Liquid Sampling-Atmospheric Pressure Glow Discharge Ionization as a Technique for the Characterization of Salt-Containing Organic Samples

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ABSTRACT: Typical ionization techniques used for mass spectrometry (MS) analysis face challenges when trying to analyze organic species in a high-salt environment. Here, we present results using a recently developed ionization source, liquid sampling-atmospheric pressure glow discharge (LS-APGD), for marine-relevant salt-containing organic samples. Using two representative sample types, a triglyceride mixture and dissolved organic matter, this method is compared to traditional electrospray ionization (ESI) under saline and neat conditions. LS-APGD produced equal or higher (15%+) ion intensities than those of ESI for both salt-containing and neat samples, although important differences linked with adduct formation in high-salt conditions explain the molecular species observed. For all sample types, LS-APGD observed a higher diversity of molecules under optimized settings (0.25 mm electrode spacing at 20 mA) compared to traditional ESI. Furthermore, because the LS-APGD source ionizes molecular species in a ~1 mm³ volume plasma using a low-power source, there is the potential for this method to be applied in field studies, eliminating desalting procedures, which can be time-consuming and nonideal for low-concentration species.
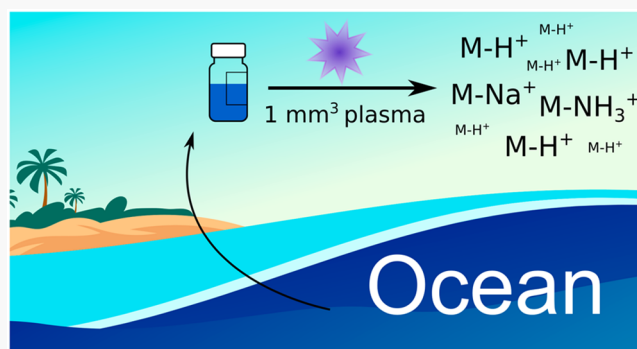
Analysis of complex environmental samples using mass spectrometry represents a challenging problem due to low concentrations of target analyte(s), chemical lability, and the presence of matrix materials such as salts.[1] Despite these challenges, numerous improvements that utilize unique methods for sample preparation, introduction, and data analysis have been made over the past several decades.[2] Samples containing dissolved organic matter (DOM), an abundant component in terrestrial and marine environments and operationally defined as molecular species that pass through a 0.45 um filter,[3] can contain over 10 000 different molecular signatures,[1] most of which are not fully characterized. Even selectively filtered samples from field studies aiming to look at specific classes of molecules, fatty acids, or lipids at the ocean—air interface for example, can contain hundreds of unique structures as well as salts.[4] Besides the complex organic nature of environmental samples, the interfering presence of salt is a limitation for in-depth mass spectrometry analysis of samples such as marine-DOM.

Electrospray ionization (ESI) is the predominant ionization method used in high-resolution mass spectrometry for environmental samples, because it can ionize a wide range of molecules with respect to polarity and molecular weight.[5] However, sea salts nominally at ~0.6 M NaCl can greatly affect signal intensity even with concentrations below 0.1 mM.[6]

There are a few modified ESI methods that can deal with elevated salt concentrations; however, these modified methods are specific to protein-relevant systems and often result in either low ion signal or high sample consumption rates.[7−9] Other methods exist to circumvent this salt issue entirely, such as using solid phase extraction (SPE) to collect marine-dissolved organic matter (m-DOM or sometimes known as SPE-DOM), described in detail by Dittmar and co-workers in 2008.[10] However, concentrating and removing salt from natural organic matter samples (via ultrafiltration, SPE, reverse osmosis, etc.) can result in recovery issues depending on the type of sample[11,12] and possibly alter the chemical nature of the sample.[13] Thus, there is a need to analyze complex salt-containing environmental samples in both the field and lab without extensive preprocessing. Herein, we have applied a new ionization method for the analysis of complex marine samples containing high concentrations of salts, liquid sampling-atmospheric pressure glow discharge (LS-APGD).
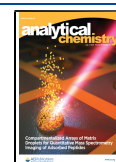
This method shows high sensitivity, can be made field-ready, and leads to reasonably low levels of molecular fragmentation.

The LS-APGD ion source has been described previously by Marcus and co-workers,[14] and briefly, the source operates similarly to a traditional atmospheric pressure chemical ionization (APCI) source using a corona discharge. However, in this case, a ~1 mm³ helium-based plasma is formed at the end of the capillary where the liquid sample would normally be vaporized before contact with the APCI corona. This plasma assists in the vaporization of the liquid samples into ionized gas phase molecules. The relatively low power (maximum of 60 mA and 500 V) of the plasma-forming electrode, compared to common 3−6 kV corona or glow discharge sources, enables practical requirements for field deployment.

Initially, LS-APGD was developed for elemental and isotopic analysis, where it produces ng/L detection limits of select metals such as Cs and U and μg/L detection for Fe, Ni, Cu, In, Cd, and Pb.[14−16] The simple and field-ready LS-APGD has detection limits that are semicompetitive with ICP-MS. Because the source is optimized for aqueous salts and metals, samples with ocean salinity levels would not be a large issue as it is with other ionization sources. With such a low-power plasma, it has already been shown that LS-APGD can analyze intact organic species; therefore, the analysis of organics in seawater is possible.[17] Thus, we show here that the capabilities of LS-APGD for the analysis of samples that are expected in a marine environment, with and without salt, are demonstrated through investigations of three distinct sample types, a simple well-characterized triglyceride mixture (C8−C16) and highly complex samples of Suwannee River fulvic acid (SRFA) and m-DOM. LS-APGD and ESI are contrasted to identify the spectral features acquired for each sample type.

■ EXPERIMENTAL METHODS

An initial model sample was prepared for this study. A certified triglyceride reference mixture was purchased from Sigma-Aldrich (Supelco). This reference mixture is composed of five saturated triglycerides of chain length C8−16 at approximately equal mass fractions. The mixture was dissolved in acetonitrile, and all analyzed samples were run at a concentration of 9 mg/L. Samples of the triglyceride mixture and environmental mimics were prepared in saltless or 0.20 M NaCl in 1:2 H_2O/MeOH and teed at 15 μL/min into an isocratic stream of 1:2 H_2O/MeOH + 0.1% formic acid with a 1:200 Ultramark calibration mix also flowing at 15 μL/min. The LS-APGD spectra were collected at a range of probe conditions from 20 to 30 mA and an electrode spacing 0.25−1.5 mm past the plasma ignition point (SI Scheme 1). Sample flow rates were chosen to maximize stability of the plasma and reduce deposition of involatile material on the inlet. Mass spectral data were extracted using Thermo XCalibur data analysis software and imported into R-Studio or Igor (Wavemetrics) for further analysis.

Ultrahigh-Resolution Mass Spectrometry. To compare the LS-APGD source to a universal ionization method, a heated electrospray ionization-linear ion trap Orbitrap high-resolution mass spectrometer (HESI-LIT-Orbitrap, Thermo Fisher Scientific) was used for this study. Samples were directly injected into the electrospray source at 5−15 μL/min. Peaks were detected and analyzed in positive mode at a capillary voltage set to 2.8 kV, where the capillary was maintained at a temperature of 325 °C. HESI gases (arbitrary units) were set to sheath at 30, auxiliary at 10, and sweep at 0. The HESI-LIT-

Orbitrap was always calibrated before both HESI and LS-APGD configurations using a calibration mix (Pierce ESI Ion Calibration Solutions, Thermo Fisher Scientific) to maintain mass accuracy better than 2 ppm. During data acquisition, the Orbitrap mass range is set to m/z 50−2000 with the mass resolution set at 120 000. All solutions in this study contained 0.1% formic acid. Mass error drift was prevented by mass locking the data acquisition to persistent signals from the calibration solutions, giving a range from m/z 195 to 1250.

Using the Orbitrap, in both HESI and LS-APGD modes, masses of thousands to tens of thousands of unique molecular signatures were observed for the complex mixtures. Molecular formula assignments were acquired using the Xcalibur Thermo Fisher Scientific software. The following element ranges were used: ^{12}C, 0−100; ^{1}H, 0−200; ^{16}O, 0−50; ^{14}N, 0−5; ^{32}S, 0−2; and ^{23}Na, 0−1. These element ranges were chosen based on past studies' attempts on mass spectral characterization of highly complex organic samples.[18,19] Formulas with an O/C ratio below 0 or greater than 2.5 as well as relative double bond equivalence values above 25 or below 0 were excluded. In addition, formulas were required to be below a mass error of 2 ppm and have a relative intensity greater than 0.1% of the base peak. Based on these strict heuristic filtering rules and depending on the sample, only between ~30−60% of the ions detected during data acquisition were assigned a molecular formula.

Two environmentally complex samples were used in this study to test the LS-APGD ability to ionize complex systems: Suwannee River fulvic acid (Standard III, International Humic Substances Society) and m-DOM (collected from Scripps Pier, La Jolla). The collection and purification of m-DOM in this study is described by Dittmar and co-workers.[10] Briefly, coastal ocean water passed through a 50 μm mesh is collected from the pier. Nutrients, f/2 algae growth medium (Proline, Aquatic Eco-Systems) as well as solutions of sodium metasilicate, were added to the water. The m-DOM was collected after the subsequent bloom and senescent phase of phytoplankton over 1−3 weeks. The water was then passed through a series of filters: 10, 0.7, and 0.2 μm pore sizes. The samples to be extracted were acidified to a pH value at or close to 2.0 using 1 M HCl (Sigma-Aldrich). The acidified solution was gravity filtered through a solid phase extraction column (Bond Elut PPL, Agilent) at no more than 5 mL/min or about 2 drops per second. The column was then washed and eluted using methanol, and the resulting yellow/orange solution was quickly (under an hour) dried using a rotary evaporator. All glassware used was combusted at 500 °C for 8 h to remove trace organics before use. The solid sample was stored at −21 °C under nitrogen.

■ RESULTS AND DISCUSSION

For the majority of measurements shown in this work, salt concentrations were kept at 0.2 M or lower. For marine samples, this was done by simply diluting with methanol. A few measurements on samples containing up to 0.6 M salt (seawater salinity) were performed; however, significant deposition of material on the MS inlet capillary prevented extended operation before cleaning was required. Further improvements of the LS-APGD source to reduce salt buildup, such as positioning the LS-APGD capillary orthogonal to the MS inlet or the introduction of an auxiliary sweep gas, are warranted. Furthermore, it is recommended that upstream instrument orifices and ion optics such as transfer capillaries

and S-lenses be cleaned more frequently than usual after sustained periods of analysis of salt-containing samples.

Analysis of a Triglyceride Reference Material Mixture. Normalized averaged mass spectra of the triglyceride mixture by electrospray and LS-APGD are shown in Figure 1
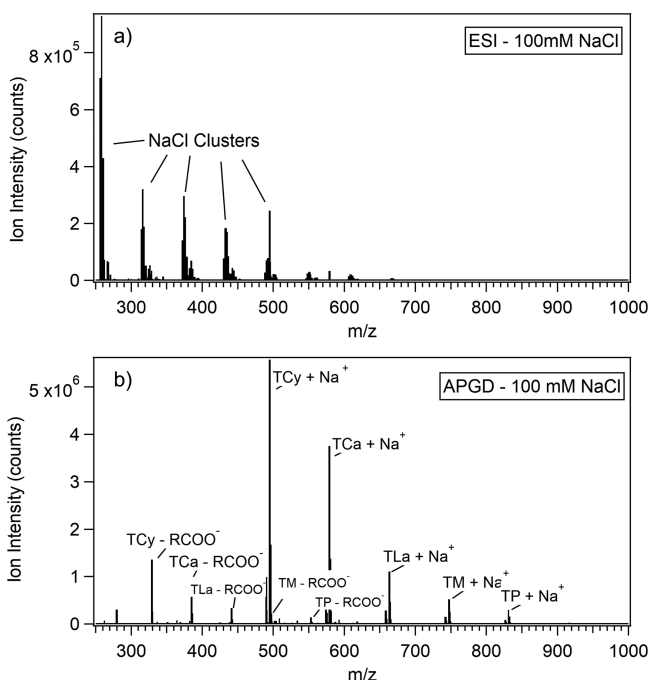
Figure 1. Averaged mass spectra obtained from HRMS analysis of a triglyceride mixture in 100 mM NaCl by ESI (a) and LS-APGD (b).

at 100 mM NaCl. Further analysis conditions of nonsaline triglyceride mixtures by LS-APGD and ESI are shown in the Figure S1. Both the neat ESI and LS-APGD analysis preferentially formed cationized triglyceride ions adducted with NH_4^+ (Figure S1a,b). However, at 0.1 M NaCl for the LS-APGD (Figure S1c), the prevalence of sodium adducted species was significantly higher in proportion to the ammoniated ion. This effect is driven by the preferential binding of sodium over ammonium to triglycerides previously observed in ESI mass spectrometric studies in lipidomics.[20,21] For ESI at 0.1 M NaCl, the production of NaCl ion clusters completely eclipses the production of the sodiated triglyceride cations (Figure 1a) and is not effective at ionizing triglycerides above 1 mM (Figure S1c).[22] Triglyceride precursor ion counts for LS-APGD were equal to or 10−20% greater than those produced by ESI, suggesting that the ionization technique is comparably sensitive for the sample type (Figures 1a,b and S1a−c). Furthermore, LS-APGD was more capable of ionizing higher-mass triglycerides in greater proportion to the total ion count than ESI (Figure 1b). Notably, significant differences in the ratio of quasimolecular ions to their primary decomposition products ($M − RCOO^−$) between neat and saline conditions stimulated an investigation to understand the influence of salinity and LS-APGD conditions (current and electrode distance) on the production and fragmentation of triglyceride species.

Here, we define the fragmentation ratio from the measured ion intensity of the triglyceride precursor and product species in eq 1

$$F_{\text{Triglyceride}} = \frac{[\text{TAG} + \text{Na}]_I + [\text{TAG} + \text{NH}_4]_I}{[\text{TAG} - \text{RCOO}^-]_I} \quad (1)$$

where I is the average raw ion intensity of each species, and the selection of the diglyceride fragment of the ammoniated and sodiated species is based on the observation that very little other fragmentation products are observed in the mass spectrum. Observations of diglyceride fragments from both collisionally activated $−Na^+$, $−NH_4^+$, and protonated triglycerides in the literature have also been commonly identified.[23−25] A list of the selected ions can be found in Table 1 of the Supporting Information.

Figure S2a−e explores the influence of discharge current and electrode distance under saline conditions. Various trade-offs were observed in the production of precursor cations, with higher ratios of precursor to product ion at further electrode distances (Figure S3). However, for the current parameters studied, higher electrode currents favored the production of precursor cations and decreased fragmentation (Figure S2). Differences in fragmentation ratio with triglyceride carbon tail chain length (Figure S3a) are likely due to general reduced stability with increased length, a common feature in organic species. These results contrast recent investigations of LS-APGD parameters for the analysis of caffeine, where electrode distance showed little effect on fragmentation conditions.[17] In addition, for the present investigations with triglycerides, there is a general increase in the fragmentation ratio with discharge current observed. In conclusion, it is further suggested that ionization behavior, especially fragmentation, in LS-APGD requires a compound-class-dependent investigation to optimize analysis conditions.

Interestingly, LS-APGD fragmentation ratios between the neat and saline samples were significantly different at the same LS-APGD conditions, with reduced fragmentation in the saline samples. To explore this behavior further, triglyceride mixture samples were analyzed over 5 orders of magnitude of [NaCl]. The resultant fragmentation ratios are shown in Figure 2. Fragmentation ratios at 0.01 mM NaCl are below 1, indicating the majority of all triglycerides under these conditions are fragmented to diglyceride or other fragments, barring differences in ion transfer efficiency. In contrast, at 1 mM, the fragmentation ratio favors the production of the sodiated cations over fragmentation. This observation is attributed to
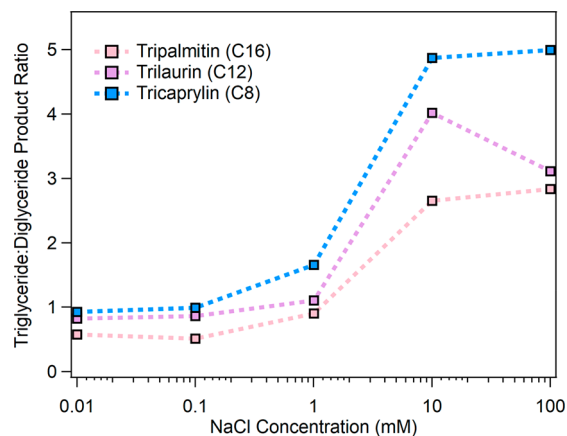
Figure 2. LS-APGD triglyceride/diglyceride fragmentation ratios from 0.01 to 100 mM for triglyceride mixture samples at a constant electrode distance (0.5 mm) and discharge current (30 mA).
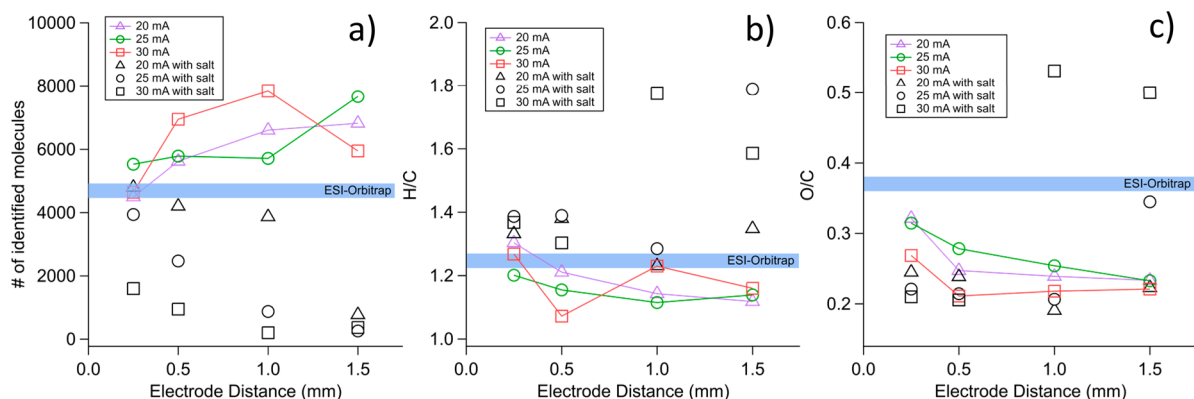
Figure 3. HRMS analysis of SRFA, with (black) and without salt (colored), at various electrode currents and positions with corresponding ESI values analyzed using SRFA (no salt) at the same concentration. Relationships shown between: (a) number of identified molecules averaged mass spectra; (b) hydrogen/carbon ratios; and (c) oxygen/carbon ratios.

the altered adduct distribution in the saline analysis, which is supported by studies of collisionally induced dissociation of triglyceride species.[26]

It has been observed that the generation of products via collisionally induced dissociation requires significantly larger collisional energies for sodiated triglycerides over ammoniated triglycerides, likely due to strong coordination between the Na$^+$ cation and the electron donating groups on the triglycerides.[21] Thus, it is proposed that in-source adduct assisted stabilization of the ionized triglyceride significantly enhanced the persistence of the quasimolecular ion from thermal decomposition in the LS-APGD source. In support of this hypothesis, Figure S4 shows the ratio of sodiated to ammoniated cations over varying NaCl concentrations, indicating a significant shift in adduct distribution toward sodium with increasing [NaCl]. This trend is driven primarily by increases in the production of sodiated molecular ions as opposed to a decrease in ammoniated precursor species, as evidenced in Figure S5a,b, where sodiated species increase with added [NaCl], and ammoniated species remain relatively constant. Curiously, the trends in both the fragmentation and adduct ratios reflect different dependencies on salt concentration. It is further hypothesized that this effect is caused by the reduction of excited but un-ionized triglyceride species at increasing salt concentrations, as they are preferentially sodiated. Unfortunately, production of protonated triglyceride species was not particularly effective and cannot be used to verify this hypothesis further. This result adds an interesting detail to the aspects of salt-containing analysis, as the alteration of the overall adduct state may enhance or possibly hinder the observation of intended species through changes in fragmentation. Although changes in adduct state with varying salinity add interesting features and detail to LS-APGD that must be considered, the source successfully analyzes triglycerides in the presence of high salt concentration in comparison to ESI where salts render the spectra unusable.

Complex Environmental Samples. DOM in the Earth's oceans is the single largest pool of reduced carbon.[27] Complex DOM samples are notoriously difficult to characterize, and therefore, a suite of instrumental techniques have been developed.[1] This study aims to provide a possible alternative to the current approaches used historically for DOM collection, extraction, and analysis. Since m-DOM is particularly understudied due to its relatively low concentration in the ocean (~1 mg/L) and high concentration of

salts, it was selected as a model system to be tested by this new approach in this study.

Since the composition of DOM and humic-like substances can change significantly based on location and/or time,[28] SRFA was used as a standard in this study as well. SRFA and Suwannee River DOM have been extensively studied over the past two decades.[18] Though much of the identity of species in terrestrial DOM remains elusive, this system provided a reasonable benchmark for LS-APGD for comparison to other ionization techniques.

The electrode distance and plasma current in the LS-APGD have a significant impact on the ability to ionize species in the SRFA sample. Figure 3 shows that the lowest current and shortest electrode distances result in the most similar spectral characteristics between neat and saline samples containing complex matter. This is largely attributed to the fact that the smaller and weaker plasma results in softer ionization. Comparisons between salt-containing and salt-free samples in LS-APGD indicate that the incidence of Na$^+$ adducts increases by 15% or more depending on the LS-APGD source parameters such as electrode distance and current, indicating that these effects must be accounted for in data analyses of salt-containing samples. Notably, fragmentation of organic species (most commonly $C_9H_7^+$ and $C_{10}H_8^+$) was prevalent in both salt-containing and salt-free samples, a drawback to the technique when the composition of the sample is mostly unknown.

In Figure 3a,b, the LS-APGD ionization of the SRFA, both with and without salt, shows good agreement when compared to ESI at the recommended settings. However, in Figure 3c, a notable difference in the O/C ratio is observed, where LS-APGD analysis of the SRFA sample consistently measures a lower O/C value (between 0.20 and 0.33). In this study, ESI of SRFA produced an O/C ratio of about 0.38, which is within the range of literature values of 0.3 to 0.6.[18,29] The observations of a lower O/C ratio in the LS-APGD experiment are attributed to the source more efficiently ionizing nonpolar or low-polarity organics compared to ESI, comparable to a corona-based ionization source such as APCI. This finding makes LS-APGD an attractive option for studying complex organic samples due to its apparently wide range of potential species, polar and nonpolar, to be ionized. A more detailed comparison of SRFA molecular composition by LS-APGD and ESI is planned for a future study.
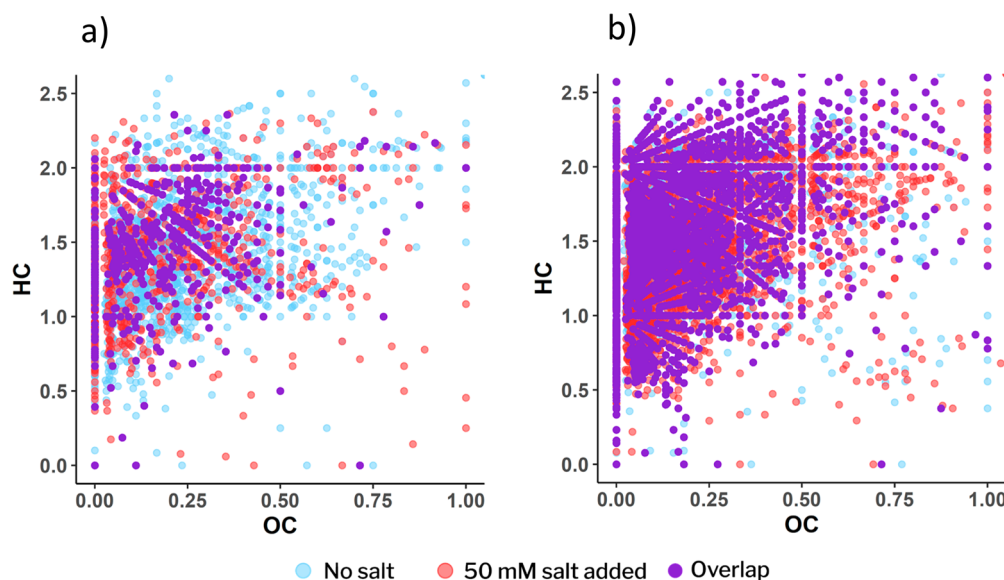
Figure 4. van Krevelen diagrams of m-DOM spectra showing oxygen/carbon (OC) and hydrogen/carbon (HC) ratios, measured by (a) traditional ESI and (b) LS-APGD. A comparison is shown for spectra obtained with (50 mM added NaCl) salt (red circles) and without salt (light blue circles), where the overlap of elemental compositions is also shown (purple circles).

A sample of m-DOM was extracted from seawater collected off Scripps Pier in La Jolla, California. The m-DOM was analyzed with both heated-ESI and the LS-APGD ion sources with direct infusion at 5 and 15 μL/min, respectively. Sample collection was relatively fast, in part due to the high throughput of the Orbitrap, resulting in a sample consumption less than 60 μL for the LS-APGD method.

The ESI and LS-APGD mass spectra of non-salt-containing m-DOM were similar in the overall spectral range from 150 to 600 m/z (Figure S6), with the LS-APGD spectra differing due to the appearance of aforementioned ion fragmentation signatures as well as a factor of 10 increase in total ion intensity. After 50 mM NaCl was added to the m-DOM sample, the ESI shows a vastly different spectrum compared to the no-salt ESI spectra, with multiple groups of peaks separated by 23 m/z units due to the formation of a large number of sodium adducts. Figure 4a shows the small overlap in the no-salt and salt-containing m-DOM (less than 20%) analyzed by ESI in a van Krevelen diagram.[30] Conversely, Figure 4b shows significant overlap between the no-salt and salt-containing m-DOM when ionizing with the LS-APGD (above 80%). There is also a significant increase in identified features (such as condensed aromatics, shown below a 0.25 O/C ratio and below a 1.25 H/C ratio) in the LS-APGD mass spectra compared to the ESI, possibly in part due to fragmentation but more likely a result of (1) LS-APGD being able to ionize nonpolar compounds more efficiently than ESI and (2) an increase in total ion signal, thus increasing sensitivity for a wider range of low-concentration compounds. Comparisons of unique molecular signatures detected using traditional ESI and LS-APGD show that around 33% of exact masses (including adducts) found in ESI were also detected using the LS-APGD (Figure S7).

The ability of LS-APGD to analyze organics in complex matrices was further demonstrated by directly measuring seawater acquired during a phytoplankton bloom with no preconcentration or extraction steps (Figure 5). This experiment cannot be compared to traditional ESI mass spectrometry due to the high amount of salt clogging the ESI probe tip
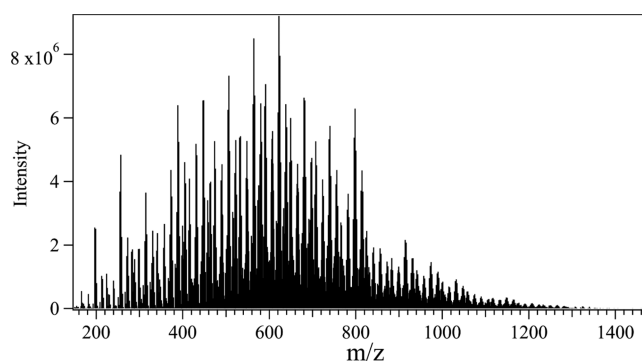
Figure 5. High-resolution mass spectrum of coastal seawater collected during a phytoplankton bloom obtained by LS-APGD Orbitrap mass spectrometry.

and rendering it unusable. The spectrum is composed of many spectral envelopes, similar to those observed in ESI Fourier transform ion cyclotron resonance mass spectra using the PPL SPE method, and contains over 7000 unique masses.[10,28] To our knowledge, this is the first full-high resolution mass spectrum of DOM in pure seawater without any sample preparation required.

■ CONCLUSIONS

In this study, liquid sampling-atmospheric pressure glow discharge ionization has been shown to ionize complex organic samples successfully in the presence of environmentally relevant salt concentrations. Optimization of the ionization source, using a triglyceride mixture, SRFA, and mDOM led to the conclusion that the operational conditions for the analysis of marine-relevant organics depend on sample type and need to be optimized on a case-by-case basis. Mass spectra of environmentally complex compounds (humics, triglycerides, etc.), in the presence of salt, produced more informative ion signals via LS-APGD in comparison to ESI. Such characterization was based on the comparison of the diglyceride/triglyceride fragmentation ratios as well as the ensemble

metrics concerning the spectra of SRFA. Notably, the presence of salts can significantly alter the fraction of adducts, which may hinder or possibly assist fragmentation depending on the stability of the coordinated ion complex. For LS-APGD, which has been shown to fragment some organic species, high-salinity analysis may enhance sensitivity to the molecular ion. Additionally, changes in the fragmentation patterns due to adducts forming in LS-APGD indicate the need for salinity-dependent calibrations when quantitatively analyzing and comparing samples that have varying salt concentrations.

Preliminary analysis of coastal seawater and m-DOM using LS-APGD points to interesting possibilities for compositional analysis, providing an avenue for field analysis of these complex systems. More work on identifying these species is planned for a future study. Besides being able to analyze discrete complex environmental samples, the LS-APGD has the potential to be used for real-time measurements of aqueous systems in the presence of salts to capture temporal changes in chemistry. Future work using LS-APGD and salt-containing samples will aim to investigate its potential for ionizing sea spray aerosol, where organic fractions can reach up to 80% by mass, and salt concentrations can exceed 10 M depending on the size of the aerosol particle.[31] The ability of LS-APGD Orbitrap mass spectrometry to successfully ionize m-DOM in seawater without any sample preparation has far-reaching implications for analyzing m-DOM in the future—where using direct analysis techniques, without inadvertent sample modification, will lead to a more complete characterization of a complex and important component in the marine environment.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.analchem.0c00361.

Supporting Figures 1−7 as well as Table 1 and Scheme 1 (PDF)

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Notes

The authors declare no competing financial interest.

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