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On the importance of reactions in the proximity of the gas–water interface: Application to direct ozone reactions of antibiotics in water

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ABSTRACT

A comparison between kinetic models of the direct ozonation in water of a mixture of fifteen antibiotics has been carried out by considering both the reactions in the proximity of gas–water interface (film reactions) and in the water bulk. Stoichiometric coefficients and rate constants of the O_3-antibiotic reaction were determined following standard procedures and compared to the values reported in the literature. The importance of stoichiometric coefficients in the establishment of the ozone kinetic regimes and kinetic modelling has been discussed. Most of the antibiotics studied react under fast or moderate regime with ozone at the conditions applied. The significance of these reactions in the proximity of gas–water interface is discussed sustained in the application of film theory. Results have been compared to those obtained from the kinetic approach where ozone reactions in the film are not taken into account. The importance of reactions in the film represents >60% of antibiotics consumption. Deviations between experimental and simulated concentrations of antibiotics are due to the contribution of reaction intermediates to ozone consumption, which is not considered in the kinetic model.

1. Introduction

There are many examples of chemical processes involving reactive gas–liquid absorption (i.e., gas–liquid reactions) such as hydrogenation of olefins and oxidation of hydrocarbons using soluble catalysts [1,2] or absorption of CO_2 into aqueous solutions of alkanolamines [3]. Environmental applications of gas–liquid reactions also include different processes such as cleansing of gases [4] and the ozonation of water and wastewater [5]. In order to design gas–liquid reactors for such applications, kinetics and mass transfer data have to be determined in the first place. Besides, a mathematical model considering an appropriate description of the gas and liquid phases and the simultaneous occurrence of the complete set of chemical reactions and inter-phase and intra-phase transport processes is required [6]. Chemical Engineering academics have been interested in the fundamentals of gas–liquid reactions since long, developing various models for the transport of mass and heat accompanied by chemical reaction such as the two-film, the penetration, the surface renewal and others [7–10]. Despite the extensive literature on gas–liquid reaction modelling, many simplifying assumptions are made in complex gas–liquid reacting systems such as ozonation of pollutants in water. Regarding this process, with a few exceptions [11–13], chemical reactions are considered to occur only in the bulk liquid (slow reactions) [14] or in the liquid film (fast reactions) [15] when applying the two-film theory. Also, simplified lumped kinetic schemes are typically used to account for complex sets of simultaneous reactions between ozone and pollutants as well as their reaction intermediates. Parameters such as chemical oxygen demand (COD) or total organic carbon (TOC) are usually considered as surrogate parameters of organic compounds in wastewater [16]. Some authors have developed a simplified approach based on ozone and hydroxyl radical ($HO^{\bullet}$) rate constants and the exposures to both oxidants, as experimentally measured, to predict the abatement of aqueous micropollutants by ozonation [17]. Unfortunately, the results of these simpler models should be experimentally validated before the design of gas–liquid reactors. Then, a study focusing on the potential pitfalls of neglecting the multiple ozone reactions taking place in the proximity of the gas–water interface in an ozonation process is recommended. An example of this process is the simultaneous reactions of ozone in water with antibiotics of different reactivity.

Antibiotics are frequently found in surface waters and effluents from municipal wastewater treatment plants (MWWTPs) at concentrations up to tens of μg L^{-1}. However, much higher concentrations of antibiotics

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and other pharma compounds are reported to be found in effluents from hospital and drug production facilities [18]. This means that ozone reactions with antibiotics at environmental conditions can be slow, moderate and/or fast gas–liquid reactions, that is, ozone reactions can simultaneously develop both in the film and in the water bulk. Since the release of antibiotics to water media from MWWTPs and pharmaceutical industries constitutes a major threat to living beings and the environment [19–22] studies on kinetic modelling of these ozone processes result attractive to many researchers. For instance, research developed in recent years has shown that antibiotics can effectively be removed by advanced oxidation processes (AOP) relying on the formation of highly oxidizing hydroxyl radicals [23–25]. Moreover, ozone based AOPs can benefit from the two possible ways of ozone action: direct and hydroxyl free radical reactions [26].

According to precedent comments, the main aim of this work was to develop a mathematical model for a perfectly mixed gas–liquid semi-batch reactor that accounts for multiple parallel ozone reactions in the entire liquid phase (i.e, film and bulk water). The model is used to compare the simulated concentration–time profile of an aqueous mixture of fifteen antibiotics (see Table 1) of different ozone reactivity to that calculated only considering water bulk reactions. Also, deviations among calculated concentrations from both kinetic models (with and without reactions in the film layer) and experimental ones are discussed to highlight the importance of ozone reaction intermediates. knowledge of stoichiometry and rate constants of ozone-antibiotic reactions results fundamental to run the kinetic model.

Literature reports the rate constants of ozone-antibiotic reactions. As seen in Table 2, discrepancies are observed in the reported values and

Table 1
Some antibiotics found in surface waters and effluents from MWWTPs:, acid dissociation constant, chemical structure and maximum concentration measured in water bodies.

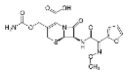
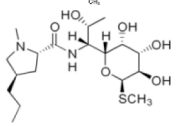
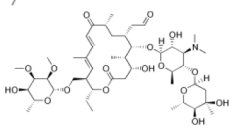
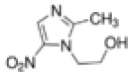
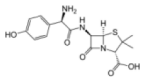
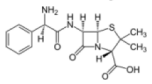
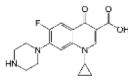
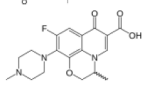
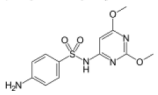
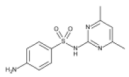
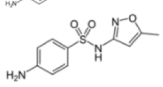
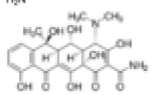
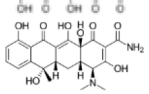
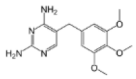
Category	Antibiotic	Abbreviation	pK_a	Chemical structure	C_{max} ($ng \cdot L^{-1}$)	Ref.
Cephalosporin (2nd generation)	Cefuroxime	CFX	3.2		3.42	[27]
Lincosamide	Lincomycin	LIN	7.8		19,401	[28]
Macrolide	Tylosin	TYL	7.7		1150 269	[29,30]
Nitroimidazole	Metronidazole	MTZ	2.6		2000	[30]
Penicillin	Amoxicillin	AMX	2.8 7.2 9.6		2000	[27]
	Ampicillin	AMP	2.5 7.3		104 383	[27,30]
Quinolone (Fluoroquinolone)	Ciprofloxacin	CIP	6.2 8.8		12,900 4287	[27,31]
	Flumequine	FLU	6.4		317	[32]
	Ofloxacin	OFX	6.0 9.3		716	[29]
Sulfonamide	Sulfadimethoxine	SDX	2.9 6.1		164	[33]
	Sulfamethazine	SMZ	2.7 7.7		3190	[28]
	Sulfamethoxazole	SMX	1.7 5.6		2260 17,000	[27,28]
Tetracycline	Oxytetracycline	OXT	3.3 7.5 8.9		107	[30]
	Tetracycline	TTC	3.3 7.8 9.7		980	[29]
Other	Trimethoprim	TMP	3.2 7.1		4010	[27]

Table 2
Summary of reported rate constant, k_D, and corresponding stoichiometric ratio, z, of ozone direct reaction with antibiotics listed in Table 1, applied methodology for k_D determination and reference compound employed [a].

Compound	Reported data k_D $M^{-1} \cdot s^{-1}$	Method	Reference compound	Ref	z and Ref
SMX	1.1×10^5	Competitive	Carbamazepine	[34]	2[b] [35]
	1.66×10^5	Competitive	Fumaric acid	[36]	
	2.7×10^5	Direct (ozone exposure)	–	[37]	
	4.15×10^5	Direct (fast kinetic regime)	–	[38]	
	5.5×10^5	Competitive	Dimethylisoxazole	[35]	
	2.5×10^6	Competitive	Phenol	[39]	
SDX	2.7×10^6	Competitive	Sulfamethoxazole	[40]	n.d.
SMZ	2.9×10^6	Competitive	Sulfamethoxazole	[40]	n.d.
FLU	1800	Direct (ozone spiking)	–	[39]	1[b] [35]
CIP	1.9×10^4	Competitive	Flumequine	[35]	2[b] [34]
OFX	1.65×10^6	Competitive	Phenol	[41]	2.5 [41]
	2.61×10^6	Competitive	Metoprolol	[34]	
CFX	$\sim 4.69 \times 10^6$	Direct (instantaneous regime)	–	[42]	1 [42]
AMP	4.1×10^5	Competitive	Cinnamic acid	[43]	n.d.
AMX	1.5×10^6	Competitive	Trimethoprim	[44]	2.6 [45]
	$\sim 7.0 \times 10^6$	Competitive	Paracetamol	[45]	
	5.98×10^6	Competitive	Phenol	[39,46]	
OXT	2.08×10^6	Competitive	Cinnamic acid	[47]	n.d.
	6.9×10^6	Competitive	Sulfamethoxazole	[40]	
TTC	1.09×10^6	Competitive	Cinnamic acid	[47]	4[b] [35]
	1.9×10^6	Competitive	MBDCH	[35]	
	9.8×10^6	Competitive	Sulfamethoxazole	[40]	
TYL	5.5×10^5	Competitive	DMCH	[35]	2[b] [35]
MTZ	253	Direct (ozone exposure)	–	[48]	n.d.
	306	Competitive	Simazine	[34]	
LIN	4.93×10^5	Direct (diffusional transition regime)	–	[49]	2[b] [35]
	6.7×10^5	Competitive	1-methylpyrrolidine	[35]	1[c] [49],
	6.75×10^5	Stopped flow	–	[50]	
TMP	2.7×10^5	Competitive	Trimethoxytoluene	[35]	2[b] [35]
	2.74×10^5	Competitive	Carbamazepine	[34]	

DMCH: N,*N*-dimethylcyclohexylamine, MBDCH: 2-(3-methylbutyryl)-5,5-dimethyl-1,3-cyclohexan-dione.
Values of k_D were determined at pH: 6.7 for LIN [49], and pH 6.7 – 7.2 for SMX, OFX, MTZ and TMP [34].
[a] pH = 7 unless otherwise indicated. [b]Theoretically deduced from feasible points of ozone attack to the antibiotic molecule. [c]pH = 5.5. n.d.: not determined.

the methods used for their assessment. Regarding the stoichiometric ratio, however, there is a lack of information since most of works dealing with the kinetics of ozone reactions assume that one mole of ozone reacts with another one of antibiotic (see also Table 2).

Therefore, another objective of the work was to determine the rate constants of the reactions between ozone and the fifteen antibiotics listed in Table 1 by the same method in as many cases as possible. Moreover, the corresponding stoichiometric coefficient of the ozone-antibiotic reaction (mole of ozone consumed per mole of antibiotic consumed in the direct reaction) has also been determined using a standard procedure. Both, rate constants and stoichiometric ratios were used together with mass-transfer parameters in the gas–liquid reaction model.

2. Materials and methods

2.1. Chemicals

All of the antibiotics listed in Table 1 (and other compounds listed below) were used as received: amoxicillin (MP Biomedicals, CAS 26787–78-0), ampicillin sodium salt (Panreac, CAS 69–52-3), cefuroxime sodium salt (Merck, CAS 56238–63-2), ciprofloxacin (ACROS Organics, CAS 85721–33-1), flumequine (Merck, CAS 42835–25-6, lincomycin hydrochloride (Alfa Aesar, CAS 859–18-7), metronidazole (TCI, CAS 443–48-1), ofloxacin (Merck, CAS 82419–36-1), oxytetracycline -(Alfa Aesar, CAS 79–57-2), sulfamethoxazole (Merck, CAS 423–46-6), sulfamethazine sodium salt (TCI, CAS 1981–58-4), sulfadimethoxine (Merck, CAS 122–11-2), tetracycline (Meck, CAS 60–54-8), trimethoprim (Merck, CAS 738–70-5) and tylosine tartrate salt (Alfa Aesar, CAS 1405–54-5). Moreover, sodium nitrite (Panreac, 7632–00-0), *t*-butanol (Panreac, 99.5 %, CAS 71–36-3), phosphoric acid (Panreac, 85 %, CAS 7664–38-2) and NaOH (Panreac, 98 %, CAS 1310–73-2) were also employed in the reaction media. Ultrapure water was obtained in a Milli-Q Integral system with a resistivity up to 18.2 MΩ·cm.

2.2. Determination of the stoichiometric coefficient and the rate constant of the ozone-antibiotic direct reaction.

The stoichiometry of the reaction between ozone and each antibiotic was determined following a method already reported in the literature [51]. Details are shown as Supplementary Material (see Text S1 and Fig. S1).

The rate constant of the direct reaction between ozone and the antibiotic (k_D) can be obtained through direct or competitive kinetic methods depending on the ozone reactivity. Both methods were applied in this work following Huber et al. [39]. Details of the procedure are also provided as Supplementary Material (see Text S2 and Fig. S2).

2.3. Ozonation of antibiotics in a mixture

A mixture of the antibiotics listed in Table 1 was prepared in phosphate buffered ultrapure water with an average concentration of 10^{-5} M of each antibiotic. In addition, an excess of *tert*-butanol (0.01–0.02 M) was spiked into the solution to quench hydroxyl radicals. Fig. S3 shows the experimental set-up used for ozonation experiments. The aqueous solution containing the antibiotics was charged into a 400-mL cylindrical reactor (see Fig. S4). An O_2-O_3 gas mixture (10 mg L^{-1} ozone) was continuously bubbled into the reactor at a gas flow rate of 30 L·h^{-1}. Magnetic agitation was provided to achieve perfect mixing in the reactor volume. Aqueous samples were steadily withdrawn from the reactor and

analyzed for antibiotic and dissolved ozone concentrations.

2.4. Analytical methods

The concentrations of antibiotics were determined in an ultra-fast liquid chromatography (UFLC) Shimadzu Prominence equipped with a degassing unit, high pressure pump (LC-20AD), autosampler, oven and a diode array detector (DAD). The stationary phase was a Phenomenex C18 column at 40 °C A mixture of acidified ultrapure water (0.1 % v/v H_3PO_4): acetonitrile (A:B) solution at 0.6 mL·min^{-1} was employed as mobile phase. The method started with 4 min of initial stabilization with a water acetonitrile ratio of 95:5. A linear gradient for 6 min to reach 70:30 A:B followed. Finally, a second linear gradient for 20 min up to 50:50 A:B was applied. Analyses were monitored at different wavelengths for the determination of antibiotics (see Table S1).

Some competitive reaction kinetic experiments were carried out using nitrate as reference compound. The concentrations of residual nitrite and formed nitrate were measured by ion chromatography in a Metrohm 881 Compact IC pro device, equipped with ion suppression and conductivity detector. An anionic column (Metrosep A sup 7–150/4.0) and a trap column (Metrosep A Trap 1–100/4.0), both thermoregulated at 45 °C, were used as stationary phase. The mobile phase was an aqueous solution of Na_2CO_3 fed at 0.7 mL·min^{-1}. A gradient program from 0.6 mM to 9.35 mM in 50 min and 10 min post-time equilibration was used for the analysis. Retention times for nitrite and nitrate were 18 and 23 min, respectively.

The concentration of aqueous ozone was measured at 600 nm with the indigo method [52] in a Shimadzu UV-1800 spectrophotometer, while ozone concentration in the gas was continuously monitored by means of an Anseros Ozomat GM-6000 Pro analyzer. Measurement of the pH was carried out with a pH-meter CRISON Basic with a CRISON 50 21 T pH electrode.

3. Results and discussion

3.1. The stoichiometry of the ozone-antibiotic reaction

Following the method described in the Supplementary Information (see Text S1), the stoichiometric ratio, z, of the ozone-antibiotic direct reactions was experimentally determined (see Fig. S1). Table 3 reports the values obtained for z, which were further used to determine the direct rate constant k_D.

As observed from Table 2, literature reports z values at pH 7 for only three of the fifteen antibiotics studies in this work (cases of OFX, CFX and AMX). Theoretically, the stoichiometric ratio can be justified considering the well-known ozone chemistry in water [53,54]. Accordingly, ozone as electrophilic agent mainly reacts with nucleophilic centers negatively charged such as amines, aromatic rings with certain substituents groups (amines, hydroxyl groups), double carbon bonds, etc. Following this, Dodd et al [35] suggested feasible sites of ozone attack to 16 antibiotic, 7 of them studied in this work. Among these antibiotics, z values experimentally determined in this work agree the ozone attack sites reported by Dodd et al [35] for LIN, TMP, SMX, CIP, TYL and FLU. Also, following ozone chemistry in water, determined values of z for AMX, CFX and OFX (not considered in the work by Dood et al.) can also be explained by the chemistry of ozone in water as their molecules possess one primary point of ozone attack. Andreozzi et al [45] and Márquez et al [41] reported z values as high as 2.6 and 2.5 for AMX and OFX, respectively, which suggests that hydroxyl reactions were not completely scavenged. Some discrepancies were observed between z results of this work and the predictions made by Dodd et al for TTC, OXT and SMX. For TTC, Dodd et al. [35] reported up to 4 possible positions of ozone attack while in this work a value of z = 1 was experimentally obtained (see Fig. S1). This main ozone attack can likely be due to the presence of a tertiary amine, or the phenol ring where the ortho position with respect to the hydroxyl group is strongly activated for ozone electrophilic aromatic substitution reactions. Regarding OXT, another tetracycline, a value of z = 1 was also experimentally determined coinciding with the one of TTC-ozone reaction (as expected from their similar molecular structures). The sulfonamides (SMZ, SMX and SDX), have at least three clear points of ozone attack: the secondary amine and the aniline ring where the ortho positions respect to the amine group are strongly activated for ozone attack. Experimentally, a value of z = 3 was obtained for SMZ and SDX ozone reactions while only z = 2 was determined for SMX-ozone reaction. In any case, z values were determined following the same method already published [51] and, as a consequence, they present the same experimental error if any. Accordingly, we have applied these z values to solve the mass balances of antibiotics and also to know the true rate constant referred to ozone that is used in the Hatta number to determine the kinetic regime of ozone absorption (see below).

3.2. The direct ozone rate constant of antibiotics

The ozone rate constants of some ozone-antibiotic reactions (k_D) have already been determined in several studies, though different direct and competitive methodologies were used. (see Table 2), Thus, reported rate constant values should be checked before their use in kinetic models dealing with the simultaneous ozonation of antibiotics. In ozone reaction kinetics, second order reaction (first order with respect to ozone and first order with respect to the organic compound) has been confirmed in previous works for organic compounds of different nature [5,39,54,55–58]. Then, in this work, second order reaction has been also assumed for the ozone-antibiotic reactions.

The rate constants, k_D of the reactions between of ozone and the antibiotics listed in Table 2 were obtained, wherever possible, with the same methodology (competitive kinetics with nitrite as reference compound) at pH 7. It is evident that this should introduce similar errors in the calculated rate constants. However, because of their low reactivity with ozone, k_D values of ozone reactions with MTZ and FLU were determined by the direct method with the addition of aqueous ozone in homogenous phase (see Text S2 and Fig. S2 of the Supplementary Information). In these cases, as shown in Table 4, the calculated values of k_D for MTZ and FLU at pH 7 were 210 ± 5 and 486 ± 11 $M^{-1}s^{-1}$, respectively. The k_D value for the O_3-MTZ reaction is close to those reported by Sánchez-Polo (306 $M^{-1}\cdot s^{-1}$) [48] and Mathon et al (253 $M^{-1}\cdot s^{-1}$) [34] while in the case of the ozone-FLU reaction the calculated value of k_D was almost four times lower than that reported by Dodd et al. [35].

The competitive method was applied to determine k_D for the rest of antibiotics studied. Nitrite was used for 12 out of 13 remaining antibiotics, and FLU, for CIP-ozone reaction due to the much lower reactivity of this compound with ozone. Rate constant of the ozone-nitrite reaction has been reported to be 3.7×10^5 $M^{-1}s^{-1}$ [57] and 5.83×10^5 $M^{-1}s^{-1}$ [59]. The procedure to determine k_D with this method is described in the supplementary section (see Text S2 and Fig. S3). Broadly speaking, k_D values are in agreement with those reported in previous studies (see Table 2). However, some values from the literature should be taken with

Table 3
Stoichiometric ratio, z, of the ozone-antibiotic reactions studied[a].

AMX	MTZ	LIN	TMP	SMZ	OXT	AMP	TTC	OFX	CIP	CFX	SMX	SDX	TYL	FLU
1	1	2	2	3	1	1	1	1	2	1	2	3	2	1

[a]In moles of ozone consumed per mole of antibiotic consumed

Table 4
Values of rate constants of the reactions of ozone and antibiotics calculated in this work[a].

Antibiotic	k_D, $M^{-1}s^{-1}$	Antibiotic	k_D, $M^{-1}s^{-1}$	Antibiotic	k_D, $M^{-1}s^{-1}$	Antibiotic	k_D, $M^{-1}s^{-1}$
SMX	3.08×10^5	SDX	6.38×10^5	SMZ	2.03×10^6	FLU	486[c]
CIP	1.10×10^4[b]	OFX	1.50×10^5	CFX	8.63×10^5	AMP	2.15×10^5
AMX	2.00×10^6	OXT	5.15×10^6	TTC	2.05×10^6	TYL	2.05×10^6
MTZ	210[c]	LIN	5.02×10^5	TMP	5.98×10^5		

[a] Competitive method with nitrite as reference compound unless indicated. [b]Competitive method with flumequine as reference compound. [c]Direct method.

caution since k_D was determined without considering the stoichiometry of ozone-antibiotic reaction or assuming a value of $z = 1$, so that they should be defined as apparent rate constants [39,36,43,47,60]. For instance, in the cases of sulfonamides, the calculated value of k_D for the ozone-SDX reaction was lower than that estimated by Ben et al. [40] (i.e. 3.08×10^5 compared to 2.7×10^6 $M^{-1}{\cdot}s^{-1}$). This discrepancy is undoubtedly due to the different reference compound since Ben et al. took SMX (with a rate constant of 2.5×10^6 $M^{-1}{\cdot}s^{-1}$). As a consequence, their estimated k_D for SDX was consequently higher [41,40]. On the contrary, SMZ-ozone rate constant of this work agrees with the value determined by these authors (i.e. 2.9×10^6 $M^{-1}{\cdot}s^{-1}$ compared to 2.7×10^6 $M^{-1}{\cdot}s^{-1}$).

3.3. The direct ozonation system

There are two ways of oxidation in ozone-based processes: the direct reaction with ozone and the reaction with hydroxyl radicals coming from ozone decomposition. In this work, however, only the direct pathway of oxidation has been studied to observe the possible effects of ozone direct reactions in the proximity of gas–water interface. This latter aspect is not commonly considered when modeling the kinetics of ozone reactions in water. To the authors knowledge, only Benbelkacem et al [11–13] studied this effect for the case of the direct ozonation of maleic and fumaric acids, compounds that react moderately fast with ozone. In moderate kinetic regimes, a fraction of ozone reacts in the proximity of the gas–water interface and the rest reacts in the water bulk. To analyze this effect, the film theory concept has been applied [13]. This theory is based on the existence of a stagnant water film close to the gas–water interface where mass transfer and reaction of the dissolved gas and target compounds (ozone and antibiotics, respectively, in this work) can take place. According to film theory, the film extension, that is, the depth in the water from the gas interface to the water bulk frontier, is the ratio between the ozone diffusivity coefficient, D_{O3}, and the liquid phase mass transfer coefficient, k_L. In this work, the film extension or width, δ_L, has a value of 26 μm. Notice that the size of molecules is only of a few Amstrongs (Å). Ozone, for example, with a molecular size of <2 Å, has to travel from the interface to the water bulk a distance about 130,000 times its size. In this space, ozone can react before reaching the bulk water. In order to model the ozone kinetic system taking into account any possible ozone reaction in the film layer, both the stoichiometric coefficient, z, and the direct reaction rate constant, k_D, were first determined as discussed before. Once the rate constant values were calculated, for an antibiotic concentration of about 10^{-5} M, the Hatta numbers [5] of the ozone reactions studied were obtained (see Table 5). The Hatta number allows for the establishment of the kinetic regime of an ozone-compound i reaction [61], and it is defined as follows:

$$Ha_i = \frac{\sqrt{k_{Di} D_{O3} C_i}}{k_L} \tag{1}$$

where C_i is the concentration of compound i in the water bulk. D_{O3} is ozone diffusivity coefficient, k_{Di} is the direct rate constant between ozone and compound i and k_L is the individual mass transfer coefficient.

From Table 5 the ozone absorption kinetic regime can be considered as fast in ozone reactions with AMX, SMZ, OXT and TTC ($Ha > 3$), moderate in ozone reactions with LIN, TMP, AMP, OFX, CFX, SDX, SDX and TYL ($0.3 < Ha < 3$) and slow with MTZ, CIP and FLU ozone reactions

Table 5
Hatta numbers of selected antibiotics[a].

Antibiotic	$C_i \times 10^5$, M	Hatta number	Kinetic regime
AMX	0.95	3.14	F
MTZ	0.69	0.03	S
LIN	1.10	1.70	M
TMP	0.95	1.72	M
SMZ	1.02	3.28	F
OXT	1.04	5.28	F
AMP	1.06	1.09	M
TTC	1.06	3.35	F
OFX	0.96	1.35	M
CIP	0.87	0.23	S
CFX	1.03	2.15	M
SMX	0.93	1.22	M
SDX	1.14	1.95	M
TYL	0.99	2.26	M
FLU	1.06	0.09	S

F = Fast, M = Moderate, S = Slow. Concentrations indicated are those of the antibiotics at the start of the ozonation run.
[a] $k_L = 5x10^{-5}$ ms^{-1}, $D_{O3} = 1.3 \times 10^{-9}$ m^2s^{-1} [62]. For values of k_D see Table 4.

($Ha < 0.3$). This means that at the concentrations used in this work, the first four compounds react with ozone at different rates mainly in the film close to the gas–water interface, the second six compounds react both in the film and water bulk while the last three exclusively react within the water bulk. Accordingly, the mass balance of a given compound i that reacts with ozone only in the water bulk, in a semi-batch perfectly mixed reactor, would be given by Eq. (2):

$$-\frac{dC_i}{dt} = \frac{1}{z_i} k_{Di} C_{O3} C_i \tag{2}$$

where C_{O3} is the concentration of dissolved ozone in the water bulk. However, Eq. (2) is only valid for compounds that react with ozone in a slow fashion (MTZ, CIP and FLU in this case). Application of Eq. (2) is not correct when moderate or fast kinetic regimes develop, that is, compounds that partially or completely react in the film layer. In these cases, mass transfer and chemical reaction phenomena simultaneously take place in the film and affects the kinetic term (right side of Eq. (2)). The concentration profiles through the film and, consequently, the amounts of reactants consumed in the film, can be determined solving the corresponding mass balances within the film layer:

$$Ozone: D_{O3} \frac{d^2 C_{O3f}}{dx^2} = -\sum_i k_{Di} C_{O3f} C_{if} \tag{3}$$

$$Antibiotic\ i: D_i \frac{d^2 C_{if}}{dx^2} = -\frac{1}{z_i} k_{Di} C_{O3f} C_{if} \tag{4}$$

where C_{O3f} and C_{if} are the concentrations of ozone and antibiotic at any point within the film layer, D_i is the diffusivity coefficient of compound i in water (see section S5 of the Supplementary Information). Eqs. (3) and (4) are valid between the limits of the film (x is the position variable in the film), so that, boundary conditions are:

$$for\ x = 0\ C_{O3f} = C_{eq} \therefore \frac{dC_{if}}{dx} = 0 \tag{5}$$

$$for\ x = \delta_L\ D_{O3}a\frac{dC_{O3f}}{dx} = \sum_i k_{Di}C_{O3f}C_{i0}.\therefore C_{if} = C_{i0} \quad (6)$$

where C_{i0} stands for the concentration of antibiotic i at $x = \delta_L$.

Boundary condition (5) implies that the null term of the derivative assumes that i is a non-volatile compound, as it happens with the antibiotics studied, while C_{eq} is the solubility of ozone in water, defined as:

$$C_{eq} = \frac{C_{O3g}RT}{He} \quad (7)$$

where C_{O3g} is the concentration of ozone leaving the reactor, T the temperature in K and R and He the molar gas and Henry constants, respectively. In the case of ozone, the application of Fick's law holds. In this expression, "a" is the specific surface area or ratio between the volumetric and individual mass transfer coefficients: $a = k_La/k_L = 10^{-2}/5 \times 10^{-5} = 200\ m^{-1}$ (see section S5 in the Supplementary Information). Solutions of Eqs (3) and (4) with boundary conditions (5) and (6) were obtained after application of *bvp5c* MatLab solver to experimental antibiotic concentrations once equations were expressed in dimensionless form (see section S6 in the Supplementary Information). Fig. 1 shows, as an example, the calculated dimensionless concentration profiles of ozone and three antibiotics within the film layer corresponding to the simultaneous direct ozonation of the 15 antibiotics studied. These three antibiotics have been chosen because their kinetic regime with ozone belongs to fast (OXT), moderate (CFX) and slow (MTZ) reactions (see Table 5) (for the rest of antibiotics see Figs. S5 in the Supplementary Information).

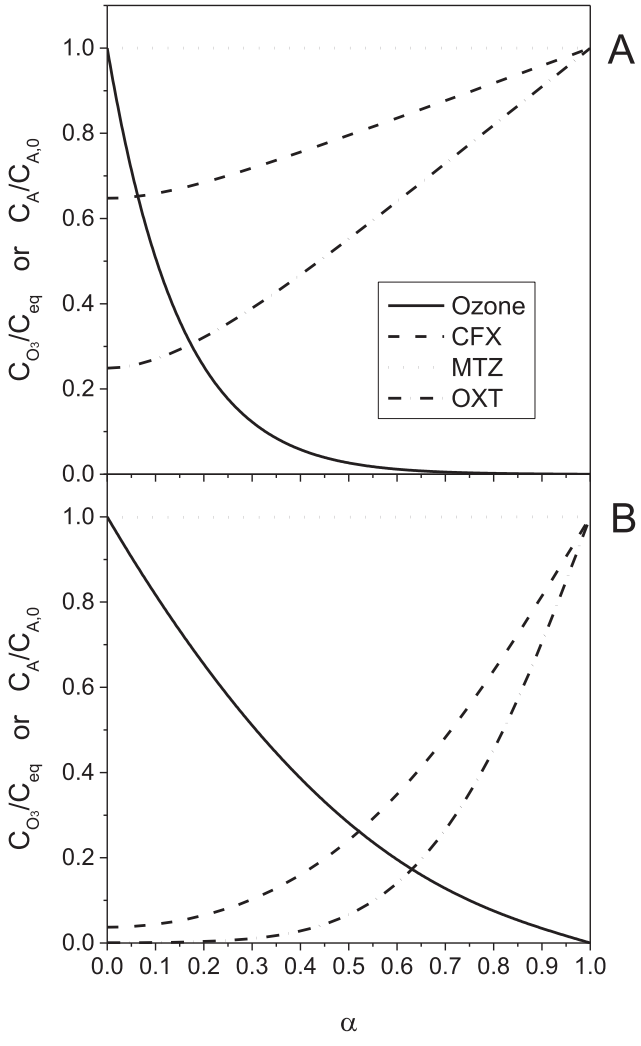


Fig. 1. Calculated dimensionless concentration of ozone and OXT, CFX and MTZ within the film layer from *bvp5c* MatLab solver applied to experimental concentrations: (A) at the start of reaction and (B) at 11 min of the ozonation of 15 antibiotics in water at pH 7 in the presence of 0.01 M *t*-butanol. Conditions Fig. 1A: Initial concentration of antibiotics (see Table 5). Fig. 1B: Experimental concentrations at 11 min of the ozonation run $\times 10^6$, M: OXT: 0.92 CFX: 5.86 MTZ: 6.9.

Fig. 1A reveals how at the start of reaction, ozone concentration drops from the interface within the liquid film layer to become negligible at the water bulk interface, consequence of ozone direct reactions with antibiotics in fast or moderate kinetic regime. Specifically, for the case shown in Fig. 1A, the calculated concentration of dissolved ozone at the water bulk, $x = \delta_L$, was 8×10^{-11} M while the drop percentage of calculated concentrations of OXT, CFX and MTZ from the water bulk to the gas water interface was 75, 35 and 7.5×10^{-4} %, respectively. These figures, however, do not represent the consumption rates of antibiotics in the film layer but the decrease of their concentrations due to their direct reactions with ozone and mass transfer process (see later determination of consumption rates in the film). The negligible amount of ozone reaching the water bulk indicates that, at the start of reactions, antibiotic consumption in the water bulk was also negligible. Drops of antibiotic concentrations depend on their reactivity with ozone, that is, on the kinetic regime. Moreover, since concentrations of ozone at the gas reactor outlet (and, as a consequence, ozone solubility) increase, and concentrations of antibiotics in the water bulk decrease, the kinetic regime changes with time. For example, Fig. 1B shows the dimensionless concentration profiles within the film layer of ozone, OXT, CFX and MTZ at 11 min reaction. These concentration profiles were obtained starting with the corresponding experimental concentration values in limiting condition (6) while for condition (5) the concentration of ozone was that corresponding to the equilibrium determined from application of Henry's law and the experimental gas ozone concentration at the reactor outlet since perfect mixing conditions were also applied. At 11 min reaction time, the calculated concentration of ozone reaching the bulk water was 9.5×10^{-9} M, still an undetectable concentration but nearly 100 times higher than at the reaction start (t = 0). Also, the percentage drop of calculated antibiotic concentrations was nearly 100 % for OXT and CFX and still negligible in the case of MTZ as expected according to the Ha values. Additionally, if a null contribution of ozone reactions in the film is assumed, the calculated concentration of aqueous ozone at 11 min of reaction would be 1.44×10^{-5} M according to the kinetic model (see later) only based on water bulk reactions, while the measured experimental ozone concentration was much lower (i.e., still undetectable experimentally). This sustains the value obtained from solving Eqs. (3) to (6), that is, the existence of ozone reactions in the film. In any case, the difference of dissolved ozone concentration would be about 4 orders of magnitude. This clearly suggests that ozone reactions in the film are more important than in water bulk for antibiotics of Ha values higher than 0.3 [63].

3.3.1. The reaction enhancement factor

Another parameter in gas–liquid reaction kinetics that allows for an estimation of the importance of ozone reactions in the film layer is the reaction enhancement factor, E. This parameter is defined as the ratio between the actual ozone absorption rate, calculated from the application of Fick's law at the gas–water interface, and the ozone physical absorption rate [63]:

$$E = \frac{-D_{O3}a\frac{dC_{O3}}{dx}\Big|_{x=0}}{k_La\left(C_{eq} - C_{O3}\right)} \quad (8)$$

When considering the ozonation of the 15 antibiotics, E has a calculated value of 7.6 at the start of ozonation, which means that the actual ozone absorption rate is 7.6 times higher than the absorption obtained without the development of ozone reactions in the film where

E = 1. Also, the bulk factor, D, similar to E but evaluated at the film-water bulk interface (at x = δ_L) is defined as follows [13]:

$$D = \frac{-D_{O3} a \frac{dC_{O3}}{dx}\Big|_{x=\delta_L}}{k_L a\left(C_{eq} - C_{O3}\right)} \quad (9)$$

It was calculated D = 0.006, which again indicates that almost no ozone reached the water bulk (see also Table S3 for calculated E and D at different reaction times assuming the development of ozone reactions in the film). However, to determine the consumption rates of antibiotics, as indicated above, this low ozone concentration cannot be disregarded since the volume of water bulk is much higher than the corresponding to the film; Volumes of water bulk and film per total volume of reaction: β-aδ_L and aδ_L, respectively, were calculated as shown in the Supplementary section. According to their values, 97.5 % of the total volume (gas plus liquid) belongs to the water bulk while only 0.5 % is the contribution of film volume. In spite of the difference between these two values, both contributions of ozone reactions in the film and in the water bulk have to be accounted for. Coming back to the reaction factor, calculated E drops to 1.97 after 11 min of reaction while D increases up to 0.32 as a result of the change of the kinetic regime of ozone-antibiotic reactions. It is evident, that at more advanced reaction times, E will equal D, becoming unity so that all reactions develop in the water bulk with no consumption of ozone in the film layer. These values of E and D result when solving Eqs. (3) to (9) feeding the *bvp5c* solver with the experimental antibiotic concentrations at start and at 11 min of ozonation.

3.3.2. *Consumed molar flow rates of ozone and antibiotics within the film layer*

The volumetric molar flow rate of ozone, V_{O3}, consumed in the film can be calculated as follows [11]:

$$V_{O3} = (E - D)\left[k_L a\left(C_{eq} - C_{O3}\right)\right] \quad (10)$$

which represents the difference between the ozone molar rates at the inlet and outlet film boundaries. As it can be inferred from Fig. 1 dimensionless concentrations of OXT and CFX, (the latter to a lesser extent), drop from the bulk water interface to inside the film layer due to mass transfer and ozone reaction effects while MTZ concentration does not practically change because of its slow reaction with ozone. From application of Fick's law at the water bulk interface, the molar flow rate of each antibiotic being transported and reacted within the film from water bulk can be calculated as follow:

$$V_i = -aD_i \frac{dC_i}{dx}\Big|_{x=\delta} \quad (11)$$

From Eqs. (10) and (11) and the corresponding stoichiometric coefficients, z_i, the contributions of V_{O3} and V_i have to be introduced in the mass balances applied to the water bulk, leading to the calculated concentrations of species with time (see later kinetic model section). Notice that at a given time the kinetic model confirms that the molar flow rate of ozone consumed was equal to the sum of the molar flow rates of the antibiotics consumed in the film once the stoichiometric ratios were considered:

$$V_{O3} = \sum_i z_i V_i \quad (12)$$

These molar flow rate contributions, V_{O3} and V_i, are not included in the ozonation kinetic models commonly proposed in the literature. This means that ozone reactions in the film are not included in the corresponding mass balances of ozone and fast and/or moderate reacting compounds. Although the importance of these contributions diminishes with time (the concentrations of antibiotics decrease and their reactions with ozone become slow (Ha < 0.3))[63], rigorously, they have to be accounted for.

3.3.3. *Dynamic kinetic model of direct ozonation*

Once the reaction and bulk factors and consumed molar flow of antibiotics within the film are known, they are included in ozone and antibiotic mass balances. That is, from the kinetic model (shown below) the changes of concentrations with reaction time can be calculated. For a semi-batch ozone perfectly mixed reactor as that used in this work, the mass balances are as follows:

For ozone gas:

$$V_r(1-\beta)\frac{dC_{O3r}}{dt} = v_g\left(C_{O3ge} - C_{O3g}\right) - Ek_L a\left(C_{eq} - C_{O3}\right)\beta V_r \quad (13)$$

where v_g is the volumetric gas flow rate, β the liquid fraction of reaction volume V_r and C_{O3g} is the actual ozone gas concentration at the reactor outlet.

For dissolved ozone in the water bulk:

$$\frac{dC_{O3}}{dt} = (E - D)k_L a\left(C_{eq} - C_{O3}\right) - \sum_i k_{Di} C_{O3} C_i [\beta - a\delta_L] \quad (14)$$

where the term in brackets is the volume of water bulk per reaction volume. Notice that the first term of the right side of Eq. (14) is the consumed ozone molar flow rate in the film, V_{O3} (Eq. (10)).

For any antibiotic:

$$\frac{dC_i}{dt} = -\left[V_i + \frac{1}{z_i} k_{Di} C_{O3} C_i [\beta - a\delta_L]\right] \quad (15)$$

where the terms in brackets are the antibiotic molar flow consumptions due to reaction in the film and in water bulk, respectively.

The whole kinetic model of the direct ozonation system consisted of Eqs. (3) to (6) and (13) to (15). The model was solved by the alternative use of *bvp5c* and *ode23tb* MatLab solvers starting with the initial values of the antibiotic concentrations (see Fig. 2 for the flowchart).

Figs. 3 and 4 show, as examples, the calculated concentration profiles of ozone and some antibiotics (OXT, CFX and MTZ, dimensionless concentrations) during the course of ozonation runs. Figs. S6 in the Supplementary Information show results obtained for other antibiotics.

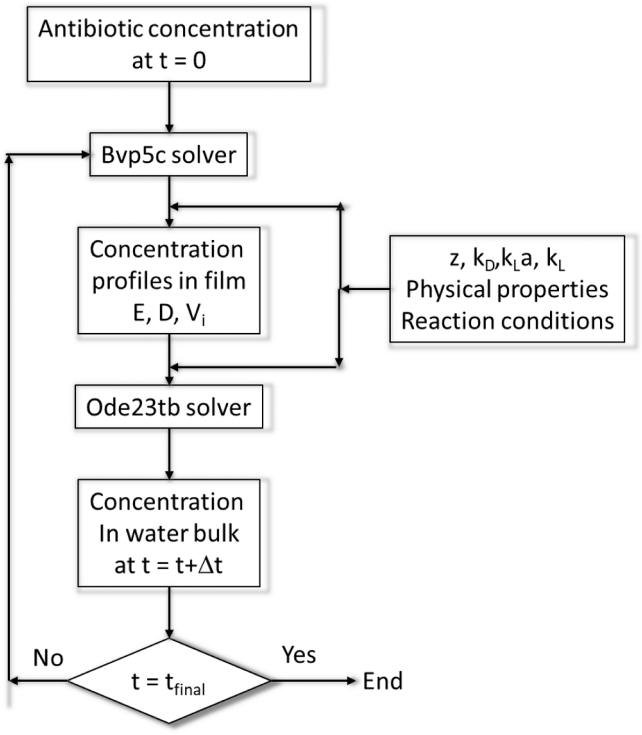


Fig. 2. Flowchart of the MatLab program to solve the kinetic model.

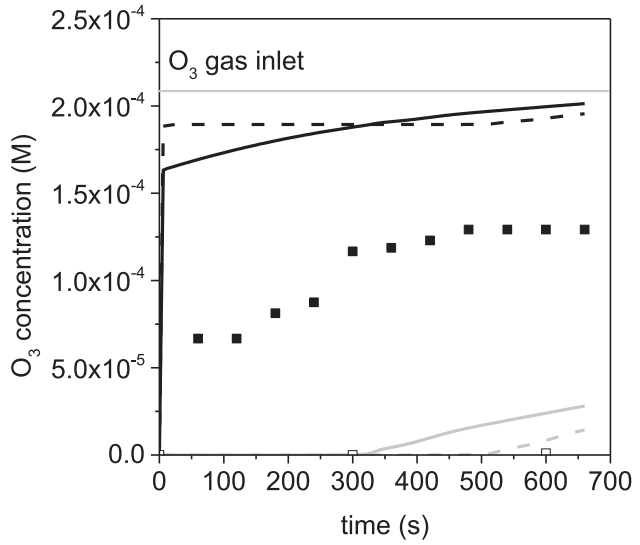


Fig. 3. Variation with time of experimental and calculated concentrations of ozone in gas and water from the simultaneous ozonation of the 15 antibiotics listed in Table 1. Conditions: Gas flow rate: 40 $L{\cdot}h^{-1}$, Ozone inlet gas concentration: 10 $mg{\cdot}L^{-1}$, Average initial antibiotic concentration: 10^{-5} M, pH 7 phosphate buffer, *t*-butanol concentration: 0.01 M. Symbols: experimental ozone gas concentrations at the reacting system outlet (■) and experimental ozone dissolved concentration in water (□). Solid and dashed black lines: calculated outlet ozone gas concentration with and without reactions in the film layer, respectively. Solid and dashed grey lines: calculated dissolved ozone concentrations with and without reactions in the film layer, respectively.

Also, in these figures the experimental concentrations and those calculated with time corresponding to the solution of the kinetic model without including molar flow rates of consumed ozone and antibiotics in the film are shown. Regardless of whether film reaction contributions are considered or not, experimental concentration of antibiotics, (with the exception of MTZ, FLU and CIP of slow reaction with ozone), are above the calculated ones, (except for the first two minutes of reaction in some cases). These differences, however, are the logical consequence of neglecting mass balances of reaction intermediate compounds in the kinetic model. In an ozonation system, especially with organics of complex molecular structures, there are multiple intermediates formed that also react fast with ozone [36,64–66]. This also happens with the ozonation of antibiotics as multiple works report. Just to mention a few examples, literature reports on ozone reaction intermediates of AMX [67], CIP [68], CFX [42], FLU [69], OXT [70], SMX [71,72], TTC [66] or TMP and SMX [73], etc. In these works, some reaction intermediates of similar structure of the parent antibiotic are reported to be formed. Then, these compounds likely have reactivities similar to the initial antibiotic to compete for the available ozone in the film layer. Inclusion of these contributions would have led to a better agreement between calculated and experimental concentrations. However, the aim of this work was to check the importance of ozone reactions in the film rather than to identify multiple reaction intermediates to include their mass balances in the kinetic model.

3.3.4. Comparison between ozone concentrations

In Fig. 3, it is seen that for the first 330 s calculated dissolved ozone concentration when reactions in the film are considered are lower than those calculated without ozone film reactions. These results are the consequence of the fast removal of antibiotics when ozone reactions in the film are considered.

On the other hand, as it is observed from Fig. 4 and Figs. S6, most of the antibiotics are removed in the first 330 s of reaction when ozone reactions in the film are accounted for. However, at this reaction time, there are still significant concentrations of some antibiotics if no ozone reaction in the film is considered. During this period of reaction, it is deduced from Fig. 3 that consumption of ozone calculated considering film reactions is closer to the experimental value than the ozone consumption without taking into account film reactions. Still, significant differences between experimental and calculated data are observed due to the absence of reactions with degradation intermediates. In Fig. 5 calculated dimensionless concentration profiles of OXT, CFX, MTZ and dissolved ozone in the film layer corresponding to 330 s are shown. These results have been obtained with the application of *bvp5c* and *ode23tb* MatLab solvers. It has to be highlighted that profiles shown in Fig. 1B were calculated from experimental concentrations at 11 min reaction, while those of Fig. 5 are calculated from calculated concentrations of Fig. 2. When simulating the process, results at 330 s led to almost 100 % conversion of fast and moderate ozone reacting antibiotics. In the actual experiment, 100 % conversion of this type of compounds is obtained at 11 min of reaction. If calculated concentrations at 330 s in the film layer (Fig. 5) are compared to those obtained from experimental concentrations at 11 min (Fig. 1B), it is seen that while concentration profiles of antibiotics are similar the profile of dissolved ozone concentration within the film layer is clearly different. Now, from Fig. 5 it is observed that the ozone concentration profile nearly follows a straight line across the film layer. This means that at this reaction time of 330 s reactions in the film can be neglected. The trend virtually corresponds to the case where ozone chemical absorption rate equals the physical absorption rate. This can be confirmed with the calculated E and D values from the kinetic model that were close to unity (E = 1.03 and D = 0.98). Contrarily, Fig. 1B, obtained from experimental concentrations, reveals that ozone concentration in the film follows a curved profile. In this case, calculated E and D values are 1.97 and 0.32, respectively (see Table S3), indicating the development of reactions in the film due to the presence of still significant concentrations of fast reacting antibiotics. Coming back to Fig. 3, after the first 330 s the opposite situation is observed in terms of ozone concentration profiles with and without ozone film reactions. After this period, if film reactions are considered, only ozone reactions with slow reacting antibiotics (MTZ, FLU and CIP) would proceed. In fact, as shown in Fig. 4 and S6, after 330 s, calculated concentrations of these antibiotics start to decrease because of the absence of fast ozone reactions. This trend is also experienced without considering ozone film reactions though this phenomenon occurs at higher reaction times for the same reason (about 550 s). Regarding dissolved ozone concentrations, this species was not experimentally observed during the period when antibiotic concentrations were detected (11 min). However, as seen in Fig. 3, calculated dissolved ozone concentration appears once most of antibiotics have been consumed (330 and 550 s with and without ozone reactions in the film, respectively). Consequently, it can be concluded that for a good kinetic modeling of any ozonation system (including or not free radical reactions) detailed knowledge of the kinetics of reaction intermediates is absolutely necessary.

3.3.5. Comparison between antibiotic concentrations

In terms of antibiotic concentration predictions, the model shows different results depending on the ozone reactivity and stoichiometry coefficients. For instance, in the case of fast ozone reacting antibiotics (OXT, AMX, TTC and SMZ) with initial Hatta numbers higher than 3 and stoichiometric ratios of one mole of ozone consumed per mole of antibiotic consumed, inclusion of film reactions leads to concentrations surprisingly higher or similar than those obtained without considering film reactions. Hence, for the first minutes, in these cases: OXT (Fig. 3A), AMX and TTC, Figs. S6), considering film reactions, calculated dissolved ozone concentration reaching the water bulk is lower than that calculated without taking into account film reactions. These results lead to faster or similar antibiotic predicted removal rate. For example, at 1 min of reaction, the kinetic model without film reactions predicts $4.13{\times}10^{-6}$ M and $8.64{\times}10^{-9}$ M for OXT and dissolved ozone bulk concentration, respectively. This represents a removal rate of

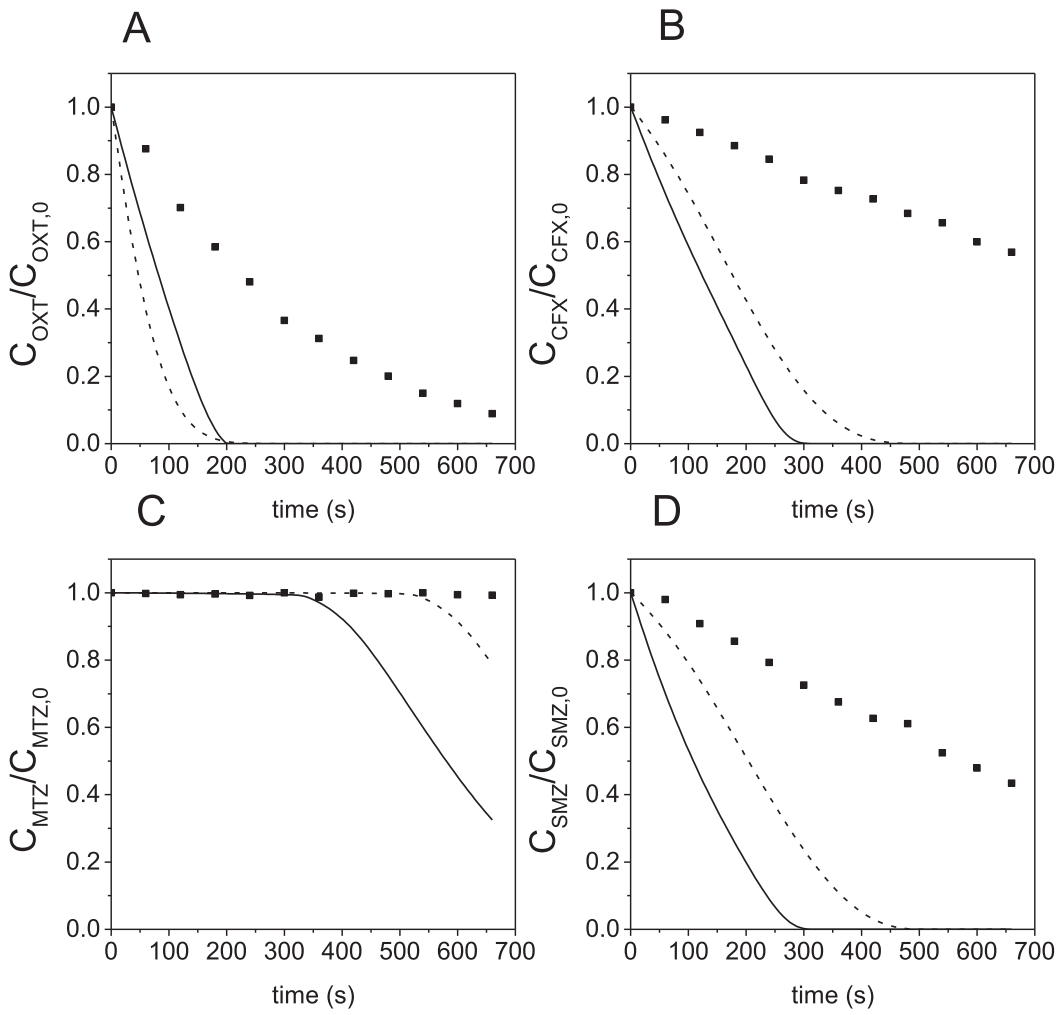


Fig. 4. Variation with time of experimental and calculated dimensionless concentration of OXT (A), CFX (B), MTZ (C) and SMZ (D) from the simultaneous ozonation of 15 antibiotics listed in Table 1. Conditions as in Fig. 3. Symbols: experimental concentrations. Discontinuous line: calculated concentration without reactions in the film layer. Continuous line: calculated concentration with reactions in the film layer (kinetic model of Fig. 2).

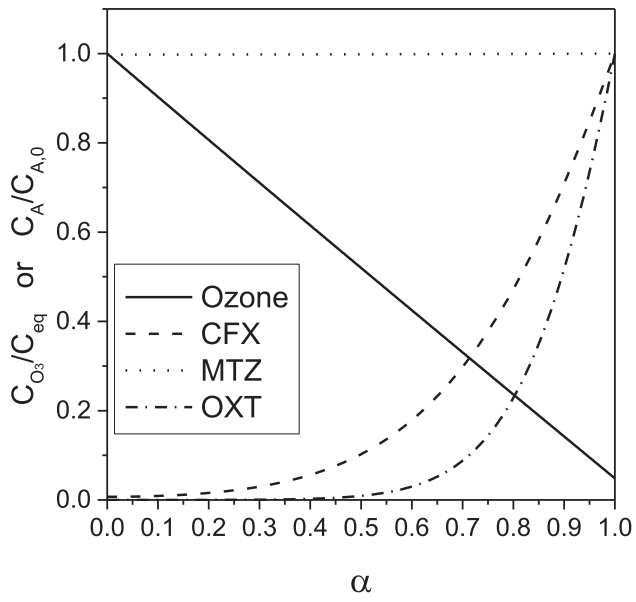


Fig. 5. Variation of calculated dimensionless concentration of ozone and OXT, CFX and MTZ within the film layer at 330 s from the application of MatLab program shown in Fig. 2.

1.83×10^{-7} Ms^{-1}. At the same reaction time, the kinetic model of Fig. 2, that includes film reactions, predicts $6{,}51\times10^{-6}$ M and 2.31×10^{-10} M for OXT and dissolved ozone bulk concentration, respectively, and the predicted removal rate due to film reaction was 5.06×10^{-8} Ms^{-1}. Hence, the sum of water bulk and film reactions rates to total OXT removal rate is: $8.02\times10^{-9} + 5.06\times10^{-8} = 5.86\times10^{-8}$ Ms^{-1} which is lower than 1.83×10^{-7} Ms^{-1}, the predicted removal rate without considering film reactions (see also section S11 for more details). However, when the stoichiometric ratio is 3 mol of ozone per mole of antibiotic (case of SMZ), the kinetic term in the water bulk ($(1/z)\ k_D C_i C_{O3}$) in the antibiotic mole balance is reduced three times, and the opposite situation is observed, that is, calculated concentrations of antibiotic is lower when reactions in the film are considered (see Fig. 4D for SMZ). When moderate reactions with ozone develop, as a general rule, predicted concentrations with the inclusion of film reactions, as expected, are much lower than those if no film reactions were included (see Fig. 4B for the case of CFX and Fig. 6S except for AMX and TTC). As a consequence, removal of these compounds is faster when including the ozone film reactions. Finally, Fig. 4C or Fig. 6S show the cases of MTZ, CIP and FLU, respectively, that slowly react with ozone. In these cases, it can be seen that there is no difference between results and only after 330 s, no inclusion of ozone film reactions leads to a slower removal of the antibiotic compared to the cases when ozone film reactions are accounted for.

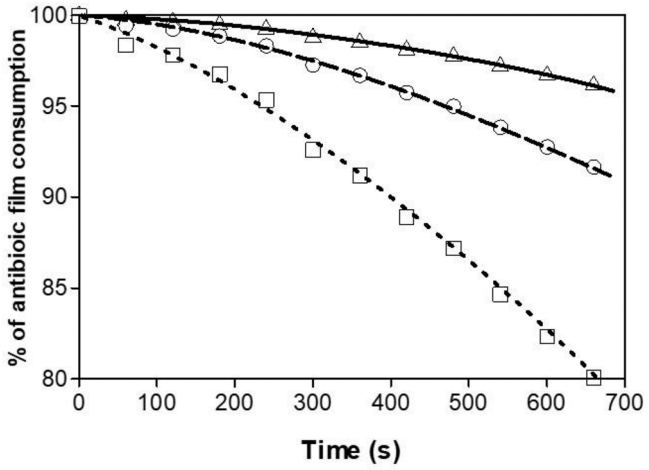


Fig. 6. Changes with time of antibiotic percentage removal from film reactions. Conditions as in Fig. 1 and application of bvp5c Matlab solver to experimental antibiotic concentrations. Symbols: △SMX, ○CFX, □OXT.

3.3.6. Comparison of antibiotic removal rates due to film and water bulk reactions.

Figs. 6 and 7 show as examples the changes with time of OXT, CFX and SMX percentage molar consumption rates due to film reactions determined from experimental concentrations by applying bvp5c Matlab solver and from the kinetic model of Fig. 2, respectively.

It is observed in Fig. 6 that when experimental concentrations are used film consumption rate always represents percentages higher than 80 %. This is due that at actual experimental conditions there are still important concentrations of antibiotics at the end of the ozonation run (11 min reaction) so that at this reaction time Hatta numbers are still higher than 0.3 (meaning at least moderate kinetic regime). Similar results were observed for the rest of antibiotics as shown in Figs. S7 except for the cases of MTZ, FLU and CIP of slow ozone kinetic regime that hardly react during the ozonation run. In these cases, there is no reaction in the film. If we look at the results from the model of Fig. 2, (see Fig. 7 and S8) it is seen that percentage contribution of film reactions decreases with time becoming water bulk reactions more important. For instance, in the case of OXT, from Fig. 7 it is observed that there is 100, 60 and 6 % contribution of film reaction at 0, 3 and 5 min, respectively. From calculated antibiotic concentrations, it can also be noted that at these reaction times, calculated Ha was 3.3, 1.4 and 0.02, respectively. This means that Ha is a good tool to specify the zones

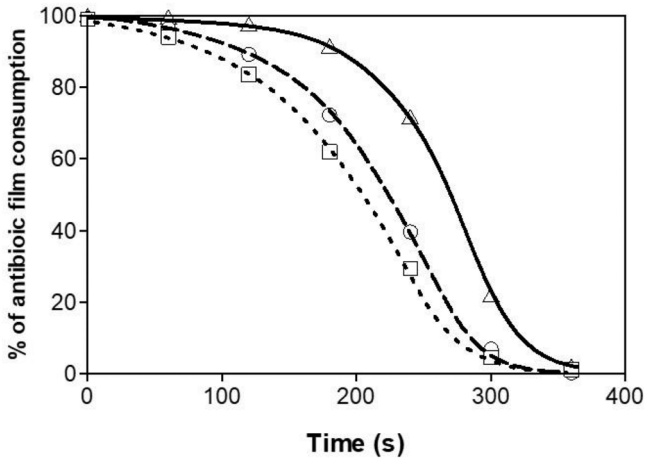


Fig. 7. Changes with time of antibiotic percentage removal from film reactions. Conditions as in Fig. 3 and kinetic model of Fig. 2. Symbols: △SMX, ○CFX, □OXT.

in the water where the reaction takes place. According to film theory, Ha > 3 means reaction exclusively in the film, Ha < 0.3 means that reaction takes exclusively in the water bulk, while there is reaction in the film and water bulk for intermediate values of Ha. This is confirmed from the percentage contribution of film reactions as shown in Fig. 7. Regarding Fig. 6 (and Fig. S7) similar conclusions can be reached, percentage contributions of film reactions are in accordance to Ha values higher than 0.3.

Finally, it can be said that if mass balances of reaction intermediate compounds would have been included, calculated antibiotic concentrations with reactions in the film layer would be closer to the experimental ones. In fact, with the presence of intermediates, calculated concentrations of antibiotics without considering ozone reactions in the film would be, in some cases, even higher than experimental ones which is not possible and would confirm the importance of film reactions. This can be deduced, for instance, from Fig. 6S, especially in the cases of AMP, SMX, SDX and TMP where there are some coincidences between experimental and calculated concentrations in spite of the absence of contribution of reaction intermediates in the kinetic model, which is an unrealistic situation.

4. Conclusions

Application of kinetic models of ozone reactions in water including film reactions are needed for the cases of high concentration (at least hundred of μg/L) of pollutants of high reactivity with ozone (high rate constants of their ozone reactions). This means that the Hatta number of these ozone reactions have to be at least higher than 0.3 as it happens with numerous antibiotics such as many studied in this work. It is evident that ozonation of natural water and effluents from MWWTPs where antibiotics are detected at low concentration, does not need the application of such models. However, literature reports on other wastewater with antibiotic concentrations of hundreds of μg L^{-1} as indicated in the introduction section. It is in these cases where kinetic models involving ozone film and water bulk reactions are necessary. Accordingly, for systems of this type, the main conclusions reached in this work are:

- Ozone rate constants and stoichiometry coefficients should be determined whenever possible at the same conditions.
- Kinetic modeling of ozone systems with moderate or fast ozone reactions must include the effects of simultaneous mass transfer and ozone reactions in the film layer or proximity of gas–water interface.
- Accurate kinetic modeling requires the inclusion of mass balances of reaction intermediates in the ozonation of complex mixtures of antibiotics.
- Antibiotics of high and moderate reactivity with ozone (Hatta numbers higher than 0.3) are almost totally or partially consumed in the proximity of the gas–water interface so that ozone consumption predictions present higher errors if ozone reactions in the film layer are not accounted for.
- For these antibiotics, however, those with very high reactivity ($k_D > 10^6$ $M^{-1}s^{-1}$) and low stoichiometry (1 mol of ozone per mole of antibiotic), no inclusion of film reactions implies erroneous predictions of lower concentrations because of the higher and erroneous calculated dissolved ozone concentrations.
- When the ozone-antibiotic reactivity is moderate (0.3 < Ha < 3) ozone film reactions once accounted for, allow a faster removal of the antibiotics which is the logical consequence of the ozone and antibiotic molar flows consumed in the film. In these cases, the increase of dissolved ozone concentration predicted when ozone film reactions are not included has not enough effect to balance the consumption in the film layer.
- Finally, when reactions of ozone and antibiotics are slow (Ha < 0.3) no differences are observed in concentrations from both kinetic

models which is a logical consequence of the negligible or null reactions in the film.

The results reported in this work will be completed in the future by considering the influence of free radical formation in the film layer. Studies of the formation of free radicals in the film layer in fast-moderate ozone kinetic regimes are also missed in literature and may deserve specific studies.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cej.2023.141408.

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