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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 (O_3) 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 O_3 doses $\geq$ 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 O_3 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 micropollutants 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 induction 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, O_3 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 O_3 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

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pharmaceutical concentrations did not exceed realistic levels. The major aims of the experiments were (i) to determine a minimal O_3 dose required for the oxidation of pharmaceuticals exhibiting a high reactivity toward O_3; (ii) to investigate the influence of suspended solids on the oxidation of pharmaceuticals in MBR, CAS, and CAS + SS effluents, including an estimation of O_3 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 $m^3\ h^{-1}$, the total hydraulic retention time amounts to 4.2 ± 0.2 min in each column. O_3 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 O_3 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 O_3 concentrations were obtained. The respective concentrations yielded transferred O_3 doses ranging from 0.5 to 5 mg L^{-1}. For the highest O_3 dose, O_3 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 O_3 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 O_3. 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 ($^{\bullet}OH$) scavenging rate by acetone ≪ $^{\bullet}OH$ scavenging rate of the wastewater matrix]. The tub was equipped with a stirrer

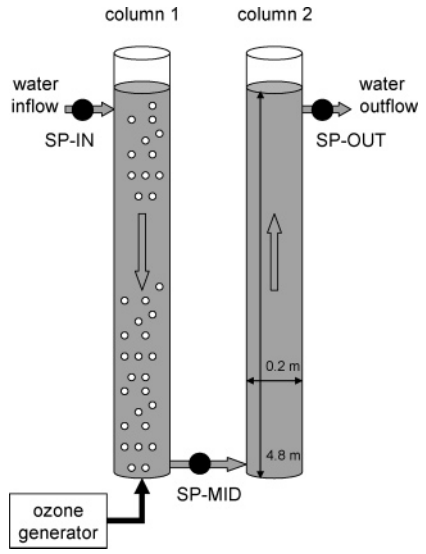


FIGURE 1. Scheme of the ozonation pilot plant. O_3 is being added only to column 1, which is operated in countercurrent mode. Black dots indicate the three sampling ports at the inlet (SP-IN) and the outlet (SP-MID) of column 1 and at the outlet of column 2 (SP-OUT).

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 $\mu g\ L^{-1}$. 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 $\mu g\ L^{-1}$, while 1 $\mu g\ L^{-1}$ 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), clofibric acid (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 $\mu g\ L^{-1}$, 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 sulfamethoxazole (CAS Registry No. 723-46-6) were chosen from the group of sulfonamide antibiotics and spiked at a concentration of 2 $\mu g\ L^{-1}$ (for structures see Table 2). Additionally, N^4-acetylsulfamethazine (0.5 $\mu g\ L^{-1}$) was added. From the group of macrolide antibiotics, 2 $\mu g\ L^{-1}$ 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). N^4-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 O_3 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).

TABLE 1. Average Water Quality Parameters of the Effluents CAS, CAS + SS, and MBR[a]

effluent	pH	T (°C)	DOC (mg L^{-1})	COD[b] (mg L^{-1})	TSS[c] (mg L^{-1})	alkalinity (mM)
CAS	7.0 ± 0.1	16 ± 1.0	7.7 ± 0.5	29 ± 3	6	3.1 ± 0.1
CAS + SS	6.95 ± 0.1	15 ± 0.5	7.0 ± 0.5	41 ± 1	20	3.2 ± 0.2
MBR	7.5 ± 0.1	17 ± 0.5	6.6 ± 0.2	22 ± 2	0	5.4 ± 0.2

[a] Errors represent one standard deviation. [b] COD includes dissolved and particulate matter. [c] Estimated from COD.

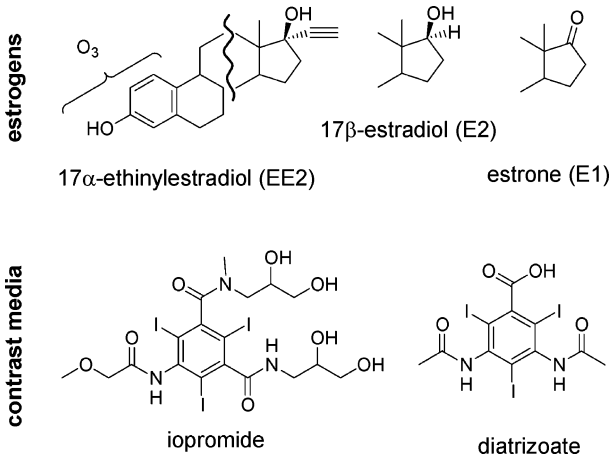
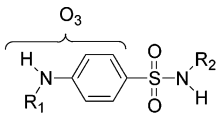
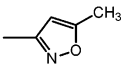
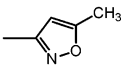
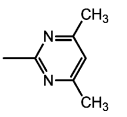


FIGURE 2. Chemical structure of estrogens and selected X-ray contrast media and proposed site of O_3 attack.

TABLE 2. Chemical Structure and pK_a of Sulfonamide Antibiotics and Proposed Site of O_3 Attack



	pK_a[a]	R_1	R_2
sulfadiazine	6.4	H	
sulfathiazole	7.2	H	
sulfapyridine	8.4	H	
sulfamethoxazole	5.7	H	
N^4-acetylsulfamethoxazole (N^4AcSMX)[b]	5.0	$COCH_3$	
N^4-acetylsulfamethazine (N^4AcSMZ)		$COCH_3$	

[a] pK_a of sulfonamide group (*38*). [b] Not spiked.

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 (60 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), fenoprop (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^4-acetylsulfamethoxazole was set to 100%. The following substances were used as surrogate standards: sulfamethazine-phenyl-$^{13}C_6$, sulfamethoxazole-d^4, sulfadiazine-d^4, sulfathiazole-d^4, N^4-acetylsulfamethoxazole-d^5, 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,

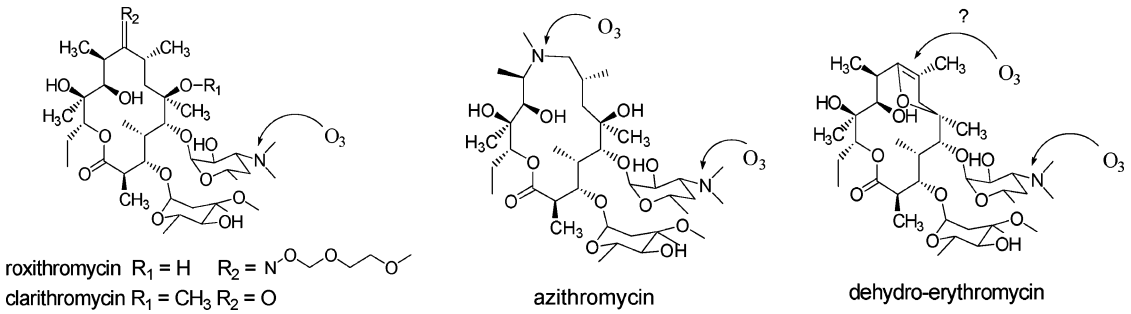


FIGURE 3. Chemical structure of macrolide antibiotics and proposed sites of O_3 attack.

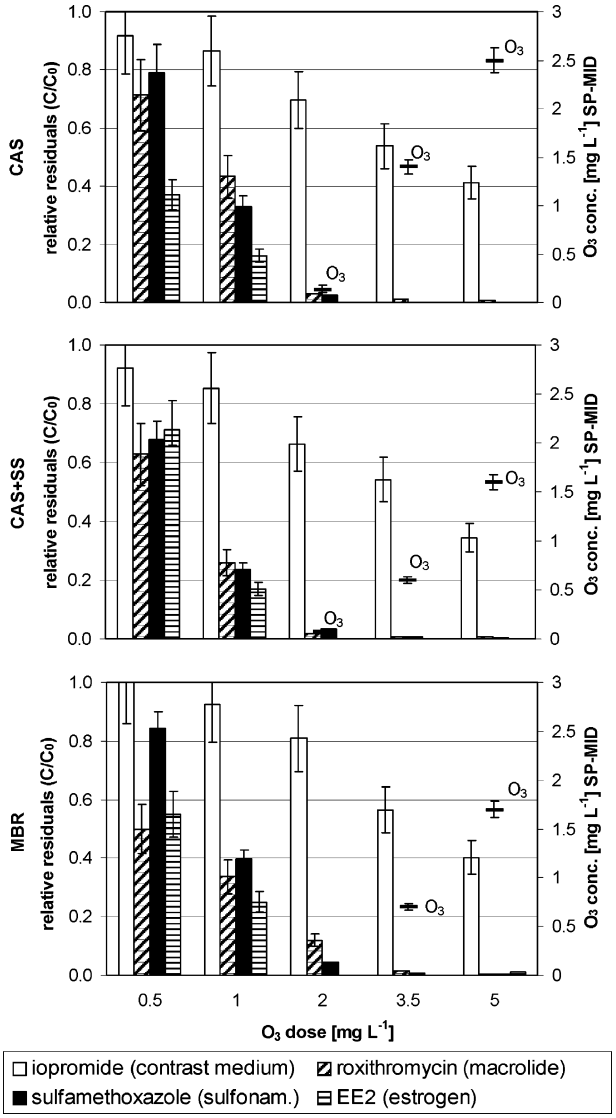


FIGURE 4. Relative residual concentrations of four compounds (iopromide, roxithromycin, sulfamethoxazole, and EE2) that represent the classes of contrast media, macrolides, sulfonamides, and estrogens, respectively. The residuals for the effluents CAS (pH = 7), CAS + SS (pH = 7), and MBR (pH = 7.5), measured at the outlet of column 2 (SP-OUT), are plotted versus O_3 dosages. Furthermore, absolute O_3 concentrations measured at the outlet of column 1 (SP-MID) are given.

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 O_3 dosage for all three effluents. Additionally, O_3 concentrations determined directly at the outlet of column 1 (SP-MID) are given. The extent of parent compound oxidation increased with increasing O_3 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 O_3 dose. In contrast, roxithromycin, sulfamethoxazole, and EE2 were efficiently oxidized in all three effluents (>90%) for O_3 doses ≥ 2 mg L^{-1}. These three compounds exhibit high second-order rate constants for the reaction with O_3 (Table 3). Therefore, a relatively low O_3 residual as present for O_3 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*.

TABLE 3. Second-Order Rate Constants for the Reaction of O_3 and •OH with Selected Pharmaceuticals[a]

compound	pK_a	apparent k_{O3}[b] (M^{-1} s^{-1})	k_{OH}[c] (10^9 M^{-1} s^{-1})
bezafibrate	3.6	590 ± 50	7.4 ± 1.2
carbamazepine		~3 × 10^5	8.8 ± 1.2
clofibric acid		<20[d]	4.7 ± 0.3[e]
diazepam		0.75 ± 0.15	7.2 ± 1.0
diclofenac	4.2	~1 × 10^6	7.5 ± 1.5
17α-ethinylestradiol	10.4	~3 × 10^6	9.8 ± 1.2
ibuprofen	4.9	9.1 ± 1	7.4 ± 1.2
iopromide		<0.8	3.3 ± 0.6
naproxen	4.5	~2 × 10^5 [d]	9.6 ± 0.5[e]
sulfamethoxazole	5.7	~2.5 × 10^6	5.5 ± 0.7
roxithromycin	8.8	~7 × 10^4	nd[f]

[a] Table adapted from ref *13*. [b] pH = 7, T = 20 °C. [c] pH = 7, T = 25 °C. [d] Rate constants determined in the present study. [e] From ref *39*. [f] Not determined.

During ozonation, micropollutants can be oxidized either by O_3 directly or by hydroxyl radicals (•OH), which are formed as a consequence of O_3 decay. The two oxidants vary strongly in their reactivity. O_3 attacks very selectively certain functional groups, whereas •OH is a nonselective oxidant that reacts very fast with a large number of moieties. Consequently, most •OH is scavenged by the water matrix in wastewater (*27*). Therefore, the oxidation of compounds that react slowly with O_3 is always less efficient than for compounds that react fast with O_3, even if the rate constants for the reaction with •OH are nearly diffusion-controlled. Because the direct reaction of iopromide with O_3 is very slow (Table 3), the observed decrease can consequently be attributed to oxidation through •OH. Due to the lower efficiency of the oxidation by •OH, iopromide residuals up to 40% were detected for an O_3 dosage of 5 mg L^{-1}. Accordingly, relative high residuals

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 O_3 demand, which would decrease the efficiency of the process for micropollutant oxidation. In Figure 5a, relative residual concentrations for diclofenac as well as O_3 residuals at SP-MID are compared for the three effluents. O_3 dosages of 0.5 and 1 mg L^{-1} did not yield measurable O_3 residuals in any of the three effluents. For 2 mg L^{-1}, low O_3 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 O_3 residual of 1.8 mg L^{-1} at SP-MID for an O_3 dose of 5 mg L^{-1}.

The loss of diclofenac as a function of O_3 dosage was similar in CAS and CAS + SS, which can be expected from comparable O_3 residuals at SP-MID for different water matrixes. Only in the case of the MBR effluent for an O_3 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 O_3 residuals determined at SP-OUT. Bezafibrate exhibits an intermediate reactivity toward O_3. Therefore, direct reactions with O_3 are not important at lower dosages and oxidation by •OH is the predominant process. The results seem to indicate that under these conditions (0.5−2 mg L^{-1} O_3) the extent of parent compound oxidation is independent of the O_3 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 O_3 doses of 3.5 and 5 mg L^{-1}, for which significant O_3 residuals are present at SP-MID, oxidation by O_3 becomes relevant. Under these conditions, the pattern of O_3 residuals at SP-OUT is well reflected by the relative bezafibrate residuals, which are lowest for high O_3 residuals. The O_3 residuals detected at SP-OUT seem to be influenced to some extent by the water matrix. CAS + SS clearly yielded the lowest O_3 residual. But the fact that the O_3 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 O_3 with the water matrix and the O_3 decay caused by radical-type chain reactions are accelerated.

Considering O_3 residuals at SP-MID and the results presented in Figures 4 and 5a for two antibiotics, EE2, and

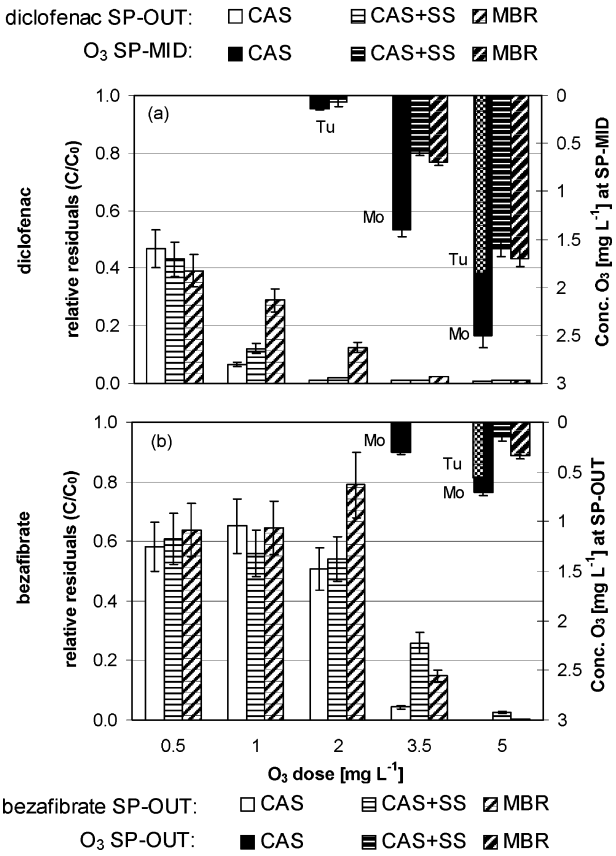


FIGURE 5. Residual concentrations of diclofenac, bezafibrate, and O_3 as a function of O_3 dosages. The given O_3 residuals were measured (a) at the outlet of column 1 (SP-MID) and (b) at the outlet of column 2 (SP-OUT). For CAS, the weekday on which the experiment was performed is indicated (Mo = Monday, Tu = Tuesday). Additionally, O_3 residuals for an O_3 dosage of 5 mg L^{-1} were determined in a second experiment conducted on a Tuesday (narrow bar). The pH values for the effluents were 7 (CAS), 7 (CAS + SS), and 7.5 (MBR).

diclofenac, it can be concluded that suspended solids have only a minor influence on the oxidation of compounds that react fast with O_3. Furthermore, the oxidation by •OH was not affected by suspended solids either, as shown for bezafibrate at low O_3 dosages or for iopromide (Figure 4). At higher O_3 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 O_3 residuals and the associated O_3 exposures.

Estimation of the O_3 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 O_3. For low O_3 dosages, the fact that suspended solids had only minor effects on the ozonation process demonstrates that O_3 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 O_3 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, O_3 mass transfer through the boundary layers surrounding the sludge floc and the gas bubble as well as the O_3 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

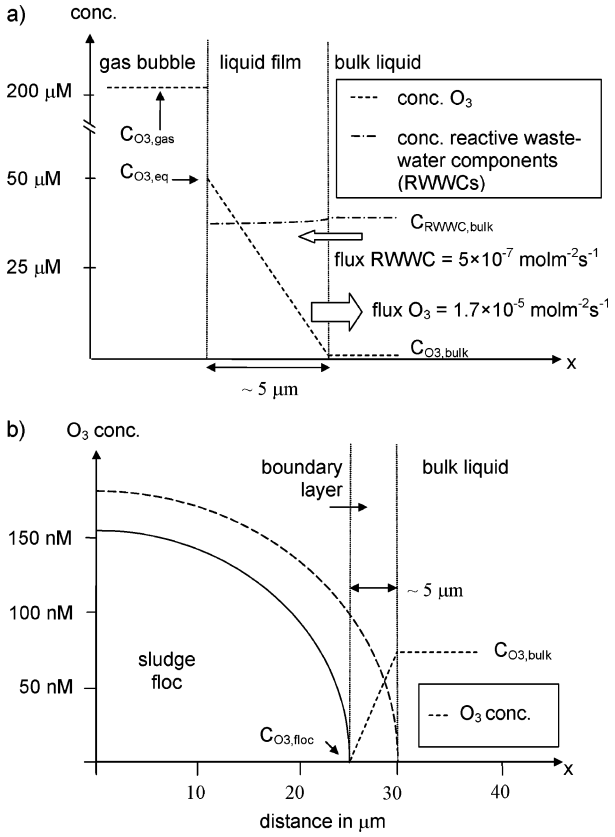


FIGURE 6. (a) Qualitative scheme of the diffusion of O_3 and reactive wastewater components (RWWC) through the liquid film according to film theory. The selected concentrations represent conditions at the bottom of column 1 for an O_3 dosage of 1 mg L^{-1}. (b) Qualitative diffusion profile of O_3 through the boundary layer of a sludge floc.

particles on the fate of adsorbed compounds and microorganisms during ozonation.

The mass transfer of O_3 from the gas phase to the liquid phase is usually calculated according to

$$N_{O3,bulk} = k_L a_b (C_{O3,eq} - C_{O3,bulk}) \text{ with } k_L = \frac{D_{O3}}{\delta_b} \quad (1)$$

where $N_{O3,bulk}$ is the O_3 absorption rate (flux per unit volume); k_L is the mass transfer coefficient for O_3, a_b is the specific interfacial area of the sum of the gas bubbles, $C_{O3,eq}$ is the equilibrium concentration of O_3 at the gas−liquid interface, and $C_{O3,bulk}$ is the concentration in the bulk liquid. The value of k_L is related to the molecular diffusion coefficient of O_3 (D_{O3}) and the thickness of the liquid film (δ_b) surrounding the bubble (see Figure 6a for illustration). The parameters k_L and a_b were not determined in the present studies. Estimations of these parameters on the basis of a study of Roustan et al. (*29*) yielded $k_L \approx 3.4 \times 10^{-4}$ m s^{-1} and $a_b \approx 18$ m^2 m^{-3}. With $D_{O3} = 1.7 \times 10^{-9}$ m^2 s^{-1} (*30*) a film thickness of $\delta_b = 5$ μm is obtained. The study of Roustan et al. was performed by use of a comparable pilot plant and covered operating conditions (bubble diameter ≈ 3 mm, gas velocity ≈ 7 m h^{-1}, and liquid velocity ≈ 70 m h^{-1}) applied in the present study.

Conditions representing the bottom of column 1 for an O_3 dosage of 1 mg L^{-1} were selected for the estimation of the O_3 absorption rate of the bulk liquid and the sludge particles. Close to the ozone diffuser, the O_3 concentration in the gas phase is $C_{O3,gas} = 10$ g m^{-3}. Henry's law relates $C_{O3,gas}$ to $C_{O3,eq}$:

$$H = \frac{C_{O3,eq}}{C_{O3,gas}} \quad (2)$$

where H is the dimensionless Henry constant. With $H = 0.24$ (*31*), eq 2 yields $C_{O3,eq} = 2.4$ g m^{-3} or 50 μM. The fact that no O_3 residuals could be measured at SP-MID for an O_3 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 $N_{O3,bulk} = 3 \times 10^{-7}$ mol s^{-1} L^{-1}.

In the presence of a high concentration of fast-reacting compounds, the O_3 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 ($C_{RWWC,bulk}$, e.g., O_3-reactive moieties of DOC and reactive inorganic compounds) and their rate constants with O_3 have to be estimated. Low O_3 residuals detected at SP-MID for O_3 dosages ≥2 mg L^{-1} indicated that the fast initial O_3 demand of the wastewater is equivalent to approximately 2 mg of O_3 L^{-1} (40 μM) under the assumption that only direct O_3 reactions with a stoichiometry of 1:1 are involved. Therefore, $C_{RWWC,bulk}$ was set to 40 μM. The rate constant for the reaction of O_3 with RWWC was estimated to be $k_{O3} = 1 \times 10^5$ M^{-1} s^{-1}. This rate constant is representative for reactive moieties such as phenols and amines. To assess the importance of the reaction of O_3 in the liquid film compared to O_3 mass transfer across the film, the Hatta number (*Ha*) was calculated with the assumiption that in the film C_{RWWC} = constant = $C_{RWWC,bulk}$:

$$Ha = \frac{\sqrt{k_{O3} D_{O3} C_{RWWC,bulk}}}{k_L} \quad (3)$$

For the selected conditions, eq 3 yields 0.2. $Ha < 0.3$ means that gas absorption follows a so-called slow kinetic regime and that reactions take place primarily in the bulk liquid (*30*). Therefore, O_3 mass transfer is well described by eq 1 and no enhancement due to consumption of O_3 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 O_3 in the liquid film (*30*) yielded very similar results.

Knowing $N_{O3,bulk}$ and $C_{RWWC,bulk}$, the following equation can be used to estimate $C_{O3,bulk}$, which is needed for the calculation of the O_3 absorption rate of the sludge flocs:

$$\frac{dC_{O3,bulk}(t)}{dt} = N_{O3,bulk}(t) - k_{O3} C_{O3,bulk}(t) C_{RWWC,bulk}(t) \quad (4)$$

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 $C_{O3,bulk} = 7.5 \times 10^{-8}$ M. This value corroborates the assumption made for the calculation of the film diffusion and is in agreement with the fact that O_3 concentrations were <0.05 mg L^{-1} (<1×10^{-6} M) at SP-MID for an O_3 dosage of 1 mg L^{-1}.

The diffusion of O_3 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:

$$F_{O3} = \frac{D_{O3}}{\delta_f} (C_{O3,bulk} - C_{O3,floc}) \quad (5)$$

The thickness δ_f of the boundary layer surrounding the flocs must be of the same order of magnitude as δ_b. Because the

flocs move more slowly than the bubbles, it is expected that δ_f is somewhat larger than δ_b. To make a conservative assumption, it was estimated that $\delta_f = \delta_b = 5\ \mu$m. Assuming that the O_3 concentration at the liquid−floc interface ($C_{O3,floc}$) is 0, a flux of $F_{O3} = 2.6 \times 10^{-8}$ mol s^{-1} 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_f) has to be calculated. An area of $a_f = 48$ m^2 m^{-3} was obtained with the assumptions of a water content of the floc of 95%, a spherical shape, and a diameter of 50 μm. Laser diffraction analysis of a different activated sludge showed that 90% of the sludge volume is formed by flocs with a diameter > 50 μm (median = 200 μm) (*32*). The resulting O_3 absorption rate by the sludge flocs is $N_{O3,floc} = F_{O3}a_f/1000 = 1.2 \times 10^{-9}$ mol s^{-1} L^{-1} compared to the absorption rate of the bulk phase of $N_{O3,bulk} = 3 \times 10^{-7}$ mol s^{-1} L^{-1}. According to this estimate, only 0.4% 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 except for unaccountable residuals of E1 for high O_3 dosages. In the case of sulfonamides, somewhat greater variations were detected, which might be caused by one of the following reasons: On one hand, it cannot be excluded that in the case of sulfathiazole the thiazole moiety is more reactive to O_3 than the aniline moiety. On the other hand, the pK_a values of the investigated sulfonamides range from 5.7 (sulfamethoxazole) to 8.4 (sulfapyridine, Table 2). Consequently, sulfamethoxazole is present in its anionic form and sulfapyridine in its neutral form, whereas the remaining sulfonamides are present as a mixture of both species. Anionic species can be orders of magnitude more reactive toward O_3 than their neutral equivalents [e.g., phenolates versus phenols (*33*)]. It is therefore rather surprising that the differences between the investigated sulfonamides are not greater. A possible explanation is that the higher electron density on the acidic nitrogen reflected by a higher pK_a extends to the adjacent moieties, making them significantly more reactive toward O_3. The reactivity of the neutral form of sulfapyridine seems, therefore, to be as high as that of the anion of sulfamethoxazole. Consequently, the reasonable agreement in the oxidation pattern seems to be rather coincidence in the case of the sulfonamides. In general, significant differences in the extent of parent compound oxidation have to be expected when the compared compounds exhibit different speciations under the investigated conditions.

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

	CAS	CAS + SS
inlet pilot plant	$\sim 5 \times 10^5$	$\sim 4 \times 10^5$
2 mg L^{-1} O_3	$\sim 2 \times 10^2$	$\sim 3 \times 10^3$
5 mg L^{-1} O_3	$< 10^2$	$\sim 6 \times 10^2$

[a] Source: ref *40*. *E. coli* concentrations are given in colony-forming units per 100 mL with an error of ±0.5 log unit.

A large share of sulfamethoxazole enters WWTPs in its acetylated form as N^4-acetylsulfamethoxazole (N^4AcSMX, Table 2) (*22*). This metabolite was also present in the investigated effluents. In Figure 7, the oxidation pattern of N^4AcSMX is given as well. The O_3-reactive aniline moiety of N^4AcSMX is protected with an acetyl group that changes the electron density of this moiety. Therefore, the metabolite N^4AcSMX reacts more slowly with O_3 and, consequently, is oxidized to a significantly lesser extent than the active compound sulfamethoxazole. Accordingly, N^4-acetylsulfamethazine, which was spiked in the wastewater, showed a very similar behavior (data not shown).

Figure 8 illustrates the oxidation of contrast media in CAS. Contrast media do not react with O_3, but due to similarities in size and structure they all exhibit similar reactivities to •OH that result in a comparable extent of parent compound oxidation. Only the anionic contrast medium diatrizoate showed a different pattern, suggesting a substantially lower reactivity to •OH. Overall, these results show that within certain limits it is possible to predict the extent of parent compound oxidation of structurally similar molecules with the same reactive moiety based on a suitable probe compound present in the wastewater.

Prediction of Parent Compound Oxidation. More important than the prediction of the oxidation of compounds within the same class of pharmaceuticals (such compounds can usually be measured with a single analytical method) would be a prediction for compounds of various classes on 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:

$$\frac{dC_P(t)}{dt} = -k_{O3}C_{O3}(t)C_p(t) - k_{OH}C_{OH}(t)C_p(t) \qquad (6)$$

where C_P, C_{O3}, and C_{OH} are the concentrations of the pollutant, O_3, and •OH, respectively, and k_{O3} 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

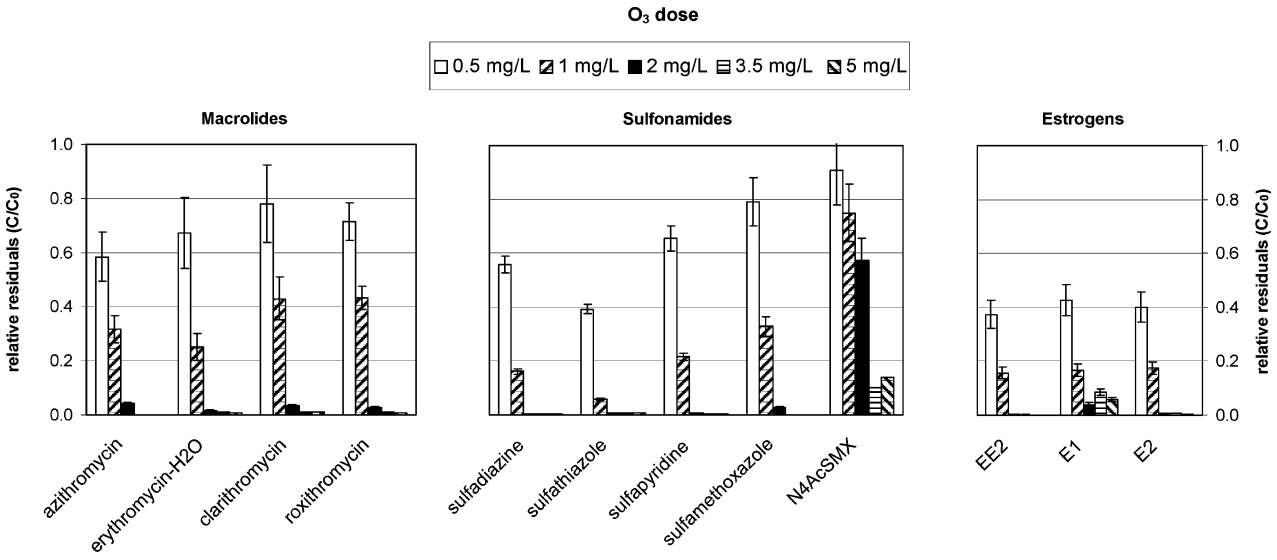


FIGURE 7. Relative residual concentrations of macrolides, sulfonamides, and estrogens in CAS effluent (pH = 7) for O_3 doses ranging from 0.5 to 5 mg L^{-1}.

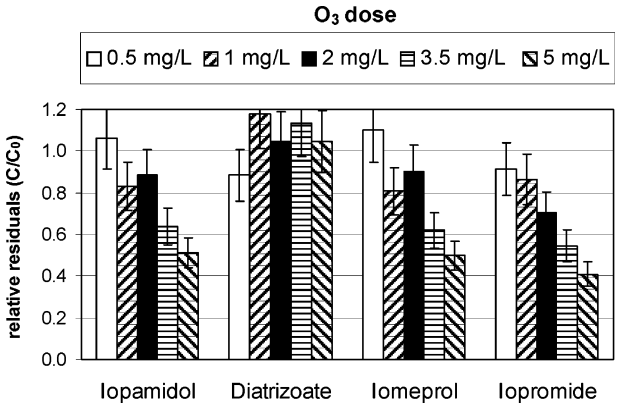


FIGURE 8. Relative residual concentrations of iodinated X-ray contrast media in CAS effluent (pH = 7) for O_3 doses ranging from 0.5 to 5 mg L^{-1}.

pollutant, the integrated form of eq 6 has to be used:

$$\frac{C_p(\tau)}{C_p(0)} = \exp[-k_{O3}\int_0^\tau C_{O3}(t)\,dt - k_{OH}\int_0^\tau C_{OH}(t)\,dt] \quad (7)$$

If k_{O3} and k_{OH} are known, only the O_3 exposure [$\int C_{O3}(t)\,dt$] and the •OH exposure [$\int C_{OH}(t)\,dt$] 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. •OH exposures were calculated with help of a probe compound and the R_{ct} value. However, •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 •OH exposure can be calculated on the basis of the relative residual concentration of the probe compound (C_{PC}) and its rate constant with •OH ($k_{OH,PC}$):

$$\int_0^\tau C_{OH}(t)\,dt = -\frac{1}{k_{OH,PC}} \ln\left[\frac{C_{PC}(\tau)}{C_{PC}(0)}\right] \quad (8)$$

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 •OH exposures. However, since all organic compounds react with •OH at appreciable rates, residuals of O_3 probes always have to be corrected for oxidation by •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 •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 •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 roxithormycin), 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 RWWCs 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 O_3 versus Oxidation by •OH. By use of ibuprofen as a probe compound, the oxidation of O_3 refractive compounds by •OH could be well predicted with the following equation:

$$\ln\left[\frac{C_P(\tau)}{C_P(0)}\right] = \frac{1}{k_{OH,IBU}} \ln\left[\frac{C_{IBU}(\tau)}{C_{IBU}(0)}\right] k_{OH} \quad (9)$$

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 O_3, even if the prediction of oxidation by O_3 failed. The comparison of the predicted oxidation by •OH with the measured residuals ($C_{P,m}$) allows us to assess the relevance of the two oxidation pathways for a selected compound according to the following equation (*27*):

$$f(\text{•OH}) = \frac{\frac{1}{k_{OH,IBU}} \ln\left[\frac{C_{IBU}(\tau)}{C_{IBU}(0)}\right] k_{OH,P}}{\ln\left[\frac{C_{P,m}(\tau)}{C_{P,m}(0)}\right]} \quad (10)$$

where f(•OH) designates the fraction of oxidation by •OH, and 1-f(•OH), the fraction of oxidation by O_3. 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 O_3 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 O_3, •OH accounts for 20−50% of the parent compound oxidation. This demonstrates clearly that in wastewater •OH radicals cannot be neglected in product studies, even if O_3 reactions would clearly predominate in a pure system. Because •OH reaches the highest concentration at first contact of wastewater with O_3, it can be assumed that higher O_3 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 O_3 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, O_3 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 micropollutant 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 O_3 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).

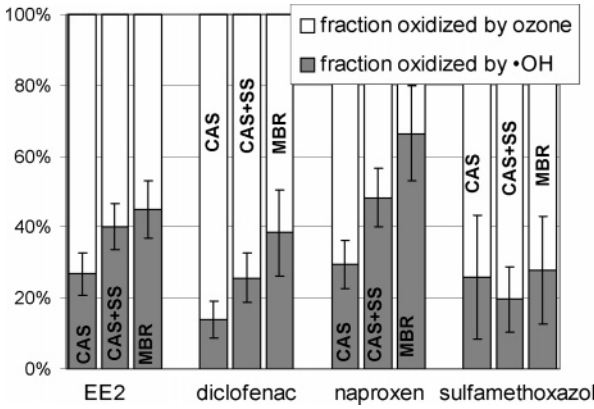


FIGURE 9. Calculated fractions oxidized by •OH and O_3 for fast-reacting pharmaceuticals for an O_3 dose of 1 mg L^{-1}. The calculation is based on the assumption that the ratio of the oxidant concentrations [•OH]/[O_3] remains approximately constant during the reaction time. The pH values for the effluents were 7 (CAS), 7 (CAS + SS), and 7.5 (MBR).

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