Journal of Hazardous Materials 177 (2010) 237–243

Contents lists available at ScienceDirect

Journal of Hazardous Materials

journal homepage: www.elsevier.com/locate/jhazmat

Oxidation products of sulfamethoxazole in ozonated secondary effluent

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ARTICLE INFO

Article history:
Received 29 October 2009
Received in revised form 2 December 2009
Accepted 4 December 2009
Available online 11 December 2009

Keywords:
Ozone
Sulfamethoxazole
Wastewater
Oxidation products

ABSTRACT

In this study the antibiotic sulfamethoxazole (SMX) was subjected to ozone treatment. Solutions of 60 mg/L and 100 μg/L SMX in pure water and secondary municipal effluent were treated. The removal profile of SMX and its oxidation products was monitored as a function of transferred ozone dose in both matrices. No difference was observed in the ozone dose required for the concentration of SMX to fall below the limit of detection in pure water and wastewater. New peaks with the same retention times were obtained on the HPLC chromatograms for all conditions studied. Solutions with an initial concentration of 60 mg/L required 83 mg/L of ozone to fall below the limit of detection and eight oxidation products were detected. Solutions with an initial concentration of 100 μg/L required 14 mg/L of ozone and only four oxidation products were detected. The four peaks obtained during experiments at low concentration were observed at the same retention times as four of the peaks obtained in higher concentration samples. In ozonated wastewater these products were identified as: 4-aminobenzene sulfonamide, N-(3-phenylpropyl)-acetamide, 2-methyl-benzoxazole and phenol. In addition, methanol, ethanol, acetic acid, methyl acetate and ethyl acetate were identified in the higher concentration samples.

1. Introduction

Water contamination by pharmaceuticals is a rising environmental concern. On the global scale, prescription and non-prescription drugs are produced and distributed in quantities that exceed thousands of metric tons annually [1]. Most of these drugs are excreted (up to 90% of administered drugs are excreted from the body without undergoing metabolism) or are disposed of in domestic wastewaters. These compounds make their way to wastewater treatment plants where they may be discharged into receiving waters. In fact, it has been found that there are significant amounts of pharmaceuticals present in the aquatic environment. Several studies have been carried out to help understand the extent of the occurrence of prescription and non-prescription drugs in wastewaters, surface and ground waters and as a result, over 100 pharmaceuticals are known to be present in waters at up to the microgram per liter level [2–9]. In addition, some research has shown that these compounds are often not eliminated during typical wastewater treatment processes and most of them are not biodegraded in the environment [10]. In such cases, the pharmaceutical compounds may stay in the aquatic environment as either the original compound or as transformation products of the parent compound.

Although at present, the effects of the presence of pharmaceuticals in wastewater on humans and aquatic life are essentially unknown, there is still cause for concern. In the case of antibiotics, these compounds may add to the antibiotic-resistance of certain pathogens that are present in the wastewater [11]. One of the treatment options being investigated is the ozonation of wastewater prior to its discharge to receiving waters.

The focus of this research is the antibiotic sulfamethoxazole (SMX, $C_{10}H_{11}N_3O_3S$), which is part of the sulfa drug class. The structure of SMX is shown in Fig. 1. It is typically prescribed in combination with trimethoprim and in 2007 it was the 6th most commonly prescribed antibiotic combination in Canada. Due to its high usage volume (amongst other contributing factors) it has often been identified in wastewater treatment effluent studies [12]. To improve the quality of wastewater effluents, ozonation and advanced oxidation processes are being considered. Ozonation is capable of oxidizing pharmaceuticals and other pollutants in the wastewater by either molecular ozone or by hydroxyl radicals (•OH). To date, most studies have used synthetic wastewater and pure water to assess the reaction of pharmaceuticals such as sulfamethoxazole with ozone [13–24]. Only a few studies have attempted to understand the reaction mechanism of this pharmaceutical with ozone [19,21]. In addition, the nature of the oxidation products that result from the ozona-

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doi:10.1016/j.jhazmat.2009.12.023

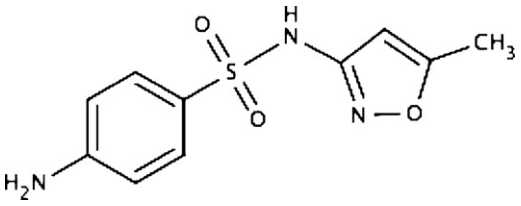

Fig. 1. Structure of sulfamethoxazole.

tion process remain mostly unknown. In our previous work, the presence of unidentified oxidation products of SMX at a high concentration of SMX in pure water was confirmed [20] and the relative toxicity of this mixture of oxidation products on mammalian cells was studied [25]. The objectives of this project were complementary to previous studies and included: the removal profile of 60 mg/L and 100 μg/L solutions of SMX, the evolution of the oxidation products as a function of transferred ozone dose in both pure water and wastewater and, the identification of these products in both matrices.

2. Materials and methods

Ozonation experiments were carried out in a 2 L acrylic reactor with continuous supply of an ozone–oxygen gas mixture to the bottom of the reactor. Ozone was produced by an OZO-4VTT generator (Ozomax) at a rate of 3.3 g/h, using oxygen as a feed gas. Volumes of 500 mL of SMX solutions of either 60 mg/L or 100 μg/L were poured into the reactor and the gas was bubbled through a porous stainless steel diffusion plate (Mott Corporation, 2 μm). The high concentration of SMX was used to facilitate the recovery and identification of the products formed during ozonation. The low concentration was chosen to be at the high end of the concentration range of pharmaceuticals that have been found in treated wastewater [5,18,26].

Experiments were carried out in pure water and treated wastewater obtained from a secondary wastewater treatment plant in Granby, Quebec, Canada (average flowrate: 56,000 m^3/day, population: 50,000 habitants (2006)) – referred to as wastewater in this paper. A partial characterization of the wastewater was carried out, which includes the concentration of metals, chemical oxygen demand (COD), suspended solids (SS) and total organic carbon (TOC). The TOC was measured prior to and after ozonation treatment. The COD was measured to be 23 mg/L using a HACH Digital Reactor Block 200 (DRB 200) and a HACH spectrophotometer DR/2500. The concentration of suspended solids was measured to be 6 mg/L using a standard method (Standard Method #2540D). TOC measurements were carried out using a Rosemount DC-80 Total Organic Carbon Analyzer and the EPA Method 415.2. The concentration of common metals was measured using a Thermo Trace Scan inductively coupled plasma-optical emission spectrophotometer (ICP-OES) and EAP Method 300.1. The most abundant metals were sodium (480 mg/L), iron (31.4 mg/L) and calcium (28.3 mg/L). All other measured metal concentrations were below 1 mg/L.

Prior to ozonation, all solutions (pure water and treated wastewater) were adjusted to an initial temperature of 17 °C and initial pH of 7.1, which correspond to the average annual values of the effluent at the Granby treatment plant. The temperature and pH were not controlled during experiments. Ozonation experiments were run for various times so that different doses could be applied (and thus transferred) and all solutions were quenched with 10 mL of a 24 mM sodium sulfite solution immediately after ozone treatment. Previous experiments showed that sodium sulfite does not react with SMX. For low concentration samples, the entire volume (500-mL) was withdrawn from the reactor and for high concentration samples; 10 mL volumes were collected. The amount of ozone transferred to solution was measured using a standard iodometric titration (Standard Method # 2350 E) and was considered to be equal to the difference in the amount of ozone entering and exiting the reactor. All ozone doses reported here correspond to the ozone transferred to solution during experiments and are referred to as ozone dose (mg/L).

The reactants used in this study were supplied by Sigma–Aldrich (Canada) and Fisher Scientific (Canada). Sulfamethoxazole, sulfamethizole and sulfanilamide, were obtained from Sigma–Aldrich (Canada) while all other chemicals were supplied by Fisher Scientific (Canada). For experiments conducted with solutions of 100 μg/L SMX, solid phase extraction (SPE) was required prior to high performance liquid chromatography (HPLC) analysis in order to pre-concentrate the samples. The performance surrogate was sulfamethizole (SMZ, $C_9H_{10}N_4O_2S_2$), which is a sulfa drug with a similar structure to SMX. The entire sample volume (500-mL) with surrogate was pre-concentrated using extraction cartridges (Waters Oasis HLB, 6 cm^3, 500 mg) and eluted with 8 mL of a 2:1 (v/v) mixture of acetone and ethyl acetate. The samples were dried under argon flow and re-dissolved in 5 mL of 20 mM sodium dihydrogen phosphate monohydrate (NaH_2PO_4) adjusted to pH 7.5 with 50% sodium hydroxide. Recoveries of 75–82% were obtained for both compounds. No matrix effects were observed, and the HPLC results were corrected using the performance surrogate recoveries. The concentration of SMX and SMZ were monitored by HPLC (Agilent 1200) equipped with a diode array detector at a wavelength of 273 nm. Eluents consisted of 20 mM NaH_2PO_4 and acetonitrile using an eluent gradient from 30% acetonitrile to 55% over 15 min (Eclipse XDB-phenyl column, 3.5-μm, 4.6 mm × 150 mm). The limit of detection and limit of analysis of the combined SPE/HPLC methods were 2 and 6 μg/L, respectively.

The oxidation product analysis was conducted using several analytical techniques. Fractions were collected from HPLC analysis in order to determine the nature of the oxidation products of SMX formed during ozonation in both pure water and wastewater. The same HPLC column and method were used, however, the buffer was changed to 20 mM ammonium acetate adjusted to pH 4.0 with formic acid, for compatibility with LC–MS analysis. The retention times of SMX and SMZ were the same as those obtained when the sodium phosphate buffer was used. Some of the fractions collected on the preparative HPLC were analyzed by gas chromatography mass spectrometry (GC–MS) and gas chromatography (GC). The GC analysis was performed using an Agilent 5890 gas chromatograph with a Stabilwax column (length: 30 m, ID: 0.32 mm, film thickness: 0.25 μm) and helium as the carrier gas. GC–MS analysis was conducted using a Thermo Trace Gas Chromatograph equipped with a Polaris-Q External Ion Trap Mass Spectrometer. In addition, some sample analysis was carried out using a Waters Time of Flight Liquid Chromatograph–Mass Spectrometer (LC-Q-TOF). Some samples were analyzed by LC-Q-TOF and were then prepared for GC–MS analysis. Preparation consisted of placing three 20-mm sections of a Rtx-5ms column (Restek, USA) in each fraction vial. They were rotated at slow speed at room temperature for 2 h. The column pieces were removed and placed in 20 mL headspace vials. The vial's atmosphere was replaced with argon to prevent oxidization and volumes of 500 μL were heated to 200 °C prior to injection. The instrument was set to several different modes based on the data obtained by LC-Q-TOF analysis: scan mode, sequential mode and single ion monitoring mode. The samples were then re-analyzed in chemical ionization mode to confirm the molecular ions. An MS^2 analysis (electron ionization mode) was also conducted to confirm the fragmentation pattern obtained by LC-Q-TOF.

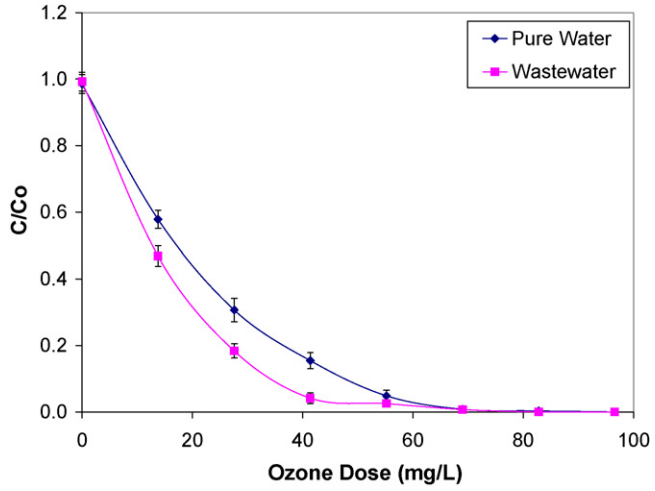

Fig. 2. Relative concentration of SMX as a function of ozone dose (C_o = 60 mg/L smx, initial pH = 7.1, error bar: one standard deviation).

3. Results and discussion

3.1. Degradation experiments at high initial concentration

Experiments were first conducted at an initial sulfamethoxazole concentration of 60 mg/L in pure water and in wastewater. Considerable removal of the antibiotic was achieved as the ozone dose was increased, as shown in Fig. 2.

From this figure it can be seen that very similar amounts ozone are required to achieve the same degree of removal in pure water and wastewater. The removal in wastewater is initially faster and requires less ozone but the dose needed to reduce the concentration of the drug below the limit of detection is 83 mg/L in both cases. It was hypothesized that the reason for the difference in removal rate is due to wastewater matrix effects and is more thoroughly discussed in Section 3.2.

As the SMX removal increased, several oxidation products were formed. These products were monitored by their peak retention times and areas obtained by HPLC analysis as a function of ozone dose. Again, these experiments were conducted in both pure water and wastewater. Peaks with the same retention times were obtained in both types of water. The evolution of these peaks as a function of ozone dose followed similar trends in both cases. Therefore, Fig. 3 shows only the results obtained using wastewater. The results indicate that the wastewater matrix does not seem to have a

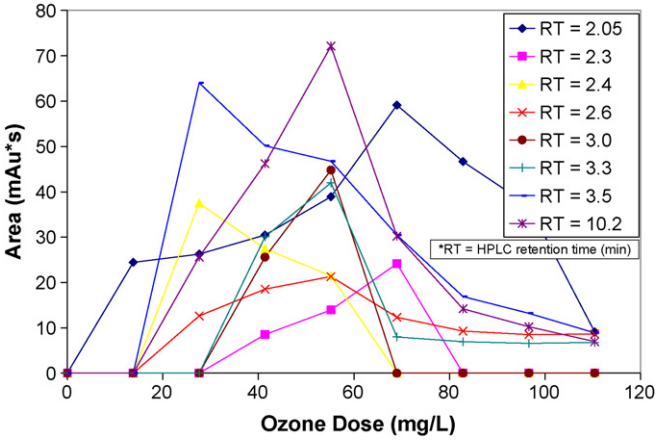

Fig. 3. Evolution of degradation products in wastewater as a function of ozone dose (C_o = 60 mg/L smx).

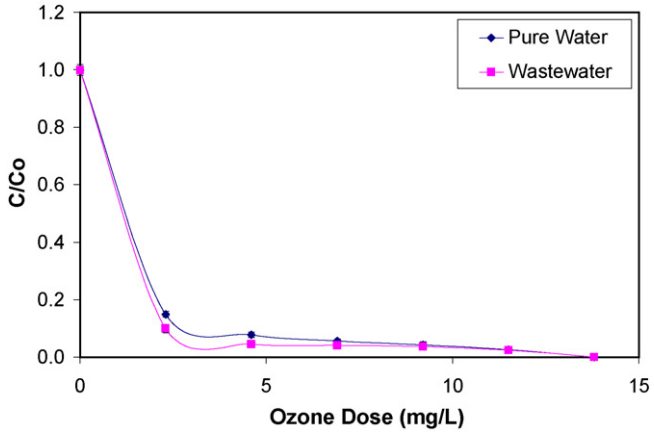

Fig. 4. Relative SMX concentration as a function of ozone dose (C_o = 100 μg/L smx, initial pH = 7.1, error bar: one standard deviation).

major effect on the oxidation products formed during the ozonation of SMX.

Eight oxidation products were detected throughout the range of ozone doses tested as shown in Fig. 3. The retention times of the products range from 2.3 to 10.2 min, while the retention of SMX is 6.3 min. SMX is no longer detected after an ozone dose of 83 mg/L however, at this dose, peaks with retention times of 2.05, 2.6, 3.3, 3.5 and 10.2 min are still detected and remain detected at the highest dose reported in Fig. 3.

Experiments were run for longer ozone bubbling times to see whether other oxidation products are produced or whether any of those already in the solution fall below the HPLC limit of detection or persist regardless of the ozone dose. It was found that the only oxidation product that persisted in solution after an ozone dose of 221 mg/L was the peak with retention time of 2.05 min.

3.2. Degradation experiments at low initial concentration

Analogous experiments were carried out with an initial SMX concentration of 100 μg/L. This corresponds to a concentration 600 times lower than in previous experiments and is more representative of what is found in wastewater treatment plant effluents. Fig. 4 represents the removal of SMX in wastewater and pure water as a function of ozone dose, adjusted to the lower initial concentration of SMX. In fact, the dose required to reduce the concentration of SMX in wastewater below the limit of detection (corresponding to a TOC removal of 5%) is six times smaller than for a 60 mg/L solution. Fig. 4 shows that again, the concentration of SMX initially decreases faster in wastewater but then falls below the limit of detection of the HPLC with the same ozone dose as the pure water solution, which is 14 mg/L. This shows that the wastewater matrix has no significant effect on the amount of ozone required to remove SMX.

Considering that the removal kinetics of SMX by reaction with hydroxyl radicals are generally negligible compared to its reaction with ozone ($k_{O_3,app}/k_{\bullet OH,app} > 10^{-5}$ [27]), the role of hydroxyl radicals was not investigated. Considering the significant concentration of metals observed in the treated wastewater, the possible effect of these metals on the removal rate was investigated. After an average metal and anion removal of 75% from the wastewater (via precipitation), ozonation experiments were conducted to see if the kinetics were different. It was found that the SMX removal profile remained unchanged after metal precipitation when compared to wastewater experiments without metal removal. Therefore, it was confirmed that the metal content of the wastewater does not influence the kinetics of the removal of SMX in wastewater. It was then hypothesized that the higher initial removal observed in

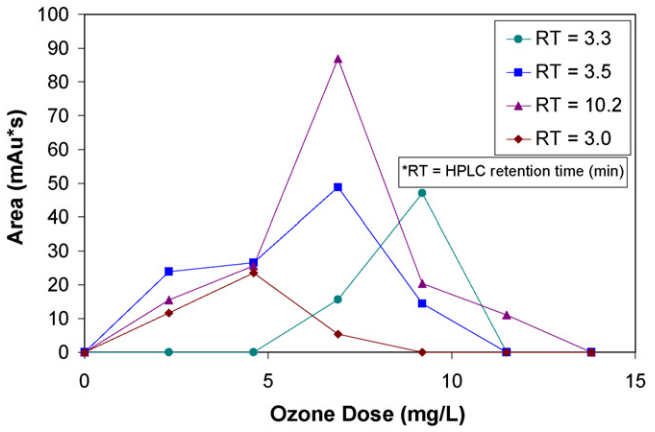

Fig. 5. Evolution of degradation products in wastewater as a function of ozone dose (C_o = 100 μg/L smx).

wastewater can be attributed to mass transfer differences between the two matrices. The rates of ozone transfer were measured for three different matrices: pure water, pure water spiked with SMX (60 mg/L) and wastewater. It was observed that the presence of SMX did not influence the rate of ozone transfer when compared to pure water. This indicated that the transfer of ozone to the solution was not affected by the reaction of ozone with dissolved constituents. However, a much faster rate of ozone transfer was observed in wastewater (26.4 mg/L/min in pure water, 34.4 mg/L/min in wastewater) indicating that wastewater constituents had an effect on the mass transfer of ozone. Experimental values for the mass transfer coefficient of ozone in wastewater are 2.5–5 times higher than for pure water depending on the organic and inorganic content of the water [28]. The initial faster decrease of SMX in wastewater, observed at both concentration levels, may therefore be explained by better mass transfer of ozone to the solution.

In addition, peaks with the same retention times were obtained for oxidation products in both matrices, as observed in the experiments at higher concentration. Fig. 5 shows the variation of the peak areas of the oxidation products formed as a function of ozone dose. Since similar trends were observed between the two matrices only the results for the wastewater experiments are shown here.

Fig. 5 shows the appearance, change and disappearance of the four peaks that were detected by HPLC. It can be seen that after an ozone dose of 14 mg/L no peaks are present and thus all detectable oxidation products are either completely degraded or have fallen below the limit of detection of the HPLC method. When compared to Fig. 3, the number of oxidation products is less, four as opposed to eight. It may be that the compounds represented by these peaks are present at too low of a concentration to be detected by HPLC even after pre-concentration with SPE. Alternatively, the SPE method may not be suitable to recover these oxidation products. Once these oxidation products are identified in the higher concentration samples, the SPE procedure can be changed to optimize the recovery of these compounds. This may confirm their presence in the samples obtained during the experiments at the low initial concentration of SMX. Although no peaks were detected in solutions with an initial concentration of 100 μg/L after an ozone dose of 14 mg/L, experiments using higher ozone doses were also conducted to ensure that no new peaks would appear. Experiments were carried out for ozone doses in the range of 28–83 mg/L and no peaks were detected.

3.3. Oxidation product identification

The oxidation products that both sets of experiments have in common are those with HPLC retention times of 3.0, 3.3, 3.5 and

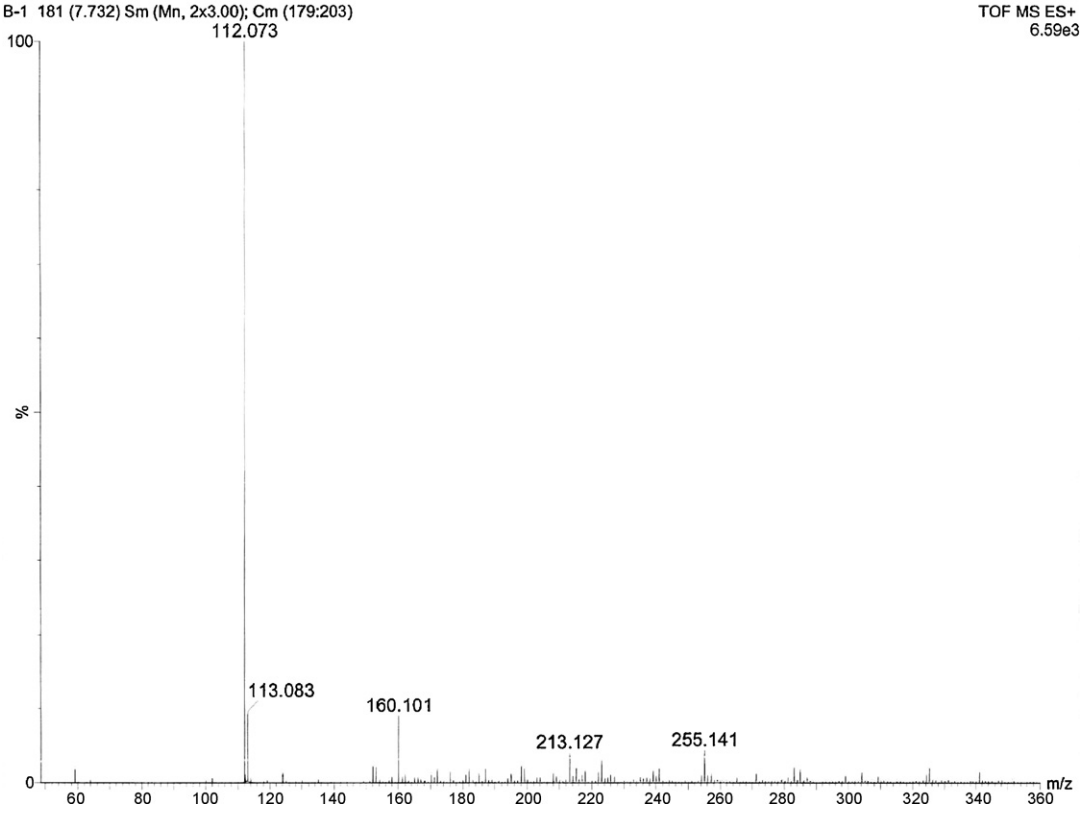

Fig. 6. Mass spectrum of the fraction with a retention time of 3.0 min.

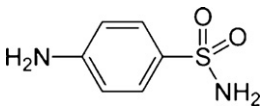

Fig. 7. Structure of sulfanilamide.

10.2 min. None of these peaks were detected when a wastewater blank was ozonated. This suggests that these compounds are oxidation products of SMX and do not come from other compounds present in the wastewater. From Figs. 3 and 5 it can be seen that the corresponding peaks follow the same trends. It can be hypothesized that the four peaks which appear in both sets of chromatograms correspond to the same compounds but the HPLC retention times are not sufficient to make this conclusion. It was necessary to determine the nature of the peaks at both concentration levels before concluding that they are the same oxidation products.

The retention times of the peaks analyzed using gas chromatography are those at 2.05, 2.3, 2.4, 2.6 and 3.5 min of which only the peak at 3.5 min is present in both low and high concentration samples. These peaks were well resolved and were clearly collected from the HPLC and analyzed on the GC by comparison with standards and on GC–MS for identification. Beltran et al. [21] identified maleic and oxalic acid as intermediates of SMX during ozone treatment. The GC retention times of these compounds were determined and compared to the GC results of the oxidation product peaks obtained from the current experiments. The retention times obtained for these acids did not match any of the GC retention times of the peaks collected. However, the retention times on the GC indicated that the peak at an HPLC retention time of 2.05 min was in fact two different compounds. For ozone doses up to 111-mg/L, the peak was a mixture of methanol and ethanol while for ozone doses above 111-mg/L, only ethanol was detected. By comparison to the National Institute of Standards and Technology (NIST) database, the GC–MS spectrum confirmed the identification of these products which are composed of the functional groups suggested by Yargeau and Leclair [20]. In addition, the oxidation products present at HPLC retention times of 2.3, 2.4, 2.6 and 3.5 min were identified using the same approach. These were as follows: acetic acid, methyl acetate, ethyl acetate and phenol, respectively. All of these products, excluding methanol and ethanol, were absent in solutions with ozone doses of 221 mg/L for high concentration samples and some fell below the limit of detection after doses as low as 69 mg/L. This implies that they readily react with ozone (or with other components in the mixture) or they escape the solution due to their volatile nature.

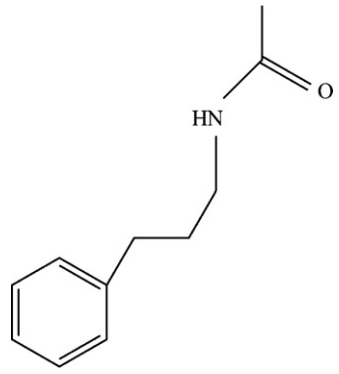

Fig. 9. Structure of N-(3-phenylpropyl)-acetamide.

The other peaks that were detected during HPLC analysis were those with retention times of 3.0, 3.3 and 10.2 min all of which were detected at high and low concentrations of SMX. These peaks were collected as fractions and analyzed by GC–MS and LC-Q-TOF in order to identify them. Fig. 6 presents the mass spectrum of the

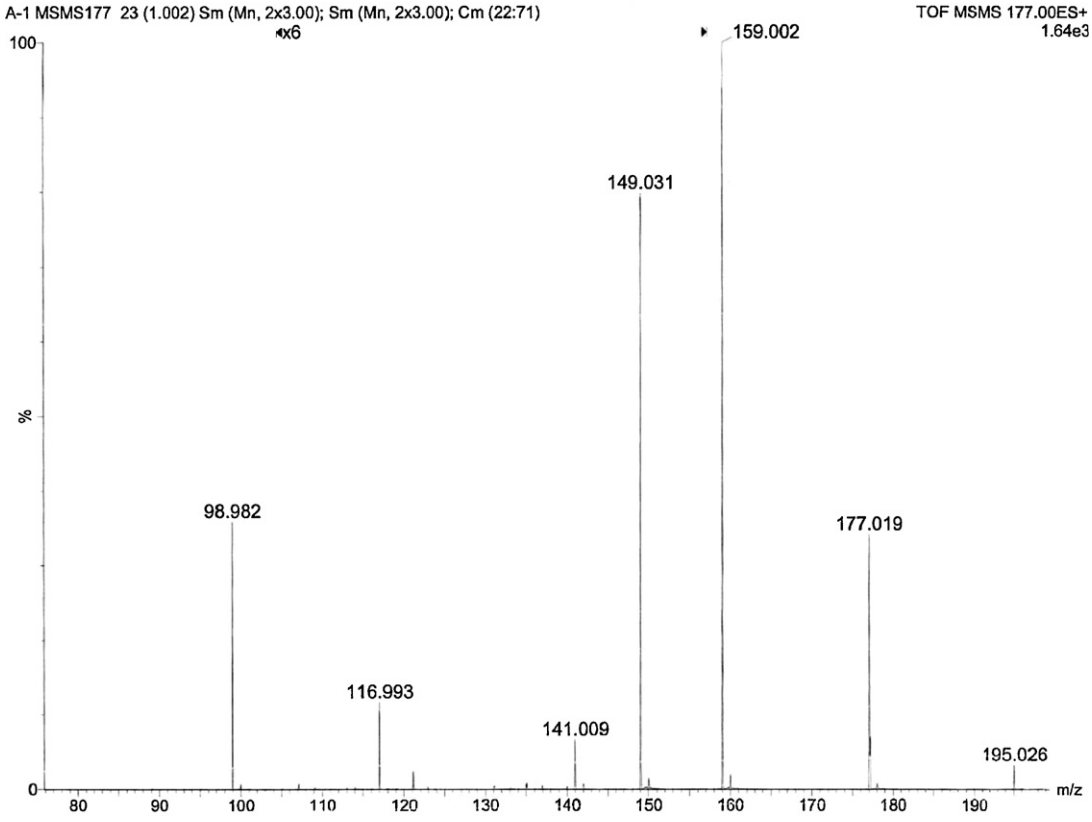

Fig. 8. Mass spectrum of the daughter ion at 177 *m*/*z* of the parent compound at 261 *m*/*z*.

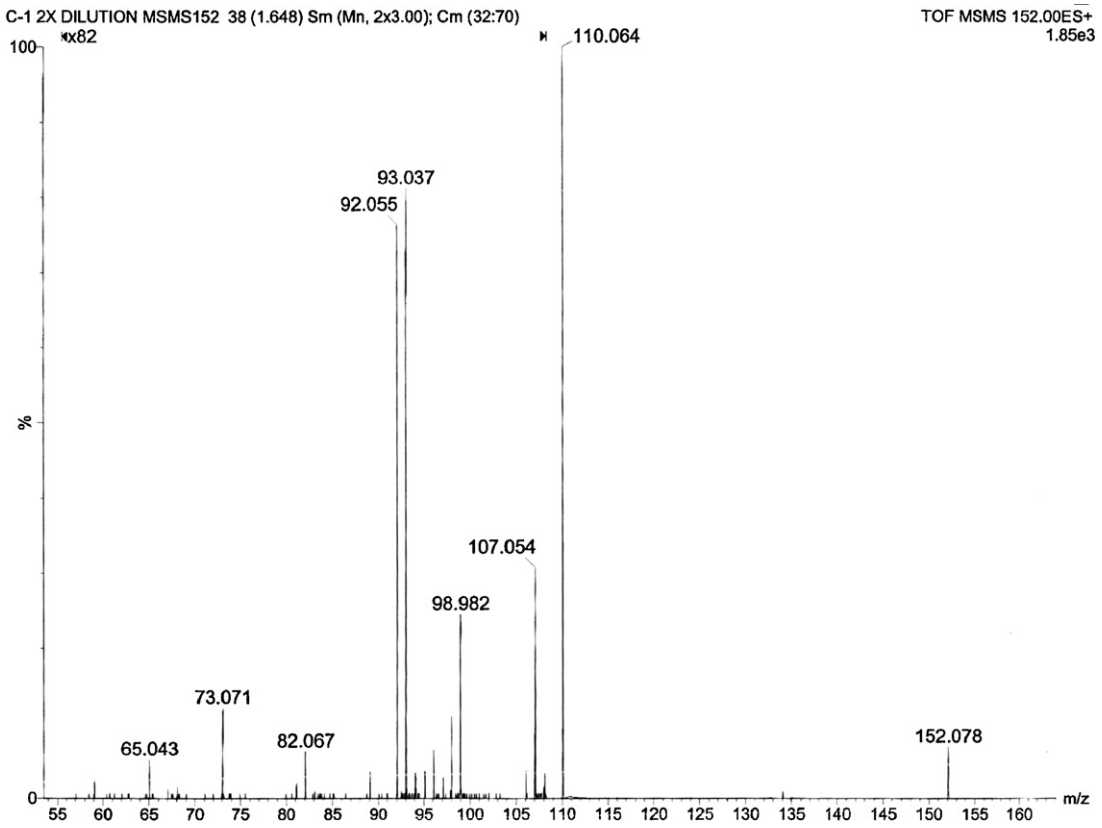

Fig. 10. Mass spectrum of the fraction with a retention time of 10.2 min.

fraction with a retention time of 3.0 min. By comparison to the National Institute of Standards and Technology (NIST) database, the GC–MS spectrum confirmed the structure of sulfanilamide (4-aminobenzene sulfonamide, $C_6H_8N_2O_2S$) in this fraction and its chemical structure is shown in Fig. 7. In addition, a standard of sulfanilamide analyzed by HPLC eluted at the same time as the oxidation product peak (3.0 min). According to Dodd et al. [29] the "potency-equivalent" value, calculated as a ratio of the EC-50 values (untreated sample/ozonated sample), decreases linearly with SMX concentration. This seems to indicate that the transient concentration of sulfanilamide observed here would not significantly affect the antibacterial activity of the solution.

The peak at the HPLC retention time of 3.3 min was analyzed by both LC-Q-TOF and GC–MS. Using the LC-Q-TOF, an ionization was performed and a key mass to charge ratio was the molecular ion at 177 m/z. The mass spectrum obtained for this molecular ion (177 m/z) of the parent compound at 261 m/z is presented in Fig. 8. This molecular ion was assumed to be an oxidation product of SMX and not simply a result of a reaction between ozone and the components in the wastewater for two reasons. Firstly, no HPLC peak was observed at this retention time in ozonated wastewater samples without SMX. Secondly, the HPLC peak was present in ozonated SMX solutions in both matrices: pure water and wastewater. This confirms that the product cannot be the result of a reaction between ozone and wastewater. This daughter ion (177 m/z) was fragmented to 50% of its initial intensity and new mass to charge ratios (fragments) were obtained. These fragments were complemented with mass to charge ratios below 100 m/z obtained by GC–MS analysis. Electron ionization mode (70 eV) was used on the GC–MS and produced a fragmentation pattern for 177 m/z. Chemical ionization mode was used to confirm the 177 m/z molecular ion. An MS^2 analysis was also performed on the fragments determined by electron ionization to confirm the parent ion (177 m/z). The results obtained from all of the analyses were combined and gave a clear picture of the fragmentation pattern of the oxidation product. Analysis of these results and a comparison with the National Institute of Standards and Technology (NIST) database allowed for the identification of N-(3-phenylpropyl)-acetamide ($C_{11}H_{15}NO$) as the main component in the fraction collected by HPLC at a retention time of 3.3 min. Its chemical structure is shown in Fig. 9.

The peak at the HPLC retention time of 10.2 min was also analyzed by both LC-Q-TOF and GC–MS. A similar set of analyses was conducted as described for the peak with HPLC retention time of 3.3 min. From the initial fragmentation pattern of this peak, the molecular ion with mass to charge ratio of 133 m/z was investigated and a peak at 5.19 min was obtained by GC–MS. From the analysis of both the LC-Q-TOF (mass spectrum presented in Fig. 10) and GC–MS results, the main component of the sample was determined to be 2-methyl-benzoxazole (C_8H_7NO) and is shown in Fig. 11.

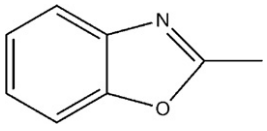

Fig. 11. Structure of 2-methyl-benzoxazole.

4. Conclusions

Ozonation was shown to be a suitable way to remove SMX from wastewater. It was demonstrated that the wastewater matrix does not have a significant effect on the amount of ozone required to reduce the concentration of SMX below the given detection limit or the nature of the oxidation products. However, comparison between pure water and wastewater indicated a significant difference in ozone transfer. This indicates that the design and oper-

ation of wastewater ozonation plants must consider the effect of the wastewater matrix on ozone mass transfer. In addition, four of the peaks obtained at the high SMX concentration (60 mg/L) were still detected at the low initial concentration of SMX (100 μg/L). The fact that these oxidation products were detected indicates that they could be present in the effluent of a wastewater treatment plant after ozonation. These compounds might be less, equally or more harmful than SMX even if lower antibacterial activity is expected. It is therefore critical that the oxidation products that have been identified be subjected to toxicity assays.

Acknowledgements

The authors wish to thank the Natural Sciences and Engineering Council of Canada (NSERC), Le Fonds Québecois de la Recherche sur la Nature et les Technologies (FQRNT) and the Eugenie Ulmer Lamothe Chemical Engineering Fund (McGill University) for the financial support for this work.

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