Sensitivity enhancement using chemically reactive gas cluster ion beams in secondary ion mass spectrometry (SIMS)

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We report for the first time on significant molecular secondary ion yield increases by modifying the chemistry of a water cluster primary ion beam. This was demonstrated using 70-keV ion beams of 0.15 eV/amu. For the neutral drug Bezafibrate, secondary ion yield enhancements ×5–10 were observed when replacing the Ar carrier gas in a water gas cluster ion beam (GCIB) source with a mixture containing 12% CO2 and 2% O2 in Ar. For the cationic drug Ranitidine, the ion yield enhancements using the CO2-containing carrier gas were up to ×20–50 in positive mode and ×2–4 in negative mode. The extent of molecular fragmentation was very similar from both cluster beams. We conclude that additional chemically reactive species are present in the impact zone using the (H2O/CO2)n projectile, which promote the formation of secondary ions of both polarity through projectile impact-induced chemical reactions. This methodology can be applied to further extend the capabilities of high-resolution 3-dimensional mass spectral imaging using reactive GCIB-SIMS.

1 | INTRODUCTION

The capabilities of secondary ion mass spectrometry (SIMS) for (bio)organic analysis have been greatly extended by the introduction of massive gas cluster primary ion beams (GCIBs). For a recent review on the subject of cluster beam interactions with surfaces, see Delcorte et al.

Sputtering of organic species by keV projectiles containing thousands of constituent atoms is characterised by the emission of intact molecules and low residual damage to the sample. This is thought to result from the localised energy deposition from the cluster projectile and the low internal energy of sputtered molecules. Importantly, this facilitates molecular depth profiling and 3D imaging, whereby underlying molecular layers are revealed in a stepwise manner as a function of primary ion fluence.

Seah and co-workers developed a generic description of molecular sputter yields under GCIB projectiles including angular-dependence and the importance of projectile energy (E) and cluster size (n). For SIMS analysis, sputtered secondary ions (SI) are required, and their internal energy and probability of ionisation is dependent on the velocity of the primary cluster. To compare ion velocity of clusters with constituents of different chemistry (mass), it is convenient to refer to projectile energy per nucleon or E/m rather than E/n. For atomic cluster beams of a given E, a more massive cluster with lower E/m results in reduced damage but also lower SI yield. The first GCIBs applied in SIMS, and still the most prevalent, consist of Arn clusters. However, the current density of Arn GCIBs remains low in comparison to liquid metal beams or C60 and 3D molecular imaging at (sub)micrometer resolution often employs a dual-beam approach where the low-damage GCIB sputtering is interleaved with a high-resolution/high-damage analytical beam, for example, Bi3+

To optimise efficient 3D molecular SIMS imaging applications using a single beam approach, a number of groups have investigated methods to increase the SI yield under GCIB bombardment. A strategy which shows particular promise, is to change the chemistry of the GCIB such that ionisation is promoted within the impact crater or the sputter plume. This methodology minimises sample modification and provides enhancement specifically at the impact site throughout a depth-profile or 3D image. An analogous approach is used in atomic SIMS analysis using Cs+ or O2+/− projectiles, but these beams are

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Combining the ionisation benefits of H2O in sample environments with the low damage properties of GCIB sputtering, Sheraz et al. developed a GCIB SIMS water source which has demonstrated a 10–100 increase in SI yield compared to Ar clusters of equivalent E/n. Tian et al. used a mixed (Ar/HCl)n GCIB in combination with D2O doping of the surface to further enhance the yield of protonated analyte ions by a factor ×20 (without the D2O doping to facilitate HCl ionisation no enhancement was observed). Mixtures of Ar/CH4, Ar/CO2, and pure CO2 have also been tested as GCIB projectiles having the potential to introduce chemically reactive species to the impact crater and thereby promote secondary ionisation. The addition of CH4 into Arn projectiles increased the [M + H]+ SI yield ×4 through an enhanced chemical ionisation mechanism which did not affect the neutral sputter yield. The optimum level of doping was found to be 3% CH4 in Ar. Interestingly, Moritani et al. report that (CH4)n and (C6H6)n clusters reduce the Si signal compared to Arn, but (CH2OH)n and particularly (H2O)n clusters provide enhancements ×4 and ×12, respectively. Tian et al. reported that (CO2)n projectiles showed very similar sputter yield and SI yield compared to Ar GCIBs of the same E/m in the range 0.1–0.5 eV/amu whereas at E/m > 0.5 eV/amu CO2 dissociation promoted oxygen adduct formation, particularly in metallic samples.

To date, the most effective GCIBs in terms of SI yield and capability for 3D molecular SIMS imaging are water clusters. Early data from (H2O)n GCIBs confirm that whereas sputter yields scale with E/n, following Seah's 'Universal Equation', SI yields are optimum at E/m ~ 0.10–0.20 eV/amu for analytes of m/z < 2000. More recently Sheraz et al. compared the SI yields from (H2O)n, (CO2)n, and (CO2/Ar)n GCIBs over a range of E/n values for a series of biomolecules and reported that at <0.2 eV/amu the positive and negative SI yields from the water beam were ×10 that of the (CO2/Ar)n cluster. Dimovska Nilsson et al. report a ×2 SI yield increase for biological lipids using 40 keV (H2O)n compared with (CO2)n at 0.15 eV/amu. The aim of this work is to explore if the H2O GCIB can be made more reactive by incorporating CO2 into the water projectiles. Our hypothesis is that this will provide an additional source of chemically reactive species including HCOO− and H+ within the impact region leading to enhanced SI yield compared to (H2O)n or (H2O/Ar)n projectiles. Here, we report for the first time on significant molecular SI yield increases by introducing CO2 into a water GCIB source.

2 METHODS

2.1 Sample preparation

SIMS is increasingly being applied to determine the localisation of pharmaceuticals within biological systems including single cells and tissues, where the limit of detection determines the level of spatial resolution that can be obtained. We therefore chose two drug compounds for this study, with a significant difference in physico-chemical properties. Bezafibrate (monoisotopic molecular mass 361.82 g/mol, pKs 3.8, log P 1.6, CAS: 41859-67-0) is a lipid-lowering agent to treat patients with hyperlipidaemia. Ranitidine (monoisotopic molecular mass 350.86 g/mol, pKs 7.8, log P 0.2, CAS: 66357-59-3) is a histamine-2 blocker used to treat ulcers of the stomach and intestines, and administered as a hydrochloride salt. The two analytes were dissolved in 10-mL HPLC-grade ethanol to 100-mM concentration. All chemicals used in this study were purchased from Sigma-Aldrich, UK. Si wafer substrates (5 × 5 mm2) were cleaned by ultrasonification sequentially in distilled water and HPLC-grade ethanol (two wash cycles each comprised 20 min in each solvent) followed by 20 min UV-ozone treatment (Ossila Ltd, UK, model L2002A2-UK) and a final ultrasonic wash cycle. Samples were prepared by a static dispensing spin coating method (Laurell Technologies, US, spin coater). Five aliquots of sample solution totalling 90 μL were pipetted onto the polished face of the Si wafer and after each aliquot the sample was spun at 500 rpm until the ethanol had evaporated. The process was repeated until 90 μL of solution had been deposited, forming a sample film that appeared uniform to the eye. The substrates were mounted on the SIMS Cu sample stub using conductive carbon tape and equilibrated under high-vacuum in the SIMS instrument for 24 h before analysis.

2.2 ToF-SIMS characterisation

ToF-SIMS measurements were performed on a J105 3D Chemical Imager (Ionoptika Ltd, UK) described previously. A 70-keV GCIB system was employed, equipped with a source which is capable of producing primary cluster projectiles of Arn (Ar/CO2)n or (H2O)n with n ≤ 50 k. Clusters are formed by adiabatic expansion from a high-pressure region into vacuum and ionised by electron bombardment. The water GCIB is formed by filling the source with superheated steam, pressurised by a carrier gas, in this case pure Ar or mixture consisting 86% Ar, 12% CO2, and 2% O2 (Argoshield universal, BOC Ltd.). The exact chemical compositions of the beams from our GCIB source are not known, but in this source design we expect them to be mostly (H2O)n, using the Ar carrier gas and incorporating CO2 using the Ar/CO2 carrier. Moritani et al. report that the SIMS characteristics of H2O GCIBs formed through an alternative bubbler source design depends on the flow rate of the Ar seed gas. The authors concluded that pure (H2O)n clusters are formed at lower Ar flow rates and mixed H2O/Ar clusters at higher rates. Heinbuch et al. noted a transition from pure water clusters through mixed clusters to predominantly CO2 clusters as the composition of CO2 in the source increased. The design of the source used by Heinbuch et al. was similar to that used by Moritani et al. and cannot be used to quantitatively predict the composition of clusters formed in our mixed-gas source. The design and other operating parameters of the source nozzle will also affect the beam composition. Because O2 is a minor constituent and O is already present in the major constituent species H2O and CO2,
we do not consider further the potential role of \( \text{O}_2 \) in the Argoshield carrier gas. This will be explored in subsequent studies using pure \( \text{Ar}/\text{CO}_2 \) mixtures. In this work the water clusters formed with pure \( \text{Ar} \) carrier gas are denoted \((\text{H}_2\text{O}/\text{Ar})_n\), and those with the \( \text{Ar}/\text{CO}_2 \) mixture \((\text{H}_2\text{O}/\text{CO}_2)_n\). The mean cluster size is determined by performing a time-of-flight measurements through the primary beam column, and once the desired cluster mass is tuned (~470 kDa in this case) it is selected by a Wien filter to impact the sample. In mixed \((\text{H}_2\text{O}/\text{CO}_2)_n\), clusters the number of molecular constituents \( n \) will depend on the composition ratio, ranging from \( n = 26 \text{,000} \) to \( 10 \text{,600} \) as the \( \text{CO}_2 \) content increases. The GCIB operates with a continuous current due to the buncher-ToF design of the J105 instrument. All GCIBs were focused to a 10-\( \mu \text{m} \) spot size at the sample. Data were acquired in positive and negative ion mode. The structures of the ions measured in this study are shown in Figure S1.

The physics of the GCIB sputtering process is determined principally by the velocity of the primary projectile. To enable comparison with projectiles of different chemistry we consider the energy per unit mass \( (E/m) \) rather than the energy per atom \( (E/n) \) in reporting cluster size. To compare the performance of 70-keV GCIBs of different chemistry, with the same velocity, we therefore selected a mean cluster size which gives \( E/m = 0.15 \text{ eV/amu} \), in the region of maximum \( \text{Si} \) yield for water GCIBs.\(^{27}\)

Depth profile analyses were performed on each sample by scanning the GCIB over an area \( 500 \times 500 \mu \text{m}^2 \). Data were acquired over 30 analysis layers. The primary ion dose density per layer was \( 4 \times 10^{11} \text{ ions cm}^{-2} \) and the total dose density used in the depth profile \( 1 \times 10^{13} \text{ ions cm}^{-2} \). For each GCIB, six etch craters were generated from the same sample wafer and within each crater data was selected from three regions of interest, giving a total of 18 depth profiles for each GCIB/analyte combination. Data were processed using the Ionoptika Image Analyzer software. To compare relative \( \text{SI} \) yields, mean signal levels from all 18 analyses of each analyte were used.

3 | RESULTS AND DISCUSSION

To investigate sample uniformity and any beam-induced damage, depth profiles were obtained with each beam on each sample. Representative positive ion depth profile data are shown in Figure 1. It can be observed that for the Bezafibrate sample there is evidence that the interface with the substrate is reached after layer 20 when using the \((\text{H}_2\text{O}/\text{CO}_2)_n\) GCIB (Figure 1A). The Bezafibrate \([\text{M} + \text{H}]^+ \) ion at \( m/z \) 362 and the fragment \([\text{CH}_2\text{J}_2\text{C}_6\text{H}_4\text{OH}]^+ \) at \( m/z \) 121 show a decay in mean signal after this layer is reached at a primary ion dose \( 8 \times 10^{12} \text{ ions cm}^{-2} \). Immediately previous to this point in the depth profile the \( m/z \) 121 fragment shows an increased signal level, which we interpret as a result of reflection of the incident beam energy from the underlying \( \text{Si} \) substrate, causing increased fragmentation. The depth profile obtained with the \((\text{H}_2\text{O}/\text{Ar})_n\) GCIB shows no signal decay. This suggests either the sputter yield with \((\text{H}_2\text{O}/\text{CO}_2)_n\) is greater than \((\text{H}_2\text{O}/\text{Ar})_n\), or the sample area where the former depth profiles were performed was thinner. Closer inspection of the

![Figure 1](https://example.com/figure1.png)

FIGURE 1 Depth profiles obtained with 70 keV \((\text{H}_2\text{O}/\text{Ar})_n\) (open markers) and \((\text{H}_2\text{O}/\text{CO}_2)_n\) (closed markers) with \( E/m = 0.15 \text{ eV/amu} \). Signal intensities were averaged over multiple regions of interest (\( N = 18 \)) using total primary ion dose of \( 1 \times 10^{13} \text{ ions cm}^{-2} \) for the full depth profile. The ions represented are the \([\text{M} + \text{H}]^+ \) of (A) Bezafibrate and (B) Ranitidine at \( m/z \) 315, respectively, and diagnostic fragments \([\text{CH}_2\text{J}_2\text{C}_6\text{H}_4\text{OH}]^+ \) at \( m/z \) 121 and \([\text{CH}_3\text{J}_2\text{NHC}(\text{CHNO}_2)\text{NHCH}_3]^+ \) at \( m/z \) 130

18 individual depth profiles contributing to the averaged depth profile shown in Figure 1A indicate that this is specific to certain regions of interest and not a general phenomenon and therefore we conclude it
is due to sample thickness variations rather than a sputter yield effect. We did not measure sputter yields specifically in this study, but previous work has indicated that $E$ and $E/n$ are the principal parameters determining sputter yield$^{11}$ and these values are identical for both GCIBs in our study. The Ranitidine depth profiles (Figure 1B) show no signal decay with either GCIB over the full 30-layer data acquisition. The ratio of Ranitidine molecular ion $[M + H]^+$ ion at $m/z$ 315 to the fragment $[\text{CH}_2\text{NHC}(\text{CHNO}_2\text{NHC})\text{H}]^+$ at $m/z$ 130 is very consistent throughout the depth profile with the $(\text{H}_2\text{O}/\text{Ar})_n$ beam. When using $(\text{H}_2\text{O}/\text{CO}_2)_n$, the yield of the molecular ion increases relative to the fragment, before both ions reach a steady state at $\sim 6 \times 10^{12}$ ions cm$^{-2}$ (layer 15). In light of the depth profile data, secondary ion yields between the two GCIBs are compared over layers 1–20 for the Bezafibrate sample and layers 1–30 for the Ranitidine sample.

Figure 2 shows the effect of changing the $\text{H}_2\text{O}$ GCIB carrier gas on the mean positive and negative SI yields obtained from Bezafibrate over layers 1–20 of each depth profile. In both positive and negative polarity, SI yields are enhanced by a factor $\times 5$–10 for this drug. The relative SI yields for Ranitidine using $(\text{H}_2\text{O}/\text{Ar})_n$ and $(\text{H}_2\text{O}/\text{CO}_2)_n$ projectiles are shown in Figure 3. Unlike Bezafibrate, the yield enhancement using the CO$_2$-containing carrier is an order of magnitude greater in positive than negative ions. It is noteworthy that both ion polarities are enhanced when introducing CO$_2$ into the water source of the GCIB. For a given peak, typical integrated intensity RSD values for each depth profile were 10–20% for both samples. These uncertainties were propagated to determine the error bars on the yield ratio plots in Figures 2 and 3.

At the fixed $E/m \sim 0.15$ eV/amu used in this study, the choice of carrier gas for the water GCIB did not significantly affect the SI yield of diagnostic fragment ions relative to that of $[M + H]^+$. The similarity in the energy deposition process between different projectiles is consistent with the similarities observed in the resulting SIMS spectra (Figure 4). On this basis, we conclude that the presence of CO$_2$ in the water source provides an enhanced efficiency for secondary ion formation. The same effect has been demonstrated previously in switching from Ar$_n$ to $(\text{H}_2\text{O})_n$, but has not previously been reported with doped water clusters.

Molecular Dynamics simulations have provided many insights into the mechanisms of the interaction of (poly)atomic projectiles with surfaces (see for example a recent review on GCIB impacts by Delcorte et al.$^8$). An important parameter is the ratio of the projectile energy per atom/molecule $E/n$ to the cohesive energy $E_{\text{coh}}$ of the cluster i.e. the total potential energy of the atomic interactions. Simulations predict the impacting projectiles are fully disintegrated into atomic/molecular constituents if $E_{\text{coh}} < 1.7 E/n$.$^{32}$ The cohesive energy amounts to $E_{\text{coh}} = 80$, 56, and 520 meV in Ar, CO$_2$, and H$_2$O clusters, respectively.$^{32,33}$ Complete atomisation requires $E/n$ of the order $100 \times E_{\text{coh}}$, that is, 5 eV for (CO$_2$)$_n$ and 50 eV (H$_2$O)$_n$. Depending on the chemical composition of the (H$_2$O/CO$_2$)$_n$ cluster of the selected mass, the average $E/n$ used in this study ranges from 2.7 eV for (H$_2$O)$_{26,000}$ to 6.5 eV for (CO$_2$)$_{10,000}$. Although these are below the bond enthalpies in H$_2$O and CO$_2$ (5.1 and 8.3 eV, respectively) molecular dissociation within (CO$_2$)$_n$ projectiles has been previously shown to be significant above 5 eV per CO$_2$ molecule.$^{26}$ For a pure (CO$_2$)$_n$ cluster, we predict a high level of atomisation under our experimental conditions, whereas a large percentage of the (H$_2$O)$_n$ constituents are predicted to be in molecular forms including (H$_2$O)$_{n+}$. 

Therefore, on an energetic basis we are likely producing reactive species within the impact zone. The extent and nature of CO$_2$ solvation or other chemical reactions in the ion source, cluster beam or impact zone remain unclear. Measuring SIMS spectra of backscattered ions related to the projectile components may give some insights$^{24}$ and will be the subject of future study. Nevertheless, preliminary data using (Ar/CO$_2$)$_n$ clusters indicate SI yields in both polarities to be significantly lower than for pure water clusters of the same $E/m$ (data not shown), in agreement with published data$^{25,29}$ and supporting the conclusion that it is chemical effects of mixed (H$_2$O/CO$_2$)$_n$ clusters which are responsible for the SI yield enhancement.

Very recently Dimovska Nilsson et al. made a similar study of lipids and biological cells using 40-keV beams.$^{29}$ The observations of that study were that SI yield enhancement of $\times 2$ were observed for (H$_2$O)$_n$ beams using both N$_2$ and CO$_2$ carrier gases, compared to pure (CO$_2$)$_n$ beams with the same $E/m \sim 0.13$ eV/amu. It should be noted that the study by Dimovska Nilsson et al. focused, in the positive polarity, mostly on salt adducts and/or pre-charged lipids such as...
phosphatidylcholines (pKa ~1.0). In contrast, Bezafibrate is an extremely weak base (predicted pKa ~3.8\textsuperscript{24}), which might explain its greater sensitivity to acid–base reactions induced by the GCIB projectile. The Ranitidine sample is prepared as a hydrochloride salt, so the Ranitidine moiety is likely to be pre-ionised in the sample. It is interesting that for this relatively small molecule, SI yield characteristics are clearly influenced by the use of CO\textsubscript{2}-containing carrier gas, in contrast to the pre-charged lipids analysed by Dimovska Nilsson et al. It may be significant that although $E/m$ values are very similar, our impact energy $E$ is greater (70 keV vs. 40 keV), which will increase the energy imparted to the surface and available for chemical reactions. The details of the energy deposition mechanism remain uncertain and require sputter yield measurements in tandem with molecular dynamics simulations\textsuperscript{35} to further understand.
4 | CONCLUSIONS

The chemistry of the carrier gas used in combination with a water cluster beam of $E/m$ 0.15 eV/amu influences the secondary ion yield of sputtered drug molecules. Given the broad experimental support for Seah’s ‘Universal Equation’ predicting similar sputter yields for these projectiles, we infer that impact-induced chemical reactions involving CO$_2$ are responsible for an increased ionisation efficiency. Our observations suggest the charge state of the sample prior to analysis affects the magnitude of this effect which may differ in each polarity. This work demonstrates the potential for further significant SIMS performance gains using reactive GCIBs. SI yield enhancements over an order of magnitude have been observed in this study, while changes in the relative fragmentation of secondary ions are within a factor of two. Further studies are needed to better understand the relationship between analyte/cluster beam physico-chemical properties and SIMS performance using novel GCIB projectiles. Although we limit our discussion in this paper to Ranitidine and Bezafibrate, similar SI yield enhancement have also been observed with Acetaminophen and Diclofenac and these will be reported as part of a wider study into matrix and primary beam effects on quantification in GCIB-SIMS.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available in Zenodo at https://doi.org/10.5281/zenodo.5727115

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**SUPPORTING INFORMATION**

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