The authors would like to thank the editor for managing the peer review process and all the reviewers for reviewing our manuscript and for providing incisive and constructive feedback to help us improve the quality of this paper and to address some issues that required further clarification and discussion. We have made revisions to our original manuscript accordingly. The colorings of text in the reviewer response are:

- Light blue: Original reviewer comments
- Dark blue: Original text in the submitted version of the manuscript. **Bolded sentences** are the text added in the revision while ~~strikethrough words~~ are the text deleted in the revised manuscript.
- Black: Authors' response to the comments and others.

Note that the line number in the response is based on the revised clean-version manuscript.

Anonymous Referee #1

Summary: The authors describe a new instrument consisting of an aerosol impactor, thermal desorption unit, GC, and split column effluent to an FID detector and an iodide adduct chemical ionization mass spectrometer. The separate components of this instrument have been described previously; the combination of the simultaneous FID and CIMS measurement is novel. The goals of this instrument are to (1) isomerically resolve chemical compounds in an aerosol sample, and (2) determine the sensitivity of the CIMS detector to each chemical species. A second novel instrument technique is also described, in which a combination of air and iodide are used as reagent ions in the CIMS. The purpose of this is to ionize both high- and low-polarity compounds.

Major comments: The manuscript is generally well-written and well-organized. The use of chromatography to interpret CIMS spectra is not especially inventive, and because it is so complicated, this instrument will likely not see widespread use in its current form. However, this is a particularly useful instrument because it addresses two major problems with CIMS in atmospheric science: the spectra may be complicated to interpret, and the sensitivities to individual species are difficult to determine. Used under carefully-controlled conditions in a small number of laboratories, this instrument could provide important reference information to interpret iodide-CIMS measurements from field studies.

The analysis of the number of detected isomers was done very well and it is very useful to see the comparison to other studies.

Response: We sincerely appreciate the reviewer's suggestions and feedback for the manuscript. In the general summary, the reviewer expressed some concerns about the instrument being too complicated to be widely used in its current form. We agree with the reviewer that the TAG-CIMS/FID is very complex, and we will simplify the design of the instrument in the future. However, we believe that the current form of the instrument, although complicated, is a reasonable starting point to demonstrate the values and capability of the simultaneous coupling of CIMS and FID to a TAG. The detailed responses of each comment can be found in the sections below.

Comment 1: The inclusion of the air/iodide mixed-reagent-ion technique is interesting, but does not seem to really belong here. It is not even indicated in the title of paper and does not address the motivations mentioned in the introduction. This is better suited to a separate manuscript. If this is retained, it needs to be better explained how the mixed-reagention approach relates to the other capabilities of the instrument. An additional figure or other concrete example should be shown to demonstrate how chemical information can be derived from this technique.

Response: We thank the reviewer for thinking that it is interesting. Both reviewers highlight multi-reagent chemistry as both interesting and perhaps not fully developed. The intention of including this approach is not necessarily to understand in great detail this specific reagent chemistry, as we agree that an in-depth exploration of such an approach would likely require a separate full manuscript (note, for example, that the core of understanding of iodide chemistry was only achieved over multiple separate manuscripts). Instead, the motivation of this work is to overcome the technical hurdles in coupling a GC with a CIMS (and an FID) and explore the benefits of such an instrument.

We have chosen to include multi-reagent chemistry within this manuscript because it is specifically a feature made possible by coupling these instruments. Adding the GC enhances the ability for CIMS to explore new or simultaneous ionization chemistry by separating analytes with the retention time, yielding "clean" interpretations of complex spectra. Just as the separation provided by the GC allows known chemistries to be explored, it also enables the extension to new approaches such as multi-reagent ionization. We demonstrate that the multi-reagent ionization extends the range of chemical species that can be identified in the form of their elemental formulas, while the FID can serve as the detector for quantification. In the manuscript, we provide an example of the implementation of the multi-reagent ionization using a mixture of known chemical standards and liquid fragrance with unknown components on Line 360. In the example, we have shown that the elemental formulas of the extra compounds that can be detected in multi-reagent ionization mode. To emphasize the example of chemical identification using multi-reagent ionization, we have put the descriptions of the example in a separate paragraph of the manuscript:

"An example of the benefit of this approach is demonstrated by the detection of compounds not accessible through iodide adduct formation; 4 times as many compounds are observed in multi-reagent ionization mode (with formulas assigned to at least half of them). For example, a known component in the sample of complex fragrance mixtures, eugenol (Peak 2 in Figure 4c), is identified in the multi-reagent ionization mode yet not detected in iodide mode. In Figure 4c, 6 other peaks are labeled that are not detected as iodide adducts, but for which formulas can be assigned using $[M-H]^-$ and $[M+O_2]^-$ as identifiers, 1: $C_{15}H_{24}O$, 3: $C_9H_{10}O_3$, 4: $C_{12}H_{24}O_2$, 5: $C_{16}H_{32}O_2$, 6: $C_{18}H_{34}O_2$, and 7: $C_{18}H_{36}O_2$. A reasonable objection to multi-reagent ionization is that the complexity of adding up signals in multiple ionization chemistry with variable sensitivities may prohibit reasonable CIMS quantification. However, using CIMS for identification of unknowns by formula or other chemical information is valuable on its own, and quantification of many components is achievable using the FID channel of this instrument. This technique is likely only useful when analytes are individually resolved (i.e., isomer resolution), as the resulting mass spectrum of the complete complex mixture would be otherwise too difficult to interpret."

Additionally, we have revised the title of this section 3.3 to clarify that this is an example of what the TAG-CIMS/FID can do:

"**3.3 Exploring new chemistries: multi-reagent ionization** ~~Iodide ionization versus multi-reagent ionization~~"

Comment 2: Instead of the mixed-reagent ion description, it would be better to include an assessment of the FID-enabled determination of CIMS sensitivities. This is stated several times as the major benefit of the FID. However there are no data shown to demonstrate this utility. This is a significant weakness of the manuscript. The manuscript could be published with some minor revisions, but would have a much larger impact if the use of the FID to determine sensitivity is demonstrated.

Response: We completely agree with the reviewer that the FID-enable determination of CIMS sensitivities is a major benefit of coupling an FID and should be discussed in detail. However, quantification of iodide CIMS is a complex topic (again, note current quantification schemes have been built up over multiple manuscripts), and a proper treatment of it here would significantly expand the scope and complexity of the present manuscript. We choose instead to focus here on the technical hurdles and the array of potential value/benefits of the coupled instrument. A forthcoming manuscript is nearly ready for submission that addresses in detail the FID-determined CIMS sensitivities, and a wide range of related topics, including an examination of the voltage scan calibration method and the correlation between GC retention time and CIMS sensitivities. We have provided the information on splitting the work as described on Line 226:

"Implementation of this calibration approach including detailed methods of quantification and determination of isomer sensitivity is complex and will be addressed in future work. **This manuscript focuses instead on the descriptions of technical hurdles overcome by TAG-CIMS/FID and its potential value in understanding existing and new ionization chemistries, as well as atmospheric systems.** ~~This manuscript focuses instead on the description of TAG-CIMS/FID, isomer-counting, and evaluation of multi-reagent CIMS.~~"

Comment 3: Specific/minor comments: Section 2.3. It would be helpful to summarize the major technical challenges of CIMS/FID split flow at the top of this section.

Response: We agree with the reviewer that summarizing the major challenges of splitting the flow at the beginning of section 2.3 would help readers to understand the section better. We have added the summary at the top of this section:

"The design of the TAG-CIMS/FID interface needs to allow the efficient transfer of analytes from GC effluent to CIMS and FID. This interface is subject to three technical challenges:1) the connections between capillary columns and fittings need to be leak-tight; 2) all components in the interfaces require proper heating to avoid cold spots and dead volume; and 3) the relative flow rates to CIMS and FID need to be controlled to maintain roughly equal split of flow. ~~The interface between the GC and detectors controls the relative transfer flow toward each detector and must avoid any degradation to the chromatography (i.e., cold spots or dead volume).~~**~~"~~**

Comment 4: Page 6 line 166- 170. I don't understand the purpose of the EI-MS experiment. Please explain.

Response: We apologize for the lack of explanation on the EI-MS experiment. The EI-MS experiment was used as a secondary way to verify the stability of the flow split in addition to the flow rate measurement. Since the split flow rate ratio is critical for quantifying analytes in this instrument, we examined the flow split using two methods. The first method is to directly monitor the flow rate at the FID side during a chromatographic run. Since the total flow rate is known and controlled by TAG, the remainder flow to the CIMS can be calculated. Details of the description can be found on Line 166:

"With these dimensions and temperatures, the flow rate to FID is approximately one-third of total GC flow (0.3 sccm, measured using Sensidyne Gilibrator-2 at the inlet of FID) with the remainder to the CIMS (0.7 sccm). To further evaluate the stability of the split ratio of flow, test runs were conducted prior to the experiments to monitor the flow rate at the inlet of FID, variability in the flow split was found to be less than 10% variation throughout a run cycle, stable enough to be quantitative."

Additionally, we examined the split ratio through the injection of a mixture of alkane standards (C8-C40). Suppose that the split flow ratio is constant throughout a chromatographic run. In this case, the ratio of chromatographic peak area between the two detectors should be the same for a series of n-alkanes, which elute at different retention times depending on their carbon number. However, this cannot be done with an iodide CIMS because it cannot detect alkanes. Since both CIMS and EI-MS is at near-vacuum, swapping CIMS to EI-MS, which can measure alkanes, does not impact the flow split ratio. We therefore replaced CIMS with the EI-MS to evaluate whether the flow split ratio between CIMS and FID is stable in a GC run cycle. We found that the ratios of EI-MS to FID peak area for observed alkanes, which linearly correlate with the flow split ratios at a given retention time, were found to vary by less than 10%.

The EI-MS experiment was conducted for validating the TAG-CIMS/FID interface design before actually coupling the FID to the CIMS. We thought there is no harm to provide more information on the ways of validating the flow split. However, based on the reviewer's comment, adding the extra EI-MS verification method may confuse the reader. Since the measurements of FID flow are sufficient to demonstrate a stable flow rate split, we have deleted the description on the EI-MS method used to validate the flow split:

~~"Additionally, the CIMS was swapped with an EI-MS while maintaining the TAG-MS/FID interface so that liquid injections of alkanes standards (i.e., alkanes mix C8-C40, AccuStandard) can be measured by both EI-MS and FID. The ratios of EI-MS to FID peak area for observed alkanes, which linearly correlate with the flow split ratios at a given retention time, were similarly found to vary by less than 10%."~~

Comment 5: Page 10 Line 235: Wouldn't decomposition during TD change the parent formula as well?

Response: We are not quite clear to the reviewer's question since the sentence has already discussed the decomposition of parent analyte during thermal desorption. In response to what we think the reviewer refers to, we have revised the sentence on Line 236 to mention that thermal desorption may change the parent formula:

"**Overestimation may occur when large parent molecules decompose to isomers of a smaller formula during thermal desorption.** ~~Overestimation may occur because peaks observed might be formed in part by thermal decomposition of analytes during thermal desorption.~~"

Comment 6: Page 11 Line 260: This statement should be qualified with the volatility- or carbon number-range analyzed.

Response: We agree with the reviewer that the conclusion needs to be further constrained on specific samples or the range of compounds. The data in the literature is collected using off-line filters.

Therefore, the compounds in the literature and our study are primarily particle-phase compounds (or some adsorbing low-volatility gases, which are known to be present on some filter samples), with ten or less carbon number. We have added this description in the manuscript on Line 260:

"Together, the published data and that collected by TAG-CIMS/FID support the conclusion that isomers are abundant **for molecular formulas with ten or less carbon number in particle-phase samples**~~atmospheric samples~~."

Comment 7: Page 11 lines 264-266: Could you not use the EI-MS and identify the isomers via matching to a NIST library?

Response: As noted in our response above, while it is possible to include all three EI, CIMS, and FID detectors, doing so was not a focus of this work; EI data was not analyzed for the samples shown here. As addressed in Comment 4, we apologize for misleading the reviewer to believe that the EI-MS was used to measure analytes in this study.

Although not described in the manuscript, we indeed tried using the EI-MS as the 3rd detector to achieve a simultaneous coupling between the TAG and three detectors (iodide CIMS, EI-Tof-MS, and FID) for some test runs during the limonene-O_3 experiments. Unfortunately, even for that data, most of the oxidation products do not have reference mass spectra in the NIST library. This is a common problem for atmospheric GC/EI-MS samples. For example, the EI mass spectra of some primary limonene oxidation products (Witkowski and Gierczak, 2017) such as ketolimononic acid and 7-hydroxy limononic acid are not reported in the NIST library. A common practice of EI-MS users is to build a customized EI-MS library for specific compound categories of their interests (Yee et al., 2018), but such customized libraries can be labor-intensive and it is often the case that the analytes can only be related to a parent molecule, so it is not clear such a task would advance the scope of the present manuscript.

Comment 8: Page 14 lines 330-358: Can you provide an example of how this can be used? This seems to subvert the main benefits of CIMS, which are a 1:1 correspondence between molecule and product ion, and the retention of the parent ion (low fragmentation). If the only benefit is that it allows detection of some other compounds with the CIMS, why not just use the FID, which detects everything and with roughly equal sensitivity? The spectra are probably too complicated to interpret without GC-preseparation. Maybe there is some information about the structure of the isomer, given the observed mixed I-/O2- product ions. If so, can you provide some examples? Please comment on the use of this method to interpret the non-adduct ions typically observable in I- CIMS spectra. Can you state anything concrete about the identity of these ions, given the results of your experiments?

Response: We agree with the reviewer that the multi-reagent chemical ionization is not practical to be used in direct-air-sampling CIMS. As discussed above, multi-reagent ionization is discussed in this manuscript precisely because it is an approach that has some benefits (extending the potential chemical range of the instrument) but is only made possible with GC pre-separation. It is certainly true that the spectra are probably too complicated to interpret without GC pre-separation. The multi-reagent ionization method proposed in this study should be used mostly in the setup of the TAG-CIMS/FID (or some other GC-CIMS) where CIMS serves as an instrument for elemental formula identification and FID quantifies the well-resolved analytes.

The reviewer asked that if the only benefit is that it allows detection of some other compounds with the CIMS, why not just use the FID, which detects everything and with roughly equal sensitivity. It is because the information provided by the FID is very limited. Since FID is a single-channel detector, simply using GC-FID alone does not provide any information on the analyte molecule except its FID abundance. Additionally, the range of FID sensitivities for oxygenated organics still vary by a factor of two (Scanlon and Willis, 1985) while it can be corrected to within 20% if the elemental formulas of the analyte are known (i.e., corrections using O/C and carbon number) (Hurley et al., 2020). As mentioned in Comment 2, this FID-assisted calibration technique will be discussed in detail in a forthcoming manuscript. Simultaneous coupling of the CIMS in multi-reagent ionization mode can identify elemental formulas of chemicals generated in the atmospheric oxidation products. Those identified formulas can serve as correction factors for the FID calibration and also provide an additional dimension of the information (i.e., formula-level information) on the molecule. In this case, increasing the number of detected compounds using multi-reagent ionization in CIMS is beneficial so that more compounds can be identified and quantified.

The example on the identification of the ions was provided on Line 357 :"For example, a known component in the sample of complex fragrance mixtures, eugenol (Peak 2 in Figure 4c), is identified in the multi-reagent ionization mode yet not detected in iodide mode. In Figure 4c, 6 other peaks are labeled that are not detected as iodide adducts, but for which formulas can be assigned using $[M-H]^-$ and $[M+O_2]^-$ as identifiers, 1: $C_{15}H_{24}O$, 3: $C_9H_{10}O_3$, 4: $C_{12}H_{24}O_2$, 5: $C_{16}H_{32}O_2$, 6: $C_{18}H_{34}O_2$, and 7: $C_{18}H_{36}O_2$."

To better clarify the applicability of the multi-reagent ionization, we have revised the section by moving the example to a separate paragraph demonstrating the more formulas can be identified.

"An example of the benefit of this approach is demonstrated by the detection of compounds not accessible through iodide adduct formation; 4 times as many compounds are observed in multi-reagent ionization mode (with formulas assigned to at least half of them). For example, a known component in the sample of complex fragrance mixtures, eugenol (Peak 2 in Figure 4c), is identified in the multi-reagent ionization mode yet not detected in iodide mode. In Figure 4c, 6 other peaks are labeled that are not detected as iodide adducts, but for which formulas can be assigned using $[M-H]^-$ and $[M+O_2]^-$ as identifiers, 1: $C_{15}H_{24}O$, 3: $C_9H_{10}O_3$, 4: $C_{12}H_{24}O_2$, 5: $C_{16}H_{32}O_2$, 6: $C_{18}H_{34}O_2$, and 7: $C_{18}H_{36}O_2$. A reasonable objection to multi-reagent ionization is that the complexity of adding up signals in multiple ionization chemistry with variable sensitivities may prohibit reasonable CIMS quantification. However, using CIMS for identification of unknowns by formula or other chemical information is valuable on its own, and quantification of many components is achievable using the FID channel of this instrument. This technique is likely only useful when analytes are individually resolved (i.e., isomer resolution), as the resulting mass spectrum of the complete complex mixture would be otherwise too difficult to interpret."

Comment 9: Technical corrections: Line 221: "magnitudes" -> "magnitude"

Response: We have revised the work on Line 220:

"However, comparing to the near-universal response of FID signals, the signals of iodide CIMS per unit mole of analytes may vary up to five orders of **magnitude**~~magnitudes~~ and highly depend on their enthalpies of binding with iodide"

Anonymous Referee #2

Received and published: 3 October 2020 Review of Bi et al., “Coupling a gas chromatograph simultaneously to a flame ionization detector and chemical ionization mass spectrometer for isomer-resolved measurements of particle-phase organic compounds”

Summary: The authors describe a new instrument configuration using a TAG column upstream of both an FID and a ToF-CIMS. The goal was to address several current measurement issues by 1) using the GC to separate isomers in the CIMS spectrum, and 2) using the FID as a means of quantifying unknown compounds in the CIMS spectrum. They also show the simultaneous use of I- and O2- as reagent ions, with the goal of expanding CIMS sensitivity to generally less oxidized compounds. Generally, this is an interesting and well written paper that attempts to address several of the critical issues with CIMS spectrum interpretation of ambient or complex data. Separation of isomers seems be useful (at least for compounds that can make it through a GC column, which will be a subset of what I- usually can measure). This technique may well be very useful (especially for simplified systems), however I don’t think the authors have fully illustrated this yet. I have a major issue with some of the methods and interpretations thereof that require major revisions. Mainly, the data shown for iodide ionization shows that the ionization process is different than in typical iodide ionization CIMS setups (at least for some compounds including vanillin). This will diminish the ability to use this instrument to guide interpretation of other typical iodide CIMS measurements. I believe the authors need to address this issue (likely by showing more measurements) before making some of the conclusions drawn here. I also have questions about decomposition, and the utility of interpreting multiple reagent ion spectra.

Response: We sincerely appreciate the reviewer for carefully reviewing this manuscript and providing insights and suggestions on the weakness of the manuscript. The main issue mentioned by the reviewer is the difference of ionization chemistry between this instrument and a direct-air-sampling CIMS. We certainly recognize this concern, but believe that much of this apparent discrepancy is due not to true differences in ionization chemistry, but rather some of the details and features of ionization are made more obvious because this instrument sees the clean spectra of individual analytes due to the pre-separation of the GC as opposed to direct-air-sampling, in which all analytes are measured simultaneously. For detailed discussions and revisions in response to the reviewer's concerns, please see our response in Comment 3 and 4. The reviewer also mentions other issues on thermal decomposition of analytes, which are addressed in the responses of Comment 1 and 2; some of these concerns are due primarily to a lack of clarity in our original manuscript around operating conditions and temperatures, which we apologize for and have tried to correct in the revision. The question on the quantification using multi-reagent ionization is addressed in the response of Comment 5.

Some of the reviewer’s comments involve questions of the capability of this instrument to do quantification of analytes. We would like to note that the main objective in this study is to demonstrate the detailed instrumental design for isomer-resolved measurements of particle-phase organics. Such an instrument could be useful to investigate several different issues, include quantification and novel ionization chemistries. In many cases, investigating any one of these questions in detail is likely complex, and we feel that it is best examined in separate manuscripts to give a proper full treatment. In fact, we are preparing another manuscript on the quantification and sensitivity of this instrument. The forth-coming manuscript will discuss the quantification of CIMS sensitivities, the variance of isomer sensitivities within a formula, examination of the voltage scan calibration method, and correlation between GC retention time and CIMS sensitivities. Including such information in this manuscript would substantially expand the complexity and scope of this manuscript, which we feel would not serve readers well either in terms of understanding the present work, or understanding issues related to quantification and sensivitity. We have provided the information on splitting the work as described on Line 226:

Implementation of this calibration approach including detailed methods of quantification and determination of isomer sensitivity is complex and will be addressed in future work. **This manuscript focuses instead on the descriptions of technical hurdles overcome by TAG-CIMS/FID and its potential value in understanding existing and new ionization chemistries, as well as atmospheric systems.** ~~This manuscript focuses instead on the description of TAG-CIMS/FID, isomer-counting, and evaluation of multi-reagent CIMS.~~"

What we would like to highlight in this manuscript is that this instrumental design provides options to investigate known and new ionization chemistries, which includes in-depth issues such as quantifying sensitivies of iodide CIMS and expanding the range of identified chemical species using multi-reagent ionization. We have added a sentence to highlight the needs of future work on Line 365:

"We demonstrate here an example of exploring new reagent chemistries: simultaneously using multiple reagent ions is only made possible by the GC separation of analytes, but expands the information provided by this instrument. An in-depth understanding of the competition between reagent chemistries in a multi-reagent system is beyond the scope of this manuscript."

Comment 1: Main comments:

Line 112: Is there a risk of decomposition of organic analyte molecules at this 225C temperature in the IMR, especially on metal surfaces? I would also be worried about fragmentation at the 300C temps upstream. Previous FIGAERO CIMS research has suggested decomposition of oligomers and/or highly functionalized molecules when heating at even lower temperatures than 300C. Please add some references to this previously observed issue, and also add some discussion somewhere in the manuscript of how decomposition would affect your measurements.

Response: We agree with the reviewer's concern about the potential for high temperatures to produce decomposition of target analytes, and we seek to address those concerns throughout our responses here and in the revised manuscript. The specific issue raised in this comment is actually simply a misunderstanding due to a lack of clarity in the original manuscript suggesting that the IMR temperature was held at 225 °C in our study. In reality, the IMR was not heated, but instead was kept at room temperature (~20 °C). The transfer line between the passivated flow splitting manifold and the IMR consisted of inert silica tubing (GC guard column) that was maintained at 225 °C using a heated metal sheath and interface. A transfer line using the same materials was also used to connect the flow splitting manifold to the FID in order to ensure that both detectors "see" the same analytes. To clarify the misunderstanding, we have revised the manuscript on Line 114:

"The inlet is a heated metal **interface**~~cartridge~~ which is kept at 225°C and has a 1/32" inner diameter bore-through center hole to allow insertion of fused-silica guard column into the ion-molecule region (IMR) **which is kept at room temperature (~20 °C)**."

Because the heated inlet was directly connected with the IMR, the outer IMR surface facing the inlet had a slightly higher temperature (~50 °C) due to the heat transfer. However, the temperature inside the IMR was room temperature and the surface temperature (50 °C) was not substantially higher than the typical CIMS operating temperature. Additionally, the room temperature reagent ion flow rate (2 slpm) was three orders of magnitudes higher than the heated GC column flow rate (~0.7 sccm @ 225 °C), so the temperature of the mixed flow in the IMR is not expected to be significantly elevated.

Although IMR temperature is a misunderstanding due to unclear aspects of the description, we acknowledge that the thermal-decomposition of analytes can impact the interpretation of the collected data. This decomposition is expected to occur primarily during the heating of TAG sampling cell where compounds may decompose to volatilize, and in the GC column and flow splitting manifold, where compounds are exposed to higher temperatures to mobilize them. As the reviewer notes, we agree it is a concern with any instrument that uses thermal desorption that some artifacts or misinterpretation may occur due to the decomposition of thermally unstable products. Some of those limitations are discussed in the manuscript on Line 285:"thermal desorption may fragment larger accretion products to form analytes not present in the original sample (Isaacman-VanWertz et al., 2016; Lopez-Hilfiker et al., 2016b), or may reverse particle-phase oligomerization reactions (Claflin and Ziemann, 2019)."

Critically, the transfer lines to both detectors are held at temperatures at or below that of the flow splitting manifold to avoid any further decomposition. This is meant to ensure that any thermal decomposition occurs upstream of the flow split and both detectors see the same effluent mixture. In other words, while the eluting analytes may not be identical to the sampled analytes, both detectors see the same eluting analytes. We agree that scientific interpretation of these atmospheric data consequently needs to consider the possibility of decomposition adequately and be interpreted within this context, but decomposition is not expected to influence the comparison of signals between CIMS and FID. To this end, we strive to be transparent and clear about the potential impacts of decomposition on the isomer analyses. As suggested by the reviewer, we have added more references to show that compounds are subject to decomposition in the thermal desorption process and elaborated the discussion of the impacts of such decomposition on the results on Line 273:

"Conversely, thermal desorption **within TAG** may fragment larger accretion products to form analytes not present in the original sample **(Buchholz et al., 2019; Isaacman-VanWertz et al., 2016; Lopez-Hilfiker et al., 2016b; Stark et al., 2017)**~~(Isaacman-VanWertz et al., 2016; Lopez-Hilfiker et al., 2016b)~~, or may reverse particle-phase oligomerization reactions (Claflin and Ziemann, 2019). **These fragments may not represent the actual molecular composition of SOA, though they nevertheless may provide insight into the formation mechanisms of SOA (Isaacman-VanWertz et al. 2016). Consequently, the potential multiple fragments from one parent compound may result in an overestimation of the number of isomers.**~~These fragments may be identified as oxidation products in this analysis and consequently overestimate the number of isomers.~~ We note, however, that similar numbers of isomers are observed when using liquid chromatography (Figure 3b), which does not involve thermal desorption. Given these uncertainties, we believe that the results presented are not a floor or a ceiling on the number of isomers in the atmosphere, but a step toward understanding a poorly constrained problem."

Comment 2: Line 211: Related to my previous comment, how much of these early eluting compounds might be fragmentation products as an artifact of the sampling technique? Fig 4: Regarding decomposition again, one way to investigate would be to show the FID signal for Fig 4 and maybe for more examples where you are injecting single known compounds. How much signal is in the FID but not the CIMS, i.e., how much fragmentation occurs throughout the sampling process? I think this would be important information for a reader to judge the utility of the technique.

Response: We interpret this comment to raise two possible and related issues on the subject of decomposition. Firstly, decomposition of sampled analytes in the TAG instrument ("upstream decomposition") may mean that detected analytes are actually transformed products of the true sampled analytes. Secondly, if decomposition impacts each detector differently ("downstream decomposition"), comparisons between chromatograms or detectors may be biased or incorrect. We discuss both here in order to address the reviewer's concerns.

Firstly, we agree that decomposition occurring during sampling or transfer of the sample to and/or through the GC column would impact the scientific interpretation of collected data. Critically, we note that decomposition upstream of the flow splitting manifold should not impact the comparison of CIMS and FID data, which would see the same (transformed) analytes. In the context of this work, the impact of upstream decomposition within TAG primarily would impact the counting of isomers, as fragmentation may lead to overestimation of isomer counts, which we have sought to make clear in the revised manuscript on Line 236 as excerpted below. In any work that uses this or any GC-based instrument, similar considerations will need to be taken in the context of any conclusions drawn. These instruments consequently always offer/suffer some tradeoffs between molecular specificity and potential for in-instrument transformations, but their ability to measure specific tracer molecules indicative of sources and chemical pathways (whether or not those tracers are actually decomposition products) has nevertheless provided a range of important atmospheric conclusions, such as the body of work from other TAG instrumentation (Isaacman-VanWertz et al., 2016; Williams et al., 2006; Zhao et al., 2013).

Line 236: "**Overestimation may occur when large parent molecules decompose to isomers of a smaller formula during thermal desorption.** ~~Overestimation may occur because peaks observed might be formed in part by thermal decomposition of analytes during thermal desorption.~~"

Secondly, we consider the possibility for downstream decomposition, such that that the early eluting compounds appeared in FID yet missing in CIMS in Figure 2 is due to the thermal decomposition of analytes in CIMS or FID. Some of this concern may again be due to the implication in the original manuscript that the IMR was heated. Instead, we have sought to design this instrument such that any decomposition occurs upstream of the flow split, as described above, so we believe decomposition is far more likely upstream of the flow splitting manifold than downstream. Specifically, we note that decomposition in transfer lines downstream of the flow splitting manifold should be minimal because the transfer lines are kept at or below the temperatures of the interface, and downstream decomposition is probably not a significant process. The compounds coming out of the TAG, which may be the fragments of a parent molecule, are therefore being measured by the CIMS and FID simultaneously.

Given these considerations, we believe the differences between FID and CIMS chromatograms can be best explained by the wide ranges in CIMS sensitivity previously reported in the literature, as described in the manuscript. While an FID provides a mass-based, near-universal response to hydrocarbons and oxygenated organics, the range of the iodide CIMS sensitivities can vary up to 6 orders of magnitudes (Iyer et al., 2016), with a general tendency to be more sensitive to polar or hydroxyl-containing compounds. Many oxidation products of monoterpenes are less-polar compounds (e.g., limona ketone (Donahue et al., 2007)) and even compounds having a single hydroxyl group is not necessarily sensitive in an iodide CIMS. Since less-polar compounds tend to elute early on a polar GC column (i.e., MXT-WAX used in this study), those early elutes are expected to be not detected or have low abundance in the iodide CIMS. In contrast, polar compounds tend to elute late in the chromatogram and can provide orders of magnitude stronger signals in CIMS.

Overall, therefore, it is not clear that decomposition could account for the observed differences in CIMS and FID chromatograms, while known trends in sensitivity provide a reasonable explanation. Some early eluting compounds may be present in the CIMS chromatogram at low signal but not visible because displaying them in a single chromatogram is difficult with a linear Y-axis due to the wide range of sensitivity.

To explain the two reasons that result in the differences between CIMS and FID chromatograms, we have added more descriptions on Line 206:

"Since the TAG-CIMS/FID interface and the capillary to the FID is held at 50 °C above the maximum column temperature, differences in the transfer of analytes to these two detectors should be negligible. Instead, these differences are due to the selectivity of the two detectors. FID is a near-universal detector, able to detect almost all organic compounds with relatively similar and predictable responses (Scanlon and Willis, 1985). **The sensitivity of the iodide-CIMS may differ by orders of magnitude and is highest for compounds that contain multiple OH groups and can therefore more readily form an adduct with the iodide ion (Iyer et al., 2016). Since the TAG here used a polar (MXT-WAX) GC column that more preferably retains polar compounds, the early-eluting compounds are likely less-polar, and consequently less sensitive or not detected in the iodide-CIMS. Some early-eluting compounds may be present but have peaks too small to be visible due to the linear display of signal in Figure 2.** ~~The sensitivity of the iodide-CIMS is highest for compounds that are more polar and can therefore more readily form an adduct with the iodide ion (Iyer et al., 2016). The wax GC column used here more readily retains polar compounds, suggesting that the early-eluting analytes are more likely to be lower-polarity compounds that exhibit low sensitivity in the iodide-CIMS.~~"

In the context of the reviewer's concerns, we understand their suggestion to add the FID chromatogram for Figure 4 in the manuscript to probe the decomposed fragments by comparing chromatograms between CIMS and FID. As above, the reviewer suggests that what is shown in the FID chromatogram yet missing in CIMS chromatograms may be decomposition fragments due to heating of the sampling process. We appreciate the reviewer for suggesting options to identify the thermal decomposition compounds in the instrument. For the reasons discussed above, we do not think decomposition is a likely explanation for the observed differences between chromatograms. In Figure R1, we have included the FID chromatogram for Figure 4. The sample injected is a mixture of know chemical standards and unknown fragrance liquids. As in the case of Figure 2, there are clearly more peaks in the FID, as some compounds in the fragrance are expected to be hydrocarbons or lightly-oxygenated compounds that an iodide CIMS cannot detect (e.g., monoterpenes, $C_{10}H_{16}$, a major component of fragrances (Steinemann et al., 2011)). However, it is not clear to us that including this chromatogram provides any additional information or insight than what is already evident from Figure 2, so we have chosen not to add this chromatogram to Figure 4 in the revised manuscript. Furthermore, compounds that are sufficiently stable to be introduced to the instrument are generally less likely to decompose upon thermal desorption, so the introduction of individual standards does not provide a clear path forward to explore the possibility of upstream decomposition

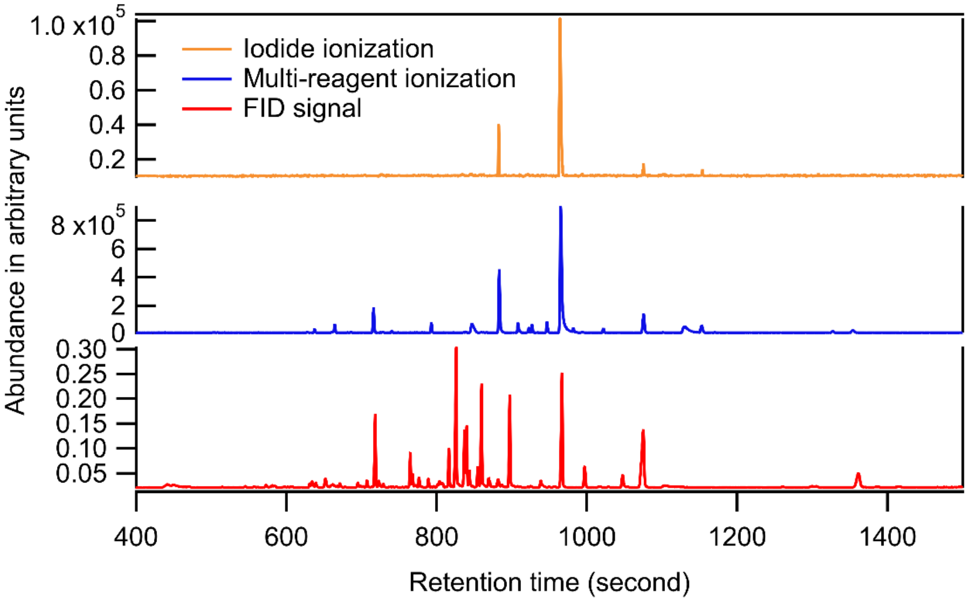

Figure R1: Comparison of chromatograms of analyte total ion counts between CIMS using iodide ionization, CIMS using multi-reagent ionization, and FID. Top two panels are recreated from Figure 4 of the manuscript.

Comment 3: Line 297: This inset in Fig 4a indicates a major issue. In a typical iodide CIMS setup, vanillin would be sampled almost completely at the [M+I]- cluster with iodide, but you're showing that in your instrument it is predominantly sampled at the deprotonated [M-H]- . Therefore, the ionization process is different from a normal iodide CIMS. I think this is a major problem that you need to address before publishing under the pretext that your instrument can be used to help generally interpret iodide CIMS measurements. The most likely answer that I see could be that holding the IMR at 225C is causing the changes? Perhaps at those temperatures (and with metal surfaces?), vanillin becomes a gas phase acid and C8H8O3 + I- –> C8H7O3- + HI proceeds? At line 300, you try to address the [M-H]- by stating that vanillin "produces a large number of detectable ions through reactions with other reagents in the IMR." But, there are no other reagent ions there (except NO2- maybe, but that is often present in typical iodide CIMS spectra and is therefore not the cause), so this statement is probably not accurate. So, please address this issue thoroughly. A first step could be to do the same vanillin injection but hold the IMR at room temp. The vanillin signal may smear, but does is show up at [M+I]-? Again, this seems like a major issue since you're trying to say (eg lines 372- 374) that you can use this method to investigate non-iodide clusters separated by the 'iodide valley', but you're apparently also drastically changing the ionization method.

Response: The reviewer raises several concerns, which are generally related to the ionization occurring within this instrument, and whether it resembles that of other iodide CIMS in use in the field, with a specific discussion of vanillin as an example. A critical difference between this instrument and direct-air-sampling instrumentation is the ability to collect “clean” mass spectra of individual analytes, which leads to some subtleties in how to compare to direct-air-sampling instruments. Consequently, while the reviewer raises very reasonable concerns, we believe that a lot of the apparent discrepancy comes from the fact that this instrument specifically provides an ability to see and explore the non-adduct ions, while a typical CIMS does not straightforwardly relate adduct ions to potential non-adduct counterparts. While iodide CIMS is indeed used in large part specifically for its ability to selectively study molecular ions, non-adduct ions (i.e., ions formed through pathways other than the formation of an iodide adduct) are commonly also generated in iodide CIMS instrumentation. This issue has been previously reported, with iodide adduct ions separated from non-adduct ions by a gap in mass defect by the so-called “iodide valley” shown in Figure R2 (Lee et al., 2014). It is not unexpected that any given analyte (e.g., vanillin) could produce non-adduct ions through side reactions with small impurities in flow streams (discussed further below).

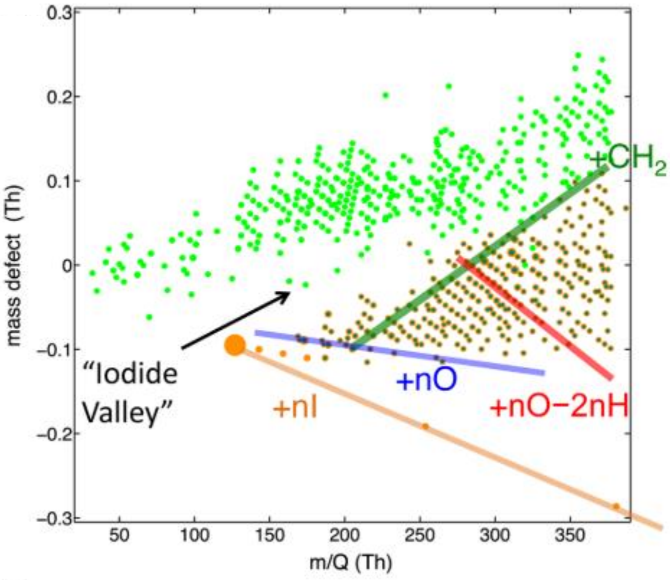

Figure R2: High-resolution mass defect spectrum obtained during ozonolysis of α-pinene (adopted from Lee et al. (2014))

One of the significant values of the described instrument is that it specifically provides an opportunity to study ions at the other side of the iodide valley (i.e., non-adduct ions) shown as the green dots in Figure R2 and their potential relationship to adduct ions. In a direct-air-sampling iodide CIMS, all analytes generate ions simultaneously, so parent ions and non-adduct ions cannot be independently studied. Consequently, researchers frequently discount the non-adduct ions when analyzing the iodide CIMS data. With the pre-separation of the GC, we can explore those non-adduct ions that are simply ignored in a direct-air-sampling CIMS. One of the reviewer’s concern is that the 225 ^{o}C IMR temperature may cause the different ionization chemistry, which is, again, confusion due to lack of clarity in our origical description of the instrument as addressed in Comment 1; in fact, the IMR was set at room temperature so it should have minor impacts on the ionization chemistry and we apologize for the confusion and have tried to clarify as described above.

To address the reviewer's specific concern with regards to vanillin, we discuss here possible reasons for observed differences, and comparison to other previously studied analytes. The reviewer suggests that in a typical iodide CIMS setup, vanillin would be sampled almost completely at the [M+I]- cluster. We agree that it is certainly possible for an instrument to be operated in such a way, but in many typical applications of CIMS, the spectra of vanillin would be sampled simultaneously with other analytes (i.e., without the pre-separation provided by GC); given the ubiquity of non-adduct ions in CIMS spectra, in such cases, the spectrum of vanillin and/or its tendency to form non-adduct ions would often not be specifically known, so direct comparisons of our individual-analyte spectra to that of a typical CIMS are primarily limited to cases where individual analytes are introduced. More broadly, we note that while a specific iodide CIMS may be tuned to optimize measurements of a specific analyte, the mass spectrum of any given instrument may be impacted by the tuning and/or the pressure of the IMR. Spectra are therefore heavily dependent on instrumental settings such as voltage settings of the atmospheric pressure inlet (API) and operating pressure, and to our knowledge, there is no consensus on a standardized operating condition of an iodide CIMS. For example, while our IMR pressure was set at 100 mbar, we are aware of other studies using 200 mbar (e.g., Isaacman-Vanwertz et al., (2018)). Indeed, even the voltage setting of the small transfer quadrupole *rf* amplitude can impart fragmenting energy into the analyte molecules and clusters.

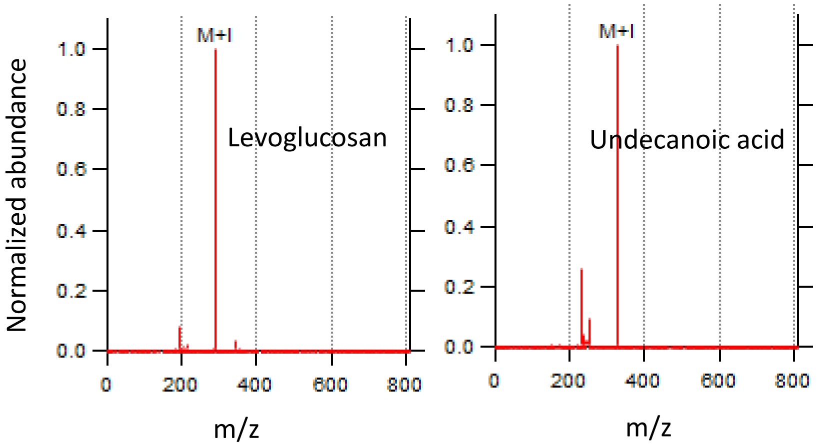

Figure R3. Iodide subtracted mass spectra for liquid standards of levoglucosan, undecanoic acid, and hexdecanoic acid in this study.

To provide the reviewer with further information on the ionization scheme of this instrument, we provide the mass spectra for liquid standards of levoglucosan and undecanoic acid in this study in Figure R3. Those compounds have [M+I]- as the most abundant ion in the "clean" mass spectrum. Levoglucosan, which was reported having the near collision-limited sensitivity in Lopez-Hilfiker et al., (2016a), is also found to form mostly iodide-adduct in this study. The results suggest that the ionization chemistry varies significantly for different compounds, and that more polar (more sensitive) compounds do tend to have more dominant adduct ions. We have revised some description on the ranking of the detectable ions in the manuscript on Line 305:

"Although the abundance ranking of the produced ions may differ on a compound-by-compound basis, we constantly observe ions other than $[M+I]^-$ in the clean mass spectrum of injected liquid standards such as undecanoic acid, hexadecanoic acid, and 1,12-dodecanediol, as well as more polar

and low volatility aerosol constituents produced in the oxidation experiments.~~ Similar trends are observed for other compounds injected as authentic standards, including undecanoic acid and 1,12-dodecanediol. In contrast, the iodide-adduct ions ([M+I]$^-$) of more polar and lower-volatility aerosol constituents produced in oxidation experiments are the dominant ions in their analyte mass spectra.~~"

Overall, the TAG-CIMS has a unique advantage of exploring ionization chemistry due to the pre-separation of a GC, but, for the same reason, there are not a lot of published spectra in the literature against which to compare to other CIMS. However, the target of this study is not to investigate the ionization chemistry for specific compounds, but to propose a proof-of-concept instrument for future studies on those specific science questions.

A second question in the comment: "At line 300, you try to address the [M-H]- by stating that vanillin "produces a large number of detectable ions through reactions with other reagents in the IMR." But, there are no other reagent ions there (except NO2- maybe, but that is often present in typical iodide CIMS spectra and is therefore not the cause), so this statement is probably not accurate."

We agree with the reviewer that the statement is not accurately explained and the "other reagent ions" were not clearly defined in this sentence. In fact, there are other reagent ions with their abundance too small to be observed in the figure. Although the abundance of O2- in the iodide ionization mode is very small, 0.03% compared with I-, it may be still competitive to react with the analytes thus produced [M-H]-. The O2- is likely produced by the impurity of UHP N2 (99.999%). Since reagent ions can have dramatically different sensitivity to the analyte, the low abundance of O2- can probably not be ignored in the ionization process. We suspect that the [M-H]- is generated mainly through the reaction between the analyte molecule and the O_2- because the abundance of [M-H]- ions of most analytes were boosted five to ten times after mixing 5% of the zero-air in the ultra-high purity (UHP) N_2 reagent ion flow. Additionally, previous studies have reported such ionization pathway of O2- as described on Line 317:"It is reported that the presence of O_2^-, which is commonly found in atmospheric pressure ion sources such as electrospray ionization (ESI) (Hassan et al., 2017), atmospheric pressure chemical ionization (APCI) (McEwen and Larsen, 2009), atmospheric pressure photoionization (APPI) (Song et al., 2007), and direct analysis in real-time (DART) (Cody et al., 2005), may result in the deprotonated molecules through oxidative ionization."

Mentioned the reaction with other reagent ions before introducing the reaction mechanism probably lead to the confusion of the reviewer. To avoid such confusion, we have deleted the description on "other reagent ions" on Line 303:

"In other words, this compound, which is generally measurable by iodide-CIMS (Gaston et al., 2016), produces a large number of detectable ions other than the iodide-adduct ions~~**through reactions with other reagents in the IMR."**~~

Comment 4: Line 303: Interesting that the lower volatility compounds or more polar compounds appear to have different ionization processes relative to the more volatile or less polar compounds like vanillin. Since one of the advantages of I- ionization has been a more consistent (and single) ionization process for the majority of compounds, do you have any thoughts on how this affects interpretation of the spectra?

Response: We agree with the reviewer that one of the main benefits of the iodide CIMS is the simple ionization chemistry. The simple adduct formation makes the quantification using an iodide CIMS straightforward by only tracking the abundance of the iodide-adduct. The findings in our study do not change this fact. However, not all analyte molecules form an adduct with iodide. Previous studies have reported some iodide-adducts, such as simple monocarboxylic acids or diols, may be rapidly disassociated when increasing the voltage differences in specific components of the API (Lopez-Hilfiker et al., 2016a). Additionally, the use of multi-reagent ionization in our study demonstrates that other reagent ions can compete with iodide and produce non-adduct ions. The finding here suggests that there is not only iodide chemistry in the IMR, but also other potential ionization pathways producing the ions at the other side of the iodide valley. As noted above, we believe this to be one of the major advantages of a coupled GC-CIMS system - to better understand ionization chemistries and examine features that are otherwise difficult to study (such as non-adduct ions). To avoid the misunderstanding that iodide ionization chemistry may change with the polarity of compounds, we have revised the manuscript on Line 305:

"**Although the abundance ranking of the produced ions may differ on a compound-by-compound basis, we constantly observe ions other than $[M+I]^-$ in the clean mass spectrum of injected liquid standards such as undecanoic acid, hexadecanoic acid , and 1,12-dodecanediol, as well as more polar and low volatility aerosol constituents produced in the oxidation experiments.** ~~Similar trends are observed for other compounds injected as authentic standards, including undecanoic acid and 1,12-dodecanediol. In contrast, the iodide-adduct ions ($[M+I]^-$) of more polar and lower-volatility aerosol constituents produced in oxidation experiments are the dominant ions in their analyte mass spectra.~~"

Comment 5: Line 318: Since you're seeing the deprotonated ions using both ionization methods (just I-, and both I- and O2-), it seems like it would be really hard to convert the signal in multiple reagent ion mode to mixing ratios as the sum of two ionization processes with variable sensitivities. Especially this would be hard if you have are sampling a complex mixture. It makes me wonder if it's feasible to use both reagent ions at the same time, or if you should instead use them one at a time in series. No doubt that O2- ionization gives you a lot of extra information about the less oxidized/polar compounds that Ican't see. Please discuss this to give the reader confidence that using two reagent ions simultaneously is actually a practical scientific improvement. Best would be to show a quantitative example of a calibration curve using both reagents, but possibly this will be the subject of a future manuscript.

Response: We fully agree with the reviewer that it is complicated to calculate the mixing ratio of an analyte by summing up concentrations/abundance in the two ionization processes of CIMS without building a deeper understanding of the O2- pathway. However, this is not what we intend to do. In the multi-reagent ionization mode, the CIMS is primarily valuable for examing elemental formulas while the quantification could be achieved by FID. We agree that alternating different modes might be helpful, but note that due to the inherent semi-continous nature of GC, that would come with its own tradeoffs in terms of time resolution and the fact that each analysis might not be examining exactly the same sampled air. We have revised the sentences on Line 360 to clarify the issue:

"A reasonable objection to multi-reagent ionization is that ~~the complexity and/or novelty of the chemistry may prohibit reasonable quantification~~**the complexity of adding up signals in multiple ionization chemistry with variable sensitivities may prohibit reasonable CIMS quantification.** However, using CIMS for identification of unknowns by formula or other chemical information is valuable on its own, and quantification of many components is achievable using the FID channel of this instrument.”

Comment 6: Technical comments: Fig. 3 Caption: extra ‘s’ after SOA

Response: We have deleted the “s” in the caption of Figure 3:

”Figure 1. …… combined datasets from **SOA**~~SOAs~~ formation ……”

Comment 7: Line 324: This sentence just needs some clarification. You’re either adding zero air to the ionizer alongside methyl iodide, or adding O2- to the ionization region (aka IMR) alongside iodide. Also “ionization region” is ambiguous because that could be the ionizer or the IMR.

Response: We agree with the reviewer that the description on Line 324 is ambiguous. We have revised the sentence on Line 328 for clarifications :

“the CIMS was operated in a multi-reagent ionization mode by adding ~~5%~~**100 sccm flow (i.e., 5%) of ultra-zero air to the 2 slpm flow of N_2 for the gas supply of the methyl iodide permeation tube**~~the ionization region alongside iodide~~**.**”

Comment 8: Line 326: This was confusing to me because you list the numbers with multi-reagent ion first and iodide second, right after referring to Figs. 4b (iodide) and 4d (multi) in the reversed order. Please reverse the order of listing the numbers in order to stay consistent with the Fig.

Response: We thank the reviewer for pointing out the reversed order of ionization mode. We have revised the manuscript on Line 330:

” the total ion counts are ~~1.4~~**2.4**×10^6 and ~~2.4~~**1.4**×10^6 ions/s and the I^- ion counts are ~~0.7~~**1.8**×10^6 and ~~1.8~~**0.7**×10^6 ions/s for ~~multi-reagent~~**iodide** ionization and ~~iodide~~**multi-reagent** ionization, respectively.”

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Coupling a gas chromatograph simultaneously to a flame ionization detector and chemical ionization mass spectrometer for isomer-resolved measurements of particle-phase organic compounds

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Abstract

Atmospheric oxidation products of volatile organic compounds consist of thousands of unique chemicals that have distinctly different physical and chemical properties depending on their detailed structures and functional groups. Measurement techniques that can achieve molecular characterizations with details down to functional groups (i.e., isomer-resolved resolution) are consequently necessary to provide understandings of differences of fate and transport within isomers produced in the oxidation process. We demonstrate a new instrument coupling the thermal desorption aerosol gas chromatograph (TAG), which enables the separation of isomers, with the high-resolution time-of-flight chemical ionization mass spectrometer (HR-ToF-CIMS), which has the capability of classifying unknown compounds by their molecular formulas, and the flame ion detector (FID), which provide a near-universal response to organic compounds. The TAG-CIMS/FID is used to provide isomer-resolved measurements of samples from liquid standard injections and particle-phase organics generated in oxidation flow reactors. By coupling a TAG to a CIMS, the CIMS is enhanced with an additional dimension of information (resolution of individual molecules) at the cost of time resolution (i.e., one sample per hour instead of per minute). We found that isomers are prevalent in sample matrix with an average number of three to five isomers per formula depending on the precursors in the oxidation experiments. Additionally, a multi-reagent ionization mode is investigated in which both zero air and iodide are introduced as reagent ions, to examine the feasibility of extending the use of an individual CIMS to a broader range of analytes with still selective reagent ions. While this approach reduces iodide-adduct ions by a factor of two, $[M-H]^-$ and $[M+O_2]^-$ ions produced from lower-polarity compounds increase by a factor of five to ten, improving their detection by CIMS. The method expands the range of detected chemical species by using two chemical ionization reagents simultaneously, enabled by the pre-separation of analyte molecules before ionization.

1 Introduction

Atmospheric aerosols can impact climate by scattering light and absorbing radiation thus changing earth's reflectivity directly, or by impacting the formation of clouds (Seinfeld and Pandis, 2016). If inhaled, they may deposit into the alveoli region of lungs and transmit into the blood to cause adverse health effects such as ischemic heart disease, cerebrovascular disease, and lung cancer (Burnett et al., 2014; Pope and Dockery, 2006). A significant fraction of sub-micrometer aerosol mass is organic, mostly formed through the oxidative conversion of gas-phase volatile organic compounds (VOCs) to lower-volatility oxygenated organic compounds that can condense to form secondary organic aerosol (SOA) (Goldstein and Galbally, 2007; Jimenez et al., 2009; Kroll and Seinfeld, 2008).

Atmospheric oxidation of volatile organic compounds produces thousands of unique chemicals that exist in a dynamic and complex mixture that span a wide range of physicochemical properties (Atkinson and Arey, 2003; Goldstein and Galbally, 2007). The detailed structure and functional groups of each individual compound controls its properties (Kroll and Seinfeld, 2008; Nozière et al., 2015). Rate of reactions, partitioning between phases, and compound toxicity are all impacted by the functional groups present in a molecule (Arangio et al., 2016), and in some cases on its physical conformation (Atkinson, 2000; Lim and Ziemann, 2009). Characterization of a compound to the level of detail of its molecular structure (i.e., isomer-resolved composition) is therefore necessary to predict whether a compound will deposit to a particle or surface, react with an oxidant, or persist in the atmosphere, and to understand its potential adverse impacts on public or ecosystem health.

A major advance in the online non-target analysis of oxygenated organics in the atmosphere has been the development and widespread adoption of the high-resolution time-of-flight chemical ionization mass spectrometer (HR-ToF-CIMS). These systems directly sample atmospheric constituents with minimal pre-treatment and classify them by their molecular formulas, providing unprecedented characterizations of thermally and/or chemically labile atmospheric constituents. Multiple negative-ion chemical ionization methods have been applied to atmospheric sampling, including acetate for the detection of carboxylic acids and some inorganic acids (Bertram et al., 2011; Brophy and Farmer, 2016; Veres et al., 2008), nitrate for the detection of highly oxidized organic matters (Ehn et al., 2010; Krechmer et al., 2015), and iodide for the detection of moderately and highly polar organic compounds (Aljawhary et al., 2013; Isaacman-Vanwertz et al., 2018; Lee et al., 2014; Lopez-Hilfiker et al., 2014; Riva et al., 2019). The latter has seen particularly wide use due to its relatively general selectivity and straightforward chemistry, in which an adduct is formed between the analyte and iodide ion. Due to the high negative mass defect of iodine, iodide adduct ions are separated from other isobaric ions in the mass spectrum by the so-called "iodide valley" in which few ions are present, so can be classified by their molecular formula with high confidence and low detection limits (Lee et al., 2014). Ions with positive mass defects (i.e., non-iodide-adduct) are observed in iodide-CIMS mass spectra of atmospheric mixtures and may represent peroxy acids (Lee et al., 2014; Mielke and Osthoff, 2012), but these ions are generally poorly understood and frequently excluded from analyses due to their uncertain interpretation.

A major barrier to understanding most reagent ion chemistries is that isomers cannot be differentiated since analytes are classified by molecular formulas. Studying instrument response requires introducing analytes as known standards, so is limited to commercially available or custom synthesized compounds. Such compounds do not fully capture the composition of real-world atmospheres, which contain compounds that are not easily synthesized or available, such as transient and short-lived oxidation products. An improved approach would be the generation of oxidized products through the simulated atmospheric oxidation of atmospherically-relevant precursors, but this approach has limited utility due to the formation of multiple isomers of each formula (Brophy and Farmer, 2016). The range of CIMS reagent ion chemistries that are practically useful is therefore limited to those, such as iodide, that yield distinguishable products, while other potentially promising techniques (e.g., acetate CIMS) have seen less use due to the complex ionization pathways. The lack of isomer-resolution afforded by CIMS introduces several other limitations as well. The fate of a compound and its impacts on the environment are dependent on molecular structure, so they may not be fully predicted or captured by molecular formulas. Furthermore, a formula may represent many isomers, but CIMS signals will preferentially represent isomers to which the ionization method is more sensitive. This may bias the interpretation and quantification of CIMS data, though the extent to which this issue has impacted the literature is unknown.

The resolution of individual components in a complex mixture is typically performed through some form of chromatography. While liquid (e.g., Gómez-González et al., 2008), ion (e.g., VandenBoer et al., 2012), and gas chromatography (e.g., Hamilton, 2010; Schauer et al., 1996) have all been used in atmospheric measurements, we limit our discussion here to gas chromatography (GC), as it has been demonstrated as a field-deployable technique for the analysis of oxygenated organics, complementary with CIMS instrumentation (Isaacman-VanWertz et al., 2016; Thompson et al., 2017; Zhang et al., 2018). GC separates compounds in a complex mixture based upon their vapor pressure and polarity and has been field-deployed for decades for the online measurement of low-polarity gas-phase components (Goldan et al., 2004; Goldstein et al., 1995; Helmig et al., 2007; Millet, 2005; Prinn et al., 2000; Vasquez et al., 2018). More recent developments on the field-deployable thermal desorption aerosol gas chromatograph (TAG) have enabled the GC analysis of semi-volatile and particle-phase air samples, through novel sampling cells, autonomous calibration via liquid injections of authentic standards, and derivatization of oxygenates for the analysis of oxygenated compounds (Isaacman et al., 2014; Williams et al., 2006; Zhao et al., 2013). Detection of analytes eluting from the GC may rely on a flame ionization detector (FID), which has near-universal response but provides no chemical information about an analyte (Kolb et al., 1977; Willmott, 1978), or an electron ionization mass spectrometer (EI-MS), which provides identification of compounds with mass spectra available in existing libraries but requiring careful interpretation to identify those not in the libraries. These techniques have allowed quantification of some individual isomers in SOA, but the substantial majority of analytes observed in GC analyses of SOA have no known structures or identification (Isaacman-VanWertz et al., 2016) due to a lack of commercially available standards of atmospheric oxidation products.

We demonstrate here a new instrument coupling the TAG, which enables the separation of isomers, with the HR-ToF-CIMS, which has the capability of classifying unknown compounds by their molecular formulas, and the FID, which provide a near-universal response to all analytes for quantification with low uncertainty. The specific objectives of this work are to 1) describe the set-up and operation of a TAG-CIMS/FID; 2) evaluate the presence of isomers in laboratory-generated SOA; 3) demonstrate the utility of this instrument for investigating ionization chemistries by resolving mass spectra of individual compounds separated from a complex mixture; and 4) expand the range of chemical species which can be measured by an individual CIMS by using multiple reagent ions.

2 Instrumentation and methods

As shown in Figure S1, the TAG-CIMS/FID integrates the use of a GC instrument, TAG, with two detectors, HR-ToF-CIMS (Aerodyne Research Inc.) and FID (Agilent 7820A). The GC column effluent is split to the two detectors using a heated and passivated tee together with heated fused-silica transfer lines. The instrument allows the collection of chromatographic signals generated by CIMS and FID simultaneously.

2.1 HR-ToF-CIMS

The HR-ToF-CIMS (Lee et al., 2014) uses a similar physical configuration as described by Isaacman-Vanwertz et al., (2018) with modification at the inlet for adapting the GC flow. The inlet is a heated metal ~~cartridge~~ interface which is kept at 225 °C and has a 1/32” inner diameter bore-through center hole to allow insertion of fused-silica guard column into the ion-molecule region (IMR) which is kept at room temperature (~20 °C) . The tip of the guard column extends 2 mm out of the heated cartridge to mix with the reagent ion flow inside the IMR.

Two different ionization modes are used in this study: iodide and multi-reagent ionization mode. The iodide ionization mode (Lee et al., 2014) is used in a similar configuration to those published in the past for a gas-phase iodide CIMS (Krechmer et al., 2016). Iodide ions are generated by passing a 2 slpm flow of humidified ultrahigh purity (UHP) N_2 over a permeation tube filled with methyl iodide and then through a radioactive source (Po-210, 10 mCi, NRD) into the IMR. The IMR pressure is maintained at 100 mbar. Besides the pure iodide ionization mode, the CIMS operated using a multi-reagent ionization mode to investigate the use of multiple reagent ions in the IMR. Instead of using pure nitrogen, the multi-reagent ionization mode uses a mixture of 1.91 slpm of UHP N_2 and 0.09 slpm of ultra-zero air as the methyl iodide sheath flow. This mixture is selected such that iodide ions (I^-) accounted for ~50% of the total reagent ion count, with the rest comprised of air-based components as described later.

To obtain a smooth chromatographic peak, raw negative-ion spectra are typically acquired at a rate of 4 Hz without time averaging, which is higher than the rate typically used for direct air sampling by CI-TOF-MS (1 Hz and 1 min averaging). Data collection as fast as 20 Hz was tested and found to be viable for applications requiring higher data frequency, but is not necessary for data collection described here. The ToF-MS is operated in “V-mode” and achieves a mass resolution of ∼4100 at m/z 212 and a mass accuracy of <5 ppm, which enables the assignment of elemental composition to observed mass-to-charge values.

2.2 TAG

The TAG used in this study is a custom-built instrument similar to those commercially available through Aerodyne Research Inc. In brief, aerosols are collected with a sampling flow rate of 9 slpm through a 9-jet impactor with a 50% collection cut-point of 0.085 µm (Williams et al., 2006). The collection cell is equipped with a liquid injection port where chemical standards can be quantitatively added through an automatic liquid injection system (Isaacman et al., 2011). After a 5-15 mins sample collection period, which is equivalent to 0.045-0.135 m^3 of air sampled, samples are thermally desorbed in helium to the head of the GC column by heating the cell to 300 °C at a rate of 50 °C /min while the GC column is held at 50 °C with ~ 3 sccm of helium carrier gas flow. Samples pass through a passivated metal manifold with restrictive capillaries to separate sample pressures from GC operating pressures without the use of in-line valves (Kreisberg et al., 2014). A polar GC column (MXT-WAX, 17 m × 0.25 mm × 0.25 µm, Restek) wrapped onto the temperature-controlled metal hub is used for the separation of oxygenated organic compounds. The GC analysis is conducted with 1 sccm of helium and the temperature of the GC column is ramped to 250 °C at a rate of 10 °C /min, then held for 25 mins. Though analysis focuses on oxygenated compounds to which the CIMS may exhibit sensitivity, we highlight that derivatization, which is typically used in the analysis of oxygenates by GC (Isaacman et al., 2014), is not employed here to minimize chemical alterations to the functionality of the analytes reaching the detectors. Although not observed with the injection of liquid standards, it is possible that skipping derivatization may bring up certain limitations of the instruments such as the decrease of the transmission efficiency and stability of the analytes (Isaacman et al., 2014).

2.3 TAG-CIMS/FID interface

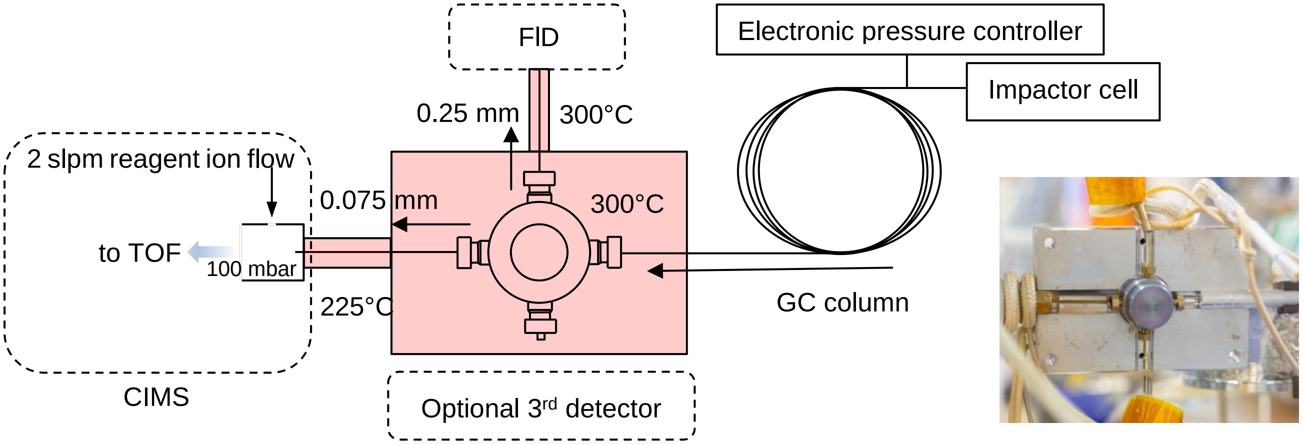

Figure 1. Schematics of the TAG-CIMS/FID interface, with a photo inserted. Details of each instrument are simplified. Restrictive capillaries to each detector are used to balance flows to each detector due to differences in pressure (dimensions and temperatures shown).

The design of the TAG-CIMS/FID interface needs to allow the efficient transfer of analytes from GC effluent to CIMS and FID. This interface is subject to three technical challenges:1) the connections between capillary columns and fittings need to be leak-tight; 2) all components in the interfaces require proper heating to avoid cold spots and dead volume; and 3) the relative flow rates to CIMS and FID need to be controlled to maintain roughly equal split of flow. ~~The interface between the GC and detectors controls the relative transfer flow toward each detector and must avoid any degradation to the chromatography (i.e., cold spots or dead volume).~~ As shown in Figure 1~~Figure 1~~, a 1/32” passivated (SilcoNert 2000, SilcoTek Corp.) metal cross (Part No. ZX.5, VICI) is covered by a two-piece heated aluminum block. The four ports on this connector allow splits from the GC to three detectors (FID, CIMS, optional third). Because the IMR pressure of the CIMS is at 100 mbar while the FID is at ambient pressure, the restriction to the CIMS side needs to be significantly higher than that of the FID side to maintain comparable flow rates. These restrictions are achieved using deactivated fused-silica guard columns which have an inner diameter of 0.075 and 0.25 mm, and a length of 0.18 and 0.5 m to connect the cross with CIMS and FID, respectively. Because the change of temperature of GC column during a run cycle may potentially influence the split flow, we mitigate the impacts by maintaining the TAG-CIMS/FID interface at a constant temperature, 300 °C, that is 50 °C higher than the maximum temperature of the GC column. The guard column to FID passes through a narrow-bore metal tube wrapped in heater cable with fiberglass insulation and heated to 300 °C to prevent the condensation of analytes in the transfer lines. The temperature of the entrance capillary to the IMR of CIMS is maintained at 225 °C in order to prevent the degradation of PTFE components of CIMS inlet; this leads to some peak broadening of low-volatility analytes in the CIMS data. With these dimensions and temperatures, the flow rate to FID is approximately one-third of total GC flow (0.3 sccm, measured using Sensidyne Gilibrator-2 at the inlet of FID) with the remainder to the CIMS (0.7 sccm). To further evaluate the stability of the split ratio of flow, test runs were conducted prior to the experiments to monitor the flow rate at the inlet of FID, variability in the flow split was found to be less than 10% variation throughout a run cycle, stable enough to be quantitative.~~ Additionally, the CIMS was swapped with an EI-MS while maintaining the TAG-MS/FID interface so that liquid injections of alkanes standards (i.e., alkanes mix C8-C40, AccuStandard) can be measured by both EI-MS and FID. The ratios of EI-MS to FID peak area for observed alkanes, which linearly correlate with the flow split ratios at a given retention time, were similarly found to vary by less than 10%.~~

2.4 Laboratory experiments

Data are collected from two sources: injection of liquid standards, and laboratory-generated SOA through the oxidation of atmospherically relevant precursors. Liquid standards include 1,12-dodecanediol (Sigma Aldrich, 99% purity), undecanoic acid (AccuStandard, 100% purity), eugenol (Sigma Aldrich, 99% purity), vanillin (Sigma Aldrich, 99% purity), vanillic acid (Sigma Aldrich, 97% purity), and oleic acid (Sigma Aldrich, 99% purity). Additionally, six commercially available liquid fragrance samples (MakingCosmetics Inc) are also used to serve as representative complex mixtures. SOA was generated via gas-phase O_3 and/or OH oxidation of limonene (Sigma Aldrich, 97% purity), 1,3,5-trimethylbenzene (Sigma Aldrich, 98% purity), and eucalyptol (Sigma Aldrich, 99% purity) in a Potential Aerosol Mass (PAM) flow reactor (Lambe et al., (2011), and collected onto the TAG impactor cell at 9 L/min sampling flow rate, and analyzed by the TAG-CIMS/FID. We hereafter label data from a given set of oxidation experiments system as “precursor-oxidant” (e.g. limonene-OH).

2.5 Data processing

CIMS and FID data are acquired as continuous timeseries throughout a single GC run. TAG sends a start signal to both CIMS and FID once the GC run starts and sends a digital signal to stop the data acquisition once a sample run is completed. For each run file, high-resolution (HR) mass spectrum peak fitting of CIMS data is conducted using the Tofware (Tofwerk, AG and Aerodyne Research, Inc., version 3.1.2) toolkit developed for the Igor Pro 7 analysis software package (Wavemetrics, Inc.). HR fitting of iodide-adduct ions was used to generate a list of potential molecular formulas present within a given set of experiments. Once the formulas are extracted and assigned in CIMS, the high-resolution time-series data with the peak list are then imported into TERN, the freely-available (https://sites.google.com/site/terninigor/) Igor-based software tool for the quantification of chromatographic data (Isaacman-VanWertz et al., 2017). The retention times of peaks between CIMS and FID are aligned based on linear regression of retention times of internal standards (i.e., vanillin and 1,12-dodecandiol) and the most abundant compounds in chromatographic runs.

3 Results and discussion

3.1 Chromatograms

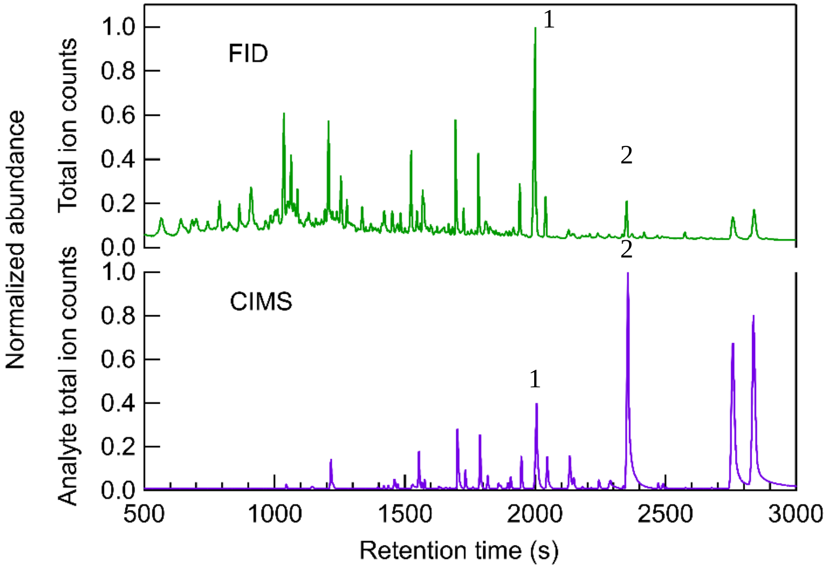

Figure 2. Comparison of chromatograms between FID and CIMS from particle sample generated from limonene-O_3 reaction. The time-series signals of CIMS are the analyte total ion counts, which are summation of all ions with the reagent ions removed while signals of FID are single-channel. The signals of both CIMS and FID are normalized to the highest peak in the chromatogram.

Figure 2 shows an example comparison of chromatograms collected by the FID and CIMS for limonene-O_3 SOA. The FID produces a total signal (y-axis) as a function primarily of the mass of carbon combusted, so each analyte (i.e., chromatographic peak eluting at a given retention time) responds with similar mass-based sensitivity. However, the total chromatogram shown is the full extent of the data available for a given sample; there is no further separation by mass or other dimension. Co-eluting peaks that are not well resolved may not be able to be accurately integrated. In contrast, the CIMS analyte total ion count signal is the sum of all observed ions with the reagent ions removed, so while two peaks may not be chromatographically resolved (i.e., co-eluting total signal), they may be mass-resolved by producing signals on different ions. The results demonstrate that the responses from FID and CIMS have distinctly different patterns with the number of peaks and the height of aligned peaks in the chromatograms of FID and CIMS differ significantly. Many early-eluting compounds (i.e., compounds having peaks with retention times less than 1500 seconds) that are observed by FID do not produce a clear signal in the CIMS. Compounds with retention time longer than 1500 seconds usually have peaks detected by both FID and CIMS chromatograms. Since the TAG-CIMS/FID interface and the capillary to the FID is held at 50 °C above the maximum column temperature, differences in the transfer of analytes to these two detectors should be negligible. Instead, these differences are due to the selectivity of the two detectors. FID is a near-universal detector, able to detect almost all organic compounds with relatively similar and predictable responses (Scanlon and Willis, 1985). The sensitivity of the iodide-CIMS may differ by orders of magnitude and is highest for compounds that contain multiple OH groups and can therefore more readily form an adduct with the iodide ion (Iyer et al., 2016). Since the TAG here used a polar (MXT-WAX) GC column that more preferably retains polar compounds, the early-eluting compounds are likely less-polar, and consequently less sensitive or not detected in the iodide-CIMS. Some early-eluting compounds may be present but have peaks too small to be visible due to the linear display of signal in Figure 2. ~~The sensitivity of iodide-CIMS is highest for compounds that are more polar and can therefore more readily form an adduct with the iodide ion (Iyer et al., 2016). The wax GC column used here more readily retains polar compounds, suggesting that the early-eluting analytes are more likely to be lower-polarity compounds that exhibit low sensitivity in the iodide-CIMS.~~

The low abundance of early-eluting peaks in the CIMS chromatogram is an example of the value of the coupled CIMS/FID detector pair for investigating CIMS response. Although compounds having larger retention times can be found in both FID and CIMS, their abundance is significantly different between the two detectors. For example, Analyte 1 ($C_{10}H_{14}IO_3^-$) with a retention time of 2000 seconds has the most abundant signals in FID while Analyte 2 ($C_8H_{10}IO_4^-$) with a retention time of 2380 seconds is the largest peak in CIMS. Since FID sensitivity differs between compounds by less than a factor of two (Hurley et al., 2020), the peak area of FID approximates the relative mass of a compound in a sample matrix. However, comparing to the near-universal response of FID signals, the signals of iodide CIMS per unit mole of analytes may vary up to five orders of magnitude~~s~~ and highly depend on their enthalpies of binding with iodide (Iyer et al., 2016; Lopez-Hilfiker et al., 2016a). The two peaks highlighted provide an example in the variability of CIMS response: Analyte 1 has a larger FID peak area, indicating a higher mass concentration in the sample mixture than Analyte 2. However, since the CIMS peak area of Analyte 1 is lower, it must be less sensitive than Analyte 2 in an iodide CIMS. With the use of FID in addition to the CIMS detector, calibration of compounds in CIMS without using authentic standards can therefore theoretically be achieved. Implementation of this calibration approach including detailed methods of quantification and determination of isomer sensitivity is complex and will be addressed in future work. This manuscript focuses instead on the descriptions of technical hurdles overcome by TAG-CIMS/FID and its potential value in understanding existing and new ionization chemistries, as well as atmospheric systems.~~This manuscript focuses instead on the description of TAG-CIMS/FID, isomer-counting, and evaluation of multi-reagent CIMS.~~

3.2 Number of isomers per formula

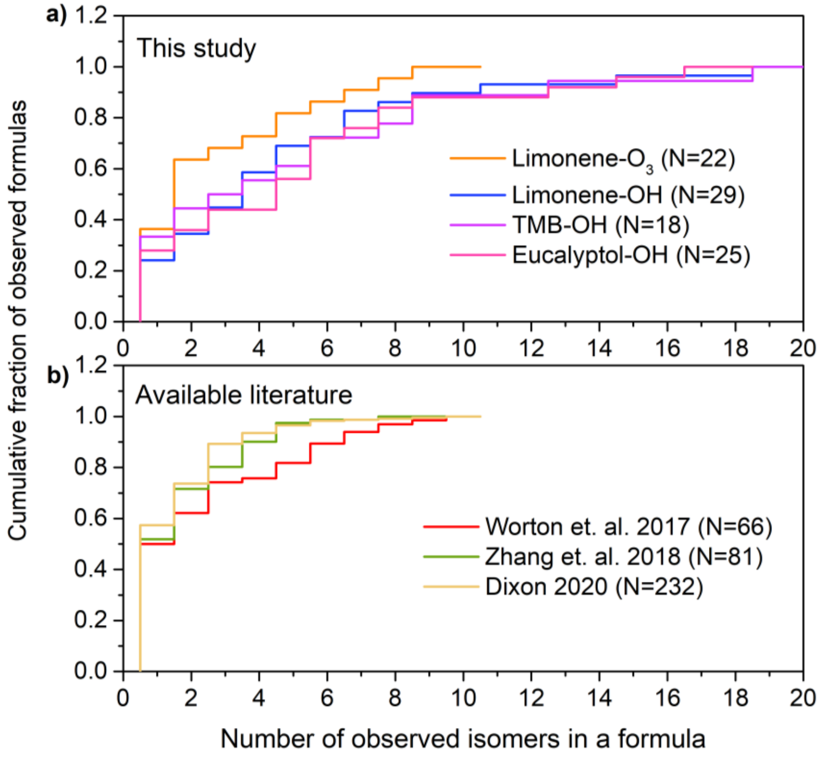

Figure 3. Number of isomers per chemical formula in (a) observed in this work in oxidation experiments, and (b) available literature. Data in (b) are from ambient atmospheres in a ponderosa pine forest in California measured by two-dimensional GC without derivatization (Worton et al., 2017), Southeastern U.S. by two-dimensional GC with derivatization (Zhang et al., 2018), and combined datasets from SOA~~s~~ formation measured by liquid chromatography (Bryant et al., 2019; Dixon, 2020). The number, N, of formulas observed in each dataset is provided in the legend.

We explore here the extent to which isomers are present in atmospherically relevant mixtures to assess the potential utility of a TAG-CIMS/FID (or, more generally, a GC-CIMS/FID). The number of isomers per molecular formula identified in the high mass resolution peak fitting can be obtained by counting the number of peaks in the chromatograms of a specific high-resolution *m/z* of the iodide-adduct (i.e., a specific molecular formula). These data should be interpreted cautiously. Overestimation may occur when large parent molecules decompose to isomers of a smaller formula during thermal desorption. ~~Overestimation may occur because peaks observed might be formed in part by thermal decomposition of analytes during thermal desorption.~~ Conversely, isomers may be undercounted if they fall below the threshold used to count them, which was selected here to be conservative. The limitations in these estimates will be discussed in detail later in this section, but these data nevertheless provide a useful, if uncertain, understanding of the prevalence of isomers in atmospherically-relevant samples.

Figure 3a shows the cumulative number of isomers found in formulas identified in the PAM oxidation experiments. In this study, compounds with a peak height higher than 1.0×10^4 ions/s are taken into the isomer counts; the number of isomers is sensitive to the selection of this threshold so we set as a threshold the approximate level at which the chromatographic peak height clearly rises above the baseline by at least a factor of 50; in many cases, peaks are present below this threshold (e.g., Figure S2, showing 12 isomers identified in ($C_9H_{12}O_4$)I). Although 30% of formulas in the oxidation experiments have only one isomer, a significant portion (34%) of formulas have more than five isomers. For limonene-O_3, limonene-OH, 1,3,5 trimethylbenzene-OH, and eucalyptol-OH reactions, the median number of isomers per formula is 2.0, 4.0, 3.5, and 5.0; the average number of isomers per formula is 3.7, 4.9, 5.1, and 5.3; and the maximum number of isomers per formula is 14, 19, 19 and, 17, respectively. The results indicate that isomers are prevalent in sample matrix with an average number of three to five isomers per formula depending on the precursors in the oxidation experiments. We compare these data to previously published studies using isomer-resolved analyses of SOA (Figure 3b). Ambient measurements from a range of environments show a qualitatively similar distribution of isomers per formula, though with somewhat lower averages of 2.7, 2.1, and 1.9, based on data collected from ambient air in a ponderosa pine forest in California measured by two-dimensional GC without derivatization (Worton et al., 2017), Southeastern U.S. by two-dimensional GC with derivatization (Zhang et al., 2018), and combined datasets from SOA formation measured by liquid chromatography (Bryant et al., 2019; Dixon, 2020). These data were collected by different instruments (two-dimensional GC with filter samples analyzed by thermal-desorption and derivatization, two-dimensional GC with filter samples analyzed by thermal desorption, and LC, respectively) that are likely not sensitive to the same compounds. Another possible reason for the lower number of isomers might be that the use of two-dimensional GC can limit the range of compounds detected since those analytes have to be such that they make it through two consecutive capillary columns. Together, the published data and that collected by TAG-CIMS/FID support the conclusion that isomers are abundant for molecular formulas with ten or less carbon number in particle-phase samples. ~~Together, the published data and that collected by TAG-CIMS/FID support the conclusion that isomers are abundant in atmospheric samples.~~ Those isomers may have significantly different physical and chemical properties that impact the formation, transport, and toxicity of SOA, and the distribution of isomers could vary temporally or spatially. The isomer-resolved classification of SOA components provided by TAG-CIMS/FID therefore provides valuable understandings of the oxidative process. Although the molecular structure of each isomer cannot be recognized directly in the chromatograph and the specific functional groups within the formula remain unknown, the chromatographic separation of the TAG-CIMS provides some comparison of polarity, which is dependent on chemical structures, for isomers within a formula.

There are certain limitations for the analysis of the number of isomers per formula in this study. The number of isomers is probably underestimated due to exclusion of peak heights less than 1.0×10^4 ions/s. Furthermore, isomers may vary in their sensitivity, with isomers having less polar functional groups possibly not detected by CIMS. Additionally, the use of a GC column, which is selective towards a certain range of volatility and polarity of compounds, limits the detection of compounds. Conversely, thermal desorption within TAG may fragment larger accretion products to form analytes not present in the original sample (Buchholz et al., 2019; Isaacman-VanWertz et al., 2016; Lopez-Hilfiker et al., 2016b; Stark et al., 2017), or may reverse particle-phase oligomerization reactions (Claflin and Ziemann, 2019). These fragments may not represent the actual molecular composition of SOA, though they nevertheless may provide insight into the formation mechanisms of SOA (Isaacman-VanWertz et al., 2016)..Consequently, the potential multiple fragments from one parent compound may result in an overestimation of the number of isomers.~~These fragments may be identified as oxidation products in this analysis and consequently overestimate the number of isomers.~~ We note, however, that similar numbers of isomers are observed when using liquid chromatography (Figure 3b), which does not involve thermal desorption. Given these uncertainties, we believe that the results presented are not a floor or a ceiling on the number of isomers in the atmosphere, but a step toward understanding a poorly constrained problem. In any case, the number of isomers observed by any single instrument is expected to be underestimated as no instrument is capable of measuring all atmospheric components with molecular speciation. The number of isomers shown in Figure 3 is therefore likely more illustrative as an example than quantitative, demonstrating the general ubiquity of isomers in the atmosphere. This issue raises significant questions the atmospheric measurement community should address as to how isomers differ in their sources, physicochemical properties, instrument sensitivities, and atmospheric transformations.

3.3 Exploring new chemistries: multi-reagent ionization~~Iodide ionization versus multi-reagent **ionization**~~

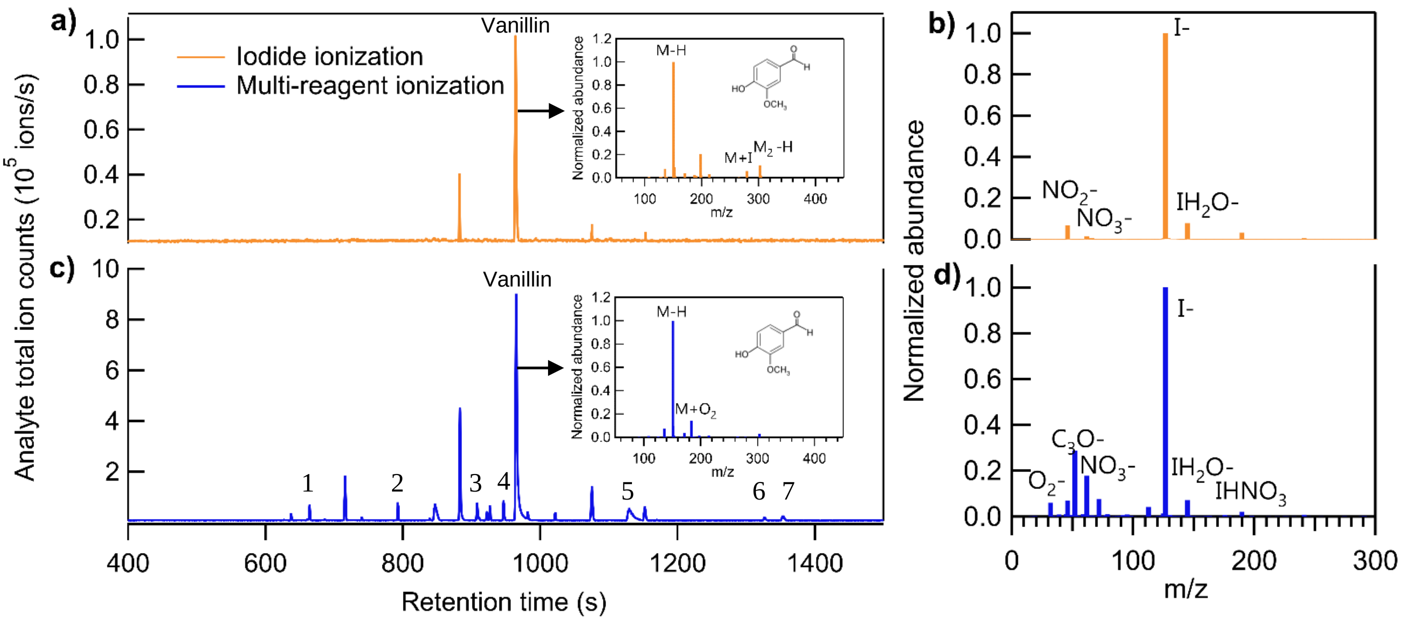

Figure 4. Comparison of chromatograms of analyte total ion counts between a) iodide ionization and c) multi-reagent ionization. Comparison of background mass spectra between b) iodide ionization and d) multi-reagent ionization.. The sample introduced in this run is the mixture of liquid chemical standards and six commercially available fragrances.

Unlike direct air sampling by CIMS, in which the mass spectrum at a given time point is the summation of all analytes, the mass spectra of TAG-CIMS/FID analytes are separated in time by chromatography. Consequently, if a chromatographic peak of a compound is well-resolved in CIMS, all signals detected from the ionization of a single analyte are observed at the same chromatographic retention time and unambiguously assignable to that specific compound, including iodide adducts, products of adduct declustering, fragments (generally not from iodide clustering), and any ions produced by simultaneous alternate chemistry with other ions present in the atmospheric pressure interface (e.g., air). This provides a clean mass spectrum for each chromatographically well-resolved analyte and consequently a significant advantage for understanding ionization chemistry. Previous work has demonstrated that coupling a GC-interface to a NO^+ CIMS can determine the products ion distributions for VOCs (Koss et al., 2016). This instrument complements this previous work by examining less volatile and more oxidized compounds, as well as other CIMS chemistries. This technique is particularly interesting in the context of iodide CIMS chemistry, as it allows us to explore ions with positive mass defects (i.e., non-adduct ions), which are not particularly well understood (Lee et al., 2014). We demonstrate the capability of the technique by showing the chromatograms of a complex sample containing a mixture of liquid chemical standards and six commercially available fragrances in Figure 4. For example, while the analyte mass spectrum of vanillin, shown in Figure 4a, in iodide ionization mode does contain an iodide-adduct ion (i.e., $[M+I]^-$), there are other ions with higher abundance including the predominant deprotonated form of vanillin (i.e., $[M-H]^-$), followed by its nitrite-adduct (i.e., $[M+NO_2]^-$), then the deprotonated form of dimer (i.e., $[M_2-H]^-$). In other words, this compound, which is generally measurable by iodide-CIMS (Gaston et al., 2016), produces a large number of detectable ions ~~through reactions with other reagents in the IMR~~. Although the abundance ranking of the produced ions may differ on a compound-by-compound basis, we constantly observe ions other than $[M+I]^-$ in the clean mass spectrum of injected liquid standards such as undecanoic acid, hexadecanoic acid, and 1,12-dodecanediol, as well as more polar and low volatility aerosol constituents produced in the oxidation experiments. ~~Similar trends are observed for other compounds injected as authentic standards, including undecanoic acid and 1,12-dodecanediol. In contrast, the iodide-adduct ions ($[M+I]^-$) of more polar and lower-volatility aerosol constituents produced in oxidation experiments are the dominant ions in their analyte mass spectra.~~ Application of this instrument to ambient samples and/or selected test systems have therefore be a pathway toward better understanding iodide adduct chemistry as and co-existing side reactions.

Using GC-CIMS not only enables the elucidation of different ionization pathways in the CI source and enables separation of interferences in the quantification, but might also be useful for exploiting these co-existing chemistries to yield additional information. While chemical ionization intrinsically offers selectivity for ease of analysis, selectivity is also negatively limiting (Munson and Field, 1966). Thus, under certain circumstances it may be useful to use multiple reagent ions to detect different classes of compounds using separate, but still soft, ionization methods. Other ions like the deprotonated form of the analyte, $[M-H]^-$ spectra might be better suited for the identification and quantification of some analytes. The deprotonated ions are believed to be produced through the reaction with O_2^- present in the IMR (Dzidic et al., 1975; Hunt et al., 1975). It is reported that the presence of O_2^-, which is commonly found in atmospheric pressure ion sources such as electrospray ionization (ESI)

(Hassan et al., 2017), atmospheric pressure chemical ionization (APCI) (McEwen and Larsen, 2009), atmospheric pressure photoionization (APPI) (Song et al., 2007), and direct analysis in real-time (DART) (Cody et al., 2005), may result in the deprotonated molecules through oxidative ionization. Therefore, using multiple reagent ions including I^- and O_2^-, it is possible that low polarity compounds tend to be ionized through proton abstraction by O_2^- while compounds with high polarity can still form iodide adducts. Although we did not find carbonate (as CO_2^- and CO_3^-) in the mass spectrum in this study, we caution that those ions, like O_2^-, can also deprotonate molecules and may interfere with the quantification of the deprotonated ions.

To explore the feasibility of using multiple simultaneous chemistries (e.g., deprotonation reactions and iodide adduct formation) to extend the utility of a CIMS with isomer resolution, the CIMS was operated in a multi-reagent ionization mode by adding ~~5%~~100 sccm flow (i.e., 5%) of ultra-zero air to the 2 slpm flow of N_2 for the gas supply of the methyl iodide permeation tube~~the CIMS was operated in a multi-reagent ionization mode by adding 5% ultra-zero air to the ionization region alongside iodide~~. Figure 4b and 4d show the background ions under the two modes. With no sample introduced into the system (i.e., pure helium as GC effluent), the total ion counts are ~~1.4~~2.4×10^6 and ~~2.4~~1.4×10^6 ions/s and the I^- ion counts are ~~0.7~~1.8×10^6 and ~~1.8~~0.7×10^6 ions/s for ~~multi-reagent ionization~~iodide and multi-reagent ~~iodide~~ ionization, respectively. In other words, by mixing the reagent ion flow with 5% air, the I^- ion reduced by half, while the abundance of additional reagent ions such as O_2^- and NO_3^- increased by approximately an order of magnitude.

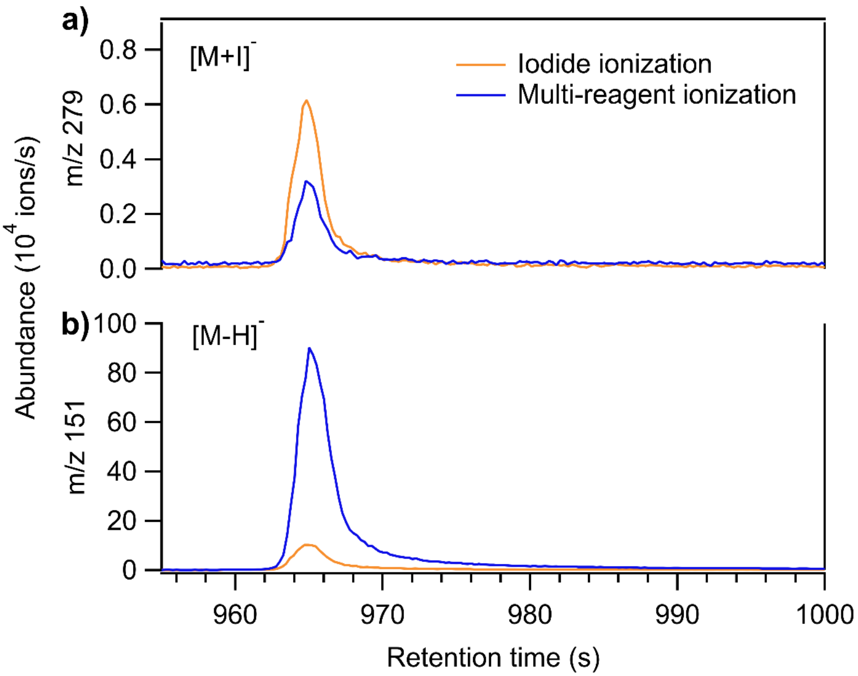

Figure 5. Comparisons of chromatograms of a) $[M+I]^-$ ion and b) $[M-H]^-$ ion from the injection of vanillin between iodide ionization and multi-reagent ionization.

As shown in Figure 4c, for compounds that can be detected by iodide ionization, the total number of ions produced by an analyte increased by a factor of five to ten after switching to multi-reagent ionization mode (note that the scale of y-axis in Figure 4c is a factor of ten higher than that in Figure 4a). For example, the analyte total ion counts of vanillin (labeled with an arrow, retention time = 965 secs), has a peak height of 1.0×10^5 ions/s in iodide ionization mode while the peak height of vanillin in multi-reagent ionization mode is 8.6×10^5 ions/s. This increase in ions is observed to occur almost entirely through the addition of new chemical pathways. In multi-reagent ionization, the three most abundant ions in the vanillin mass spectrum are deprotonation (i.e., $[M-H]^-$), the cluster with O_2^- (i.e., $[M+O_2]^-$), and the deprotonated dimer (i.e., $[M_2-H]^-$). Because of the presence of oxygen in the reagent ion flow, the abundance of $[M-H]^-$ and $[M+O_2]^-$ is enhanced significantly. Though the $[M+I]^-$ is no longer observed in the spectrum, this is only due to the significant increase in other signals; the actual impact on the iodide adduct formation pathway is minor. To demonstrate, we plot the comparisons of the $[M-H]^-$ and $[M+I]^-$ of vanillin between the two ionization modes in Figure 5. The peak height of the $[M-H]^-$ ion of vanillin increases by a factor of 10, from 9.0×10^4 to 90×10^4 ions/s while the $[M+I]^-$ of vanillin reduces by a factor of only 2, from 0.58×10^4 to 0.32×10^4 ions/s after switching from iodide ionization mode to multi-reagent ionization mode, consistent with the factor of 2 decrease in the reagent I^- ion. The results suggest that the instrument selectivity to other classes of compounds can be enlarged by bringing in O_2^- as an additional reagent ion, without significantly suppressing the iodide ionization pathway. In other words, the sensitivity of compounds that tend to be ionized by O_2^- or other side reactions are significantly enhanced in multi-ionization CIMS with only minor decreases in the sensitivity of compounds typically observed by an iodide-CIMS. As long as individual analytes enter the CIMS at separate times, as in the case of chromatography, combining multiple ionization chemistries can provide additional information or selectivity.

An example of the benefit of this approach is demonstrated by the detection of compounds not accessible through iodide adduct formation; 4 times as many compounds are observed in multi-reagent ionization mode (with formulas assigned to at least half of them). For example, a known component in the sample of complex fragrance mixtures, eugenol (Peak 2 in Figure 4c), is identified in the multi-reagent ionization mode yet not detected in iodide mode. In Figure 4c, 6 other peaks are labeled that are not detected as iodide adducts, but for which formulas can be assigned using $[M-H]^-$ and $[M+O_2]^-$ as identifiers, 1: $C_{15}H_{24}O$, 3: $C_9H_{10}O_3$, 4: $C_{12}H_{24}O_2$, 5: $C_{16}H_{32}O_2$, 6: $C_{18}H_{34}O_2$, and 7: $C_{18}H_{36}O_2$. A reasonable objection to multi-reagent ionization is that the complexity of adding up signals in multiple ionization chemistry with variable sensitivities may prohibit reasonable CIMS quantification~~the complexity and/or novelty of the chemistry may prohibit reasonable quantification~~. However, using CIMS for identification of unknowns by formula or other chemical information is valuable on its own, and quantification of many components is achievable using the FID channel of this instrument. This technique is likely only useful when analytes are individually resolved (i.e., isomer resolution), as the resulting mass spectrum of the complete complex mixture would be otherwise too difficult to interpret. We demonstrate here an example of exploring new reagent chemistries: simultaneously using multiple reagent ions is only made possible by the GC separation of analytes, but expands the information provided by this instrument. An in-depth understanding of the competition between reagent chemistries in a multi-reagent system is beyond the scope of this manuscript.

4 Conclusions

We couple a thermal desorption aerosol gas chromatograph with a chemical ionization mass spectrometer as a technique for isomer-resolved analysis of particle-phase organics in the air. The GC column effluent is also split to a flame ionization detector, which provides a near-universal response to carbon-containing analyte, to calibrate the compounds identified by CIMS. We demonstrate that the TAG-CIMS/FID can measure compounds from liquid injections as well as compounds in SOA generated in an oxidation flow reactor. By coupling a TAG to a CIMS, the CIMS is enhanced with an additional dimension of information (resolution of individual molecules) at the cost of time resolution (i.e., one sample per hour instead of per min). This trade-off may be valuable in ambient atmospheres, as the number of isomers per formula, although subject to the positive bias during thermal decomposition and the negative bias due to the vapor pressure limit of the GC column, is observed in ambient samples and oxidation experiments to be typically 2 to 5, and as high as 10 to 20, depending on the instrument and the environment.

A key advantage of coupling a TAG to a CIMS is in characterizing the reagent-analyte reactions occurring in the IMR of a CIMS by resolving mass spectra of individual analytes that might not be commercially available. While the iodide-adduct ions do exist in the mass spectrum of individual analytes, we also observe high abundance of non-adduct ions such as $[M-H]^-$ and $[M+O_2]^-$, which likely account for many ions in the non-adduct region of the iodide valley. By separating analytes chromatographically, these non-adduct ions can be used for the identification of some compounds. These non-iodide ionization pathways can be further enhanced by the intentional introduction of multiple reagent ions.

A multi-reagent ionization mode is investigated in which both zero air and iodide are introduced as reagent ions, to examine the feasibility of extending the use of an individual CIMS for detection of a broader range of analytes. While this approach reduces iodide-adduct ions by a factor of two, $[M-H]^-$ and $[M+O_2]^-$ ions produced from less polar compounds increase by a factor of five to ten, improving their detection by CIMS. The method expands the range of chemical species, which can be measured by CIMS without losing the advantage of identifying chemical formula using the iodide adducts. This novel multi-reagent approach is made possible by combining GC and CIMS detection together with co-measurements from FID. The advantage of simultaneously measuring FID signal for isomer-resolved quantification of I-CIMS sensitivity will be discussed in more detail in a forthcoming paper. Thus, taken together, the GC-CIMS/FID instrument not only inherently valuable for its resolution of isomers in complex atmospheric samples, but also for its ability to characterize and calibrate known CIMS chemistries and to investigate novel and complex chemistries.

Data availability

All raw and processed data collected as part of this project are available upon request.

Author contributions

CB led hardware design, instrumentation, data collection, and data analysis under the guidance of GIVW. GIVW, JEK, BML, and MRC contributed to the development of the theory of the described approach. GIVW, GOF, JEK, JTJ, and DRW contributed to hardware design and instrumentation. JEK, WX, ATL, MSC contributed to data collection. CB prepared the manuscript with contributions by all authors.

Competing interests

The authors declare that they have no conflicts of interest.

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