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Real-Time Detection and Identification of Aqueous Chlorine Transformation Products Using QTOF MS

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A screening technique has been developed that allows the rapid, real-time detection and identification of major transformation products of organic contaminants during aqueous oxidation experiments. In this technique, a target contaminant is dissolved in buffered water and chlorinated by the addition of sodium hypochlorite to give a free chlorine residual of 3 mg/L. Solution from the reaction vessel is combined with methanol and pumped directly into the electrospray ionization source of a quadrupole time-of-flight mass spectrometer (QTOF MS). The real-time decay of the target contaminant and the formation/decay of transformation products are then monitored using the QTOF MS. Subsequently, accurate mass measurements with internal mass calibration (<5 ppm mass error) and product ion scans are employed to identify these transformation products. Unlike other techniques, it requires no liquid chromatography, derivatization, or quenching of residual chlorine, all of which can interfere with transformation product analysis. To validate the technique, aqueous chlorination experiments were performed on triclosan, a previously studied environmental contaminant. Earlier research showing that triclosan underwent chlorine addition to form mono- and dichlorinated transformation products was successfully reproduced, demonstrating the feasibility of the technique. In addition, the technique revealed the formation of a stable oxygen radical-containing transformation product resulting from the oxidation of either mono- or dichlorinated triclosan. This triclosan transformation product was determined to have an empirical formula of $C_{12}H_4O_3Cl_4$ with 3.9 ppm mass error. Furthermore, atorvastatin, a commonly prescribed medication and environmental contaminant, was subjected to aqueous chlorination and studied with the technique. Atorvastatin underwent hydroxylation to form two transformation products with the empirical formulas $C_{33}H_{34}FN_2O_6$ (1.8 ppm mass error) and $C_{26}H_{29}O_5NF$ (2.9 ppm mass error).

Organic contaminants such as pharmaceuticals, personal care products, and endocrine-disrupting compounds have been the subject of study due to their presence in surface and ground waters.[1–6] Because many surface waters that contain these contaminants are used as raw water sources for drinking water supplies, their removal by drinking water treatment processes has been investigated.[7–10] Chemical disinfectants, such as chlorine and ozone, can effectively remove many organic contaminants;[10–12] however, removal entails chemical alteration of the contaminant, producing transformation products. As some research has shown the potential toxicity of these transformation products,[13–19] their identification and study has been a topic of recent work.

To study the transformation of an organic contaminant during oxidative treatment, a compound is typically dissolved in a solution of buffered water to which a disinfectant is added. At various time intervals, a sample aliquot is taken from the reaction vessel and quenched with a reducing agent to remove residual oxidant and prevent further oxidation of the sample until analysis can begin. The most common quenching agent currently in use for transformation product studies is sodium thiosulfate;[13,14,16,20–27] how-

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(1) Vanderford, B. J.; Pearson, R. A.; Rexing, D. J.; Snyder, S. A. *Anal. Chem.* **2003**, *75*, 6265–6274.
(2) Vanderford, B. J.; Snyder, S. A. *Environ. Sci. Technol.* **2006**, *40*, 7312–7320.
(3) Snyder, S. A.; Kelly, K. L.; Grange, A. H.; Sovocool, G. W.; Snyder, E. M.; Giesy, J. P. In *Pharmaceuticals and Personal Care Products in the Environment: Scientific and Regulatory Issues*; Daughton, C. G., Jones-Lepp, T. L., Eds.; ACS Symposium Series 791; American Chemical Society: Washington, DC, 2001; pp 116−140.
(4) Snyder, S. A.; Villeneuve, D. L.; Snyder, E. M.; Giesy, J. P. *Environ. Sci. Technol.* **2001**, *35*, 3620–3625.
(5) Richardson, S. D. *Anal. Chem.* **2007**, *79*, 4295–4323.
(6) Richardson, S. D.; Ternes, T. A. *Anal. Chem.* **2005**, *77*, 3807–3838.
(7) Petrovic, M.; Gonzalez, S.; Barcelo, D. *TrAC, Trends Anal. Chem.* **2003**, *22*, 685–696.
(8) Westerhoff, P.; Yoon, Y.; Snyder, S.; Wert, E. *Environ. Sci. Technol.* **2005**, *39*, 6649–6663.
(9) Heberer, T.; Reddersen, K.; Mechlinski, A. *Water Sci. Technol.* **2002**, *46*, 81–88.
(10) Snyder, S. A.; Wert, E. C.; Lei, H.; Westerhoff, P.; Yoon, Y. *Removal of EDCs and Pharmaceuticals in Drinking Water and Reuse Treatment Processes*; American Water Works Association: Denver, Colorado, 2007.
(11) Huber, M. M.; Canonica, S.; Park, G.-Y.; von Gunten, U. *Environ. Sci. Technol.* **2003**, *37*, 1016–1024.
(12) Snyder, S. A.; Wert, E. C.; Rexing, D. J.; Zegers, R. E.; Drury, D. D. *Ozone: Sci. Eng.* **2006**, *28*, 445–460.
(13) Shah, A. D.; Kim, J.-H.; Huang, C.-H. *Environ. Sci. Technol.* **2006**, *40*, 7228–7235.
(14) Canosa, P.; Morales, S.; Rodriguez, I.; Rubi, E.; Cela, R.; Gomez, M. *Anal. Bioanal. Chem.* **2005**, *383*, 1119–1126.
(15) Rule, K. L.; Ebbett, V. R.; Vikesland, P. J. *Environ. Sci. Technol.* **2005**, *39*, 3176–3185.
(16) Hu, J.-Y.; Cheng, S.; Aizawa, T.; Terao, Y.; Kunikane, S. *Environ. Sci. Technol.* **2003**, *37*, 5665–5670.
(17) Bedner, M.; MacCrehan, W. A. *Chemosphere* **2006**, *65*, 2130–2137.
(18) Oliveira, D. P.; Carneiro, P. A.; Rech, C. M.; Zanoni, M. V. B.; Claxton, L. D.; Umbuzeiro, G. A. *Environ. Sci. Technol.* **2006**, *40*, 6682–6689.
(19) Buth, J. M.; Arnold, W. A.; McNeill, K. *Environ. Sci. Technol.* **2007**, *41*, 6228–6233.
(20) Mascolo, G.; Lopez, A.; James, H.; Fielding, M. *Water Res.* **2001**, *35*, 1705–1713.
(21) Hu, J.-Y.; Aizawa, T.; Ookubo, S. *Environ. Sci. Technol.* **2002**, *36*, 1980–1987.

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ever, sodium sulfite,[15,17,28] ascorbic acid,[14,28] ammonium chloride,[19,23,24] and others have been utilized. Although these chemicals effectively quench residual oxidants, some have been shown to negatively affect transformation product determinations. Dodd and Huang[23] reported that transformation products of sulfamethoxazole could be reduced back to the parent compound by sodium thiosulfate. Canosa et al.[14] demonstrated that both sodium thiosulfate and ascorbic acid interfered with the determination of labile transformation intermediates of triclosan. Ascorbic acid was also shown by Duirk and Collette[28] to be problematic during the study of chlorpyrifos in the presence of aqueous chlorine. However, these reactions may be compound-specific. Shah et al.[13] found that measurements to determine carbadox reaction kinetics with free chlorine were unaffected by quenching with sodium thiosulfate. Similarly, Bedner and MacCrehan[17] concluded that acetaminophen transformation products 1,4-benzoquinone and *N*-acetyl-*p*-benzoquinone imine are reduced back to acetaminophen by sodium sulfite, whereas chloro- and dichloro-4-acetamidophenol are not.

After the sample has been quenched, it is usually analyzed for parent compound degradation and transformation product identification/formation by either liquid chromatography (LC) coupled with UV and/or mass spectrometric (MS) detection[13,16,17,20–27,29] or gas chromatography (GC) with or without derivatization coupled with MS.[14,15,28] When using LC, a common method employed to avoid the problem of quenching is to leave the residual oxidant unquenched and immediately inject an aliquot of the reaction mixture into an LC system.[22–25] However, because mobile phase modifiers frequently used in LC analysis contain ammonia (e.g., ammonium acetate, ammonium formate), unquenched free chlorine can react to form chloramines.[17] Furthermore, pH buffers (such as acetate) used in batch experiments have been shown to form transformation products in the presence of free chlorine,[13] thereby making the determination of the source of detected products less obvious. This phenomenon could also be extended to mobile phase modifiers because many contain the acetate anion. Therefore, the uncertainty with regard to the effect of chemical quenching agents, mobile phase modifiers, and pH buffers on transformation product analyses makes their selection difficult.

In addition to limitations associated with quenching and LC, identification of transformation products with traditional analysis techniques can be challenging. UV−vis detection lacks the mass-related information afforded by an MS detector and is restricted to compounds that absorb light between 200 and 800 nm, making difficult the identification of transformation products that no longer absorb light in this region (i.e., through loss of conjugation). GC/MS is primarily used for nonpolar and nonthermally labile compounds. Derivatization to make GC/MS more amenable to polar or thermally labile compounds is time-consuming, labor-intensive, and has the potential to degrade chemically unstable transformation products. LC−MS has been found to be useful for product identification through product ion analysis; however, confirmation standards[14,15,17] and separate identification techniques such as NMR[21,23,26,30] are often necessary to verify transformation product identities. Liquid chromatography coupled with quadrupole time-of-flight mass spectrometry (LC−QTOF MS) has been used recently to successfully study environmental unknowns[31,32] and transformation products of triazine herbicides in water.[33] The main advantages of this technique are higher mass resolution (>5000) and accurate mass measurements (<5 ppm mass error) to determine empirical formulas; however, it has not been attempted for the study of pharmaceutical transformation products and may be susceptible to the problems associated with LC modifiers.

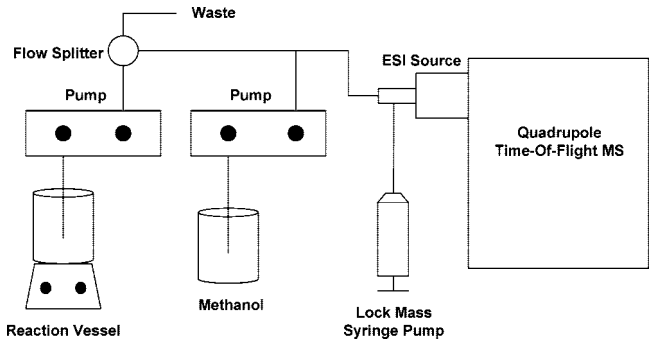

Figure 1. Schematic of experimental setup.

The goal of this study was to produce a screening technique capable of rapidly identifying major organic contaminant transformation products for further study without being susceptible to the aforementioned limitations. This was made possible by directly coupling the reaction vessel to the electrospray (ESI) ionization source of a QTOF MS with the addition of methanol as an ionization promoter. This technique eliminates the use of LC with its associated buffers/reagents and the need for quenching the residual oxidant in the reaction vessel, both of which can lead to undesirable effects on the chlorination experiments and their interpretation. Additionally, it provides a real-time technique that is much faster at identifying major transformation products and less labor-intensive than traditional analysis techniques. Furthermore, it is capable of determining empirical formulas of major transformation products using accurate mass measurements and providing structural information through product ion analysis.

To validate the technique, aqueous chlorination experiments were performed on triclosan, a commonly used antibacterial agent found in hand soaps and toothpaste that has been previously examined using traditional methods. Accurate mass measurements using internal mass calibration and product ion analysis were employed to detect previously reported major transformation products of triclosan. In addition, atorvastatin, a commonly

(22) Pinkston, K. E.; Sedlak, D. L. *Environ. Sci. Technol.* **2004**, *38*, 4019–4025.
(23) Dodd, M. C.; Huang, C.-H. *Environ. Sci. Technol.* **2004**, *38*, 5607–5615.
(24) Dodd, M. C.; Huang, C.-H. *Water Res.* **2007**, *41*, 647–655.
(25) Dodd, M. C.; Shah, A. D.; Von Gunten, U.; Huang, C.-H. *Environ. Sci. Technol.* **2005**, *39*, 7065–7076.
(26) McDowell, D. C.; Huber, M. M.; Wagner, M.; Von Gunten, U.; Ternes, T. A. *Environ. Sci. Technol.* **2005**, *39*, 8014–8022.
(27) Sandin-Espana, P.; Magrans, J. O.; Garcia-Baudin, J. M. *Chromatographia* **2005**, *62*, 133–137.
(28) Duirk, S. E.; Collette, T. W. *Environ. Sci. Technol.* **2006**, *40*, 546–551.
(29) Mascolo, G.; Lopez, A.; James, H.; Fielding, M. *Water Res.* **2001**, *35*, 1695–1704.
(30) Mehrsheikh, A.; Bleeke, M.; Brosillon, S.; Laplanche, A.; Roche, P. *Water Res.* **2006**, *40*, 3003–3014.
(31) Ibanez, M.; Sancho, J. V.; Pozo, O. J.; Niessen, W. M. A.; Hernandez, F. *Rapid Commun. Mass Spectrom.* **2005**, *19*, 169–178.
(32) Bueno, M. J. M.; Aguera, A.; Gomez, M. J.; Hernando, M. D.; Garcia-Reyes, J. F.; Fernandez Alba, A. *Anal. Chem.* **2007**, *79*, 9372–9384.
(33) Ibanez, M.; Sancho, J. V.; Pozo, O. J.; Hernandez, F. *Anal. Chem.* **2004**, *76*, 1328–1335.

Table 1. Instrument Parameter Settings

parameter	all experiments	parameter	product ions of m/z 336	product ions of m/z 573
source temperature (°C)	500	collision energy (V)	−22	−25
pulse duration (μs)	10	collision gas	5	5
gas 1 − nebulizer gas	40			
gas 2 − turbo gas	90			
curtain gas	15			
ion spray voltage (V)	−2000			
declustering potential (V)	−30			
declustering potential 2 (V)	−5			
focusing potential (V)	−265			

prescribed pharmaceutical for the reduction of cholesterol that has not yet been studied, was subjected to aqueous chlorination and investigated using the technique.

EXPERIMENTAL SECTION

Materials. Triclosan was obtained from Sigma-Aldrich (St. Louis, MO), and atorvastatin was from Toronto Research Chemicals (Toronto, Canada). Potassium bromate was purchased from Grace Davison Discovery Sciences (Deerfield, IL), and perfluorooctanesulfonic acid (PFOS) was from Wellington Laboratories (Guelph, Ontario, Canada). Sodium bicarbonate and trace analysis grade methanol were obtained from Burdick and Jackson (Muskegon, MI). Stocks of chlorine were prepared from a commercial solution of sodium hypochlorite (purified grade 4−6% NaOCl) from Fisher Scientific (Pittsburgh, PA). Three N hydrochloric acid was obtained from Red Bird Service (Osgood, IN). Reagent water was generated from deionized water that had been passed through a Millipore (Billerica, MA) Milli-Q water purification system.

Experimental Setup. A schematic showing the experiment setup is shown in Figure 1. Fluid from the reaction vessel was pumped to a flow splitter at 4 mL/min using an Agilent (Palo Alto, CA) 1311A pump that had been modified to bypass the solvent switching valve and pulse dampener. This minimized the amount of time necessary for the solution to travel from the reaction vessel to the mass spectrometer. Removing the sample tubing from the beaker to introduce air into the system demonstrated that the travel time from the beaker to the QTOF MS was ~8 s. The flow was split five ways using a flow splitter to achieve a flow rate of approximately 900 μL/min after the flow splitter. This was accomplished by varying the lengths of tubing exiting the flow splitter that were plumbed to waste. The split flow was then teed into a flow of 1.5 mL/min of methanol from an Agilent 1312A pump. The methanol was used to promote ionization of the target compounds and their transformation products. This combined flow was directed into the ESI source of the QTOF MS.

Chlorination experiments were performed in a 600 mL glass beaker containing 500 mL of a 1 mM sodium bicarbonate solution in reagent water, adjusted to pH 7.0 with 3 N hydrochloric acid. The pH of the reaction mixture was measured using a pH meter at the start and end of each experiment to verify that the pH was constant. Appropriate volumes of triclosan or atorvastatin stock solutions in methanol were added to the reaction vessel to give a final concentration of ~200 μg/L, and the solution was allowed to mix using a stir bar and stir plate. Blank methanol experiments were conducted to verify that the amount of methanol added did not exhibit a chlorine demand (data not shown). Both pumps were started and the intensity of the target compound on the QTOF MS was allowed to stabilize. Once a stable signal was observed, data collection on the QTOF MS began. Two minutes later, an aliquot of a 1/10 dilution of the 6% sodium hypochlorite solution was added to give a final free chlorine concentration of 3 mg/L as Cl_2. Free chlorine concentrations were measured using DPD colorimetry,[34] and free chlorine residuals were found to be constant throughout the experiments. The reactions were allowed to progress for 1 h, during which data was collected using the QTOF MS.

QTOF MS Methodology. The QTOF MS employed in this study was an Applied Biosystems QStar Elite (Foster City, CA). This instrument is capable of operating in TOF MS mode and in QTOF (MS/MS) mode, in which a precursor ion selected by the quadrupole is fragmented and the product ions analyzed using the TOF mass analyzer. The instrument was calibrated daily using a solution of potassium bromate and PFOS in negative electrospray ionization mode. Although this initial calibration provided mass accuracy within ±10 ppm mass error over a typical workday, these experiments were conducted using internal mass calibration. This procedure produced a calibration for each spectrum collected using internal calibrant ions and helped correct for calibration changes caused by environmental factors such as fluctuations in room temperature. In these experiments, the internal calibrants were the negative ions generated from the ionization of potassium bromate and PFOS. A methanol solution of these calibrants was

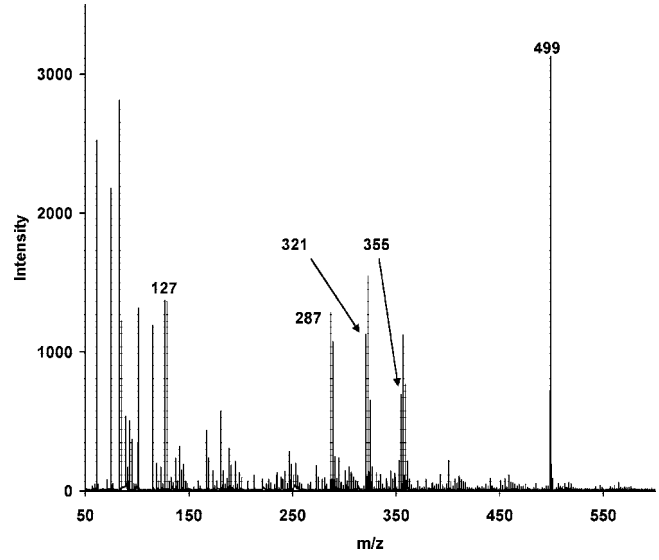

Figure 2. Mass spectrum at 1 min postchlorination showing lock masses bromate (m/z 127) and PFOS (m/z 499), triclosan (m/z 287), and formation of mono- (m/z 321) and dichlorinated (m/z 355) triclosan transformation products. (Nominal masses are shown for clarity.)

Table 2. Parent and Transformation Product Accurate Mass Measurements

compound	accurate mass measurement (m/z)	proposed empirical formula	theoretical mass (m/z)	mass error (ppm)
	Knowns			
triclosan	286.9430	$C_{12}H_6O_2Cl_3$	286.9438	2.9
monochlorinated triclosan	320.9037	$C_{12}H_5O_2Cl_4$	320.9049	3.7
dichlorinated triclosan	354.8672	$C_{12}H_4O_2Cl_5$	354.8659	3.7
atorvastatin	557.2479	$C_{33}H_{34}O_5N_2F$	557.2457	3.9
	Unknowns			
monochlorinated triclosan radical	335.8907	$C_{12}H_4O_3Cl_4$	335.8920	3.9
monochlorinated triclosan radical product ion	190.9313	$C_6HO_3Cl_2$	190.9308	2.6
hydroxylated atorvastatin	573.2396	$C_{33}H_{34}O_6N_2F$	573.2406	1.7
hydroxylated atorvastatin with loss of phenylaminocarbonyl group and hydroxylated atorvastatin product ion A	454.2022	$C_{26}H_{29}O_5NF$	454.2035	2.9
hydroxylated atorvastatin product ion B	294.1286	$C_{19}H_{17}ONF$	294.1299	4.4

added with a syringe pump through a tee ahead of the ESI source (Figure 1). The flow rate was adjusted between 5 and 25 μL/min to maintain the intensity of the calibrants and ensure the accuracy of the mass measurements.

The instrument software allowed the control of a variety of instrument parameters that affected the intensity of the observed ions. These included parameters such as the voltage applied to the electrospray needle, the pressure of nebulizing gas, and the collision energy applied during MS/MS experiments. The optimal instrumental settings at the flow rates used in these experiments were determined prior to data collection and are listed in Table 1. In addition, the rate of data collection used in these experiments was set to 1 spectrum/s.

RESULTS AND DISCUSSION

Experimental Conditions. During initial method development, it was found that direct infusion of the reaction solution into the QTOF MS did not produce enough sensitivity to reliably make accurate mass measurements of the target compounds and their transformation products. Methanol and acetonitrile were tested as ionization promoters by combining their flow with the flow from the reaction vessel using a tee. After several attempts, it was determined that syringe pumps were incapable of providing sufficient backpressure to prevent the solution from the reaction vessel from being pumped into the body of the syringe being used for solvent infusion. Therefore, a piston-driven pump was used instead. After determining a suitable method of solvent introduction, it was determined that methanol produced greater signal intensity than acetonitrile for both target compounds and therefore was chosen for all experiments, even though acetonitrile produced fewer extraneous background peaks.

To successfully make accurate mass measurements for empirical formula calculations, a continuously infused internal mass calibrant (lock mass) was found to be necessary. This allowed the mass calibration of each mass spectrum to be corrected for any variation in calibration during an experiment. Due to the presence of an oxidizing agent in the flow from the reaction vessel, care had to be taken to find a lock mass that would not be oxidized under those conditions. Initial attempts to use iodide as a lock mass failed because it was found that iodide was oxidized by the residual chlorine and consequently was unreliable. Therefore, bromate and PFOS were chosen because they were unlikely to be further oxidized under the conditions of the chlorination experiment and their mass-to-charge ratios bracketed the desired calibration range.

Triclosan Experiments. Triclosan has been previously studied under various reaction conditions.[14,15,35] These studies agreed that triclosan reacted with free chlorine or chloramines to initially form two monochlorinated triclosan derivatives (5,6-dichloro-2-(2,4-dichlorophenoxy)phenol and 4,5-dichloro-2-(2,4-dichlorophenoxy)phenol). Subsequently, a dichlorinated derivative (4,5,6-trichloro-2-(2,4-dichlorophenoxy)phenol) was formed via further oxidation of the monochlorinated triclosan. To determine whether the technique would provide results comparable to those found by previous researchers, triclosan was selected for study.

As discussed in the Experimental Section, triclosan was spiked into the buffered reagent water and allowed to equilibrate with stirring. During this time, the QTOF MS was operated in negative ESI mode and monitored for triclosan. A large peak for the deprotonated form ($[M - H]^-$) of triclosan was observed at m/z 286.9430 (Figure 2 and Table 2). Considering the theoretical m/z of deprotonated triclosan is 286.9438, the mass error was calculated to be 2.9 ppm. After the signal for triclosan had stabilized, hypochlorite was added and the QTOF MS was monitored for triclosan transformation products. Over the next 10 min, two dominant ion clusters were observed to increase and then decrease in intensity. Figure 2 shows a mass spectrum corresponding to 1 min postchlorine addition. Accurate mass measurements were performed to obtain mass-to-charge ratios of 320.9037 and 354.8672 for the monoisotopic mass ions of each ion cluster. Empirical formula calculations on these m/z values yielded formulas of $C_{12}H_5O_2Cl_4$ and $C_{12}H_4O_2Cl_5$, respectively, both with mass errors of 3.7 ppm (Table 2). These empirical formulas equate to replacements of hydrogen(s) with chlorine(s) and are the monochlorinated and dichlorinated triclosan species found by other researchers.

In contrast to previous research, the degradation products of the major monochlorinated and dichlorinated triclosan transformation products were not detected by this technique with sufficient intensity to perform empirical formula calculations. In general, as contaminants degrade, they tend to lose mass and become more volatile, making them less suitable for LC−MS analysis. As a result, they may become less amenable to detection by this technique, and in the case of triclosan, degradation products such

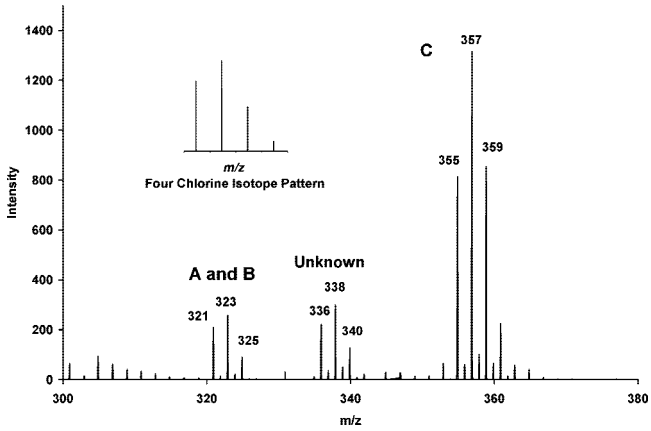

Figure 3. Mass spectrum of 2 min prechlorination subtracted from 10 min postchlorination showing an unknown transformation product at *m/z* 336. The four-chlorine isotope pattern is shown for comparison. (Nominal masses shown for clarity: (A) 5,6-dichloro-2-(2,4-dichlorophenoxy)phenol; (B) 4,5-dichloro-2-(2,4-dichlorophenoxy)phenol; (C) 4,5,6-trichloro-2-(2,4-dichlorophenoxy)phenol.)

as 2,4-dichlorophenol and chloroform that were detected in previous studies are less likely to be identified.

To elucidate possible products of triclosan that had not been previously published, the mass spectral data were further analyzed. Mass spectra from the first 2 min of data collection (prior to chlorination) were subtracted from the mass spectra collected during the first 10 min after chlorination. This revealed the mono- and dichlorinated transformation products mentioned previously but also showed the presence of an unknown product at *m/z* 335.8907 (Figure 3). When the relative isotope ratios of a hypothetical compound with four chlorines (inset in Figure 3) are compared with those of the products, it was evident that the unknown compound contained four chlorine atoms. In addition, it was noted that the nominal mass of the compound was even. According to the nitrogen rule, an even-numbered mass must either have (1) an odd number of nitrogens and an even number of electrons or (2) an even number of nitrogens and an odd number of electrons. Because triclosan has no nitrogens and ESI produces even-electron ions, it was concluded that the unknown transformation product must have either gained a nitrogen atom or contained an odd number of electrons (i.e., be a radical). With the use of an empirical formula calculator, it was determined that the unknown product was an odd-electron ion having a molecular formula of $C_{12}H_4O_3Cl_4$ with a mass error of 3.9 ppm (Table 2). This mass accuracy is in agreement with the previously discussed measurements of triclosan and the mono- and dichlorinated triclosan products. Furthermore, the substitution of nitrogen into the formula yielded mass errors of >25 ppm (data not shown), which is consistent with there being no obvious source of reactive nitrogen in the system. The formula of $C_{12}H_4O_3Cl_4$ is therefore consistent with the replacement of two hydrogen atoms by a chlorine atom and an oxygen radical (Figure 4).

To further study this radical, product ion experiments were initiated. The radical was fragmented in the collision cell, and a major product ion was found at *m/z* 190.9313. Because the nominal mass was now odd, this indicated that the product ion most likely had both an even number of nitrogens and electrons. The molecular formula was determined to be $C_6HO_3Cl_2$ with a mass error of 2.6 ppm, confirming an even number of nitrogens (i.e.,

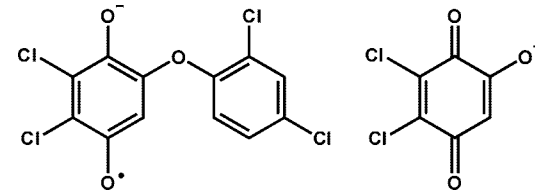

Figure 4. Proposed structures for triclosan radical (left) and triclosan radical product ion (right).

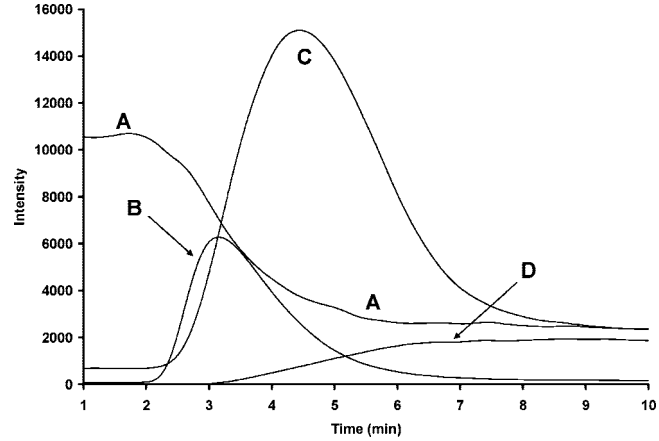

Figure 5. Plot of decay of triclosan (A) and formation/decay of 5,6-dichloro-2-(2,4-dichlorophenoxy)phenol and 4,5-dichloro-2-(2,4-dichlorophenoxy)phenol (B), 4,5,6-trichloro-2-(2,4-dichlorophenoxy)phenol (C), and triclosan radical (D).

zero) and indicating the molecule had fragmented and rearranged to yield an even-electron ion (Figure 4). The molecular formula suggests that the oxygen radical was added to the hydroxylated side of triclosan because it contains three oxygen atoms, with the most likely position being para to the hydroxyl group.

With the use of this technique, the intensity of an organic contaminant and its identified transformation products can also be plotted over the course of an experiment, as shown in Figure 5. These data can be used to determine the sequence of oxidation events with a high degree of resolution. In contrast to techniques in which a small number of discrete samples are periodically taken over the course of an experiment and analyzed, this technique allows the acquisition of 3600 data points/h. This greater data resolution can lead to a better understanding of the sequence of events during the reaction.

In the case of triclosan, it can be seen in Figure 5 that the formation of monochlorinated triclosan begins first and dichlorinated triclosan formation begins shortly thereafter, confirming the reaction sequence proposed by Rule et al.[15] The monochlorinated triclosan radical, however, begins to form approximately 1 min after the mono- and dichlorinated triclosan species, coinciding with the maxima of the monochlorinated triclosan peak. Figure 5 also shows that the mono- and dichlorinated triclosan species quickly rise in intensity, reach a maximum, and rapidly degrade. Conversely, the intensity of the monochlorinated triclosan radical slowly rises during the first several minutes of the reaction and then stabilizes over the first 15 min of the experiment (Supporting Information Figure S1).

Atorvastatin Experiments. Although atorvastatin has been detected in surface water,[2] its potential to form transformation products has not been previously examined. After spiking atorv-

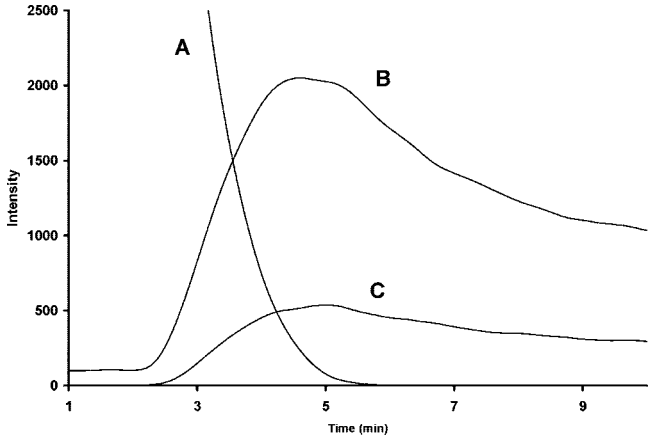

Figure 6. Plot of decay of atorvastatin (A) and formation/decay of its two transformation products at *m/z* 573 (B) and 454 (C) during the first 10 min of reaction. Due to its large initial intensity, atorvastatin is only partially displayed.

astatin into the reaction vessel, the QTOF MS was monitored for its presence. It was found to deprotonate in negative mode yielding an $[M - H]^-$ ion at m/z 557.2479 with a mass error of 3.9 ppm (Table 2).

After the addition of hypochlorite, the intensity of atorvastatin rapidly decreased while the intensity of two other ions at m/z 573.2396 and 454.2022 initially increased and then slowly decreased over the course of the experiment (Figure 6). Elemental formula calculations on the more intense of the two ions at m/z 573.2396 generated an empirical formula of $C_{33}H_{34}O_6N_2F$ with a mass error of 1.7 ppm (Table 2). This formula differs from that of atorvastatin by the net gain of one oxygen atom, probably via the replacement of a hydrogen atom with a hydroxyl group. The empirical formula of the second major ion at m/z 454.2022 was determined to be $C_{26}H_{29}O_5NF$ with a mass error of 2.9 ppm. This formula suggests the hydroxylation of atorvastatin via the substitution of C_7H_5ON, which, due to the molecular structure of atorvastatin, can only result from a loss of the phenylaminocarbonyl group. From an enlarged version of Figure 6 (Supporting Information Figure S2), it can be seen that the two products form simultaneously, although the rate of increase is different.

A product ion scan was performed on the m/z 573 transformation product to attempt to determine the most likely location of the hydroxyl addition. The fragmentation yielded product ions at m/z 454.2022 and 294.1286 (Figure 7 and Table 2). The product ion at m/z 454.2022 was identical to that of the main transformation product at m/z 454, suggesting the phenylaminocarbonyl bond is relatively weak. In addition, two previous fragmentation studies using LC−MS/MS showed that atorvastatin in positive ionization mode produced a fragment at m/z 440,[2,36] corresponding to m/z 438 in negative mode and m/z 454 after oxidation. These studies concluded that m/z 440 was due to the loss of the phenylaminocarbonyl group, adding further evidence of the tendency of the molecule to lose that group.

The product ion at m/z 294.1286 resulted in a molecular formula of $C_{19}H_{17}ONF$ with a mass error of 4.4 ppm. As this indicates a loss of $C_7H_{12}O_4$ from the product ion at m/z 454.2022, the only possible neutral loss is that of the heptanoic acid moiety. These product ion experiments suggest that the hydroxyl group is added either to the pyrrole group, resulting in the substitution of the phenylaminocarbonyl moiety, or the phenyl or fluorophenyl rings that are bonded to the pyrrole group; however, the exact site of hydroxyl addition was not determined.

Limitations. As discussed above, transformation products tend to become less massive and more volatile over time as they degrade during oxidation. This poses a challenge for analysis by a single technique as most are suitable for only a limited set of chemical properties. Hence, as contaminants degrade, they are less likely to be detected and identified by this technique as QTOF MS is typically more suitable for higher molecular weight, nonvolatile compounds. In addition, only compounds that are ionizable using ESI will be detected by the QTOF MS. Depending on the changes that occur to the functional groups of the target compound during oxidation, there is the possibility that its transformation products will no longer be ionizable by ESI. This is unlikely to prevent the identification of the initial transformation products; however, it may affect the ability of the QTOF MS to detect certain products further along in the pathway as compounds are progressively degraded. Although it was outside the scope of this paper, additional ionization techniques such as atmospheric pressure chemical ionization (APCI) and atmospheric pressure photoionization (APPI) have the potential to be used as alternatives to ESI. Another limitation of the technique is its inability to differentiate between isomers. As a screening technique, it will be able to quickly identify major transformation products; however, to determine the number of isomers, another technique such as fraction collection with chromatographic separation will be necessary.

CONCLUSIONS

The screening technique described above provides a rapid method for the real-time identification of major transformation products of organic contaminants during chlorination reactions. It requires no quenching of the reaction, liquid chromatography, or derivatization, all of which can interfere with transformation product analysis. The technique was able to detect and identify two major triclosan transformation products and was used to identify novel transformation products of triclosan and atorvastatin, including a radical that probably would not be detected by other techniques due to its reactivity. In addition, the technique yielded a high degree of resolution for the sequence of oxidation events due to the large number of data points collected. It is anticipated that the information from these data can prevent the incorrect assignment of formation maxima that may result from an inadequate number of data points and lessen the chance of not observing a short-lived transformation product.

It is also expected that the technique can be used to provide information on chemical kinetics and oxidative reaction mechanisms. To accomplish this, the intensity of the parent would need to be related to its concentration. This would allow the determination of the rate constant for the reaction of the parent

(34) Clesceri, L. S., Greenberg, A. E., Eaton, A. D., Eds. *Standard Methods for the Examination of Water and Wastewater*, 20th ed.; APHA, AWWA, WEF: Washington, DC, 1998.
(35) Greyshock, A. E.; Vikesland, P. J. *Environ. Sci. Technol.* **2006**, *40*, 2615–2622.
(36) Jemal, M.; Ouyang, Z.; Chen, B.-C.; Teitz, D. *Rapid Commun. Mass Spectrom.* **1999**, *13*, 1003–1015.

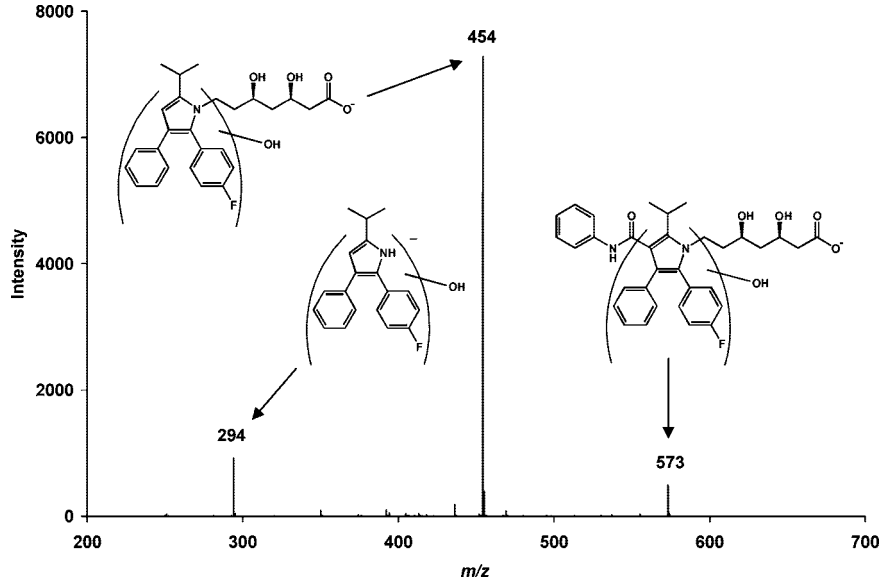

Figure 7. Product ion spectrum of hydroxylated atorvastatin showing product ions at *m*/*z* 454 and 294. Product ion structures shown for *m*/*z* 573, 454, and 294. (Nominal masses are shown for clarity.)

compound with the oxidant. Although it was outside the scope of this paper, initial attempts at using the technique for this purpose were promising; however, the degree of ionization suppression caused by the addition of hypochlorite will be an important consideration.

Additionally, it is likely that the technique can be used to detect and identify the major transformation products that result from the reaction of organic contaminants with other chemical oxidants such as ozone, chloramines, and chlorine dioxide, as well as ozone and UV-based advanced treatment processes. The only requirement of the technique is for the fluid in the reaction vessel to be directly transferable from the vessel to the mass spectrometer. Because most bench-scale work for these oxidants is performed in reaction vessels similar to those used in this experiment, adapting the technique to use a different oxidant should be relatively simple.

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SUPPORTING INFORMATION AVAILABLE

Additional information as noted in text. This material is available free of charge via the Internet at http://pubs.acs.org.

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