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Oxidation of Pharmaceuticals during Ozonation and Advanced Oxidation Processes

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This study investigates the oxidation of pharmaceuticals during conventional ozonation and advanced oxidation processes (AOPs) applied in drinking water treatment. In a first step, second-order rate constants for the reactions of selected pharmaceuticals with ozone (k_{O_3}) and OH radicals (k_{OH}) were determined in bench-scale experiments (in brackets apparent k_{O_3} at pH 7 and T = 20 °C): bezafibrate (590 ± 50 M^{-1} s^{-1}), carbamazepine (~3 × 10^5 M^{-1} s^{-1}), diazepam (0.75 ± 0.15 M^{-1} s^{-1}), diclofenac (~1 × 10^6 M^{-1} s^{-1}), 17α-ethinylestradiol (~3 × 10^6 M^{-1} s^{-1}), ibuprofen (9.6 ± 1.0 M^{-1} s^{-1}), iopromide (<0.8 M^{-1} s^{-1}), sulfamethoxazole (~2.5 × 10^6 M^{-1} s^{-1}), and roxithromycin (~7 × 10^4 M^{-1} s^{-1}). For five of the pharmaceuticals the apparent k_{O_3} at pH 7 was >5 × 10^4 M^{-1} s^{-1}, indicating that these compounds are completely transformed during ozonation processes. Values for k_{OH} ranged from 3.3 to 9.8 × 10^9 M^{-1} s^{-1}. Compared to other important micropollutants such as MTBE and atrazine, the selected pharmaceuticals reacted about two to three times faster with OH radicals. In the second part of the study, oxidation kinetics of the selected pharmaceuticals were investigated in ozonation experiments performed in different natural waters. It could be shown that the second-order rate constants determined in pure aqueous solution could be applied to predict the behavior of pharmaceuticals dissolved in natural waters. Overall it can be concluded that ozonation and AOPs are promising processes for an efficient removal of pharmaceuticals in drinking waters.

Introduction

In recent years, there has been growing concern about the occurrence of pharmaceuticals in the aquatic environment. Comprehensive review articles on the environmental relevance of pharmaceuticals have recently been published by Halling-Sørensen et al. (*1*), and Daughton and Ternes (*2*). Moreover, several studies have reported the occurrence of a great variety of pharmaceuticals in surface waters (*3*−*5*).

Surface water is widely used as water resource for drinking water. Therefore, the widespread occurrence of pharmaceuticals in surface waters may pose a problem to water utilities. Only a few pharmaceuticals have been detected in drinking waters so far (*6*, *7*). Concentrations were typically in the lower nanogram/L-range. Up to now, there has been no proof that very low concentrations of pharmaceuticals have any adverse health effects. Nevertheless, based on precautionary principles, drinking water should be free from these compounds to minimize the risk of unpredictable long-term effects. Hence, it is important to assess water treatment processes with regard to their potential for removing pharmaceuticals. Only limited information is available concerning this question. In a recent study, the removal of some selected pharmaceuticals during drinking water treatment was investigated in lab, pilot, and full-scale experiments (*8*). It was demonstrated that among different treatment steps only ozonation and filtration with granular activated carbon were effective in removing pharmaceuticals. The potential of ozonation and advanced oxidation processes (AOPs) for removing pharmaceuticals was confirmed in another study (*9*). However, both studies were performed using natural water samples, yielding case-specific information on the removal efficiency. To assess the removal efficiency of ozonation and AOPs in different natural waters, it is indispensable to determine the rate constants for the reaction of pharmaceuticals with the oxidants, i.e., ozone and OH radicals. In addition, information about oxidant concentrations is required.

The aim of the research presented here was to assess the potential of ozonation and AOPs for the oxidation of pharmaceuticals. A list of nine pharmaceuticals was selected on the basis of consumption and environmental relevance (Table 1). A major task of this study was to establish a database with second-order rate constants for the reactions of the selected pharmaceuticals with ozone and OH radicals. The determination of the rate constants was carried out in bench-scale systems in pure aqueous solution. To predict the oxidation of micropollutants during ozonation processes, Elovitz and von Gunten (*10*) developed the R_{ct} concept, which allows the prediction of the time-dependent transformation of a compound based on rate constants and oxidant behavior. The R_{ct} concept was successfully applied to predict the oxidation of atrazine (*11*) and MTBE (*12*) and the formation of their oxidation products during ozonation and AOPs. In the present study, this concept was applied to the selected pharmaceuticals in order to show the effect of the water matrix on the oxidation efficiency. To apply the R_{ct} concept, experiments were performed with surface waters and groundwaters under realistic treatment conditions.

Materials and Methods

Standards and Reagents. Bezafibrate, carbamazepine, diclofenac, ibuprofen, sulfamethoxazole, and roxithromycin were obtained from Sigma-Aldrich with a purity higher than 99% (roxithromycin > 91%). Iopromide and 17α-ethinylestradiol were provided by Schering/Berlin, Germany. Diazepam was offered by Roche AG/Basel, Switzerland. Stock solutions of these pharmaceuticals were prepared with Milli-Q purified water (Millipore). All chemicals used for solutions (buffer, eluents, etc.) were reagent grade and were used without further purification. Ozone stock solutions (~1 mM) were produced by sparging O_3-containing oxygen through Milli-Q water that was cooled in an ice bath (*13*). For some experiments, ozone stock solutions were prepared without cooling to obtain less concentrated solutions.

Natural Water Systems. To simulate real treatment conditions, experiments were performed using four natural waters that differed in dissolved organic carbon content (DOC) and alkalinity. They covered the range of typical raw waters used for drinking water production in Europe (for water quality parameters, see Table 2) and included the following: (i) raw water from Lake Zurich, Switzerland col-

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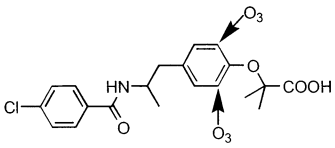
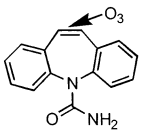
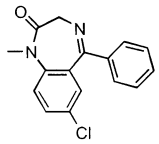
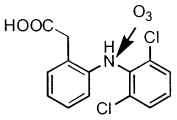
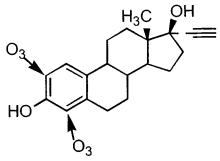
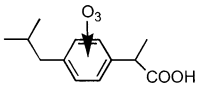
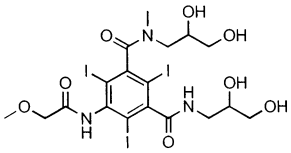
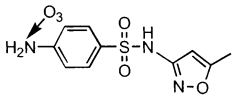
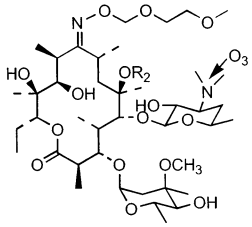
TABLE 1. Selected Pharmaceuticals (Arrows Show the Sites of the Molecules where Ozone Attack can be Expected)

Compound	Bezafibrate	Carbamazepine	Diazepam
Use	lipid regulator	antiepileptic/analgesic[a]	tranquilizer
Structure			
Compound	Diclofenac	17α-Ethinylestradiol	Ibuprofen
Use	antiphlogistic	ovulation inhibitor	antiphlogistic
Structure			
Compound	Iopromide	Sulfamethoxazole	Roxithromycin
Use	contrast medium	antibiotic	antibiotic
Structure			

[a] Used in the treatment of nerve pain.

TABLE 2. Water Quality Parameters

sample (abbreviation)	pH	DOC (mg/L)	alkalinity (mM HCO_3^-)
lake water, Zurich (LZ)	7.9	1.2	2.6
bank filtrate River Seine, Paris (RS)	7.8	1.3	4.1
well water, Porrentruy (WP)	7.2	0.8	5.8
lake water, Finland (LF)	7.5	3.7	0.7

lected from a depth of 30 m was obtained from a drinking water plant in Zurich (LZ water); (ii) bank filtrate from River Seine was received from a drinking water plant in Paris, France (RS water); (iii) filtered well water was provided by a drinking water plant in Porrentruy, Switzerland (WP water); (iv) flocculated, sandfiltered water from a lake in Finland was received from Tampere University of Technology, Finland (LF water). All waters were filtered (0.45-μm cellulose nitrate) upon arrival and stored at 4 °C until use.

Analytical Methods. All pharmaceuticals and *p*-chlorobenzoic acid (*p*CBA) used as reference compound for the determination of OH radical rate constants and R_c values were determined by high-performance liquid chromatography (HPLC, Hewlett-Packard, 1050 series) equipped with a variable wavelength detector. Eluents consisted of 10 mM phosphoric acid and methanol or acetonitrile. Depending on compounds and experiments, isocratic or gradient elutions were used with varying eluent ratios (column: Nucleosil 100, 5-μm C18, Machery-Nagel). The sample volumes injected varied from 25 to 250 μL depending on concentrations analyzed. Quantification limits of about 0.05−0.1 μM (10−40 μg/L) were achieved. The 95% confidence intervals for a single measurement were typically ±3−10% and the recoveries in natural waters ranged from 95% to 100%. Dissolved ozone was determined with the indigo method (*13*) or spectrophotometrically by measuring the absorbance at 258 nm ($\epsilon = 3000\ M^{-1}\ cm^{-1}$).

Determination of Rate Constants for the Reaction of Pharmaceuticals with Ozone. All experiments were performed in Milli-Q purified water using *tert*-butyl alcohol (10−50 mM) as the OH radical scavenger. The solutions were adjusted to the desired pH with phosphate buffer (5 or 50 mM). If not stated otherwise, experiments were carried out at 20 °C. If possible, the second-order rate constants were determined under conditions where either ozone or the target compound was in excess.

Ozone in Excess. Experiments with bezafibrate, diazepam, and ibuprofen were conducted with ozone in excess at pH 6. As a reaction vessel, 500-mL glass bottles with a dispenser system mounted onto the screwtop were used (*14*). For bezafibrate, the kinetic runs were started by adding 10 mL of the ozone stock solution to the solution containing bezafibrate (1 μM), yielding a final ozone concentration of 20 μM (1 mg/L). After 20 s, the first sample (5 mL) was withdrawn with a dispenser system. Subsequently, sampling was performed in 15-s time intervals. The ozone residual was quenched immediately by adding 0.1 mL of a fresh sodium sulfite solution (24 mM). After 2.5 min the last sample was directly transferred into a UV-cell without adding sulfite, and ozone was determined spectrophotometrically. Pre-

liminary experiments performed under the same conditions showed that ozone decrease is <5% during the sampling period of 2.5 min. Therefore, it was assumed that the ozone concentration remained constant during the experiments. The samples were immediately analyzed by HPLC. To determine the activation energy for the reaction of ozone with bezafibrate, the same experiments were carried out at 5, 10, and 15 °C.

For diazepam and ibuprofen, the procedure for bezafibrate had to be adapted to higher ozone concentrations (0.2 and 0.1 mM, respectively) and longer sample intervals (10 and 5 min, respectively). As a consequence, it is necessary to measure the ozone decay, and the data were evaluated by plotting pharmaceutical concentrations versus ozone exposure, i.e., ozone concentration integrated over time. The slope of the resulting straight line represented the rate constant.

Pharmaceuticals in Excess. Second-order rate constants for iopromide and roxithromycin, as well as the activation energy for ibuprofen, were determined under conditions where the pharmaceutical compounds were in excess. In this case, the ozone decrease was monitored instead of the disappearance of the target compound. Due to the absorption of iopromide and ibuprofen in the range of 258 nm, ozone could not be quantified by measuring the direct UV absorption at 258 nm. Therefore, the indigo method was applied for these experiments (*15*). To determine the activation energy of ibuprofen, experiments were carried out at 5° to 25 °C. Because roxithromycin exhibits no UV absorption at 258 nm, the ozone concentration could be determined by measuring its UV absorption. Kinetic runs were performed in spectrophotometric cells of 35-mL volume with Suprasil quartz window and 10-cm optical path length. The cell was mounted in a temperature-stabilized metal block inside the spectrophotometer (Kontron Instruments, Uvikon 940). The ozone decay was monitored directly in the spectrophotometer with a sampling interval of 1.2 s. Because of the pH-dependent rate constant, pH values ranging from 4.5 to 3.3 were selected. The resulting ozone half-lives ranged from 0.2 to 5 min. The experimental setup did not allow the measurement of shorter half-lives, which would occur at higher pH values.

Competition Kinetics. The methods described above are limited to rate constants that are lower than about 1000 M^{-1} s^{-1}. Only pH-dependent rate constants can be extrapolated to higher values. In this study, competition kinetics was used to determine high rate constants. For 17α-ethinylestradiol, phenol ($k_{O_3,\text{phenolate}} = 1.4 \times 10^9$ M^{-1} s^{-1}, $pK_a = 9.9$ (*16*)) was selected as a reference compound because a similar reaction mechanism and a similar rate constant were expected. The experiments were carried out in 25-mL serum vials at pH 6 with solutions containing equal concentrations of 17α-ethinylestradiol and reference compound (4 μM). Different understoichiometric concentration levels of ozone ranging from 1.5 to 7.5 μM were added with a glass syringe to a series of serum vials. During ozone injection the solutions were vigorously stirred. Remaining concentrations of target and reference compound in the serum vials were then analyzed by HPLC. The data were evaluated based on eq 1, where $k_{O_3}(R)$ and $k_{O_3}(M)$ are the rate constants for the reference (R) and target compound (M), respectively. The different ozone doses are represented by n.

$$\ln\left(\frac{[M(n)]}{[M(0)]}\right) = \ln\left(\frac{[R(n)]}{[R(0)]}\right)\frac{k_{O_3}(M)}{k_{O_3}(R)} \qquad (1)$$

The apparent rate constant $k_{O_3}(M)$ could be determined from a plot of $\ln([M(n)]/[M(0)])$ versus $\ln([R(n)]/[R(0)]$ with $k_{O_3}(M)/k_{O_3}(R)$ as the slope of the straight line. To confirm the results, the same experiments were also performed with the pairs 17α-ethinylestradiol/4-chlorophenol and phenol/4-chlorophenol. The second-order rate constant for the dissociated 17α-ethinylestradiol was calculated from the measured apparent rate constant based on the assumption that the reactivity of the neutral 17α-ethinylestradiol can be neglected at pH 6.

A very similar experimental setup was used to determine the rate constants for diclofenac and sulfamethoxazole. Phenol was chosen as the reference compound. In contrast to the method mentioned above, the ratio of the target compound to the reference compound was varied from 1:3 to 3:1 and experiments were carried out at pH 7. Preliminary experiments showed that at this pH the apparent rate constants of phenol were similar to the rate constants of the target compound. Phenol reacts about 10 times faster at pH 7 than at pH 6. To check whether competition kinetics can be applied under these conditions, additional experiments were conducted at pH 6.7 for diclofenac and pH 7.3 for sulfamethoxazole. At pH 6.7 phenol reacts slightly more slowly with ozone than diclofenac, whereas at pH 7 phenol reacts slightly faster. Correspondingly, the reactivity of phenol at pH 7.3 is higher than that of sulfamthoxazole and lower at pH 7. The variation of pH resulted in only small changes for the calculated rate constants showing that the results are consistent. Competition kinetics between diclofenac and sulfamethoxazole directly could not be performed due to secondary reactions between a product of sulfamethoxazole and diclofenac.

A method developed by Muñoz and von Sonntag (*17*) was adapted to determine the rate constant of carbamazepine. A constant ozone dose (10 μM) was added to solutions containing 80 μM carbamazepine and varying concentrations of the reference compound nitrite (3.7×10^5 M^{-1} s^{-1} (*18*)) or buten-3-ol (7.9×10^4 M^{-1} s^{-1} (*19*)), respectively. The product formed through the reaction of ozone with carbamazepine was monitored (the structure of this product is not known, its UV spectra is similar to that of carbamazepine). The rate constant was then derived by comparing product formation in the presence and in the absence of the reference compound. The experiments were carried out at pH 7 in 25-mL serum vials. Ozone was added with a glass syringe while the reaction solution was vigorously stirred.

Determination of Rate Constants for the Reaction of Pharmaceuticals with OH Radicals. Competition kinetics was used to determine the second-order rate constants for the reaction with OH radicals. The reference compound was *p*CBA exhibiting a rate constant of $k_{OH} = 5 \times 10^9$ M^{-1} s^{-1} (*20*). All experiments were carried out with Milli-Q water at 25 °C and the pH was kept constant at 7 using 5 mM phosphate buffer. For most experiments, OH radicals were generated by photolysis of H_2O_2 at 313 nm. These experiments were performed in quartz tubes using a merry-go-round photoreactor (DEMA model 125, Hans Mangels GmbH, Bornheim-Roisdorf, Germany) equipped with a medium-pressure mercury lamp (Hanau model TQ718) driven at a power of 500 W. A UVW-55 glass band-pass filter (supplied by DEMA) was used to eliminate radiation of wavelengths shorter than 308 nm in order to minimize direct photolysis of the pharmaceuticals. Further details about the irradiation equipment are given elsewhere (*21*, *22*). For compounds undergoing direct photolysis, OH radicals were generated with γ-radiolysis. The experiments were performed in a ^{60}Co γ-radiation source with lead shielding (type GAMMACELL, Atomic Energy of Canada; dose rate for water = 2.1 $kGyh^{-1}$ ± 20% in the center of source with lead shielding). Solutions were saturated with a 4:1 mixture of N_2O and O_2 (*23*). N_2O is necessary to convert solvated electrons into OH radicals. The rate of OH radical formation was about 0.1 μM s^{-1}. Initial pharmaceutical and reference compound concentrations were 1 μM in UV/H_2O_2 experiments and 10 or 50 μM in γ-radiolysis experiments. In both experiments, samples were

TABLE 3. Second-Order Rate Constants for the Reaction of Ozone with the Investigated Pharmaceuticals

compound	pK_a	method[a]	k_{O_3} (T = 20 °C)[b] (M^{-1} s^{-1})	reactive species
bezafibrate	3.6	HPLC	590 ± 50	dissociated
carbamazepine		CK	~3×10^5	neutral
diazepam		HPLC	0.75 ± 0.15	neutral
diclofenac	4.2	CK	~1×10^6	dissociated
17α-ethinylestradiol	10.4	CK	~7×10^9	dissociated
ibuprofen	4.9	HPLC/indigo	9.6 ± 1	dissociated
iopromide		indigo	<0.8	neutral
sulfamethoxazole	5.7	CK	~2.5×10^6	dissociated
roxithromycin	8.8	UV	$(4.5 \pm 0.5) \times 10^6$	neutral

[a] HPLC: decrease of target compound. Indigo: measurement of ozone decrease with indigo method. UV: direct measurement of ozone at 258 nm. CK: competition kinetics. [b] Rate constants for the most reactive species given in the last column.

repeatedly irradiated for constant time intervals. Between irradiation periods, samples were withdrawn for HPLC analysis. The data were evaluated based on eq 2, where k_{OH}(R) and k_{OH}(M) are the rate constants for the reference (R) and target compound (M), respectively. The irradiation time is represented by t.

$$\ln\left(\frac{[M(t)]}{[M(0)]}\right) = \ln\left(\frac{[R(t)]}{[R(0)]}\right)\frac{k_{OH}(M)}{k_{OH}(R)} \qquad (2)$$

For iopromide, OH radicals were also generated by the O_3/H_2O_2 system. Instead of repeated sampling, different ozone doses were added to solutions with varying ratios of iopromide and *p*CBA (from 1:3 to 3:1).

Ozonation of Natural Waters. Two different experimental setups were used to investigate the oxidation of pharmaceuticals during the ozonation of natural waters. Pharmaceuticals with rate constants $k_{O_3} > 10^3$ M^{-1} s^{-1} were investigated with the setup for fast-reacting compounds, pharmaceuticals with rate constants < 100 M^{-1} s^{-1} were investigated with the setup for slow-reacting compounds. Bezafibrate was tested with both setups.

Fast-Reacting Compounds. RS or LF water (Table 1) was buffered to pH 8 by adding 10 mM borate buffer and adjusting the pH with HCl. The water was then spiked with one pharmaceutical compound (0.5 μM) and transferred into five 25-mL serum vials. In a next step, ozone doses of 0.1, 0.2, 0.5, 1, and 2 mg/L were injected into the vials while the water was vigorously stirred for a few seconds. As soon as ozone was completely consumed (up to 10 h for RS water), residual pharmaceutical concentrations were measured with HPLC. All experiments were performed at 10 °C. To determine bromate formation under the applied conditions, one experiment was carried out without adding a pharmaceutical compound. Instead, 50 μg/L bromide was added to LF water to achieve a bromide level of 60 μg/L. RS water already contained about 60 μg/L bromide and no spiking was necessary. Bromate was determined according to a method developed by Salhi and von Gunten (*24*).

Slow-Reacting Compounds. Natural water samples were buffered to pH 8 by adding 10 mM borate buffer and adjusting the pH with HCl. The water was then spiked with one pharmaceutical compound (0.5 μM) and the probe compound *p*CBA (0.25 μM), which does not react with ozone directly. The spiked concentrations were low enough to avoid significant changes in ozone half-lives or OH radical scavenging-capacities of the investigated waters. The experiments were carried out at 10 °C in order to mimic realistic treatment conditions. Amber bottles (500 mL) equipped with a dispenser system (*14*) served as reaction vessels. The experiments were started by adding 2 mg/L ozone and, subsequently, samples were withdrawn in regular time intervals. The reaction was stopped with indigo for residual ozone measurements. For pharmaceutical and *p*CBA analysis, ozone was quenched with sodium sulfite. For analysis methods with gradient elution, samples had to be adjusted to acidic pH by adding HCl before analysis.

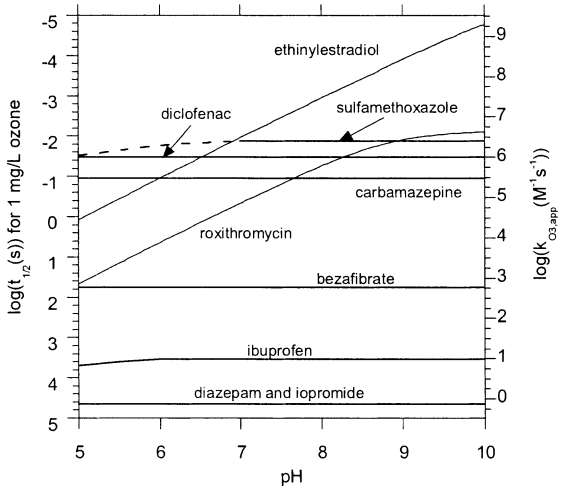


FIGURE 1. Half-lives and apparent second-order rate constants for the reactions of the investigated pharmaceuticals with ozone as a function of pH at 20 °C. The half-lives are calculated for an ozone concentration of 1 mg/L (20 μM) neglecting reactions with OH radicals.

Results and Discussion

Rate Constants for the Reaction of Selected Pharmaceuticals with Ozone. Second-order rate constants for the reaction of pharmaceuticals with ozone have been determined to assess the oxidation of these compounds during conventional ozonation or ozone-based AOPs. Table 3 and Figure 1 summarize the results. Measurements were performed at least three times and the errors given are 95% confidence intervals. For competition kinetics, errors are larger and more difficult to estimate, partly due to the errors induced by the use of reference compounds. We expect rate constants measured with this method to vary up to a factor of 2. Methods monitoring the ozone decay (indigo/UV) yield a rate constant which differs from the second-order rate constant by the stoichiometric factor η, which defines the number of ozone molecules consumed per molecule of target compound under the experimental conditions. According to ref *15* values for η range from 1 to 2.5. Deviations from $\eta = 1$ can be caused by fast side reactions of ozone with products of the primary reactions.

Figure 1 shows half-lives (O_3 = 1 mg/L) and apparent second-order rate constants as a function of pH. Ozone rate constants typically depend on speciation. Generally, deprotonated species react faster with the electrophilic ozone,

TABLE 4. Examples of Pharmaceuticals, Personal Care Products, and Endocrine Disrupters for Which High Ozone Rate Constants Are Expected

compound/class	use/origin	reactive group	estimated rate constant at pH 7, $T = 20$ °C (M^{-1} s^{-1})
β-blockers	β-blocker	amine	$(1-10) \times 10^3$
fluoroquinolones	antibiotic	amine	$(1-10) \times 10^3$
macrolides	antibiotic	amine	$> 10^5$
sulfonamides	antibiotic	amine	$> 10^5$
tetracyclines	antibiotic	phenol	$(1-10) \times 10^6$
triclosan	antimicrobial disinfectant	phenol	$> 10^6$
oxybenzone	sunscreen agent	phenol	$(1-10) \times 10^6$
estradiol	reproductive hormone	phenol	10^6 [a]
testosterone	reproductive hormone	double bond	10^5
4-nonylphenol	nonionic detergent metabolite	phenol	$(1-10) \times 10^6$
bisphenol A	plasticizer	phenol	$(1-10) \times 10^6$

[a] Measured.

because they are stronger nucleophiles (*16*). The rate constants given in Table 3 refer to the most reactive species, which are listed in the last column of the table. For most pharmaceuticals, the reactive species correspond to the predominant species in the pH range from 5 to 10. As a consequence, their apparent rate constants are stable in this pH range. However, rate constants for 17α-ethinylestradiol and roxithromycin depend strongly on pH because their pK_a values are higher than 8 and the deprotonated phenolic group of 17α-ethinylestradiol and the nonprotonated amine of roxithromycin react many orders of magnitude faster than their protonated forms.

Oxidation reactions with ozone are highly selective reactions. As a result, rate constants range over about 10 orders of magnitude (*25*, *26*). Among the pharmaceuticals investigated, the dissociated form of 17α-ethinylestradiol exhibited the highest rate constant reacting at nearly diffusion-controlled rate. Experiments with 17β-estradiol instead of 17α-ethinylestradiol yielded the same rate constant (data not shown) and a similar product, demonstrating that the reaction takes place at the phenolic group and not at the ethinyl group. This implied that the rate constant for 17α-ethinylestradiol is pH dependent. Knowing the pK_a (10.4), the rate constant for the dissociated form could be extrapolated. This rate constant is in accordance with rate constants for other phenolic compounds.

For diclofenac and sulfamethoxazole the rate constants are 1×10^6 and 2.5×10^6 M^{-1} s^{-1}, respectively. These compounds react more slowly than dissociated 17α-ethinylestradiol; however, apparent rate constants at pH 7 are in the same order of magnitude. The main reaction sites are the aromatic amino groups (see Table 1). Because protonated amino groups do not react with ozone (*16*), the reactivity of amines is strongly related to their pK_a values. Compared to other amines, diclofenac and sulfamethoxazole react particularly fast because the pK_a values of the amino groups are <3. This means that at pH > 5, the nonprotonated amine (reactive species) is the predominant species. By contrast, the amino group in roxithromycin has a pK_a of 8.8 and at pH < 8 the nonreactive protonated amine is predominant, leading to a diminished reactivity. The rate constant for sulfamethoxazole might be weakly pH dependent at pH < 7 due to the protonation of the dissociated sulfonamide group (pK_a = 5.7). The high reactivity of carbamazepine can be assigned to the reaction of ozone at the double bond which connects the two phenyl moieties (see Table 1). The rate constant is slightly higher than that for other olefins, but in very good agreement with the rate constant for styrene (3×10^5 M^{-1} s^{-1} (*15*)).

For water treatment conditions (pH 7–8, O_3 = 1 mg/L) half-lives for 17α-ethinylestradiol, carbamazepine, roxithromycin, diclofenac, and sulfamethoxazole are <0.5 s. This indicates clearly that, for these pharmaceuticals, the parent compound is completely transformed during ozonation processes and ozone-based AOPs. The remaining pharmaceuticals have considerably lower rate constants. The intermediate reactivity of bezafibrate is caused by the R-oxy substituent ($-O-C(CH_3)_2COOH$) on one of the aromatic rings. R-oxy substituents have an activating effect on aromatic rings similar to that of hydroxy substituents (*15*). However, R-oxy substituents cannot be deprotonated and consequently the overall rate constant at pH > 4 is much lower. Nevertheless, this compound will also be largely transformed by most ozonation processes. Ibuprofen reacts with a rate constant of 9.6 M^{-1} s^{-1}. The low rate constants can be explained by the absence of reactive groups and an aromatic ring that is only slightly activated, similar to toluene (*15*). Because of the low rate constant, direct reactions with ozone will play a minor role during ozonation processes and the oxidation of this compound will be caused mainly by OH radicals originating from ozone decay. The reaction of ozone with iopromide is very slow which allows only an estimate of an upper limit. Iopromide exhibits three nitrogen atoms as amides. In contrast to amines, amides have a very low reactivity to ozone. The rate constant for the reaction of diazepam with ozone is also very low. Therefore, during ozonation processes direct ozone reactions are in both cases less important than oxidation by OH radicals.

For two pharmaceuticals with intermediate to low ozone rate constants, activation energies were determined to calculate their rate constants at temperatures below 20 °C. Ibuprofen exhibited an activation energy of 57 ± 8 kJ/mol and bezafibrate had one of 39 ± 6 kJ/mol. Typically, activation energies for reactions with ozone range from 35 to 50 kJ/mol (*15*).

Expected Reactivity of other Pharmaceuticals. Table 4 lists different classes of pharmaceuticals as well as some important personal care products and endocrine disrupters together with the ozone-reactive moieties. On the basis of these characteristics and our results, expected second-order rate constants can be estimated. Generally, many pharmaceuticals, personal care products, and endocrine disrupters contain phenol or amino groups in their structures. Sulfamethoxazole and roxithromycin belong to the antibiotic classes of sulfonamides and macrolides, respectively. The reactive groups (aromatic amine and tertiary amine, respectively) are characteristic for all the compounds in these two groups. Therefore, rate constants for all sulfonamides and macrolides will be very similar to the rate constants for sulfamethoxazole and roxithromycin, respectively. The endocrine disrupter 17α-ethinylestradiol is a synthetic steroid hormone. Many steroid hormones have a phenolic group

TABLE 5. Rate Constants for the Reaction of OH Radicals with the Investigated Pharmaceuticals and Some Other Important Micropollutants

Investigated Pharmaceuticals		
compound	method	k_{OH} (10^9 M^{-1} s^{-1})[a]
bezafibrate	UV/H_2O_2	7.4 ± 1.2
carbamazepine	UV/H_2O_2	8.8 ± 1.2
diazepam	UV/H_2O_2, γ-radiolysis	7.2 ± 1.0
diclofenac	γ-radiolysis	7.5 ± 1.5
17α-ethinylestradiol	UV/H_2O_2	9.8 ± 1.2
ibuprofen	UV/H_2O_2	7.4 ± 1.2
iopromide	O_3/H_2O_2, γ-radiolysis	3.3 ± 0.6
sulfamethoxazole	UV/H_2O_2	5.5 ± 0.7

Other Micropollutants		
compound	function	k_{OH} (10^9 M^{-1} s^{-1})[b]
atrazine	pesticide	2.4
MTBE	fuel additive	1.6
perchloroethylene	solvent	2−3
trichloroethylene	solvent	3−4

[a] Experimental conditions pH = 7, T = 25 °C, errors = 95% confidence intervals. [b] Reference: (*20*).

(e.g., 17α-estradiol, 17β-estradiol, estrone, and equilin) and, therefore, will exhibit about the same reactivity as 17α-ethinylestradiol. For 17β-estradiol, this was confirmed by measurements. Other steroid hormones lack the phenolic group but have a double bond (progesterone, testosterone). These compounds will react about 1 order of magnitude slower than phenolic steroid hormones.

Rate Constants for the Reaction of Pharmaceuticals with OH radicals. Besides the direct reaction with ozone, reactions with OH radicals also contribute to the oxidation of micropollutants during ozonation (*26*). Moreover, OH radicals are the main oxidants in AOPs. Therefore, the rate constants for the reaction of 8 selected pharmaceuticals with OH radicals were determined. Results are summarized in Table 5.

Most rate constants were measured with the UV/H_2O_2 method. Some pharmaceuticals, however, were photolyzed by UV-radiation. Direct photolysis accounted for 75, 13, and 7% of the observed rate constant for diclofenac, iopromide, and sulfamethoxazole, respectively. Because direct photolysis followed first-order kinetics, as did the oxidation by OH radicals, the rate constant for sulfamethoxazole was corrected for the percentage mentioned above. Rate constants for diclofenac and iopromide were determined using γ-radiolysis.

The rate constants for the reactions of pharmaceuticals with OH radicals range from 3 to 10×10^9 M^{-1} s^{-1}. For half of the investigated compounds, rate constants lie between 7 and 9×10^9 M^{-1} s^{-1} demonstrating the relatively nonselective nature of OH radical reactions in aqueous solution. The X-ray contrast medium iopromide has the lowest reactivity. Compared to other important micropollutants (atrazine, MTBE, perchloroethylene, and trichloroethylene (*20*)) the selected pharmaceuticals react about two to three times faster with OH radicals. This indicates that AOPs, even if not ozone-based, would oxidize the selected pharmaceuticals more efficiently than many other relevant micropollutants. Also, pharmaceuticals that do not react with ozone directly will be partly removed during conventional ozonation through reactions with OH radicals.

Product Formation. The reactions with ozone and OH radicals during an ozonation process will not result in the complete mineralization of pharmaceuticals. However, as pharmaceuticals generally react with specific receptors in the target organisms, transformation of the parent molecules by the above oxidants may be sufficient to reduce the intended pharmaceutical effects. In ongoing research the degradation pathways of the selected pharmaceuticals are investigated. From the literature, the transformation pathways for certain functional groups are known. An overview is given in ref *26*. Reactions of ozone with phenolic compounds result in the cleavage of the aromatic ring (*27*). Ozone attack at double bonds leads to bond cleavage and formation of carbonyl compounds (*19*, *28*). Hydroxylamines and amine oxides are formed in ozone reactions with secondary (*29*) and tertiary amines (*30*), respectively. Hydroxylamines undergo further reactions with ozone. For the pharmaceuticals investigated, a major part of the reactions with OH radicals will take place at benzene rings, resulting in the formation of phenolic compounds or ring cleavage. In ozone-based processes phenolic compounds will quickly react with ozone. On the basis of this information, it can be concluded that modifications caused by ozonation or AOPs should be sufficient to eliminate the intended pharmaceutical effects of most of the investigated compounds. However, it cannot be ruled out that for some compounds modifications may not be important or may even lead to the formation of toxic byproducts. For instance, the formation of hydroxylamines could be problematic from a toxicological point of view, as in the case of sulfonamides, for which the hydroxylamine is associated with hypersensitivity reactions to this class of antibiotics (*31*).

Oxidation of Fast-Reacting Pharmaceuticals in Natural Waters and Bromate Formation. Experiments have been performed in different natural waters to confirm the determined rate constants and to apply them to real treatment conditions. For pharmaceuticals with ozone rate constants >100 M^{-1} s^{-1}, batch experiments were carried out with RS and LF waters, which exhibit high alkalinity and low DOC, and low alkalinity and high DOC, respectively. Ozone half-lives (O_3 = 2 mg/L, pH = 8, T = 10 °C) were 75 min for RS and 4 min for LF water. Figure 2 shows the transformation of the selected pharmaceuticals in these two waters as a function of different ozone doses. In RS water, an ozone dose of 0.2 mg/L was sufficient to achieve a transformation >97% with the exception of bezafibrate. LF water has a higher ozone demand, and an ozone dose of 0.5 mg/L was necessary for the same transformation. The ozone rate constant of bezafibrate is at least 100 times lower than the rate constants of the other compounds and bezafibrate can obviously not compete with the initial ozone demand of these waters. The generally low transformation for the ozone dose of 0.1 mg/L in LF and RS water may be partly caused by the fact that the ozone concentration exceeds the pharmaceutical concentration by only a factor of 4. At more realistic pharmaceutical concentrations a better transformation can be expected. Results for ozone doses of > 0.2 mg/L can be directly extrapolated to pharmaceutical concentrations in the ng/L range. Overall, the results demonstrate that relatively low ozone doses are sufficient to achieve a complete transformation of pharmaceuticals exhibiting rate constants of $>10^5$ M^{-1} s^{-1}.

Besides the transformation of pharmaceuticals, the formation of bromate, the major byproduct of concern during ozonation processes, was measured as well. The concentration of the bromate precursor bromide was 60 μg/L in RS (natural level) and LF water (fortified). This represents a medium bromide concentration. In RS water the highest ozone dose led to a bromate concentration of 12 μg/L, which is slightly higher than the drinking water standard of 10 μg/L set by the EU and the U.S. Because samples were measured only after all ozone was consumed, the high ozone stability in RS water led to a large ozone exposure, and, as a consequence, to a high bromate formation. For lower ozone doses, bromate formation was <2 μg/L. In LF water bromate formation was <2 μg/L for all ozone doses. Generally, the

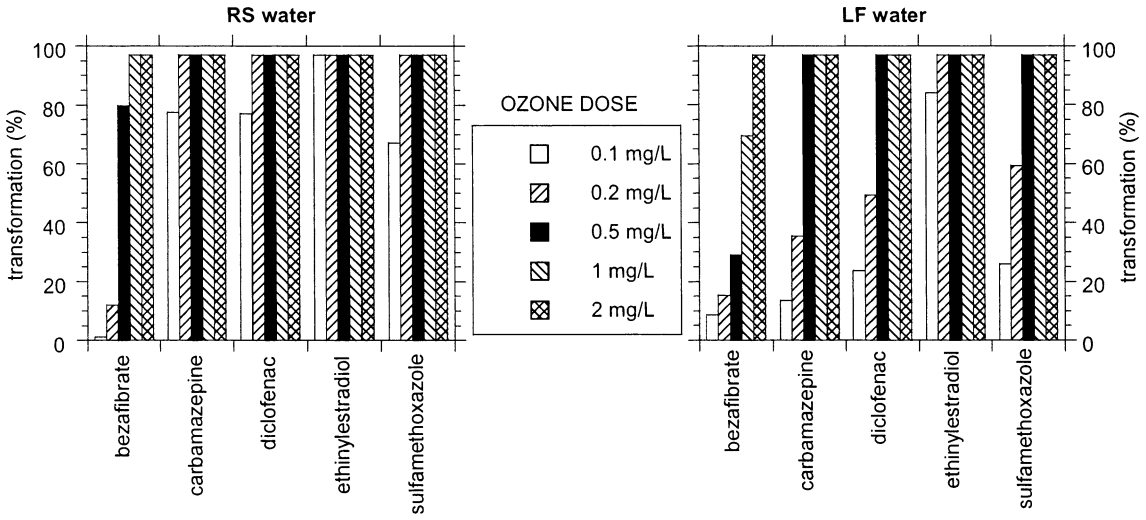


FIGURE 2. Oxidation of fast-reacting pharmaceuticals in RS water (DOC = 1.3 mg/L, alk = 4.1 mM) and LF water water (DOC = 3.7 mg/L, alk = 0.7 mM) as a function of the ozone dose. Experimental conditions: pH = 8, T = 10 °C, [pharmaceuticals]$_0$ = 0.5 μM. Samples were measured after all ozone was consumed. Transformations up to 97−99% could be measured with the existing detection limits.

results show that bromate formation is not a problem for ozone doses that are necessary to oxidize fast-reacting pharmaceuticals.

Oxidation of Slow-Reacting Pharmaceuticals during Ozonation of Natural Waters. Compared to fast-reacting pharmaceuticals, which are completely transformed for typical ozone doses applied in drinking water treatment, it is more difficult to predict the oxidation of pharmaceuticals exhibiting lower ozone rate constants. In this case, reactions with ozone and OH radicals have to be considered and it is essential to know their concentrations during the ozonation process, or more precisely their exposures (i.e., concentration integrated over the reaction time). The R_{ct} concept (*10, 26*) is an experimental approach to calibrate ozonation processes and ozone-based AOPs with respect to ozone and OH radical exposure. This calibration is done by determining the ratio of the OH radical exposure to the ozone exposure in the investigated water (R_{ct} value). After an initial phase, the R_{ct} value remains constant for the rest of the ozonation process and therefore, also represents the ratio of OH radical concentration to ozone concentration (R_c value). The OH radical exposure is obtained by measuring the degradation of a probe compound (pCBA) that does not react with ozone. Simultaneously, the ozone decrease is followed in order to determine the ozone exposure. With eq 3 it is then possible to predict the oxidation of a micropollutant (M) as a function of ozone exposure ($\int[O_3]dt$), R_c ($[^{\bullet}OH]/[O_3]$), $k_{OH,}$ and k_{O_3}:

$$\ln\left(\frac{[M]}{[M]_0}\right) = -\left(\int [O_3]\, dt\right)(k_{OH}R_c + k_{O_3}) \qquad (3)$$

where k_{OH} and k_{O_3} are the second-order rate constants for the reactions of a micropollutant (M) with OH radicals and ozone, respectively.

Experiments with four natural waters were performed to apply the determined rate constants to real treatment conditions. The corresponding water quality parameters are given in Table 2. The selected waters differed in DOC and alkalinity, two parameters controlling ozone stability as well as OH radical formation and scavenging in natural waters. On the basis of the concept presented above, R_c values were determined for the natural waters, and the oxidation of the selected pharmaceuticals was predicted using eq 3. Ozone rate constants were adjusted to the experimental conditions using the measured activation energies for bezafibrate (39 kJ/mol) and ibuprofen (57 kJ/mol) and an average activation energy of 40 kJ/mol (*15*) for diazepam and iopromide. In the same experiments, the oxidation of the pharmaceuticals was measured to verify the predictions. Table 6 summarizes the results.

The measured oxidation of bezafibrate was >95% in all ozonation experiments. This is mainly due to the relatively high second-order rate constant for its reaction with ozone. The measured oxidation of diazepam, iopromide, and ibuprofen ranged from 24% (diazepam and iopromide in WP water) to 77% (ibuprofen in LF water). The oxidation of these compounds is largely controlled by reactions with OH radicals. The oxidation efficiencies increased with increasing DOC and decreased with increasing alkalinity. An increased DOC leads to an enhanced rate of ozone transformation into OH radicals, whereas alkalinity stabilizes ozone. The effect of DOC and alkalinity was less pronounced for ibuprofen due to a higher ozone rate constant. In WP and RS water with a high ozone stability, the higher ozone rate constant resulted in a better oxidation of ibuprofen than diazepam, whereas in LZ and LF water, where ozone reactions are less relevant, the oxidation efficiencies were about the same. For bezafibrate, diazepam, and ibuprofen predictions were in reasonable agreement with the measured data. However, the oxidation of iopromide could no be predicted accurately. No explanation has yet been found for this discrepancy.

For RS water, Figure 3 illustrates the oxidation of three pharmaceuticals during ozonation (symbols represent experimental data; lines represent predictions). Bezafibrate, which has an intermediate rate constant with ozone, was oxidized within 5 min to the detection limit, mainly through the direct reaction with ozone. Ibuprofen exhibits a much lower k_{O_3} and its removal is to a large extent caused by reactions with OH radicals. For iopromide, it is expected that reactions with OH radicals are the major oxidation pathway. However, k_{OH} is rather small and the predicted removal underestimates the measured oxidation with OH radicals. Due to high alkalinity and low DOC the ozone stability is rather high in RS water. In LZ and LF water, lower ozone stability leads to an accelerated OH radical formation. As a result, compounds that react mainly with OH radicals are oxidized significantly faster in these waters.

For waters with high ozone stability, the oxidation of micropollutants can be considerably accelerated by adding H_2O_2 to the ozonation process. In the O_3/H_2O_2 AOP, ozone is converted into OH radicals within a few minutes. It has to be emphasized that the overall OH radical formation does

TABLE 6. Predicted and Measured Oxidation of Slow-Reacting Pharmaceuticals during Conventional Ozonation and Advanced Oxidation of Natural Waters[a]

	WP water		RS water		LZ water		LF water	
	predicted	measured	predicted	measured	predicted	measured	predicted	measured
Conventional Ozonation								
bezafibrate	>99%	nd	>99%	>99%	>99%	nd	97%	98%
diazepam	23%	24%	29%	nd	57%	65%	74%	nd
iopromide	6%	24%	14%	27%	31%	58%	46%	68%
ibuprofen	31%	41%	37%	40%	56%	62%	69%	77%
AOP (O_3/H_2O_2)								
ibuprofen	80%	84%	80%	78%	90%	90%	nd	nd
bezafibrate	98%	nd	92%	nd	95%	97%	nd	nd

OH Radical Scavenging Capacity	WP water	RS water	LZ water	LF water
total [s^{-1}]	7.6×10^4	7.2×10^4	5.5×10^4	9.9×10^4
DOC [s^{-1}][b]	2.0×10^4	3.2×10^4	3.0×10^4	9.2×10^4
HCO_3^-/CO_3^{2-} [s^{-1}][c]	5.6×10^4	4×10^4	2.5×10^4	0.7×10^4

[a] Conditions: ozone dose = 2 mg/L, contact time = 10 min, pH = 8, T = 10 °C; for AOP, H_2O_2 dose = 0.7 mg/L). For water quality parameters see Table 2. [b] Scavanging capacity (DOC) = k_{OH}(DOC) × [DOC]. [c] Scavanging capacity (HCO_3^-/CO_3^{2-}) = $k_{OH}(HCO_3^-) \times [HCO_3^-] + k_{OH}(CO_3^{2-}) \times [CO_3^{2-}]$.

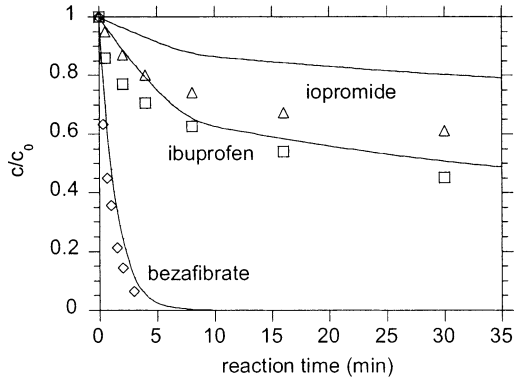


FIGURE 3. Oxidation of three pharmaceuticals during ozonation of RS water (DOC = 1.3 mg/L, alk = 4.1 mM). Experimental conditions: pH = 8, T = 10 °C, ozone dose = 2 mg/L, [pharmaceuticals]$_0$ = 0.5 μM. Symbols represent measured data, and lines represent model calculations.

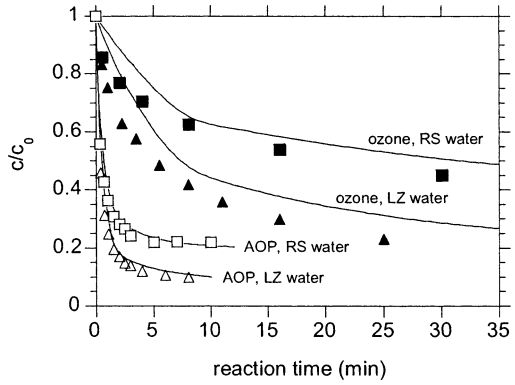


FIGURE 4. Oxidation of ibuprofen during ozonation and advanced oxidation of RS water (DOC = 1.3, alk = 4.1 mM) and LZ water (DOC = 1.2, alk = 2.6 mM). Experimental conditions: pH = 8, T = 10 °C, ozone dose = 2 mg/L, [pharmaceuticals]$_0$ = 0.5 μM, ratio of H_2O_2/O_3 = 0.34 w/w (AOP). Symbols represent measured data, and lines represent model calculations.

not change significantly compared to that of conventional ozonation in which the ozonation process is not stopped before all ozone is consumed. Table 6 presents data for the predicted and measured oxidation in the O_3/H_2O_2 AOP. Oxidation of bezafibrate is slightly lower in this AOP than during conventional ozonation (10-min contact time). This is due to a reduced ozone exposure, which cannot be fully compensated by OH radical reactions. However, the oxidation of ibuprofen could be considerably increased. The efficiency of an AOP strongly depends on the OH radical scavenging capacity of the selected natural water. Therefore, the highest oxidation was achieved in LZ water, which has the lowest scavenging capacity. Transformation in WP water was similar to the one in RS water. This can be explained by the comparable OH radical scavenging capacity. In LF water, it would not be possible to increase the oxidation efficiency of the ozonation process by adding H_2O_2, because the ozone half-life is already quite short and the scavenging capacity of the water is rather high.

Figure 4 compares the ibuprofen oxidation in conventional ozonation and in the O_3/H_2O_2 AOP. The oxidation of ibuprofen could be increased from 40% to over 80% for a hypothetical contact time of 10 min. These results can also be applied to diazepam, which has a similar k_{OH} and barely reacts with ozone. Other important micropollutants such as atrazine and MTBE showed a substantially lower transformation in the O_3/H_2O_2 AOP under similar conditions. In River Seine water, atrazine oxidation was about 50% (*11*). MTBE oxidation in different natural waters ranged from 30% to 50% (*12*).

For the investigation of oxidation products formed during the ozonation of pharmaceuticals, it will be important to know the fraction of a pharmaceutical compound reacting with ozone and OH radicals, respectively. Figure 5 shows which fraction of the slow-reacting pharmaceuticals reacts with either of the two oxidants as a function of the R_c value (R_c= ([•OH]/[O_3]), see eq 3). For LZ, RS, and WP water, conventional ozonation yielded R_c values ranging from 10^{-10} to 5×10^{-9}. Under these conditions both ozone and OH radicals contribute to the oxidation of ibuprofen, iopromide, and diazepam, whereas bezafibrate is oxidized by ozone alone. Ozonation of LF water and AOPs resulted in R_c values ranging from 10^{-8} to 10^{-7}. In this case, only OH radical reactions are relevant for the oxidation of ibuprofen, iopromide, and diazepam. However, both ozone and OH radicals are involved in the oxidation of bezafibrate under these conditions. In contrast to the slow-reacting pharmaceuticals, fast-reacting pharmaceuticals are almost exclusively oxidized by ozone for all treatment conditions.

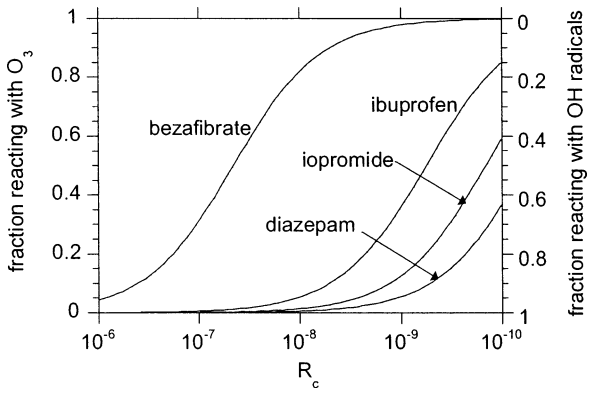


FIGURE 5. Comparison of the contribution of ozone and OH radicals to the overall oxidation of slow-reacting pharmaceuticals at $T = 10$ °C. The fraction of pharmaceuticals reacting with ozone and OH radicals, respectively, is plotted as a function of the R_c value ($R_c = [^{\bullet}OH]/[O_3]$). Ozone rate constants were corrected for $T = 10$ °C.

The batch experiments with natural waters represent ozonation processes or AOPs in ideal plug-flow reactors. To make exact predictions for real water treatment, it is necessary to account for reactor hydraulics. However, only small deviations are expected between different reactor types because the degree of transformation of slow-reacting pharmaceuticals is lower than one log unit.

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Literature Cited

(1) Halling-Sørensen, B.; Nors Nielsen, S.; Lanzky, P. F.; Ingerslev, F.; Holten Lützhøft, H. C.; Jørgensen, S. E. *Chemosphere* **1998**, *36*, 357−393.
(2) Daughton, C. G.; Ternes, T. A. *Environ. Health Perspect.* **1999**, *107*, 907−938.
(3) Ternes, T. A. *Water Res.* **1998**, *32*, 3245−3260.
(4) Kolpin, D. W.; Furlong, E. T.; Meyer, M. T.; Thurman, E. M.; Zaugg, S. D.; Barber, L. B.; Buxton, H. T. *Environ. Sci. Technol.* **2002**, *36*, 1202−1211.
(5) Heberer, T. *Toxicol. Lett.* **2002**, *131*, 5−17.
(6) Heberer, T.; Stan, H.-J. *Vom Wasser* **1996**, *86*, 19−31.
(7) Ternes, T. A. In *Pharmaceuticals and Personal Care Products in the Environment: Scientific Regulatory Issue*; Daughton, C. G., Jones-Lepp, T. L., Eds.; ACS Symposium Series; American Chemical Society: Washington, DC, 2001.
(8) Ternes, T. A.; Meisenheimer, M.; McDowell, D.; Sacher, F.; Brauch, H.-J.; Haist-Gulde, B.; Preuss, G.; Wilme, U.; Zulei-Seibert, N. *Environ. Sci. Technol.* **2002**, *36*, 3855−3863.
(9) Zwiener, C.; Frimmel, F. H. *Water Res.* **2000**, *34*, 1881−1885.
(10) Elovitz, M. S.; von Gunten, U. *Ozone Sci. Eng.* **1999**, *21*, 239−260.
(11) Acero, J. L.; Stemmler, K.; von Gunten, U. *Environ. Sci. Technol.* **2000**, *34*, 591−597.
(12) Acero, J. L.; Haderlein, S.; Schmidt, T. C.; Suter, M. J.-F.; von Gunten, U. *Environ. Sci. Technol.* **2001**, *35*, 4252−4259.
(13) Bader, H.; Hoigné, J. *Water Res.* **1981**, *15*, 449−456.
(14) Hoigné, J.; Bader, H. *Ozone Sci. Eng.* **1994**, *16*, 121−134.
(15) Hoigné, J.; Bader, H. *Water Res.* **1983**, *17*, 173−183.
(16) Hoigné, J.; Bader, H. *Water Res.* **1983**, *17*, 185−194.
(17) Muñoz, F.; von Sonntag, C. *J. Chem. Soc., Perkin Trans. 2* **2000**, 661−664.
(18) Hoigné, J.; Bader, H. *Water Res.* **1985**, *19*, 993−1004.
(19) Dowideit, P.; von Sonntag, C. *Environ. Sci. Technol.* **1998**, *32*, 1112−1119.
(20) Buxton, G. V.; Greenstock, C. L.; Helman, W. P.; Ross, W. P. *J. Phys. Chem. Ref. Data* **1988**, *17*, 513−886.
(21) Wegelin, M.; Canonica, S.; Mechsner, K.; Fleischmann, T.; Pescaro, F.; Metzler, A. *J. Water SRT* **1994**, *43*, 154−169.
(22) Canonica, S.; Jans, U.; Stemmler, K.; Hoigné, J. *Environ. Sci. Technol.* **1995**, *29*, 1822−1831.
(23) von Sonntag, C.; Schuchmann, H.-P. In *Peroxyl Radicals*; Alfassi, Z. B., Ed.; John Wiley & Sons Ltd.: Chichester, U.K., 1997.
(24) Salhi, E.; von Gunten, U. *Water Res.* **1999**, *33*, 3239−3244.
(25) Hoigné, J. In *The Handbook of Environmental Chemistry, Vol. 5, Part C: Quality and Treatment of Drinking Water II*; Hubrec, J., Ed.; Springer: Berlin, 1998.
(26) von Gunten, U. *Water Res.* **2002**, in press.
(27) Yamamoto, Y.; Niki, E.; Shiokawa, H.; Kamiya, Y. *J. Org. Chem.* **1979**, *44*, 2137−2142.
(28) Bailey, P. S. *Ozonation in Organic Chemistry, Vol 1: Olefinic Compounds*; Academic Press: New York, 1978.
(29) Mark, G.; Hildenbrand, K.; von Sonntag, C., in preparation.
(30) Muñoz, F.; von Sonntag, C. *J. Chem. Soc., Perkin Trans. 2* **2000**, 2029−2033.
(31) Sisson, M. E.; Rieder, M. J.; Bird, I. A.; Almaw, W. Y. *Int. J. Immunopharmacol.* **1997**, *19*, 299−304.

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