Characterization of Unknown Brominated Disinfection Byproducts during Chlorination Using Ultrahigh Resolution Mass Spectrometry

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S Supporting Information

ABSTRACT: Brominated disinfection byproducts (Br-DBPs), formed from the reaction of disinfectant(s) with natural organic matter in the presence of bromide in raw water, are generally more cytotoxic and genotoxic than their chlorinated analogues. To date, only a few Br-DBPs in drinking water have been identified, while a significant portion of Br-DBPs in drinking water is still unknown. In this study, negative ion electrospray ionization ultrahigh resolution Fourier transform ion cyclotron resonance mass spectrometry (ESI FT-ICR MS) was used to characterize unknown Br-DBPs in artificial drinking water. In total, 441 formulas for one-bromine-containing products and 37 formulas for two-bromine-containing products, most of which had not been previously reported, were detected in the chlorinated sample. Most Br-DBPs have corresponding chlorine-containing analogues with identical CHO composition. In addition, on-resonance collision-induced dissociation (CID) of single ultrahigh resolved bromine containing mass peaks was performed in the ICR cell to isolate single bromine-containing components in a very complex natural organic matter spectrum and provide structure information. Relatively abundant neutral loss of CO₂ was observed in MS–MS spectra, indicating that the unknown Br-DBPs are rich in carboxyl groups. The results demonstrate that the ESI FT-ICR MS method could provide valuable molecular composition and structure information on unknown Br-DBPs.

INTRODUCTION

During disinfection treatment of drinking water, naturally occurring bromide present in source water can be rapidly oxidized by chlorine to hypobromous acid (HOBr), which has been noted to be more powerful in reacting with natural organic matter (NOM) to form disinfection byproducts (DBPs) than hypochlorous acid (HOCl).^{1–3} Toxicological studies have shown that brominated DBPs (Br-DBPs) are generally more cytotoxic and genotoxic than their chlorinated analogues.^{4–7} For example, bacterial studies have shown that bromoacetic acid is approximately 20 times more cytotoxic and 200 times more mutagenic in *Salmonella typhimurium* strain TA100 than chloroacetic acid.⁶ Mammalian cell studies have shown that bromoacetic acid is 90 times more cytotoxic and 25 times more genotoxic in Chinese hamster ovary cells than chloroacetic acid.⁶ Identifying and controlling Br-DBPs have thus been important issues in securing drinking water safety.

To date, approximately 110 Br-DBPs have been reported as drinking water DBPs, most of which were identified by gas chromatography/mass spectrometry (GC–MS) with or without derivatization.^{6,8–10} Even with derivatization, however, GC–MS generally is not amenable to the detection of polar/highly polar Br-DBPs. Zhang et al.¹¹ have recently developed the precursor ion scan (PIS) method using electrospray ionization-triple quadrupole mass spectrometry (ESI-tqMS)

for fast selective detection of polar/highly polar Br-DBPs. In this method, precursor ion scans of m/z 79 and 81 were used to selectively detect the Br-DBPs, and product ion scans were then performed to confirm the presence of bromine and provide structure information. Although many polar/highly polar Br-DBPs were successfully detected and identified in artificial and actual drinking water samples, one problem related to this method is that the unit mass resolution is too low to allow nominally isobaric ions to be mass-resolved. Because of the extremely complex nature of NOM, molecular ions of NOM and their chlorinated (or brominated) products could be present at almost every nominal mass, and mass differences of isobaric ions of NOM and chlorinated (or brominated) DBPs could be as low as 36.4 mDa, 15.3 mDa, or even lower (as shown in the Supporting Information, Table S1).^{12,13} Therefore, unit resolution product ion scans may include several isobaric parent ions and bias the compositional interpretation of single brominated compounds.

On the other hand, ultrahigh resolution Fourier transform ion cyclotron resonance mass spectrometry (FT-ICR MS) is an

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emerging technique to determine the molecular composition of NOM^{12–20} and chlorinated DBPs.^{12,13,20} The ultrahigh resolution and mass accuracy of FT-ICR MS provides molecular masses accurate to within 1 ppm, which often enables the determination of molecular formulas by mass measurement alone.^{14,15,21} In our previous studies, molecular formulas of chlorine-containing DBPs have been identified with negative ion electrospray ionization (ESI) FT-ICR MS in both artificial and actual drinking water samples.^{12,13} It is thus anticipated that the ESI FT-ICR MS method could also be suitable for detecting unknown polar Br-DBPs and identifying their molecular formulas. Furthermore, on-resonance collision-induced dissociation (CID) of single ultrahigh resolved mass peaks in the ICR cell allows us to perform MS–MS fragmentation of Br-DBP with identical mass formulas,²² which could help in better proposing structures of unknown Br-DBPs in a very complex NOM matrix.

The main objective of this study was to characterize unknown Br-DBPs in artificial drinking water using FT-ICR MS. In addition, MS–MS fragmentation of single Br-DBPs with identical mass formulas was performed using CID FT-ICR MS. The FT-ICR MS method developed in this study may facilitate the characterization of structurally complicated halogenated DBPs, and the results will improve our knowledge of Br-DBPs.

■ EXPERIMENTAL SECTION

Materials. Suwannee River fulvic acid (SRFA) was purchased from the International Humic Substances Society. LC–MS grade methanol and p.a. grade hydrochloric acid were purchased from Merck (Darmstadt, Germany). Hypochlorite sodium solution (analytical grade, Sinopharm Chemical Reagent, Beijing) was diluted and used to prepare free chlorine. Ultrapure water (18.2 M Ω -cm) was prepared by a Milli-Q purification system (Millipore, USA).

Preparation of Artificial Drinking Water Samples. Artificial drinking water samples were prepared with ultrapure water containing 3.0 mg/L SRFA (as C), 90.0 mg/L NaHCO₃, and 2.0 mg/L NaBr (as Br[−]) according to Zhai and Zhang.²³ Concentrations of bromide in fresh water typically range from trace amounts to about 0.5 mg/L,²⁴ with the highest natural level of ~2 mg/L present in Israel's source water.²⁵ A nationwide survey of bromide ion concentrations in drinking water sources in the U.S. has shown that the overall average bromide level in random samples was between 60 and 65 μ g/L, with a range of 2 to 429 μ g/L.²⁶ A relatively high bromide concentration (2 mg/L) was used to amplify brominated DBPs so that unknown brominated DBPs could be detected and identified by the FTICR MS method. Bromide at such a high level (2 mg/L) has also been used to amplify and observe the possible brominated DBPs in previous studies.^{23,25,27} Water samples were chlorinated in sealed 1-L amber glass bottles with a chlorine dose of 5.0 mg/L as Cl₂ at 20 °C in darkness. Immediately after chlorine addition, all the samples were adjusted to pH $\approx$ 7.5 with 1.8 M hydrochloric acid. The reaction was halted 5 days later by the addition of excess Na₂S₂O₃.

To determine whether there were any impurities in the reagents or any artifacts in the disinfection and subsequent pretreatment, control samples were generated by repeating the same procedure with samples of the aforementioned artificial water without chlorination, and chlorination control samples

were generated by repeating the same chlorination procedure with artificial water samples without NaBr.

Pretreatment of Artificial Drinking Water Samples. Procedures for water sample pretreatment were carried out according to previous studies.^{12,13} Briefly, water samples were acidified with hydrochloric acid to pH 2 and pumped through a Sep-pak C₁₈ solid-phase extraction cartridge (1 g, 6 mL) (Waters, USA) at a flow rate of $\sim$ 5 mL/min. The cartridges had been previously rinsed with methanol and acidified (pH 2) ultrapure water. For complete removal of salt, the cartridges were rinsed with 20 mL of acidified ultrapure water before elution. Immediately after extraction, each cartridge was eluted with 30 mL of methanol. The eluted samples were freeze-dried and stored at -18 °C in the dark. The artificial drinking water sample composition and treatment applied are summarized in the Supporting Information, Table S2.

FT-ICR MS. The MS analyses were performed using a Bruker apex ultra FT-ICR MS equipped with a 9.4 T superconducting magnet. Sample extract was dissolved in methanol and injected into the electrospray source at 180 μ L/h using a syringe pump. The operating conditions for negative ion formation consisted of a 4.0 kV emitter voltage, 4.5 kV capillary column introduce voltage, and -320 V capillary column end voltage. Ions accumulated in the ion source for 0.1 s in a hexapole. All of the ions passed through a quadrupole and accumulated in an argon filled hexapole collision pool, in which ions accumulated for 1 s. The delay was set to 1.2 ms to transfer the ions from the collision pool to an ICR cell by electrostatic focusing of transfer optics. The mass range was set at m/z 150–800. The data size was set to 4 M words, and the time-domain data sets were coadded with 256 acquisitions.

MS–MS Analysis. The MS–MS analysis was performed according to a previous fragmentation study of NOM.²² Briefly, the selected precursor masses were preisolated with an external quadrupole (window of 20 mass units) and stored in a collision cell consisting of a hexapole for continuous accumulation of selective ions (CASI) for 1 s to increase the S/N of the parent ion. These preselected ions were transferred to the ICR cell and isolated with a 1 Da window applying correlated harmonic excitation field (CHEF) isolation. With the exception of the target ion for fragmentation, all the remaining mass peaks were ejected out of the ICR cell by single shots. With this technique, ions are excited with their resonance frequency using a long and, therefore, sharp pulse of 10–20 ms. Very narrow excitation pulses are needed to avoid the excitation of other ions close to the target ions. Nitrogen was pulsed into the ICR cell to a final pressure of about 10^{-7} mbar in the analyzer cell. The isolated parent masses were excited with their resonance frequency for 400 μ s using a peak-to-peak voltage of 3–5 V. A pump delay of 3 s was applied to regain a lower pressure ($\sim 10^{-10}$ mbar) prior to mass detection. The ions were then excited with a frequency sweep and detected for about 0.55 s in the mass range m/z 120–500. The size of the acquired data set was 1 M words for MS–MS spectra. The mass accuracy of the parent and fragment ions was within 1 ppm. The data were zero filled once before sine apodization; 256 scans were added for one mass spectrum.

Mass Calibration and Data Analysis. The FT-ICR mass spectra were externally calibrated for a mass range of 150–800 using a sodium formate aqueous solution and internally recalibrated with a known homologous series of the NOM sample.^{12,13} Elemental compositions were assigned from the m/z peaks by a mass calculator program^{12,13} limited to molecular formulas consisting of up to 100 ¹²C, 2 ¹³C, 200 ¹H, 3 ¹⁴N, 30

Figure 1. Negative-ion ESI FT-ICR mass spectra for bromine-containing products at nominal mass 361: (a) control sample without chlorination, (b) chlorination control sample without Br[−], and (c) chlorination water sample with Br[−].

¹⁶O, 1 ³²S, 3 ³⁵Cl, and 3 ⁷⁹Br atoms. All assigned formulas must meet basic chemical criteria:²⁸ (1) the number of H atoms must be at least 1/3 the number of C atoms and cannot exceed 2C + N + 2; (2) the sum of H and N atoms must be even (the “nitrogen rule”); and (3) the number of N or O atoms cannot exceed the number of C atoms. Halogens (Cl, Br) are treated like H atoms. These criteria ensure that the formulas generated can at least chemically exist. Additionally, molecular formulas of chlorine-containing peaks and bromine-containing peaks were cross validated using the ³⁷Cl isotopomer and ⁸¹Br isotopomer, respectively. Because the focus of this paper was on characterization of unknown Br-DBPs, only molecular formulas containing C, H, O, Cl, and C, H, O, Br were further investigated.

Limitations. It should be noted that, in this study, C₁₈ solid phase extraction (SPE) was used to isolate and concentrate the analyte from samples and for desalting because ESI FT-ICR MS analysis requires salt-free samples. Only molecules that can be adsorbed on C₁₈ and desorbed by an organic solvent were analyzed by mass spectrometry. Highly hydrophilic (incomplete adsorption) or highly hydrophobic (incomplete desorption) molecules were not considered. During the ESI process, the newly formed halogen-containing components may compete with the original NOM components. Some of the changes in

relative peak abundances may be due to increased ion suppression and/or signal enhancement caused by the additional complexity added by the newly formed halogen-containing components. In addition, the FT-ICR MS used in this study has a mass cutoff at 150 Da. Therefore, this study mainly characterized the C₁₈ extractable Br-DBP molecules, and the detected formulas do not represent the entire pool of Br-DBPs formed after chlorination. On the other hand, although the molecular formulas of Br-DBPs were assigned using the ultrahigh FTICR MS data, each identified formula could represent a variety of different structural isomers.

RESULTS AND DISCUSSION

Detection of Br-DBPs. In our previous studies,^{12,13} FT-ICR MS was successfully used to characterize chlorinated DBPs in drinking water. In this study, with a similar FT-ICR MS method, many Br-DBPs were detected in artificial Br[−]-containing drinking water after chlorination. Figure 1 shows close-up views of expanded mass spectra at the nominal mass *m/z* 361, as an example. Newly formed Br-DBPs were clearly observed in the mass spectrum (Figure 1c). Similar to the previously detected chlorinated DBPs,^{12,13} Br-DBPs also have a characteristic mass difference of 36.4 mDa for the replacement of O by CH₄. In total, molecular formulas of 441 peaks

containing one bromine and 37 peaks containing two bromines were identified in this study.

An approach for examining molecules that differ from each other only in number of CH_2 groups (i.e., members of homologous series) is Kendrick mass defect analysis.^{14,29–31} The Kendrick mass is based on assigning the mass of CH_2 to be 14.0000 Da instead of the IUPAC 14.015 65 Da. The IUPAC mass of a molecule is converted to Kendrick mass (KM) according to eq 1^{14,29–31}

$$\text{KM} = \text{IUPAC mass}_{\text{measured}} [14.0000/14.01565] \quad (1)$$

The Kendrick mass defect (KMD) is the difference between the nominal IUPAC mass (NM) and the accurate KM (eq 2).^{29–31} All members of a homologous series of molecules differing only in the number of CH_2 groups have the same KMD value.

$$\text{KMD} = [\text{NM} - \text{KM}] \quad (2)$$

Because it is possible for different homologous series to have very similar KMDs, it is necessary to presort the ions based on another, independent parameter. The z^* (eq 3)^{14,31–33} value has been shown to be a useful parameter for presorting homologous series of fulvic acids. In eq 3, the modulus is the remainder of the division of nominal mass by 14. Figure 2 panels a and b show the KMD analysis of formulas containing one bromine and formulas containing two bromines,

Figure 2. Kendrick mass defect analysis with z^* of (a) one-bromine-containing formulas and (b) two-bromine-containing formulas.

respectively. The bromine-containing formulas can be sorted out into a homologous series based on KMD analysis and z^* , suggesting they may arise from homologous series of parent NOM components.

$$z^* = (\text{modulus}[\text{NM}/14]) - 14 \quad (3)$$

Another widely used tool for the visualization of FT-ICR MS data is the van Krevelen diagram, in which individual molecular formulas are plotted on the basis of their molar H/C and O/C ratios.^{31,34} Each dot in the diagram represents one or more molecular formulas with a specific O/C and H/C ratio. The types of formulas (for example, lignin and tannin, etc.) can be classified based on their locations in the van Krevelen diagram.^{17,31,35,36} The stoichiometric ranges used to establish boundaries of the classification in such (van Krevelen) diagrams for the components found in NOM are quite variable in the literature.³⁶ Figure 3 panels d and e show the van Krevelen diagrams of the one-bromine-containing DBPs and two-bromine-containing DBPs in the chlorinated artificial water fortified with Br^- , respectively. Detailed molecular formulas for these Br-DBPs are listed in the Supporting Information, Table S3. All assigned CHO, CHOCl, and CHOBr formulas are available in a spreadsheet file in the Supporting Information for download.

Comparison of Patterns of Br-DBPs and Cl-DBPs. All 478 Br-DBPs identified in this study were compared to the chlorinated components identified in the chlorination control sample, which were generated by repeating the same chlorination procedure with an artificial water sample without NaBr. In total, 684 formulas of one-chlorine-containing components, 495 formulas of two-chlorine-containing components, and 191 formulas of three-chlorine-containing components were identified in the chlorination control samples. Detailed molecular formulas for these chlorine-containing components are listed in the Supporting Information, Table S4. Among the 441 one-bromine-containing DBPs, 392 of them have corresponding one-chlorine-containing analogues (which have identical CHO composition). Among the 37 two-bromine-containing DBPs, 28 have corresponding two-chlorine-containing analogues. Figure 3 shows the comparison of the distribution patterns for the Br-DBPs and chlorine-containing components.

It should be noted that in this study, 74 formulas of one-chlorine-containing components (Supporting Information, Table S5) were also identified in the control sample (artificial water samples without chlorination). Among the 74 formulas of chlorine-containing organic components, 63 overlapped with the “already present” chlorine-containing formulas listed in the drinking water DBPs study by Lavonen et al.²⁰ Lavonen and colleagues developed a classification method for differentiating formulas of chlorine-containing DBPs from “already present” chlorine-containing formulas (which are present before disinfection).²⁰ They suggested that the “already present” chlorine-containing formulas should not be considered as DBPs. However, in this study we observed that, compared to the SRFA control sample, the peak intensities of the already present chlorine-containing components increased 4 to 18 times after chlorination (Supporting Information, Figure S1, S2). Furthermore, all of the 74 already present chlorine-containing formulas have corresponding bromine-containing analogues. Since no bromine-containing formulas were identified in the control sample, it is reasonable to deduce that the already present chlorine-containing formulas could also

Figure 3. van Krevelen diagram of chlorinated components and brominated components identified in chlorination SRFA samples without and with NaBr, respectively: (a) one-chlorine-containing, (b) two-chlorine-containing, and (c) three-chlorine-containing components in chlorination SRFA samples without NaBr; (d) one-bromine-containing, and (e) two-bromine-containing components in chlorination SRFA samples with NaBr. Color bar represents the relative abundance of a formula.

be formed during chlorination as DBPs. All of this shows that further study to clarify the relationship of “already present” chlorine-containing components and DBPs is still needed.

MS–MS Analysis. On-resonance CID MS–MS experiment was performed to facilitate proposal of possible structures for unknown Br-DBPs. Single parent ions of Br-DBPs were selected and isolated for fragmentation analysis. The parent masses were isolated maintaining >70% of the precursor ion intensity. Figure 4 panels a and b show the MS–MS spectra of the parent mass at m/z 276.899 and 360.835, which correspond to molecular ions of the one-bromine-containing molecule ($C_7H_3BrO_7$) and two-bromine-containing molecule ($C_{10}H_4Br_2O_5$), respectively. Series of neutral loss of CO_2 were observed in both spectra (Figure 4a,b). The observation of decarboxylation is in agreement with previous fragmentation studies of fulvic acid.^{14,22,37} However, losses of H_2O , CO , or CH_4 , which have been previously reported in MS–MS analysis of fulvic acid,^{14,22} were not observed. This difference may be attributed to the differences in the structures of the precursor ions. For example, These et al.³⁸ observed different types of fragment ions for three isobaric ions of fulvic acid at nominal mass 297 in an MS–MS study. They observed loss of CO_2 alone for precursor ion $C_{13}H_{13}O_8^-$, losses of CO_2 and CO_2 plus H_2O for precursor ion $C_{14}H_{17}O_7^-$, and losses of CO_2 , H_2O , and

CO_2 plus H_2O for precursor ion $C_{15}H_{21}O_6^-$, respectively. Previous investigations have shown that the fulvic acid molecules detected by ESI-MS are dominated by carboxylate moieties with a limited number of hydroxy groups.^{22,33,37,38} In addition, it was previously suggested that in the course of oxidative alteration of very diverse source materials of fulvic acid, all functional groups that can be hydrolyzed will be hydrolyzed, erasing functional groups such as ethers, esters, and lactones.³³ With this knowledge, the observation of decarboxylation suggested that most likely carboxyl groups are present in the molecular structure of these Br-DBP molecules.

On the basis of the fragmentation patterns, possible structures can be assigned. Possible molecular structures that are in agreement with the observed fragments are shown in Figure 4 panels a and b, respectively. It should be noted that the fragmentation of the proposed structures shown in Figure 4a,b is only an example. Since one molecular formula can represent a multitude of different structural isomers, the fragmentation pattern can also be a result of a mixture of several isomers. Nevertheless, the combination of the exact mass and fragmentation patterns could provide valuable information regarding the possible molecular moieties of Br-DBPs.

Comparison with Br-DBPs Detected Previously. Richardson compiled a review on drinking water DBPs in

Figure 4. In-cell CID fragmentation spectra of the parent ion at m/z (a) 276.899 ($C_7H_2BrO_7^-$) and (b) 360.835 ($C_{10}H_3Br_2O_5^-$) with annotation of fragment losses and proposed structures.

which she listed approximately 600 chlorination DBPs, among which 110 compounds contain at least one bromine atom, and almost all of them were identified by gas chromatography/mass spectrometry (GC–MS) or derivatization-GC/MS.^{6,8–10} There was no match between Br-DBPs observed in this study and those listed by Richardson. The Br-DBPs detected in this study fall in a molecular mass range from 200 to 500 Da, and may be rich in carboxyl groups, which make these polar Br-DBPs suitable for analysis with negative ion ESI-MS. Recently, Zhang et al.¹¹ successfully developed the PIS method using ESI-tqMS for fast selective detection of polar Br-DBPs and studied the formation of new and unknown Br-DBPs during chlorination.²³ They detected 38 ion clusters of possible Br-DBPs, five of which were confirmed or proposed as brominated acetic acids, 11 could be confirmed or proposed to be identified chemical structures, and 22 were bromine-containing compounds with unknown molecular formula. Because their samples were prepared using a liquid–liquid extraction method and the formulas of most of Br-DBPs in their study are not available, a comprehensive comparison was difficult. When comparing only the formulas they confirmed or proposed, five of the 11 formulas with proposed chemical structures could be found in

the list of this study. Brominated acetic acids were not found in this study. This could possibly be caused by the limitations of the SPE method adopted in this study, because the highly polar brominated acids were not recovered by the nonpolar C18 stationary phase.

In total, 473 Br-DBPs with identified molecular formulas were for the first time reported in this study. Our results demonstrated that ESI FT-ICR MS is a powerful tool for the detection of the Br-DBPs, and the combination of the exact mass and MS–MS fragmentation could provide valuable molecular composition and structure information on Br-DBPs. Further work with offline or online chromatographic pre-separation, which could help to separate molecules with identical mass formulas and different molecular structures, will be needed to supply additional structure information and improve our knowledge on the unknown Br-DBPs.

■ ASSOCIATED CONTENT

Supporting Information

Additional figures and tables as well as formulas for Br-DBPs and chlorinated components noted in the text. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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