Response to Reviewer #1

We thank the reviewer for the helpful comments on the manuscript. Our point-to-point responses to each comment are as follows (reviewer comments are in black, and author responses are in blue).

I. General Comments

I recommend for this manuscript to be published in Atmospheric Measurement Techniques after revision. The manuscript is a significant contribution to the atmospheric TOF-CIMS literature providing a new method for generating a broad suite of reagent ions via electrospray. The elimination of radioactive ion sources is of great importance as these instruments are routinely deployed throughout the world. Moreover, the authors do a good job implementing the full suite of available procedures for characterizing the novel chemical ionization source (flow rate considerations, calibration with authentic standards, determination of backgrounds and LODs, high-resolution analysis of a complex mixture, voltage scanning, and multiple reagent ion comparisons). I would also like to applaud the authors for acknowledging that this is a work in progress; off-axis spray configurations, sheath gas flow, the positioning of the emitter to tune the reaction time, curtain gas (or counter) N_2 gas flow are all standard features on modern ESI-MS instruments and should improve this system's performance, but these considerations are outside the scope of prototype design and proof of concept experiments.

My only general concern with this manuscript is with the introduction. The authors provide good context for why this work is important and where it fits within the development TOF-CIMS methods and applications. It has, however, been known since 1986 that the electrospray of pure solvents are capable of ionizing gas phase species (see C.M. Whitehouse, F. Levin, C.K. Meng, J.B. Fenn, Proceedings of the 34th ASMS Conference on Mass Spectrometry and Allied Topics). This technique was formalized by Herbert Hill's group and termed secondary electrospray ionization (SESI) in 2000. Arguably, the authors have better controlled the chemistry of this ion source by isolating the electrospray plume from the incoming sample making this truly a chemical ionization source and not SESI. Even this claim is not entirely clear as the mechanism of SESI has been studied for years and no clear conclusion has been reached as to whether SESI ionization proceeds via interaction with small droplets, gas phase ions or other phenomenon. With this being the case, the extensive literature and the diversity of instrumental configurations utilizing electrosprays for the detection of gas-phase species and vapors necessitates placing this work in the broader context of the field. I highly encourage the authors to revisit the broader mass spectrometry literature and at a minimum comment on past work with electrospray plumes for detecting gas-phase species.

I have split my specific comments section into two parts: Major Specific Comments and Minor Specific Comments. There are claims in this manuscript that lack evidence, but I think some of these concerns are addressable with available data. My hope is that these Major Specific

Comments will only lead to a more convincing publication as the claims about ELVOC dimers have been highly contentious to some critics.

Response: Thanks for your overall positive evaluation of our manuscript and yours suggestion on commenting past work with secondary electrospray ionization (SESI) technique for detecting gas-phase species. We have added the following paragraph to the introduction.

"It has been known since 1986 that the electrospray plumes cannot only ionize solvated analytes, but also are capable of ionizing gas phase species (Whitehouse et al., 1986; Chen et al., 1994). The later technique was termed secondary electrospray ionization (SESI) (Wu et al., 2000; Tam and Hill, 2004). SESI-MS has been demonstrated promise in the real-time analysis of a variety of gas phase analytes, including drugs (Wu et al., 2000; Meier et al., 2012), explosives (Tam and Hill et al., 2004; Aernecke et al., 2015), human metabolites (Martínez-Lozano et al., 2011; García-Gómez et al., 2015), electronic cigarette vapors (García-Gómez et al., 2016), as well as volatile emissions from bacteria cultures (Zhu et al., 2010), food (Bean et al., 2015; Farrell et al., 2017), and plants (Barrios-Collado et al., 2016). In SESI, the electrospray plume and incoming sample flow intersect in the ionization region, and analyte ionization proceeds likely via interactions with both small charged droplets and electrospray-produced gas phase reagent ions (Wu et al., 2000). In the present study, by coupling the electrospray source to an orthogonal continuous-flow atmospheric pressure IMR region via an evaporation region, we separate the electrospray plume from the incoming samples to avoid SESI, and instead allow for gas-phase chemical ionization."

II. Major Specific Comments

1. Lines 337-339: This is not an entirely correct interpretation of clustering and high-resolution peak fitting in the HR-TOF-CIMS. It is absolutely possible to determine whether ions observed using acetate CIMS are ion-neutral clusters or individual ions via voltage scanning techniques and/or a properly configuring the instrument. This is clearly shown in Brophy and Farmer, 2016, which the authors cite in this section. The HR-TOF-CIMS can be operated such that the probability of observing clusters is ridiculously small, but as Brophy and Farmer point out, operation in this mode may cause fragmentation of high molecular weight ELVOC-like molecules.

At sufficiently high m/Q, the ability to unambiguously distinguish iodide containing clusters from either non-iodide containing ion-neutral clusters and individual ions also becomes potentially nebulous. While the large negative mass defect of iodide certainly aids high-resolution analysis, it is not a panacea for high-resolution molecular formula assignment and the identification of clusters.

This manuscript deals with many other reagent ions that undergo clustering (meaning the instrument is operated in a cluster-transmitting mode), it would also be worthwhile to discuss the

limitations and advantages of Li^+, Na^+, K^+, and NH_4^+ for high-resolution analysis. I would imagine that confident assignment of high-resolution ions would be as problematic for this set of positive ion as running acetate in a cluster-transmitting mode with no voltage scanning experiments.

Response: We agree with the reviewer that voltage scanning techniques and/or a proper instrument configuration may enable distinguishing between the ion-neutral clusters and the individual ions in the acetate mode, and that confident assignment of ions in the iodide mode may become difficult at sufficiently high m/Q. High resolution analysis showed that the vast majority of ions in Li^+, Na^+, K^+, NH_4^+, and NO_3^- modes could be assigned to the respective reagent ion-neutral clusters with reasonable molecular formulae based on the minimal mass error criteria and with a spectral pattern very similar to that of Iodide clusters. The unique m/Q and in some cases presence of nitrogen helped identify the cluster composition. While our focus did not include organic nitrates, we would suggest using ^{14}N labeled NH_4^+ or NO_3^- in such cases.

In the revised manuscript, we have modified the statements in lines 334-339 (changes underlined):

"The iodide clusters can be easily distinguished from iodide-free molecular ions due to the large negative mass defects of iodide (Lee et al., 2014), although this advantage weakens at sufficiently high masses (> ~ 500 m/Q for a resolution of 5000). In contrast, broadly distinguishing between acetate-neutral clusters and individual ions in the acetate mode remains a challenge when using non-isotopically labeled acetate as the reagent ion and operating the instrument in a cluster-transmitting mode with no comprehensive voltage scanning experiments (Lopez-Hilfiker et al., 2015; Brophy and Farmer, 2016), as is the case in the present study. As a result, the high-resolution ions observed in the acetate mode cannot be confidently assigned to α-pinene ozonolysis products and are excluded from further discussions."

2. Lines 423-430: Brophy and Farmer 2016 performed voltage scanning experiments using multiple adjacent components throughout the atmospheric pressure interface. If clusters are being formed in the first or second quadrupole regions (or during the transitions from one stage to another), then it would not have been possible to eliminate the presence of acetate clusters using adjacent components in the first quadrupole. Additionally, the reagent ion-clusters are most likely ejected from a stable trajectory after an energetic collision. This makes it very unlikely that the reagent ion will 1) re-combine with a neutral species, 2) find its way back into the ion beam or remain in the ion beam and 3) be transmitted through the second segmented quadrupole with a stable enough trajectory to make it to the last portions of the atmospheric pressure interface. This argument as to why a signal increase occurs as the voltage difference is initially increased is highly unlikely if not completely incorrect. The argument presented in lines 422-423 is simple and makes much more sense: ion transmission efficiency in positive mode simply increases a bit with a slight increase in voltage difference for this specific set of components. Slight increases in

voltage difference should drive ions into the second quadrupole more efficiently, and since these ion-neutral clusters are quite stable, the increased kinetic energy basically doesn't matter. The observation would probably be different for very weakly bound clusters.

Response: We have not done detailed ion trajectory modeling of ions and neutral collisions within the quadrupole ion guides and so we cannot comment on the reviewers' suggestion, though it is certainly a reasonable hypothesis. We have tempered our conclusion regarding secondary ion chemistry in the ion guides, and instead combined it directly with the explanation of potential changes in mass transmission.

We have deleted the discussions in lines 422-429 and added the following statement to the revised manuscript.

"The reason for the initial increase in cluster signals is unclear, but might involve secondary ion chemistry and/or slight changes in ion transmission efficiency of the instrument."

3. Lines 434-444: "…the cluster signals for smaller dimers generally decay more slowly than those for large dimers, suggesting these positive ions can more strongly bind to the smaller dimers, likely due to the higher polarity or the smaller steric effect for smaller dimers... This behavior implies these dimers are most likely covalently-bound species… rather than noncovalently-bound species formed during alpha-pinene ozonolysis"

The fact that smaller dimers decay more slowly than large dimers could also be explained with the alternative hypothesis that two smaller monomers (or one monomer and another small oxidation product) are clustered to the reagent ion. In this scenario, the smaller neutrals would also be more strongly bound to the reagent ion for the exact same reasons (less steric effects and higher polarity) than the larger monomers (or other oxidation products) clustered as a 3-body cluster.

This argument can be made more convincingly by showing the monomer declustering scans. Does this same trend hold true for the C-8 through C-10 monomers (which are most like the >C-10 dimers)? Does this same behavior hold true for dimers detected with nitrate CI and iodide CI?

The authors may already have the data to further understand the behavior of single vs multiple neutral-ion clusters. They note earlier in the manuscript (line 349) that they observe $NO_3(NaNO_3)_n^-$. While this is substantially different from ELVOC/HOM type hydrocarbons, this does present an interesting example of 3-body and higher-order clusters. What do the voltage scans of these clusters look like? What is the dV50 as a function of the number of $NaNO_3$ neutrals? Should we expect 3-body clusters consisting of two neutrals to be more or less stable than 2-body ion-neutral clusters?

This is a contentious area of HR-TOF-CIMS and nucleation/cluster chemistry. This is not "direct" evidence that these potential-dimers are strongly bound as we don't really know they are, in fact, covalently bonded molecules given the data presented.

I recommend either substantially reworking this section or providing additional evidence via the largest monomers, $NO_3(NaNO_3)_n^-$ clusters, and behavior of the dimers in iodide an nitrate experiments. Given the amount of additional data I am suggesting here, it may be better to actually remove this claim from this paper as it is outside the scope of characterizing and showing the promise of ESCI. This could be an impactful standalone paper if the additional data are consistent. Further study is likely warranted.

Response: We cannot rule out the possibility that two smaller monomers are strongly bound to the reagent ions forming non-covalently bound dimers based on the data presented in the manuscript. We have rephrased the conclusion that these dimer ions have a binding energy approaching that of a covalent bond. A ΔV_{50} of ~ 15V is a binding enthalpy of ~ 80 kcal/mol according to Figure 4 of Lopez-Hilfiker et al., AMT, 2016. Additional data on declustering scans of monomers, $NO_3(NaNO_3)_n^-$ clusters, and dimers in iodide and nitrate modes may help further understand the behavior of ion-neutral clusters and the formation mechanism of dimers. However, as the reviewer pointed out, this is out of the main scope of the present study. Therefore, as suggested by the reviewer, we have removed the discussion on the dimers presented in lines 437-444.

III. Minor Specific Comments

1. Lines 126-128: Here the author's present "preliminary fluid dynamic simulations" that suggest the flow rates in which the flow profiles remain laminar. Previous work with the Aerodyne/Tofwerk HR-TOF-CIMS have evaluated this problem in the IMR by simply introducing a calibration gas flow until a stable signal is reached. Then, the calibration gas is shut off and the decay monitored to determine an e-folding time (or similar metric). This is an easy and direct method for understanding the mixing of gases in these reactors. If this source improves the e-folding time over the conventional Aerodyne/Tofwerk IMR design, this ion source could be quite an improvement!

Response: We have determined the e-folding time of ESCI source/atmospheric pressure orthogonal IMR design using nitric acid standard gas in the iodide mode. Figure R2 shows the changes in ion signal for $I(HNO_3)^-$ upon adding or shutting off the standard gas at an ion source flow of 1 slpm and sample flow of 5 or 10 slpm. The increase and decay of ion signal give an e-folding time of about 1s for nitric acid under two different flow conditions. This time response value is comparable to or better than that for the low pressure IMR (1 second to a few seconds).

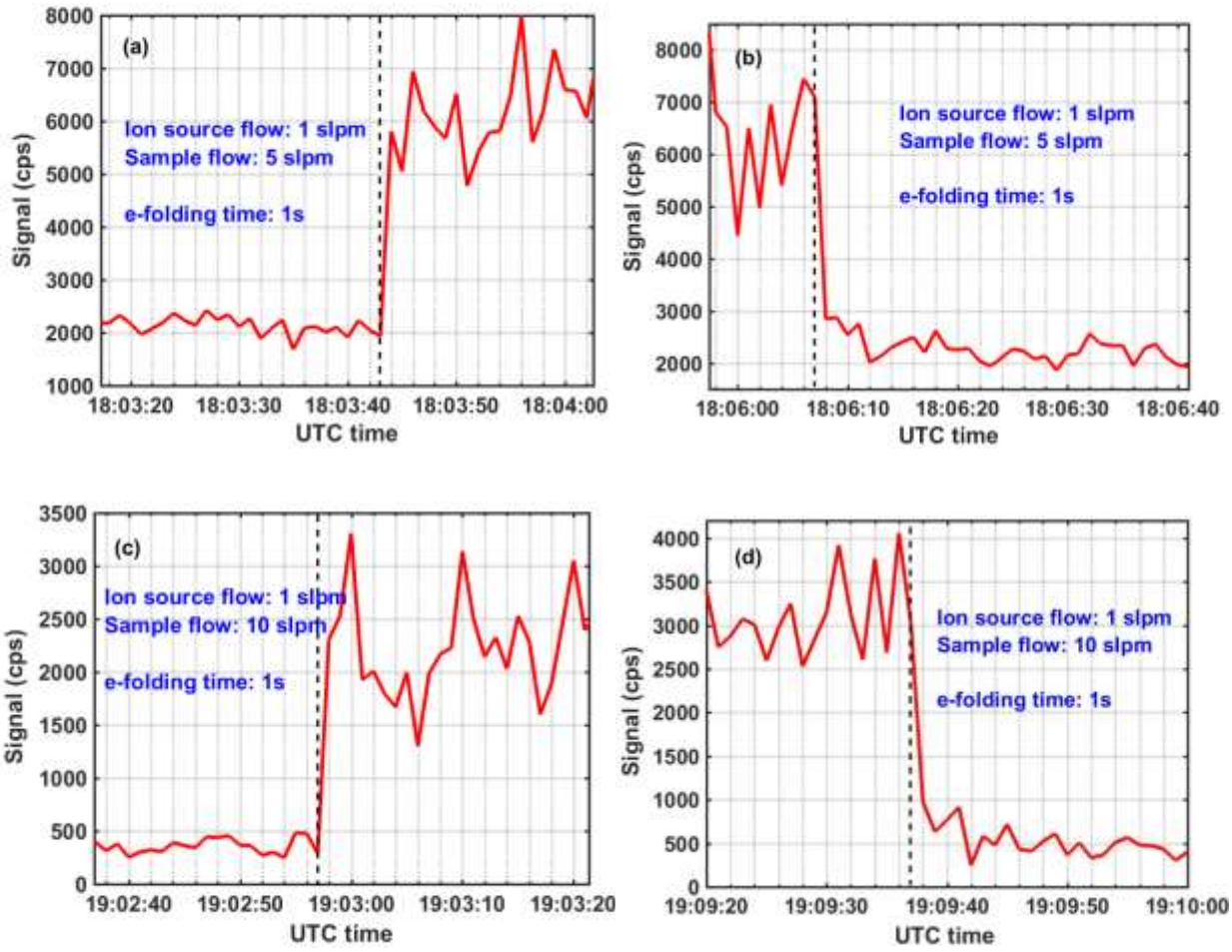

Figure R2 Time series of $I(HNO_3)^-$ observed when sampling (a, b) 5 slpm or (c, d) 10 slpm humid room air containing HNO_3 gas. The ion source flow was 1 slpm. The dashed line indicates the time at which the standard gas was added or shut off.

We have added the above discussion and Figure R2 to the revised manuscript.

2. Lines 138-146: This section could use some clarification as to how the electrospray solvent is being pushed through the electrospray emitter. Conventional electrospray configurations use syringe pumps or HPLC/UPLC style solvent pumps with online feedback control making the use of a pressure driven solvent flow a bit different. This could, perhaps, be addressed in Figure 1 by showing the pressure controller, electrospray liquid reservoir, and high voltage connections. Additionally, have the authors measured the solvent flow rate? This is commonly used to distinguish between nano-ESI and standard ESI sources.

Response: To clarify how the electrospray solvent is driven through the electrospray emitter and how the voltage is applied to the electrospray solvent, we have added the pressure controller, electrospray liquid reservoir, and high voltage connections to the schematic of ESCI module (see Figure R3). In addition, we have modified the descriptions in lines 138-141 (changes underlined).

"During operation, a dilute salt solution (~0.05 wt%) in HPLC-grade methanol (MEOH) is biased at the reservoir to +/- (2-5) kV depending on the ion mode by connecting a stainless steel rod immersed into the solution to a high voltage power supply. The solution reservoir is maintained at approximately 50 mbar above atmosphere using a commercial pressure controller (FLUIGENT, model MFCS-EZ) with 0.05 mbar precision. As a result, the salt solution is pushed through the fumed silica capillary tube to the spray needle by the pressure in the reservoir bottle."

We have not measured the solvent flow rate through the spray needle, but based on macroscopic volume changes in the reservoir, the flow rates are likely less than 100 nL/min.

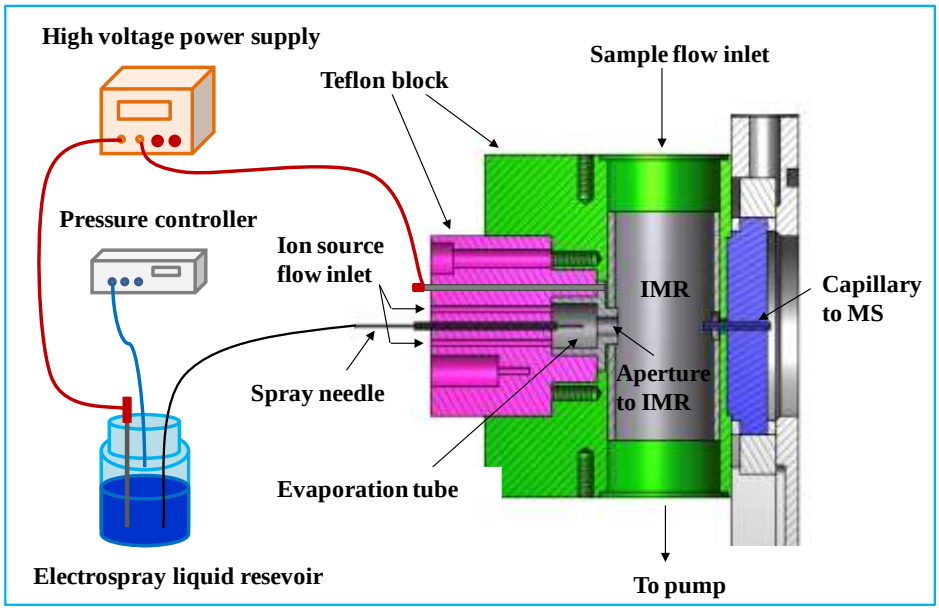

Figure R3 Schematic of the electrospray chemical ionization (ESCI) source module

3. Lines 138-146: I am also curious why the electrospray voltage to reagent ion signal relationship was not investigated? The electrospray voltage is typically a key parameter and is more complex in this source; the authors point this out by addressing that the ion drift/reaction time depends on the voltage difference between the emitter and the inlet capillary.

Response: We regret leaving this information out. We have investigated the effect of the electrospray voltage on reagent ion signals by varying the reservoir solution voltage (V_R) from +/- (2-5) kV. At a given V_R, the voltage applied to the evaporation tube and IMR (V_L) was carefully tuned to get the best ion signals (S_{max}), as well as the corresponding V_L, i.e., $V_L(S_{max})$. In the V_R range of 2-5 kV, a larger V_R (with a larger $V_L(S_{max})$) gives a higher reagent ion signal. In general, we found a fairly smooth curve above a threshold voltage for the reservoir, below which the spray was not stable. We found optimal performance with V_R values of 5 kV (corresponding $V_L(S_{max}) = 2.8$ kV) and -5 kV (corresponding $V_L(S_{max}) = -3.5$ kV) for positive

ion and negative modes, respectively. We did not probe V_R values higher than 5 kV due to limitations of various power supplies available.

We have modified the sentences in lines 138-139 (changes underlined):

"During operation, a dilute salt solution (~0.05 wt%) in HPLC-grade methanol (MEOH) is biased at the reservoir to +/- (2-5) kV depending on the ion mode by connecting a stainless steel rod immersed into the solution to a high voltage power supply. At a given reservoir solution voltage (V_R), the voltage applied to the evaporation tube and IMR (V_L) was carefully tuned to get the best ion signals (S_{max}), as well as the corresponding V_L, referred to as $V_L(S_{max})$. In the V_R range of 2-5 kV, a larger V_s (with a larger $V_L(S_{max})$) gives a higher reagent ion signal. In order to obtain good ion signals, for most of the measurements performed in this study, V_R values of 5 kV (corresponding $V_L(S_{max})$ = 2.8 kV) and -5 kV (corresponding $V_L(S_{max})$ = -3.5 kV) were used in the positive ion and negative ion modes, respectively."

4. Lines 165-170: The use of methanol and salts is an interesting choice of reagent ion precursors. Have the authors considered the possibility or looked for any evidence of methanol/protonated-methanol clustering? Additionally, other solvents could be used such as acetonitrile, which typically exhibits less clustering effects in standard electrospray ion sources.

Response: We did not see evidence of protonated methanol clustering in the positive mode, but did see iodide-methanol clustering in the iodide mode when the voltage difference between the first and second quadrupoles is small ($\Delta V < 2V$). However, under typical operating conditions in the present study ($\Delta V = 4$), the iodide-methanol cluster signals became negligible due to declustering.

We have added following sentences after line 170.

"No evidence of protonated methanol clustering was observed when electrospraying a methanolic solution of the described salts except at the extreme voltage differences between the lens and entrance capillary where it was likely a discharge developed. Although the reagent ion is likely solvated by methanol initially, the sensitivity of the ionization to various trace gases did not appear to be significantly affected in the present study."

We have not tried acetonitrile, but will certainly consider it in the further development and characterization of the ESCI source.

5. Lines 268-273: Here the authors address the differences in calibrations between atmospheric pressure ESCIMS and low-pressure CIMS. They attribute the differences to ion source configuration, pressure and ion-optics voltage settings. Tofwerk's Thuner voltage optimization tool would be a great way to ensure that the voltage configurations are optimized across sources.

This also appears later in the manuscript where the authors comment on the differences between positive and negative ion modes.

Response: We agree. The present study focuses on the characterization and performance assessment of the ESCI source. The voltage configurations within the vacuum chamber of the instrument were not optimized in this work, and voltage optimization will be considered for the further characterization and application of the ESCI source.

6. Line 328-329: why was the 5 cps criteria chosen for the high-resolution fitting cutoff? Does this correspond to some significant signal-to-noise ratio? Eyeball test? Some justification of this number is required as various other recommendations have been suggested in the HR-TOF-CIMS literature for what constitutes a significant signal.

Response: This cutoff was somewhat ad hoc, and not based on a rigorous signal to noise criterion as we were interested in comparing several different spectra in a broad sense. As we argued in the manuscript, many of these ions might be of importance to various mechanisms of particle growth or organic radical chemistry, but identifying the composition of ever ion in these spectra is beyond the scope of this paper.

To clarify why 5 cps criteria was chosen for the high-resolution fitting cutoff, we have modified sentences in lines 327-331 (changes underlined):

"High resolution peak fitting was performed and reasonable molecular formulae were assigned for detected ions that have intensity higher than 5 cps in all seven ion modes. Many ions are present at < 5 cps, which were excluded from the high-resolution fittings to ease the number of identifications required for comparison of several different spectra. Although these lower signal ions might be of importance to various mechanisms of particle growth or organic radical chemistry, identifying their compositions was deemed beyond the scope of this paper."

7. Lines 348-350: The presence of $I(NaI)^-$ and $NO_3(NaNO_3)_n^-$ suggests that the reagent ions generated from this ESCI source are not identical to the reagent ions generated from conventional Po-210 based methods. This may explain why the mass spectrum obtained for alpha-pinene ozonolysis are similar but not identical to Lopez-Hilfiker et al., 2015 results.

Response: The difference in the composition of reagent ions generated by ESCI and Po-210 sources may help explain why the mass spectra obtained for α-pinene ozonolysis are not identical in the two studies. However, different voltage settings and instrument configurations in the two studies can also lead to differences in the mass spectra. Iodide adducts are likely weaker than most of the other adducts studied, and thus most sensitive to instrumental parameters.

8. Lines 368-371: It might be worth adding a figure to better illustrate the difference between these various reagent ions. For example, a histogram of O:C or oxidation state by high-resolution

assignment could help to highlight these differences. This provides a great opportunity to further show that reagent ions are compound-class specific and parallels the previous work of Aljawhary et al., 2013. I think that bulk metrics (i.e. average oxygen:carbon ratio) would be less informative.

Response: We have added a figure showing boxplots with 5 different percentiles for the O:C ratio of monomeric products from α-pinene ozonolysis detected in I^-, NO_3^-, and Na^+ modes (See Figure R4). We have also added the following paragraph to the revised manuscript.

"Figure 9 shows boxplots for the O:C ratio of monomeric products from α-pinene ozonolysis detected in I^-, NO_3^-, and Na^+ modes. The O:C values for all the percentiles observed in I^- and NO_3^- modes are overall similar, whereas the corresponding values observed in Na^+ mode are obviously smaller. In addition, more than half of products observed in the three modes have a O:C ratio larger than 0.8. These results are consistent with the observations from Figure 8, where I^-, NO_3^-, and Na^+ are all sensitive to highly oxygenated organics, but the former two reagent ions are less sensitive or completely insensitive to less oxygenated organics as compared to Na^+."

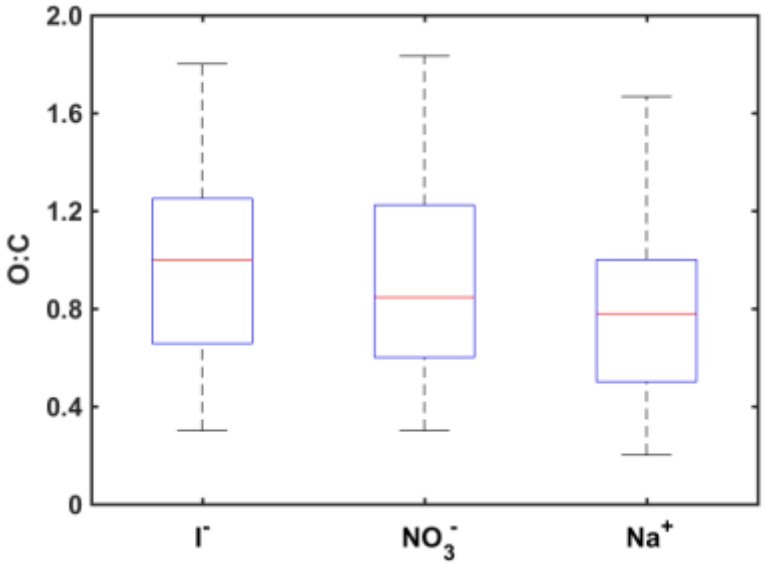

Figure R4 Boxplots showing the 5th, 25th, 50th, 75th, and 95th percentiles for the O:C ratio of monomeric products from α-pinene ozonolysis detected in different ion modes.

IV. Technical Corrections

1. Line 85: remove double ".."

Response: We have revised it.

2. Line 116: please specify the manufacturer/model if this is a commercial silica spray needle or simply a piece of fused silica tubing

Response: We have specified the manufacturer/model of the silica spray needle and fused silica tubing.

3. Line 126: what type of pump was used to back the IMR? Was the flow controlled via mass flow controller or some other device?

Response: The IMR was backed by a dry scroll vacuum pump (IDP-3, Agilent Technologies) and the flow was controlled by a mass flow controller. We have stated this in the revised manuscript.

4. Line 139: the electrospray solvent reservoir is biased between 3-5 kV. Should this read something like "+/- 3-5 kV depending on the ion mode"? Typical electrospray systems require different voltage magnitudes depending on the ion mode (positive vs negative) with negative mode typically requiring higher negative potentials. This would be useful information.

Response: We have changed "…biased at the reservoir to 3-5 kV" to "…biased at the reservoir to +/- (3-5) kV depending on the ion mode".

For both positive and negative ion modes, voltages magnitudes applied to the electrospray solvent reservoir (V_R) are the same, but the voltages applied to the evaporation tube and IMR (V_L) are different. For example, when Vs = +/- 5 kV, V_L for the best ion signals is 2.8 kV in the positive ion mode and -3.9 kV in the negative ion mode (see the reply to Minor Specific Comments #3).

5. Similar to item 2 in the specific comments section: It would be useful to show the electrospray solvent reservoir, pressure controller, and HV connections in Figure 1 as the experimental configuration is not totally clear.

Response: We have added electrospray solvent reservoir, pressure controller, and HV connection components to the schematic of the ESCI module (see Figure R2).

6. Figure 2a appears to have error bars while figure 2b does not.

Response: Figure 2b shows the dependence of the ion signal on the sample flow with an ion source flow/sample flow ratio of 0.1. We did not repeat the experiments for the same conditions, but instead we did the same measurement at ion source flow/sample flow ratios ranging from 0.02-0.2. The trend of the ion signal vs. the sample flow at each flow ratio is very similar to that shown in Figure 2b, though the absolute ion signal values are different.

7. Figure 3's caption reads "normalized sensitivity" while the y-axis reads signal in counts per second. Should the units be normalized counts per second (ncps) and/or "normalized signal"?

Response: We have changed y-axis label in Figure 3 to "normalized signal".