Oxidation of Pharmaceuticals during Ozonation of Municipal Wastewater Effluents: A Pilot Study

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To reduce the release of pharmaceuticals and endocrine disruptors into the aquatic environment or to remove them from wastewater intended for direct or indirect reuse, the application of advanced wastewater treatment may be required. In the present study, municipal wastewater effluents were treated with ozone (O₃) in a pilot-scale plant consisting of two bubble columns. The investigated effluents, which varied in suspended solids concentrations, comprised an effluent of conventional activated sludge treatment (CAS), the same effluent dosed with 15 mg of TSS L⁻¹ of activated sludge (CAS + SS), and the effluent of a membrane bioreactor pilot plant (MBR). Selected classes of pharmaceuticals were spiked in the wastewater at realistic levels ranging from 0.5 to 5 μg L⁻¹. Samples taken at the inlet and the outlet of the pilot plant were analyzed with liquid chromatography (LC)—electrospray tandem mass spectrometry (MS). Macrolide and sulfonamide antibiotics, estrogens, and the acidic pharmaceuticals diclofenac, naproxen, and indomethacin were oxidized by more than 90—99% for O₃ doses ≥ 2 mg L⁻¹ in all effluents. X-ray contrast media and a few acidic pharmaceuticals were only partly oxidized, but no significant differences were observed among the three effluents. These results show that many pharmaceuticals present in wastewater can be efficiently oxidized with O₃ and that suspended solids have only a minor influence on the oxidation efficiency of nonsorbing micropollutants.

Introduction

In recent years, various studies have reported the occurrence of a large number of pharmaceuticals in the aquatic environment (1—3). Even though the detected concentration levels are typically in the nanogram to microgram per liter range, it cannot be excluded that molecules designed to be biologically active affect sensitive aquatic organisms even at such low concentrations. Furthermore, the large number of pharmaceuticals and other micropolliants that are present in surface waters could produce additive effects (4, 5). Immediate effects caused by pharmaceuticals may be subtle and difficult to detect but nevertheless could lead to important long-term consequences in aquatic ecosystems (6).

Among the various classes of pharmaceuticals, three merit special concern: antibiotics, pharmaceuticals acting as endocrine disruptors, and antineoplastics. Primarily used for chemotherapy, antineoplastics are highly toxic agents that have a high potential to affect aquatic organisms. The release of antibiotics into the environment could promote the dissemination of antibiotic resistance, especially in human pathogens. Endocrine disruptors in general are thought to be responsible for feminizing and masculinizing effects observed in various animals that live in ecosystems affected by anthropogenic pollution (7). A prominent endocrine disrupting pharmaceutical is 17α-ethinylestradiol (EE2). Laboratory studies have already shown that environmentally relevant concentrations of EE2 and natural estrogens elicit estrogenic responses in fish (8—10). Among the estrogens and estrogenic chemicals associated with the introduction of feminizing effects in fish exposed to effluents of wastewater treatment plants (WWTPs), EE2 is likely to be of considerable importance due to its high in vivo potency, its persistence in the environment, and its capacity to bioaccumulate (5).

Municipal wastewater is the major source of pharmaceuticals in the aquatic environment (6). In developed countries, wastewater is usually treated in WWTPs before it is discharged into receiving waters. Since it is highly unrealistic to reduce the consumption of pharmaceuticals, the improvement of wastewater treatment is one of the few options to significantly diminish the release of these compounds into the aquatic environment. Conventional activated sludge treatment was shown to degrade pharmaceuticals to varying extents that ranged from complete to very poor degradation (11, 12). Applying longer sludge retention times resulted in partly improved degradation, but most of the investigated compounds could not be completely degraded. Therefore, advanced treatment technologies have to be implemented to achieve further removal of pharmaceuticals.

Ozonation has been shown to have a high potential for the oxidation of pharmaceuticals in drinking water (13, 14) and wastewater (15). In wastewater, O₃ doses ranging from 5 to 15 mg L⁻¹ led to a complete disappearance of most of the pharmaceuticals except for iodinated X-ray contrast media. For O₃ doses typically applied in water treatment, ozonation only results in partial oxidation of pharmaceuticals and therefore could yield biologically still active oxidation products. However, recent studies on EE2 (16) and carbamazepine (17) have shown that partial oxidation was sufficient to significantly reduce pharmacological activity and toxicity, respectively.

In the present study, pilot experiments were conducted to get a better understanding of the oxidation of pharmaceuticals during ozonation of wastewater effluent. The experiments were carried out on a wastewater with a DOC concentration representative for good-quality secondary or tertiary effluent. DOC was substantially lower compared to the wastewater investigated in ref 15. The selected pharmaceutical classes (macrolide and sulfonamide antibiotics, iodinated X-ray contrast media, estrogens, and three acidic pharmaceuticals) were spiked to the wastewater to be able to determine 95—99% removal. Except for estrogens, resulting
pharmaceutical concentrations did not exceed realistic levels. The major aims of the experiments were (i) to determine a minimal O₃ dose required for the oxidation of pharmaceuticals exhibiting a high reactivity toward O₃; (ii) to investigate the influence of suspended solids on the oxidation of pharmaceuticals in MBR, CAS, and CAS + SS effluents, including an estimation of O₃ absorption by sludge particles; and (iii) to assess the feasibility of the prediction of pharmaceutical oxidation by means of suitable probe compounds. Therefore, the paper also includes a brief presentation of an oxidant exposure-based model for the prediction of micropollutant oxidation.

**Experimental Section**

**Ozonation Pilot Plant.** The pilot plant consisted of two columns operated in series with an active reactor volume of 140 L each and a filling level of 4.8 m (0.193 m nominal inner diameter, 5.2 m total height; Figure 1). The first column is operated in the downstream mode, and the second, upstream. Tracer experiments with a salt spike showed slightly better plug flow behavior in the second column as compared to the first (the salinity profile at the outflow of columns 1 and 2 could best be simulated by modeling the reactor volume as a series of, respectively, three and four fully mixed compartments with comparable total volume). With a flow rate of 2 ± 0.1 m³ h⁻¹, the total hydraulic detention time amounts to 4.2 ± 0.2 min in each column. O₃ was continuously supplied by an ozone generator (Ozomatic SWO 200) fed with oxygen and bubbled into column 1 at a gas flow rate of 200 ± 10 L h⁻¹ (countercurrent). No O₃ was applied to column 2. Ozone concentrations in the feed and off gas were measured with a UV ozone monitor (BMT 936 Vent, 0.1–50 g m⁻³). By adjusting the power input of the ozone generator, the desired O₃ concentrations were obtained. The respective concentrations yielded transferred O₃ doses ranging from 0.5 to 5 mg L⁻¹. For the highest O₃ dose, O₃ residuals in the off gas were <1 g m⁻³ compared to 50 g m⁻³ in the feed gas. Because it is unlikely that the transfer efficiencies decreased with decreasing O₃ doses, transfer efficiencies were assumed to be always >98%.

**Feed Wastewater.** The pilot plant was operated on site at the municipal wastewater treatment plant (WWTP) in Kloten-Opfikon, Switzerland. Three types of WWTP effluents spiked with selected classes of pharmaceuticals were treated with O₃. The investigated effluents were effluent of conventional activated sludge treatment (CAS); the same effluent dosed with 15 mg of TSS per liter of activated sludge (from the aerobic zone of the full-scale plant), simulating an activated sludge treatment with suboptimal clarification (CAS + SS); and the effluent of a membrane bioreactor pilot plant (MBR; for water quality parameters see Table 1).

On the CAS plant, the combined sewage of 55,000 population equivalents (PE) is treated by use of a conventional activated sludge system equipped with grit, sand, and oil trap, primary clarifier, nitrification, and denitrification (11 ± 2 days sludge age). The MBR pilot plant (100 PE) is operated in parallel with proportional inflow of primary effluent (i.e., primary clarified wastewater) of the CAS plant. It is equipped with anaerobic, denitrifying, and nitrifying compartments (sludge age > 70 days; see ref 11 for a detailed description of both plants).

**Spiking of Analytes.** The biologically treated wastewater of either plant was continuously pumped into a 300 L tub, where it was spiked continuously with an aqueous solution containing representative compounds from different classes of pharmaceuticals. Care was taken that acetone residuals from primary stock solutions were low enough that they did not influence the ozonation process [i.e., hydroxyl-radical (OH) scavenging rate by acetone ≪ OH scavenging rate of the wastewater matrix]. The tub was equipped with a stirrer to ensure good mixing. A ~500-fold dilution of the spiking solution with wastewater effluent resulted in the approximate final concentrations given. Four iodinated contrast media, iopamidol (CAS Registry No. 60166-93-0), diatrizoate (CAS Registry No. 737-31-5), iopromide (CAS Registry No. 73334-07-3), and iomeprol, were spiked at concentrations of 5 µg L⁻¹. The concentration for the natural estrogens estrone (CAS Registry No. 53-16-7) and 17β-estradiol (CAS Registry No. 50-28-2) was 0.5 µg L⁻¹, while 1 µg L⁻¹ 17α-ethinylestradiol (CAS Registry No. 57-63-6) was added (for structures see Figure 2). The group of acidic pharmaceuticals comprised ibuprofen (CAS Registry No. 15687-27-1), diclofenac (CAS Registry No. 15307-86-5), bezafibrate (CAS Registry No. 41859-67-0), naproxen (CAS Registry No. 22204-53-1), gemfibrozil (CAS Registry No. 25812-30-0), clofibrate (CAS Registry No. 882-09-7), and indomethacin (CAS Registry No. 53-86-1). While only the first three were spiked at a concentration of 2 µg L⁻¹, the latter four were also included in the chemical analysis due to their presence in the effluents at concentrations well above the detection limits. Sulfadiazine (CAS Registry No. 68-35-9), sulfathiazole (CAS Registry No. 72-14-0), sulfapyridine (CAS Registry No. 144-83-2), and sulfa-methoxazole (CAS Registry No. 723-46-6) were added to the group of sulfonamide antibiotics and spiked at a concentration of 2 µg L⁻¹ (for structures see Table 2). Additionally, N²-acetylaminofluorene (0.5 µg L⁻¹) was added. From the group of macrolide antibiotics, 2 µg L⁻¹ roxithromycin (CAS Registry No. 80214-83-1), clarithromycin (CAS Registry No. 81103-11-9), and the environmental metabolite dehydroerythromycin were spiked (for structures see Figure 3). N²-Acetylsulfamethoxazole and azithromycin (CAS Registry No. 83905-01-5) were not spiked but were already present in the wastewater effluents investigated.

**Sampling and Chemical Analysis.** Samples were taken from the sample port at the inflow of column 1 (SP-IN), the sample port between the two columns (SP-MID), and at the outflow of column 2 (SP-OUT, Figure 1). Concentrations of dissolved O₃ were determined in the latter two samples, by the indigo method (18). The detection limit was 0.05 mg L⁻¹. For the analysis of pharmaceuticals, water samples of the inflow (SP-IN) and the outflow (SP-OUT) were enriched within 20 h after sampling by solid-phase extraction. Immediately after sampling, ozone was quenched with a thiosulfate solution (final concentration in samples 0.1 mM).
The dried cartridges were then frozen and transported to the laboratory, where they were eluted within 1 week. Filtration of the samples prior to enrichment was performed in the case of the acidic pharmaceuticals and the iodinated contrast media. The limits of quantification were in all cases sufficient to determine a reduction of ≥95% by ozonation. Details on the methods used have generally been published elsewhere and, therefore, only a short description is given here (19–22).

For the iodinated contrast media, 250 mL samples were adjusted to pH 2.8 and enriched on a copolymer material (ENV+, 200 mg). Detection was performed in the electrospray positive mode (19). In the case of the acidic pharmaceuticals, the samples (250 mL inflow and 500 mL outflow) were adjusted to pH 2 and enriched on prepacked Oasis MCX cartridges (80 mg) (20). Electrospray ionization in the negative ion mode was used for detection. The selected estrogens were extracted from 250 mL inflow and 500 mL outflow samples at pH 3 with prepacked Isolute C18 cartridges (500 mg) followed by a silica cleanup as described by Ternes et al. (23). Electrospray ionization in the negative ion mode was performed for the estrogens (24). For the quantification of iodinated contrast media, acidic pharmaceuticals, and estrogens, a calibration (including SPE and further sample preparation) in local groundwater was used with desmethoxyiopromide (CAS Registry No. 76350-28-2), fenoprofen (CAS Registry No. 93-72-1), and 17β-estradiol 17-acetate (CAS Registry No. 1743-60-8), respectively, as surrogate standards. Separation was achieved in all cases with reversed-phase chromatography coupled to tandem mass spectrometry. Instead of an API 365 tandem MS as described in refs 19 and 20, an API 4000 (Applied Biosystems, Foster City, CA) was used for detection, maintaining most crucial method parameters such as the MRM transitions.

For the analysis of antibiotics, 100 mL of inflow and 250 mL of outflow were taken (n = 2), adjusted to pH 4, and enriched unfiltered by solid-phase extraction on Oasis HLB polymeric cartridges (22). Measurement was performed by reversed-phase liquid chromatography coupled to electrospray positive tandem mass spectrometry (TSQ Quantum Discovery, Thermo Finnigan, San Jose, CA). Quantification was performed by use of an external calibration curve in deionized water. Results were corrected by relative recovery rates determined in the same experiment and sample matrix (n = 2–4). The relative recovery for N-acetyl-sulfamethoxazole was set to 100%. The following substances were used as surrogate standards: sulfamethazine-phenyl-13C6, sulfamethoxazole-d4, sulfadiazine-d4, sulfathiazole-d4, N-acetyl-sulfamethoxazole-d4, and tylosin (for the suppliers of the analytical standards see ref 22).

Calculation of Relative Residuals. In general, pharmaceutical concentrations measured in the inflow agreed reasonably well with the spiked amounts (e.g., deviation <±30% for sulfonamides and <±50% for macrolides). Deviations may partly have occurred due to the presence of respective compounds in the nonspiked wastewater. To compensate differences in the input concentrations, the outflow concentrations are reported as relative concentrations, which were calculated by dividing the concentration measured in the outflow by the respective concentration measured in the inflow. The resulting error was calculated by linear error propagation under the assumption that the errors of both measurements are independent of each other.

Results and Discussion

An overview of the results of the pilot experiments is provided in Figure 4. Relative residual concentrations of iopromide,
roxithromycin, sulfamethoxazole, and 17α-ethinylestradiol (EE2), representing the classes of X-ray contrast media, macrolide antibiotics, sulfonamide antibiotics, and estrogens, respectively, are plotted as a function of O₃ dosage for all three effluents. Additionally, O₃ concentrations determined directly at the outlet of column 1 (SP-MID) are given. The extent of parent compound oxidation increased with increasing O₃ dosage, but great differences were observed among the different compound classes. For iopromide and other contrast media, relative residual concentrations >40% were measured even at the highest O₃ dose. In contrast, roxithromycin, sulfamethoxazole, and EE2 were efficiently oxidized in all three effluents (>90%) for O₃ doses ≥ 2 mg L⁻¹. These three compounds exhibit high second-order rate constants for the reaction with O₃ (Table 3). Therefore, a relatively low O3 residual as present for O3 doses ≥ 2 mg L⁻¹ is sufficient to cause the observed loss of the parent compound. The same behavior was observed for the rest of the investigated compounds belonging to the respective classes and for the acidic pharmaceuticals diclofenac, naproxen, and indomethacin (data not shown). Because of the relatively high polarity of the investigated compounds, gas stripping and sorption onto sludge are negligible. Consequently, the observed loss of pharmaceuticals can be fully attributed to oxidation. For a more detailed discussion of the role of gas stripping and sorption during biological treatment of selected pharmaceuticals, see refs 25 and 26.

During ozonation, micropollutants can be oxidized either by O₃ directly or by hydroxyl radicals (•OH), which are formed as a consequence of O₃ decay. The two oxidants vary strongly in their reactivity. O₃ attacks very selectively certain functional groups, whereas •OH is a nonspecific oxidant that reacts very fast with a large number of moieties. Consequently, the observed loss of pharmaceuticals can be fully attributed to oxidation. For a more detailed discussion of the role of gas stripping and sorption during biological treatment of selected pharmaceuticals, see refs 25 and 26.

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of ibuprofen (20%) were detected under the same conditions (data not shown; for rate constants see Table 3).

**Influence of the Water Matrix.** To investigate the effect of suspended solids on micropollutant oxidation, the present study was performed with three effluents that varied in the concentration of suspended solids. MBR represented a wastewater practically free of suspended solids, CAS an average effluent quality, and CAS + SS an activated-sludge process with suboptimal clarification. From studies that investigated the fate of the investigated pharmaceuticals during activated sludge treatment, it was clear that sorption onto suspended solids is not a relevant process for the selected compounds (25, 26). However, suspended sludge particles could result in an increased O₃ demand, which would decrease the efficiency of the process for micropollutant oxidation. In Figure 5a, relative residual concentrations for diclofenac as well as O₃ residuals at SP-MID are compared for the three effluents. O₃ dosages of 0.5 and 1 mg L⁻¹ did not yield measurable O₃ residuals in any of the three effluents. For 2 mg L⁻¹, low O₃ residuals were detected in CAS and CAS + SS. For 3.5 and 5 mg L⁻¹, residuals in CAS + SS (0.5 and 1.6 mg L⁻¹) and MBR (0.6 and 1.7 mg L⁻¹) were very similar, whereas residuals in CAS were significantly higher (1.4 and 2.5 mg L⁻¹). However, this difference has to be attributed to the fact that the latter experiments (CAS) were performed on a Monday, when the wastewater was still diluted from the weekend (DOC and COD were 10–20% lower than for the other weekdays). Similar experiments (CAS) performed with the same settings on a Tuesday, yielded a much lower O₃ residual of 1.8 mg L⁻¹ at SP-MID for an O₃ dose of 5 mg L⁻¹.

The loss of diclofenac as a function of O₃ dosage was similar in CAS and CAS + SS, which can be expected from comparable O₃ residuals at SP-MID for different water matrixes. Only in the case of the MBR effluent for an O₃ dosage of 1 and 2 mg L⁻¹ were significantly higher diclofenac residuals observed. This deviation seems to be related to a high turbidity caused by very fine particles that occurred for unknown reasons in the MBR permeate during these two experiments. Due to the large surface area created by these particles (probably much smaller particles than the sludge particles in CAS + SS), the turbidity may have had a significant influence on the ozonation process.

Figure 5b depicts relative residuals of the acidic pharmaceutical bezafibrate and O₃ residuals determined at SP-OUT. Bezafibrate exhibits an intermediate reactivity toward O₃. Therefore, direct reactions with O₃ or OOH are not important at lower dosages and oxidation by *OH is the predominant process. The results seem to indicate that under these conditions (O₃ < 2 mg L⁻¹ O₃) the extent of parent compound oxidation is independent of the O₃ dosage. However, the expected trend might be within the standard deviation of the analytical method and is therefore not visible. For iopromide, the extent of oxidation seems dosage-dependent as shown in Figure 4, but this trend is not significant either. At O₃ doses of 3.5 and 5 mg L⁻¹, for which significant O₃ residuals are present at SP-MID, oxidation by O₃ becomes relevant. Under these conditions, the pattern of O₃ residuals at SP-OUT is well reflected by the relative bezafibrate residuals, which are lowest for high O₃ residuals. The O₃ residuals detected at SP-OUT seem to be influenced to some extent by the water matrix. CAS + SS clearly yielded the lowest O₃ residual. But the fact that the O₃ residual for CAS is higher than for the particle-free MBR indicates that in this case the pH difference is more important than suspended solids. The pH of MBR effluent was approximately 7.5 as compared to 7 for CAS and CAS + SS. At higher pH, reactions of O₂ with the water matrix and the O₂ decay caused by radical-type chain reactions are accelerated.

Considering O₃ residuals at SP-MID and the results presented in Figures 4 and 5a for two antibiotics, EE2, and diclofenac, it can be concluded that suspended solids have only a minor influence on the oxidation of compounds that react fast with O₃. Furthermore, the oxidation by *OH was not affected by suspended solids either, as shown for bezafibrate at low O₃ dosages or for iopromide (Figure 4). At higher O₃ dosages, however, the oxidation of compounds with intermediate reactivity seems to be influenced to some extent by the concentration of suspended solids and the pH due to significant differences in O₃ residuals and the associated O₃ exposures.

**Estimation of the O₃ Absorption Rate of Sludge Particles.** During ozonation of wastewater, reactive compounds dissolved in the aqueous bulk phase and colloidal matter compete with sludge particles for O₃. For low O₃ dosages, the fact that suspended solids had only minor effects on the ozonation process demonstrates that O₃ must be consumed by dissolved components of the wastewater before it reaches the sludge particles. We hypothesize that the ozone transfer from the bulk phase to the sludge particles is governed by the diffusion-limited transfer of ozone across the boundary layer of the particles. As a consequence, the O₃ transfer is proportional to the surface area of the sludge particles. Under the investigated conditions, the surface area was obviously too small to result in substantial ozone consumption by sludge particles. To check the plausibility of this hypothesis, O₃ mass transfer through the boundary layers surrounding the sludge floc and the gas bubble as well as the O₃ concentration in the bulk solution were estimated on the basis of film theory (28). The result of this estimate will also be crucial for the understanding of the effect of sludge...
particles on the fate of adsorbed compounds and microorganisms during ozonation.

The mass transfer of O3 from the gas phase to the liquid phase is usually calculated according to

\[ N_{O3,bulk} = k_1 a_b (C_{O3,eq} - C_{O3,bulk}) \]  

where \( N_{O3,bulk} \) is the O3 absorption rate (flux per unit volume); \( k_1 \) is the mass transfer coefficient for O3; \( a_b \) is the specific interfacial area of the sum of the gas bubbles; \( C_{O3,eq} \) is the equilibrium concentration of O3 at the gas–liquid interface; and \( C_{O3,bulk} \) is the concentration of O3 in the bulk liquid. The value of \( k_1 \) is related to the molecular diffusion coefficient of O3 \( (D_{O3}) \) and the thickness of the liquid film \( (\delta_b) \) surrounding the bubble (see Figure 6a for illustration). The parameters \( k_1 \) and \( a_b \) were not determined in the present studies. Estimations of these parameters based on the basis of a study by Roustan et al. (29) yielded \( k_1 \approx 3.4 \times 10^{-4} \text{ m s}^{-1} \) and \( a_b \approx 18 \text{ m}^2 \text{ m}^{-3} \). With \( D_{O3} = 1.7 \times 10^{-9} \text{ m}^2 \text{ s}^{-1} \) (30) a film thickness of \( \delta_b = 5 \mu \text{m} \) is obtained. The study of Roustan et al. was performed by use of a comparable pilot plant and covered operating conditions (bubble diameter \( \approx 3 \text{ mm} \), gas velocity \( \approx 7 \text{ m h}^{-1} \), and liquid velocity \( \approx 70 \text{ m h}^{-1} \)) applied in the present study.

Conditions representing the bottom of column 1 for an O3 dosage of 1 mg L\(^{-1}\) were selected for the estimation of the O3 absorption rate of the bulk liquid and the sludge particles. Close to the ozone diffuser, the O3 concentration in the gas phase is \( C_{O3,\text{gas}} = 10 \text{ g m}^{-3} \). Henry’s law relates \( C_{O3,\text{gas}} \) to \( C_{O3,eq} \):

\[ H = \frac{C_{O3,eq}}{C_{O3,\text{gas}}} \]  

where \( H \) is the dimensionless Henry constant. With \( H = 0.24 \) (31), eq 2 yields \( C_{O3,eq} = 2.4 \text{ g m}^{-3} \) or 50 \( \mu \text{M} \). The fact that no O3 residuals could be measured at SP-MID for an O3 dosage of 1 mg L\(^{-1}\) indicates that \( C_{O3,bulk} \ll C_{O3,eq} \). Assuming that \( C_{O3,bulk} \approx 0 \), eq 1 yields \( N_{O3,bulk} \approx 3 \times 10^{-7} \text{ mol s}^{-1} \text{ L}^{-1} \).

In the presence of a high concentration of fast-reacting compounds, the O3 mass transfer can be enhanced by reactions taking place in the liquid film. To check whether such an enhancement has to be considered in the present case, the concentration of reactive wastewater components in the bulk liquid \( (C_{\text{RWWC,bulk}}) \) e.g., O3-reactive moieties of DOC and reactive inorganic compounds) and their rate constants with O3 have to be estimated. Low O3 residuals detected at SP-MID for O3 dosages \( \geq 2 \text{ mg L}^{-1} \) indicated that the fast initial O3 demand of the wastewater is equivalent to approximately 2 mg of O3 L\(^{-1} \) (40 \( \mu \text{M} \)) under the assumption that only direct O3 reactions with a stoichiometry of 1:1 are involved. Therefore, \( C_{\text{RWWC,bulk}} \) was set to 40 \( \mu \text{M} \). The rate constant for the reaction of O3 with RWWC was estimated to be \( k_{O3,RWWC} = 1 \times 10^{9} \text{ M}^{-1} \text{ s}^{-1} \). This rate constant is representative for reactive moieties such as phenols and amines. To assess the importance of the reaction of O3 in the liquid film compared to O3 mass transfer across the film, the Hatta number \( (H_a) \) was calculated with the assumption that in the film \( C_{\text{RWWC}} = \text{constant} = C_{\text{RWWC,bulk}} \):

\[ H_a = \frac{\sqrt{K_{O3} D_{O3} C_{\text{RWWC,bulk}}}}{k_1} \]  

For the selected conditions, eq 3 yields 0.2. \( H_a < 0.3 \) means that gas absorption follows a so-called slow kinetic regime and that reactions take place primarily in the bulk liquid (30). Therefore, O3 mass transfer is well described by eq 1 and no enhancement due to consumption of O3 in the film has to be considered. Figure 6a gives a qualitative representation of the diffusion profiles resulting from the above-described conditions. Solving the differential equations that describe diffusion and reaction of O3 in the liquid film (30) yielded very similar results.

Knowing \( N_{O3,bulk} \) and \( C_{\text{RWWC,bulk}} \), the following equation can be used to estimate \( C_{O3,bulk} \), which is needed for the calculation of the O3 absorption rate of the sludge flocs:

\[ \frac{dC_{O3,bulk}(t)}{dt} = N_{O3,bulk}(t) - k_{O3} C_{O3,bulk}(t) C_{\text{RWWC,bulk}}(t) \]  

Under steady-state conditions the left side of eq 4 is 0 and the variables become time-independent. Solving eq 4 for \( C_{O3,bulk} \) results in a concentration of \( C_{O3,bulk} = 7.5 \times 10^{-4} \text{ M} \). This value corroborates the assumption made for the calculation of the film diffusion and is in agreement with the fact that O3 concentrations were \( < 0.05 \text{ mg L}^{-1} \) (\(< 1 \times 10^{-4} \text{ M} \)) at SP-MID for an O3 dosage of 1 mg L\(^{-1} \).

The diffusion of O3 through the boundary layer of a sludge floc can be represented as shown in Figure 6b. The diffusive transport from the bulk liquid to the sludge flocs can be assessed:

\[ F_{O3} = \frac{D_{O3}}{\delta_f} (C_{O3,bulk} - C_{O3,floc}) \]  

The thickness \( \delta_f \) of the boundary layer surrounding the flocs must be of the same order of magnitude as \( \delta_b \). Because the
flocs move more slowly than the bubbles, it is expected that $\delta_b$ is somewhat larger than $\delta_w$. To make a conservative assumption, it was estimated that $\delta_b = \delta_w = 5 \mu m$. Assuming that the O$_3$ concentration at the liquid–floc interface ($C_{O_3,\text{floc}}$) is 0, a flux of $F_{O_3} = 2.6 \times 10^{-8} \text{ mol s}^{-1} \text{ m}^{-2}$ is obtained by use of eq 5.

To estimate the O$_3$ absorption rate for 20 mg of TSS L$^{-1}$ (5 mg of TSS L$^{-1}$ CAS + 15 mg of TSS L$^{-1}$ dosed), the specific interfacial area of the sludge flocs ($a_\ell$) has to be calculated. An area of $a_\ell = 48 \text{ m}^2 \text{ m}^{-3}$ was obtained with the assumptions of a water content of the floc of 95%, a spherical shape, and a diameter of 50 $\mu m$. Laser diffraction analysis of a different activated sludge showed that 90% of the sludge volume is formed by flocs with a diameter $> 50 \mu m$ (median = 200 $\mu m$) (32). The resulting O$_3$ absorption rate by the sludge flocs is $N_{O_3,\text{floc}} = \frac{F_{O_3}a_\ell}{1000} = 1.2 \times 10^{-4} \text{ mol s}^{-1} \text{ L}^{-1}$ compared to the absorption rate of the bulk phase of $N_{O_3,\text{bulk}} = 3 \times 10^{-7} \text{ mol s}^{-1} \text{ L}^{-1}$. According to this estimate, only 0.14% of the O$_3$ transferred into the bulk solution is consumed by sludge particles. Changing the estimated parameters by a factor of 2 in any direction will not significantly increase the absorption rate of the sludge particles. Due to the unambiguity of the result, the rough estimate of mass transfer demonstrates clearly that the O$_3$ absorption rate must be limited by O$_3$ diffusion across the boundary layer surrounding the sludge particles. The fact that O$_3$ absorption by sludge particles is relatively low also explains why oxidation by *OH is relatively unaffected by suspended solids. Because the highest share of O$_3$ reacts in the bulk liquid, *OH is formed in the bulk liquid as well and does not come into contact with sludge particles due to its extremely low lifetime.

The considerations presented above also imply that micropollutants sorbed to sludge particles will not be oxidized efficiently. Furthermore, the inactivation of microorganisms present in the floc will be difficult to achieve, because these microorganisms will only experience a relatively low O$_3$ exposure. In Table 4, the snapshot of Escherichia coli concentrations (duplicate samples for one point in time) before and after ozonation of CAS and CAS + SS effluent demonstrates the negative impact of suspended solids on disinfection efficiency.

**Oxidation Patterns.** For macrolides, sulfonamides, estrogens, and contrast media, several compounds of each class have been analyzed. Within these classes, compounds are structurally very similar and it can be assumed that O$_3$ attack takes place on the same functional groups. The reactive functional groups in macrolides, estrogens, and sulfonamides are the tertiary amino groups, the phenol moiety, and the aniline moiety, respectively (Figures 3 and 2, Table 2). As mentioned above, contrast media do not react with O$_3$ directly. Since the chemical environment of these reactive moieties is in most cases quite similar within one class, it can also be assumed that the rate constants for the reaction with O$_3$ must be very similar. Consequently, for a given O$_3$ exposure, the extent of parent compound oxidation should be similar for all compounds of a class. The oxidation patterns of macrolides, sulfonamides, and estrogens in CAS are shown in Figure 7. As expected, parent compound oxidation for four macrolide antibiotics was very similar. Also, the relative residuals measured for three estrogens were comparable for the basis of second-order rate constants for their reaction with O$_3$ and *OH and appropriate probe compounds. The rate of oxidation of a pollutant during ozonation is given by the rate law:

$$\frac{dC_p(t)}{dt} = -k_{O_3}C_{O_3}(t)C_p(t) - k_{OH}C_{OH}(t)C_p(t)$$  

(6)

where $C_{O_3}$, $C_{OH}$, and $C_p$ are the concentrations of the pollutant, O$_3$, and *OH, respectively, and $k_{O_3}$ and $k_{OH}$ are the second-order rate constants for the reaction of the pollutant with the respective oxidants. To predict residual concentrations of a

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**TABLE 4. Snapshot of E. coli Concentrations before and after Ozonation of CAS and CAS + SS Effluent**

<table>
<thead>
<tr>
<th></th>
<th>CAS</th>
<th>CAS + SS</th>
</tr>
</thead>
<tbody>
<tr>
<td>inlet pilot plant</td>
<td>$\sim 5 \times 10^8$</td>
<td>$\sim 4 \times 10^6$</td>
</tr>
<tr>
<td>2 mg L$^{-1}$ O$_3$</td>
<td>$\sim 2 \times 10^2$</td>
<td>$\sim 3 \times 10^3$</td>
</tr>
<tr>
<td>5 mg L$^{-1}$ O$_3$</td>
<td>$\sim 10^2$</td>
<td>$\sim 6 \times 10^2$</td>
</tr>
</tbody>
</table>

---

*Source: ref 40. E. coli concentrations are given in colony-forming units per 100 mL with an error of ±0.5 log unit.*
polllutant, the integrated form of eq 6 has to be used:

\[ \frac{C_p(t)}{C_p(0)} = \exp(-k_{O3} \int_0^t C_{O3}(t) \, dt - k_{OH} \int_0^t C_{OH}(t) \, dt) \]  

(7)

If \( k_{O3} \) and \( k_{OH} \) are known, only the \( O_3 \) exposure \( [C_{O3}(t) \, dt] \) and the \( ^\cdot OH \) exposure \( [C_{OH}(t) \, dt] \) have to be determined to make a prediction. On the basis of eq 7, Elovitz and von Gunten (34) developed the \( R_{ct} \) concept, with which the oxidation of pharmaceuticals that exhibit an intermediate or low \( k_{O3} \) was successfully predicted in bench-scale experiments performed under drinking water treatment conditions (13). In the cited study, \( O_3 \) exposures were determined by integrating the measured \( O_3 \) concentrations over time. \(^\cdot OH \) exposures were calculated with help of a probe compound and the \( R_{ct} \) value. However, \(^\cdot OH \) exposures can also be determined without the \( R_{ct} \) value simply by use of a probe compound that has a known \( k_{OH} \) and that does not react with \( O_3 \). If \( k_{O3} = 0 \), eq 7 can be rearranged and the \( ^\cdot OH \) exposure can be calculated on the basis of the relative residual concentration of the probe compound (\( C_{PC} \)) and its rate constant with \( ^\cdot OH \) (\( k_{OH,PC} \)):

\[ \int_0^t C_{OH}(t) \, dt = -\frac{1}{k_{OH,PC}} \ln \left( \frac{C_{PC}(t)}{C_{PC}(0)} \right) \]  

(8)

If it is not possible to measure \( O_3 \) concentrations during an ozonation process, it should be possible to determine an \( O_3 \) exposure with an appropriate probe compound in the same way as for \(^\cdot OH \) exposures. However, since all organic compounds react with \(^\cdot OH \) at appreciable rates, residuals of \( O_3 \) probes always have to be corrected for oxidation by \( ^\cdot OH \).

In the present study it was tested whether predictions for fast-reacting pharmaceuticals can be made on the basis of this concept. Ibuprofen and naproxen were used as the \(^\cdot OH \) and \( O_3 \) probes, respectively. To account for the relatively high uncertainties associated with the high rate constants and the residual concentrations of the probe compounds, Monte Carlo simulations were performed with a Matlab script (MathWorks, Inc.) to calculate 90% confidence intervals for the predictions.

As for drinking water, the prediction of the oxidation by \(^\cdot OH \) radicals worked reasonably well for compounds such as clofibric acid and iopromide that exhibit a low reactivity to \( O_3 \) (data not shown). To assess the quality of the predictions for fast-reacting pharmaceuticals, only data for an \( O_3 \) dosage of 1 mg L\(^{-1} \) could be used among the \( O_3 \) dosages considered (1, 2, and 3.5 mg L\(^{-1} \)), because the low residuals of fast-reacting compounds cannot be properly measured for higher dosages. Out of the four considered compounds (EE2, sulfamethoxazole, diclofenac, and roxithromycin), the predictions for EE2 and sulfamethoxazole deviated strongly from the measured value. Taking into account the model uncertainty, maximal residuals of <1–2% were calculated compared to measured residuals of 15–30%. Also, naproxen, diclofenac, and roxithromycin were oxidized to a higher extent than EE2 and sulfamethoxazole despite their lower rate constants. Obviously, the ozonation process under these conditions is too complex to allow predictions for fast-reacting compounds to be made with this relatively simple concept.

Reasons for the poor predictions might be the sorption of some compounds to sludge particles that prevented oxidation or the interaction of pharmaceuticals with colloids (35), which also might offer some protection against \( O_3 \) attack. On the basis of film theory, it can be concluded that diffusion limitations as a consequence of the relatively high rate constants for the reaction of \( O_3 \) with BWWCs and pharmaceuticals were most probably not the cause for the poor predictions, because \( O_3 \) reactions take predominantly place in the bulk liquid and not in the film as shown in Figure 6.
Oxidation by O₃ versus Oxidation by OH. By use of ibuprofen as a probe compound, the oxidation of O₃ refractive compounds by OH could be well predicted with the following equation:

\[
\ln \left( \frac{C_p(t)}{C_p(0)} \right) = \frac{1}{k_{OH,IBU}} \ln \left( \frac{C_{IBU(t)}}{C_{IBU(0)}} \right) k_{OH} \tag{9}
\]

where \( C_{IBU} \) is the concentration of ibuprofen and \( k_{OH,IBU} \) is the rate constant for the reaction of ibuprofen with OH. In the same way, the oxidation by OH can be calculated for compounds that react fast with O₃, even if the prediction of oxidation by O₃ failed. The comparison of the predicted oxidation by OH with the measured residuals (\( \Delta C_{m,OH} \)) allows us to assess the relevance of the two oxidation pathways for a selected compound according to the following equation (27):

\[
f(OH) = \frac{1}{k_{OH,IBU}} \ln \left( \frac{C_{IBU(t)}}{C_{IBU(0)}} \right) k_{OH,LP} \ln \left( \frac{C_{P,m(t)}}{C_{P,m(0)}} \right) \tag{10}
\]

where \( f(OH) \) designates the fraction of oxidation by OH, and \( 1-f(OH) \), the fraction of oxidation by O₃. The knowledge of these values is important because different products will be formed depending on the oxidation pathway. In Figure 9, the ratio between oxidation pathways of four fast-reacting compounds is plotted for an O₃ dose of 1 mg L⁻¹. The calculated ratios are most probably pH-dependent and, consequently, only valid for the investigated neutral conditions. Despite the high reactivity of the selected compounds toward O₃, the fraction of oxidation by OH reaches the highest concentration at first contact of wastewater with O₃. This demonstrates clearly that in wastewater OH radicals cannot be neglected in product studies, even if O₃ reactions would clearly predominate in a pure system. Because OH reaches the highest concentration at first contact of wastewater with O₃, it can be assumed that higher O₃ dosages do not diminish the role of the oxidation pathway by OH.

**Practical Implications.** The results of the present study have shown that important classes of pharmaceuticals present in wastewater effluents such as macrolide and sulfonamide antibiotics as well as synthetic and natural estrogens can be selectively oxidized by use of relatively low O₃ doses. Furthermore, the results demonstrated that suspended solids have only a minor effect on the oxidation of pharmaceuticals. DOC seems to be the water quality parameter that has a stronger influence on the efficiency of the ozonation process. In another study, O₃ doses > 5 mg L⁻¹ had to be applied to achieve a comparable result for wastewater with a higher DOC (15). Ozonation of wastewater effluents will mainly be a viable solution when the treatment objectives include micropollutant oxidation and disinfection. Though suspended solids have limited effect on micro-pollutant oxidation, they have a clearly negative impact on disinfection as shown in ref 36 and indicated by the inactivation data for E. coli in the present study. In the regular CAS effluent, an O₃ dosage of 5 mg L⁻¹ seems sufficient to achieve the guideline values (100 fecal coliforms/100 mL) set by the EU bathing water quality directive (37). In contrast, this standard was not achieved with the higher suspended solids concentration in CAS + SS effluent (Table 4).

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