^+$ ,  $O_2^+$  and  $NO_2^+$  constitute minor signals, consistent with previous descriptions of similar sources.<sup>23</sup> The transport and mixing of ions into the sample flow is aerodynamic. The flow of  $C_{16}H_{10}$ -doped nitrogen continues even when the discharge is turned off. Assuming thermal velocity and an

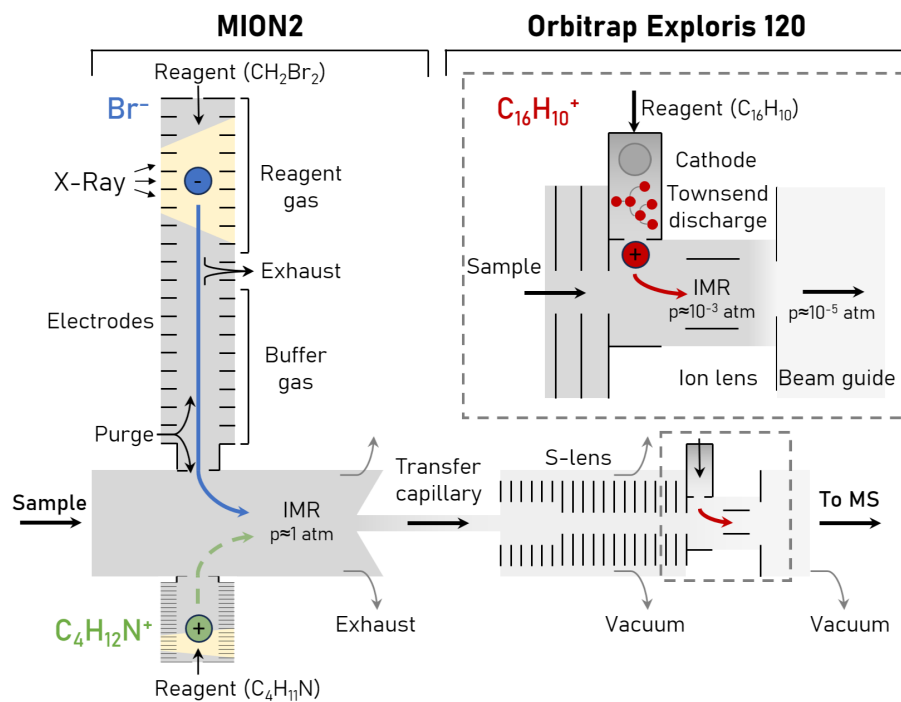


Figure 2: Experimental setup used for MPCIMS. The high-pressure ionization occurs in a MION2 CI inlet<sup>22</sup> (in the example either  $\text{Br}^-$  or  $\text{C}_4\text{H}_{12}\text{N}^+$ ,  $p \approx 1$  atm), the low-pressure ionization occurs within the Orbitrap Exploris 120 mass spectrometer ( $\text{C}_{16}\text{H}_{10}^+$ ,  $p \approx 10^{-3}$  atm).  $\text{C}_{16}\text{H}_{10}^+$  is generated from the ionization of fluoranthene ( $\text{C}_{16}\text{H}_{10}$ ) by pulsed cathode discharge and advectively introduced into the gas jet.

effective low-pressure IMR length of 1 cm, the reaction time (at  $\approx 1$  mbar) is 3  $\mu\text{s}$ .

During the fluoranthene injection time, which is only a few ms per scan, the source is actively regulated to maintain a preset abundance of  $\text{C}_{16}\text{H}_{10}^+$  (intensity approximately  $2 \cdot 10^6 \text{ s}^{-1}$ ) in the mass spectrum. This is ideal for the original objective of creating a stable mass calibration signal, but can complicate the normalization of signals in the demonstration setup when high analyte concentrations lead to reagent ion depletion and the ion source duty cycle is adjusted to re-capture the target ion intensity.

### Orbitrap mass spectrometer

Mass spectra were determined with an Orbitrap Exploris 120 (Thermo Fisher Scientific)<sup>24</sup> using a constant microscan integration time of 1 s and 10 microscans.<sup>25</sup> Data were analyzed with the Orbitool software package.<sup>26</sup>

### Measurement data

The sensitivity and linearity of the low pressure source was characterized by dosing a number of compounds from a PTR calibration bottle (Apel-Riemer Environmental, Inc) to attain volume mixing ratios (VMR) in the range of 50 ppt to 5 ppb. The calibration was carried out as duplicate either in dry ( $\text{RH} < 2\%$ ) or humidified nitrogen ( $\text{RH} \approx 30\%$ , by bubbling a fraction of the carrier gas through ultra-pure water).

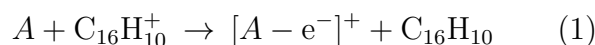
To generate a spectrum of atmospherically relevant compounds with different levels of oxidation, a-pinene was oxidized in an oxidative flow reactor.<sup>21</sup> In brief, a-pinene is dosed into a flow reactor filled with dry air. Ozone formed from irradiation with UV light reacts with a-pinene and initiates the formation of a spectrum of products.<sup>27,28</sup> During the experiment, the reagent ion was cycled between (1)  $\text{C}_{16}\text{H}_{10}^+$ , (2)  $\text{C}_{16}\text{H}_{10}^+$  together with  $\text{C}_4\text{H}_{12}\text{N}^+$ , (3)  $\text{C}_4\text{H}_{12}\text{N}^+$ , and (4)  $\text{Br}^-$ . These reagent ions were chosen to detect a wide range of oxidation states of the a-

pinene oxidation products, while, in principle, the selection of reagents can be adjusted to the experiment needs.

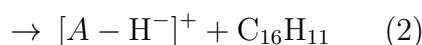
## Results and discussion

### Calibration of low-pressure ionization source

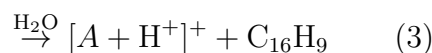
Based on the detected species, the ionization of a compound  $A$  by  $C_{16}H_{10}^+$  in the low-pressure IMR occurs via three major mechanisms:



( $e^-$  abstraction)



( $H^-$  abstraction)



( $H^+$  transfer)

For each compound  $A$  shown in Fig. 3, the predominant signal is the electron-abstracted mass  $A^+$ . The traces where  $A$  is missing  $H^-$  ( $H^-$  abstraction) occur at approximately 10% relative intensity, with only little dependence on humidity.  $AH^+$  (proton transfer) exhibits a notable sensitivity to humidity, being approximately 1% under dry, and 10% under humid (30% RH) conditions. This suggests an active role of  $H_2O$ , likely proton transfer from  $C_{16}H_{10}^+$  to form  $H_3O^+$ . The proton affinity/gas basicity of fluoranthene exceeding that of water (828.6/800.9 kJ mol<sup>-1</sup> and 695.6/660.0 kJ mol<sup>-1</sup>,<sup>29</sup> respectively) is compatible with the observation that  $C_{16}H_{10}^+$  does not lose its charge to water appreciably. The only marginal humidity sensitivity of the traces further corroborates that the chemistry experienced in the low-pressure IMR is effectively a single-collision chemistry.

Figure 3 shows the signal intensities for the calibration experiment, normalized to the primary ion, but not background corrected. Backgrounds, especially originating from the water bubbler, lead to non-zero signals at low VMR (e.g., toluene). Under humid conditions, water

and other trace gases are sinks for  $C_{16}H_{10}^+$ , leading the regulating system of the low-pressure ion source to increase its output. The normalization for the humidified data in Fig. 3 therefore uses a normalization intensity that is 1.13 times larger than the measured  $C_{16}H_{10}^+$  intensity. The detection of the VOCs is linear over two orders of magnitude of VMR, from 5 ppb down to 50 ppt, the lowest VMR attainable with the available setup. The sensitivity appears to be better for compounds less prone to fragmentation (i.e., aromatics), and worse for more reactive hydrocarbons known to more likely fragment in PTR,<sup>11,16</sup> too. The respective limits of detection in the demonstration setup range from single ppb (methyl vinyl ketone, MVK) to few 10 ppt (e.g., xylene).

### Multi-pressure CIMS demonstration

Figure 4 shows selected time series of the a-pinene oxidation experiment, acquired with switching reagent ion schemes. The three experiment stages shown are (1) the steady state in a dark reactor, with a-pinene being dosed (14:43), (2) the system response to turning on the UV-lamps (15:01), initiating the formation of ozone, and (3) the system response to increasing the a-pinene dosing (15:26). Each stage is sampled by  $C_{16}H_{10}^+$ ,  $C_{16}H_{10}^+$  together with  $C_4H_{12}N^+$ ,  $C_4H_{12}N^+$ , and  $Br^-$ .

The current of the  $C_4H_{12}N^+$  high-pressure reagent ion does not change if the low-pressure  $C_{16}H_{10}^+$  ion source is added or removed. Likewise, the current of  $C_{16}H_{10}^+$  is insensitive to whether the high-pressure source  $C_4H_{12}N^+$  is on or off. This is expected, as the small carrier flow for  $C_{16}H_{10}^+$  in the low-pressure ion source is constantly on and space-charge as a source for ion losses is insignificant. Additionally, the regulation system maintains the preset  $C_{16}H_{10}^+$  current, even if a large fraction is lost to a high analyte concentration. While enabling the low-pressure source, the current is temporarily enhanced, likely due to the Orbitrap adjusting the scan integration time to maintain the target ion saturation for individual injections. The combination of  $Br^-$  and a positive reagent

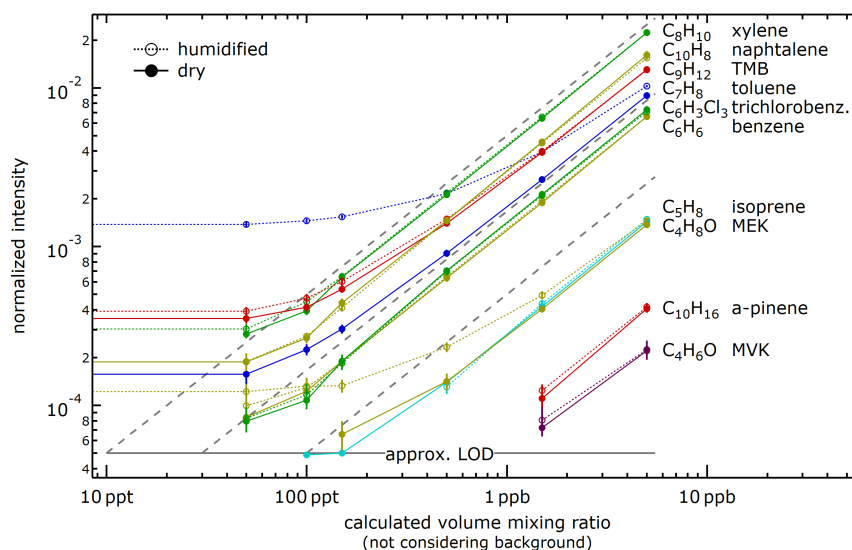


Figure 3: Humidity independent detection of volatile organic trace gases by  $C_{16}H_{10}^+$  low-pressure ionization with dry and humidified carrier gas (solid and hollow markers).

ion is not shown, as anion-cation recombination quickly scavenges the less abundant reagent ion.<sup>30</sup> However, structural information could in principle be obtained from a controlled anion-cation interaction leading to characteristic fragments (tandem MS, e.g., collision-induced dissociation,<sup>31</sup> electron-capture dissociation and electron-transfer dissociation<sup>32</sup>).

Figure 4 further shows the normalized time series (the ratio of the electron-abstracted target molecule trace intensity to the respective reagent ion intensity) of  $C_{10}H_{16}O_N$ ,  $N = 0 \dots 6$ , i.e., a-pinene and increasingly oxygenated reaction products. The low-pressure ionization by  $C_{16}H_{10}^+$  allows the monitoring of the non- and less-oxygenated precursors ( $N = 0, 1, 2$ ), while high-pressure  $C_4H_{12}N^+$  ionization tracks moderately oxygenated compounds ( $N = 2, 3, 4$ , detection as cluster with  $C_4H_{12}N^{+21}$ ), and finally  $Br^-$  more oxygenated compounds ( $N = 4, 5, 6$ , detection as cluster with  $Br^-$ ).<sup>27,28</sup> In principle, the sensitivity range could be further expanded by using other or more reagent ions (e.g.,  $NO_3^-$  at high pressure for higher oxidation states,  $H_3O^+$  at low pressure). While the ability of variously configured CIMS to study the above system has been shown previously, the value of MPCIS lies in achieving comprehensive sensitivity with a single instrument and inlet,

overcoming the need to employ separate dedicated high- and low-pressure CIMS.<sup>33</sup> Moreover, the MION inlet used here allows quasi-simultaneous use of two high pressure reagent ions.

The simultaneous ionization and quantification by  $C_4H_{12}N^+$  and  $C_{16}H_{10}^+$  is possible (Fig. 4), as the ionization schemes lead to dissimilar product ions (clustering with  $C_4H_{12}N^+$  versus electron abstraction, respectively): The interpretation of ions is unambiguous, enabling the normalization to the respective reagent ion. There is no space-charge loss of either reagent ion as evidenced by the stable reagent ion signal with or without the other reagent (Fig. 4). The simultaneous ionization comes not without cost - expecting that duplication an ionization scheme doubles the sensitivity would be erroneous: The introduction of  $C_{16}H_{10}^+$  into the sample gas flow occurs convectively, thereby slightly diluting the  $C_4H_{12}N^+$ -ionized gas. However, because  $C_{16}H_{10}^+$  is formed efficiently and constitutes a large fraction of the introduced gas, the dilution is minimal. We hypothesize that the simultaneous combination of reagent ions is most efficient (i.e., dilution losses are minimal) when distributed to high and low pressure, because of the high brightness of low pressure ion sources.

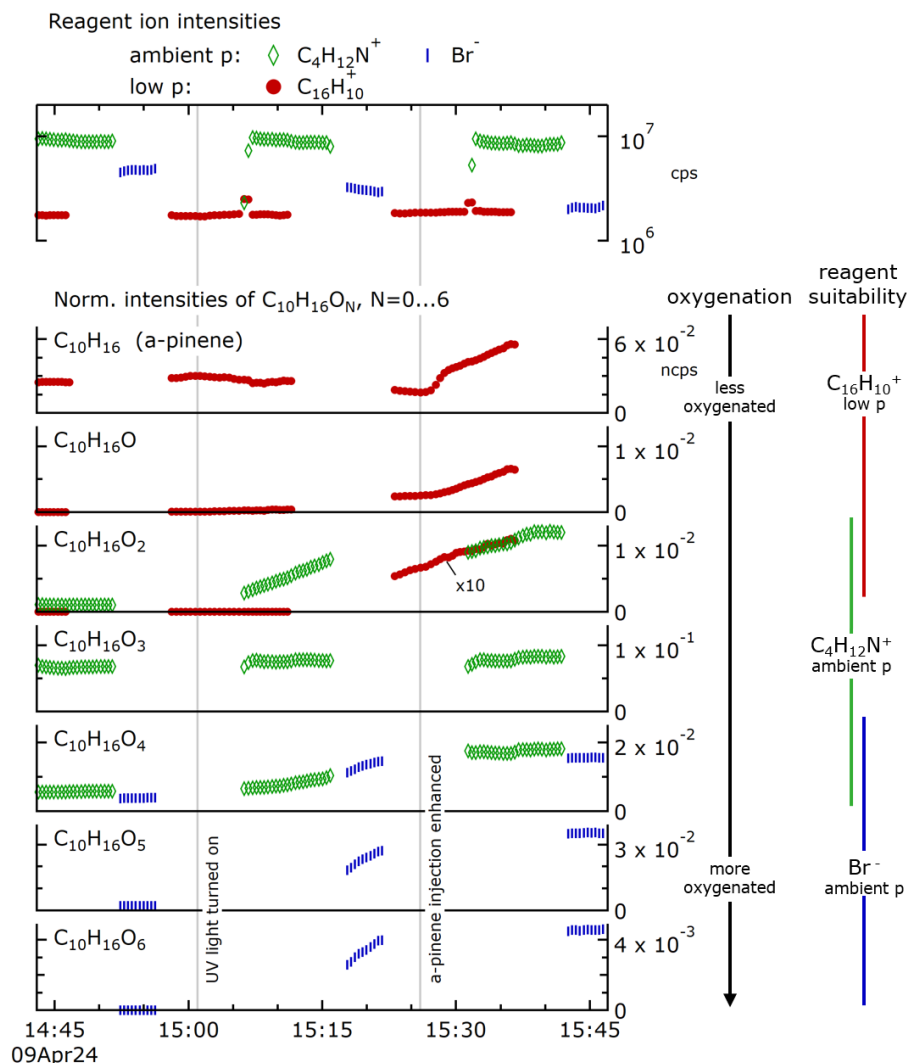


Figure 4: Detection of a-pinene oxidation product spectrum by MPCIMS. The UV lights are turned on at 15:01; the a-pinene injection is enhanced at 15:26. Combining multiple reagent ions at different pressures allows detecting the non-oxygenated precursor and its oxidation products.

In the system tested in this study, the quantification of measured signals from the low-pressure ionization is complicated by the regulated yet non-monitored dosing of  $C_{16}H_{10}^+$ : Under high analyte conditions with large sinks for the reagent ion the approach of normalizing by measured reagent ion concentration no longer applies. Future MPCIMS implementations can overcome this limitation by deregulating the source or tracking its duty cycle, and will likely also achieve much higher sensitivity from substantially increased dosing rates of reagent ions. We were unable to deplete the  $C_{16}H_{10}^+$  ion signal even when sampling directly from the head space of various solvent containers, sug-

gesting orders of magnitude of attainable gain in ion delivery, and a realistically achievable detection limits of single ppts within seconds.

## Conclusions

MPCIMS goes beyond reagent switching at the same pressure, by combining high-pressure reagent ions robust against multiple collision, thereby attaining excellent detection limits, and less soft low-pressure reagent ions needed for the non-selective ionization of less polar compounds. The low-pressure ion source demonstrated in this study was not originally developed for ionizing neutral molecules; there



is substantial potential to optimize its brightness, location (pressure and reaction time), and choice of reagent ion. Positively charged fluoranthene appears to be a little explored yet promising reagent ion with the benefit of being trivial to provide, i.e., the reagent supply only needs to be replaced yearly. The use of  $\text{H}_3\text{O}^+$  for PTR in MPCl is an obvious avenue for investigation. Orbitrap Exploris mass spectrometers already incorporate a suitable low-pressure ion source, but in principle MPCl can be used with any mass spectrometer with sufficient resolving power. If both anions and cations are used, the capability to rapidly switch between polarities is also required. MPCl, particularly when used with a versatile and clean high pressure ion source that selectively introduces the reagent ion, avoiding biases by contaminating the sample gas with reagent gas or dopant, gives the flexibility to combine appropriate reagent ions at high and low pressure to meet analytical requirements, and should help future studies by enhancing the sensitivity range and reducing the need for separate instruments and technical complexities associated with it.

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