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Fate of Carbamazepine during Water Treatment

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Seven transformation products of carbamazepine generated by at least one of three common water treatment technologies (UV-radiation, oxidation with chlorine dioxide (ClO_2), and biological treatment with activated sludge) were identified by complementary use of ion trap, single quadrupole, and quadrupole-time-of-flight mass spectrometers. Acridine was formed during all of the three treatment processes, while acridine 9-carbaldehyde was identified as an intermediate during ClO_2 oxidation. Further treatment of acridine with ClO_2 produced 9-hydroxy-acridine. UV-treatment resulted in the formation of acridone, hydroxy-(9*H*,10*H*)-acridine-9-carbaldehyde, acridone-*N*-carbaldehyde, and 1-(2-benzaldehyde)-(1*H*,3*H*)-quinazoline-2,4-dione, while biological breakdown of acridine yielded acridone. In parallel, the transformation product iminostilbene was observed during sample analysis. In addition, this study compared the treatment technologies according to the removal of carbamazepine and the production and decay of its transformation products. The most successful method for the removal of carbamazepine was UV treatment, while acridine and acridone were more susceptible to biological treatment. Therefore, based on the enhanced biodegradability of carbamazepine residues achieved by UV irradiation, we propose a coupled treatment technology involving an initial UV treatment step followed by biological treatment, which may satisfactorily remove the parent compound and its transformation products.

Introduction

Carbamazepine (CBZ) is a dibenzadiazepine derivative used for its antiepileptic and psychotropic activity, for severe pain syndromes associated with neurological disorders, and is a global pharmaceutical. It is administered chronically and usually in high dosages (100−2000 mg daily) and hence its annual production is high (*1*−*3*). The drug is excreted with <3% remaining in its unaltered form, with the pharmacologically active 10,11-epoxycarbamazepine as the major metabolite, which is then hydrolyzed to dihydroxy derivatives and excreted principally as glucuronide conjugates. Additionally, CBZ is inactivated by hydroxylation of the aromatic ring and N-glucuronidation of the carbamyl moiety (*4*). It is a relatively polar pharmaceutical and lacks sites for specific interactions with soils and sediments, which leads to its nonappreciable sorption properties (*5*−*7*). It is persistent to biodegradation and shows almost no elimination during wastewater treatment (*1, 7, 8*), which makes CBZ a pharmaceutical of high environmental relevance. Studies have reported its presence in wastewaters (up to 6.3 $\mu g\ L^{-1}$) (*1, 9*), in surface waters (up to 1.1 $\mu g\ L^{-1}$) (*1, 10, 11*), and in drinking water (30 $ng\ L^{-1}$) (*12*). In contrast with conventional biological wastewater treatment (*8*) and ClO_2 treatment (*13*), CBZ is effectively removed by ozonation (*5*), by UV/H_2O_2 induced photolytic degradation (*14*), photocatalytic degradation with TiO_2 (*15*), or by direct photolysis (*16*). Although these technologies remove CBZ, the result is not always complete mineralization and the disappearance of CBZ provides only a partial indication of treatment efficiency, since transformation products (TPs) more resilient to degradation may form. In addition, the overall toxicity of treated water arising from a mixture of stable TPs may worsen the environmental and health impact (*17, 18*). Thus, it is important not to overlook TPs when comparing the efficiency of different water treatment technologies. Albeit, abiotic transformation studies of CBZ have been made (*14*−*16, 19*), to our knowledge, the formation of TPs by biological treatment and more generally the degradation of CBZ's TPs is yet to be investigated (*20*).

In this paper, we study the efficiency of three water treatment technologies: UV treatment, chlorine dioxide treatment, and biodegradation with activated sludge, with respect to the removal of CBZ and its TPs. At the core of the present study is a comparison of these approaches, where the importance of biological treatment of TPs is underlined. Finally, solutions for the efficient removal of both CBZ and its TPs are proposed.

Experimental Section

Standards, Solvents, and Other Chemicals. Carbamazepine (99%, CAS 298-46-4) was purchased from Acros Organics (New Jersey), while acridine (ACIN: 97%, CAS 260-94-6) and 9(10*H*)-acridone (ACON: 99%, CAS 578-95-0) were both obtained from Sigma-Aldrich (St. Louis, MO). *N*-Methyl-*N*-[tert-butyldimethyl-silyl]trifluoroacetimide (MTBSTFA) was purchased at Acros Organics.

Treatment Experiments. *UV Treatment.* UV treatment was performed in an UV reactor with a circulating flow system setup. The apparatus consisted of a steel container (8 L), a water pump (85 $L\ h^{-1}$), and a medium pressure metal−halogen UV lamp (690 W). The UV lamp (Bau 42, Scan Research A/S, Denmark) emitted a polychromatic light at 400−185 nm, with an enhanced emission within the photochemical relevant wavelength range of 250−190 nm. The emission spectrum is given in the Supporting Information. The fate and behavior of CBZ and its TPs were studied during a 30 min irradiation time. Spiked tap water solutions containing 100 $\mu g\ L^{-1}$ of the test substance were sampled at set time-intervals. Photodegradation experiments were also performed separately with ACIN and ACON as respective starting compounds. Finally, to determine the impact that a radical scavenger has 1.2%, 2.5%, and 6.2% (V/V) of methanol was added to the starting solution.

Chlorine Dioxide Treatment. A ClO_2 solution was prepared by adding 25 mL of 9% (w/V) HCl and 25 mL of $NaClO_2$ (7.5% w/V) to 400 mL of deionized water. After 12 h the volume was made up to 1000 mL with deionized water giving an approximately 1 $g\ L^{-1}$ ClO_2 stock solution. The stock solution

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TABLE 1. Bioreactor Test Parameters

	bioreactor	test compound	c_X (μg L^{-1}) removal	c_X (μg L^{-1}) TPs	$c(O_2)$ mg L^{-1}
	R0	control: NO			9.0 ± 1.4
	R1	CBZ	50	200	9.5 ± 0.7
	R2	CBZ	50	500	9.3 ± 1.5
	R3	ACIN	50	200	9.5 ± 1.4
	R4	ACIN	50	500	9.5 ± 1.6
	R5	ACON	50	200	7.6 ± 1.7
aerobic	R6	ACON	50	500	9.5 ± 1.4
	R7	control: NO			0.12 ± 0.04
	R8	CBZ	50	200	0.12 ± 0.04
	R9	ACIN	50	200	0.12 ± 0.04
anoxic	R10	ACON	50	200	0.12 ± 0.04

was then normalized using the "DPD-method" and an Allcon spectrophotometer (Alldos GmbH Germany). A neutral pH was achieved by adding 0.11 M Na_2HPO_4 and the test solutions were exposed to concentrations of ClO_2, ranging from 0.7 to 13.5 mg L^{-1}. The experiments were made in distilled water spiked with 100 μg L^{-1} of either CBZ or ACIN. The test mixtures were left to react for 2 h, whereupon the reaction was interrupted by the addition of 20 mg of Na_2SO_3.

Biological Treatment. Experiments were performed in laboratory bench scale flow-through bioreactors (*21*−*23*) containing activated sludge, which were operated in parallel under identical conditions: nutrient, hydraulic retention time, and biomass concentration. Table 1 gives the different test parameters.

Seven aerobic and four anoxic bioreactors were operated. Prior to sampling, the bioreactors were kept under test conditions for a period sufficient to allow for adaptation. Temperature was maintained at 23.3 ± 1.3 °C.

Control Studies. In the biodegradation experiments, the R0 (aerobic) and R7 (anoxic) outlets were used to distinguish between the products of matrix biodegradation or bacteria lyses and actual pharmaceutical degradation. As an additional control, the spiked inlet samples R1, R2, or R8 (for CBZ); R3, R4, or R9 (for ACIN), and R5, R6, or R10 (for ACON) were also analyzed to exclude the possibility of other potential breakdown mechanisms such as light, thermal, or hydrolysis. For the photodegradation and ClO_2 experiments, untreated spiked solutions were used as controls.

Sample Preparation. Sample preparation was based on solid phase extraction, followed by gas chromatography−mass spectrometry (GC-MS) or liquid chromatography−mass spectrometry (LC-MS). For quantitative purposes, the sample preparation involved an additional derivatization step prior to GC-MS analysis (see Supporting Information).

Instrumental Analysis. *GC-MS.* Qualitative analyses were made using a Varian 3800 GC hyphenated with an ion trap

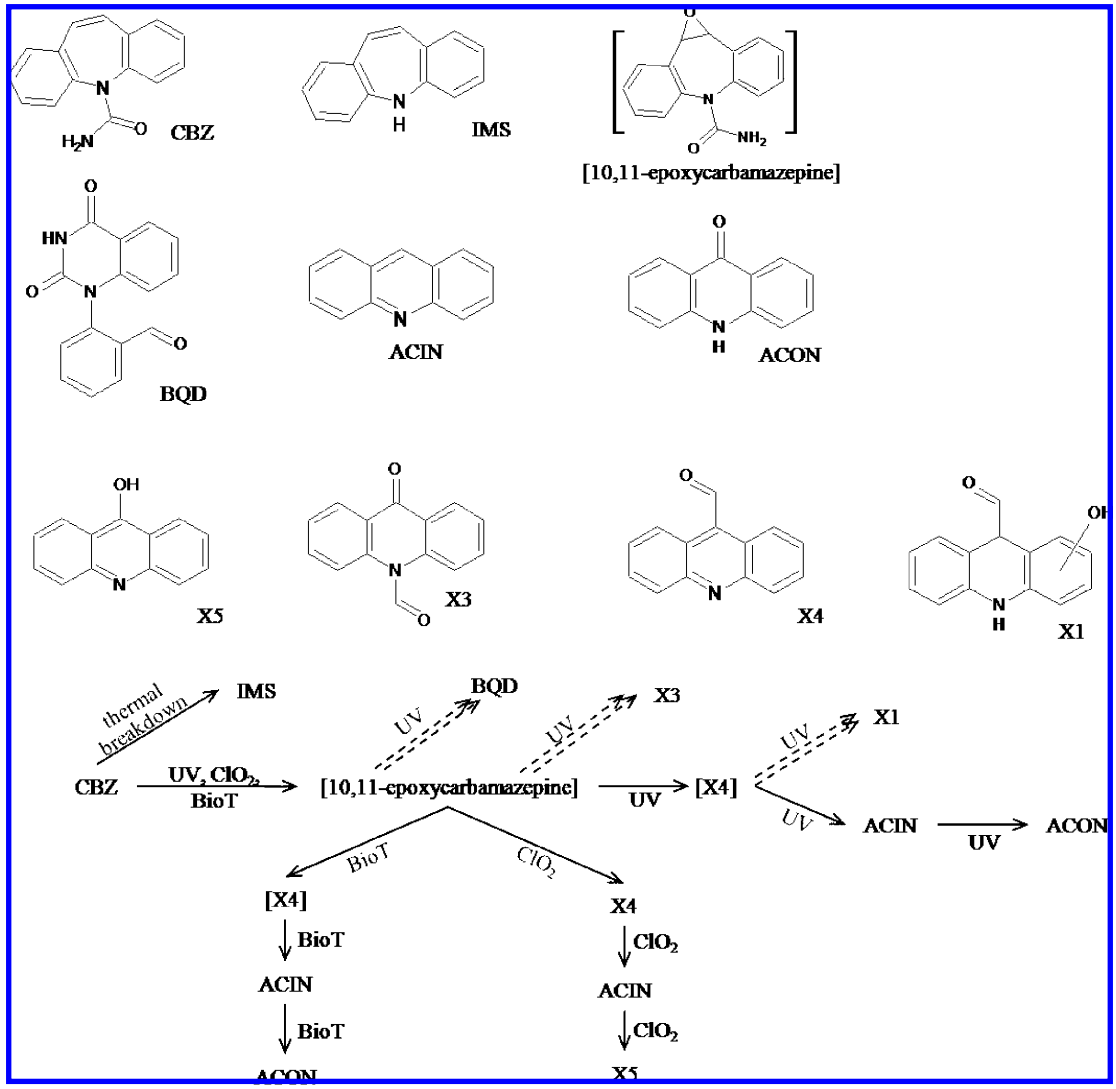

FIGURE 1. Proposed chemical structures of TPs and the proposed breakdown pathway of CBZ. BioT: biotransformation; ClO_2: chlorine dioxide treatment; UV: UV irradiation.

TABLE 2. Carbamazepine and Identified TPs

compound	abb.	elemental formula	molecular weight[a]	breakdown mechanism	identification/ confirmation method
carbamazepine	CBZ	$C_{15}H_{12}N_2O$	236 ($[M + H]^+ = 237.1030$)	parent compound	LC-QqTOF, GC-IT, GC-MSD, NIST library, authentic standard
iminostilbene	IMS	$C_{14}H_{11}N$	193	thermal degradation in GC liner	GC-IT, GC-MSD, NIST library
acridine	ACIN	$C_{13}H_9N$	179 ($[M + H]^+ = 180.0814$)	photolysis, ClO_2 oxidation, biodegradation	LC-QqTOF, GC-IT, GC-MSD, NIST library, authentic standard
acridone	ACON	$C_{13}H_9NO$	195 ($[M + H]^+ = 196.0765$)	photolysis, biodegradation of ACIN	LC-QqTOF, GC-IT, GC-MSD, NIST library, authentic standard
hydroxy-(9*H*,10*H*)-acridine-9-carbaldehyde	X1	$C_{14}H_{11}NO_2$	225	photolysis	GC-IT
acridone-*N*-carbaldehyde	X3	$C_{14}H_9NO_2$	223	photolysis	GC-IT
1-(2-benzaldehyde)-(1*H*,3*H*)-quinazoline-2,4-dione	BQD	$C_{15}H_{10}N_2O_3$	266	photolysis	GC-IT, McDowell et al. (*19*)
acridine-9-carbaldehyde	X4	$C_{14}H_9NO$	207	ClO_2 oxidation	GC-IT
9-hydroxy-acridine	X5	$C_{13}H_9NO$	195 ($[M + H]^+ = 196.0767$)	ClO_2 treatment of ACIN	LC-QqTOF

[a] The accurate mass of the protonated molecule is provided in brackets, when determined by a high resolution instrument (i.e. QqTOF).

Saturn 2000 mass spectrometer (GC-IT). Quantitation was achieved using a HP6890 series gas chromatograph fitted with a mass selective detector (GC-MSD). Both spectrometers were operated in the electron impact ionization mode (EI). For further mass fragmentation the capabilities of an IT mass analyzer, i.e., multiple reaction monitoring (MRM), tandem MS (MS/MS), and multiple MS (MS^n) ion preparation modes in the resonant waveform, were utilized.

LC-MS. LC-MS analyses were performed using a Waters Acquity ultra-performance liquid chromatograph (Waters Acquity UPLC, Waters Corp., Milford, MA) hyphenated to a hybrid quadrupole orthogonal acceleration time-of-flight mass spectrometer (QqTOF Premier, Waters). The instrument was equipped with an electrospray ionization interface operating in the positive electrospray ionization mode (ESI(+)). Further details about the GC-MS and LC-MS methods are given in the Supporting Information.

Results and Discussion

Methodology of Detection and Practical Issues Encountered in the Determination of CBZ and its TPs. To include the broadest range of TPs, screening was made by operating the GC-MS and LC-MS analyses on parallel samples. The detection of TPs in the GC samples was made by comparing the total ion chromatograms (TIC) of the treated samples with those of the control. Any new peaks appearing in the treated samples were then investigated further. In the LC analysis the transformation products were detected by applying the spectral and chromatographic algorithm MetaboLynx, a software package embedded in MassLynx v4.1 (Waters Corp.).

While LC-QqTOF and GC-IT were used to identify new compounds, GC-MSD was used for quantitative purposes. Optimization and validation of the GC-MSD method was made using CBZ, ACIN, and ACON, for which authentic standards are available. Optimization took into account chromatographic separation, peak shape and response, possible matrix effects, and the linearity of the mass spectrometer's response. A crucial step in optimizing this procedure was the use of the derivatization reagent MTBSTFA, whereas samples analyzed by GC-IT were not derivatized as this could affect the screening and identification of TPs. Both ACON and CBZ were transformed into their *tert*-butyl-dimethylsilyl ethers (ACON-MTBS and CBZ-MTBS), while ACIN was left underivatized. The use of MTBSTFA improved both separation and peak shape; moreover, the chromatographic response increased by 58% and 74% for ACON-MTBS and CBZ-MTBS, respectively. It also avoided the artifactual formation of iminostilbene (IMS, Figure 1), believed to form from the thermal breakdown of CBZ in the injector. In the underivatized GC samples, the amount of IMS corresponds to the amount of CBZ; furthermore, in LC its formation is not observed, which supports the hypothesis of it being a thermal breakdown product.

When extracting samples after chlorine dioxide treatment, there is the potential for the salt-effect to give misleading results. To evaluate this, two calibration curves were prepared, one in deionized water and the other in a 1.8 mM NaCl solution containing the relevant analyte in the concentration range 15−150 $\mu g\ L^{-1}$. The results show an almost complete overlap of the curves for each of the investigated compounds in both solutions and thus any salt-effect can be discarded. In addition, despite not using an internal standard, a satisfactory linearity with r^2 0.992, 0.989, and 0.985 was achieved for CBZ, ACIN, and ACON, respectively.

Identification of Transformation Products. By utilizing the capabilities of the QqTOF mass spectrometer: tandem mass fragmentation and accurate mass measurement, in combination with the IT mass analyzer enabling MS^n fragmentation, eight TPs were identified. In support to the proposed chemical structures, confirmatory methods were also used including matching the TP fragmentation patterns with those held in the NIST mass spectral library or published mass spectra and, where possible, a comparison of the compound's chromatographic and mass spectrometric behavior with that of a commercially available authentic compound. Table 2 summarizes all the applied identification and confirmation techniques.

Under UV irradiation of CBZ, the following TPs became evident (see Supporting Information, Figure S3): ACIN, ACON, X1, X2, X3, and BQD. According to its EI-MS and EI-MS/MS fragmentation pattern and a match with the NIST library (Table 2) the most abundant peak was acridine (ACIN). Further, its identity was confirmed by comparing its retention time and mass fragmentation pattern to that of the authentic compound. In parallel, ACIN was detected using MetaboLynx processing, while for its structural elucidation QqTOF tandem mass fragmentation and accurate mass measurement were performed. The latter gave a 0.6 ppm deviation from the theoretical mass of the

protonated acridine. For a detailed description of the identification process for ACIN see the Supporting Information.

The second TP, which was formed during UV irradiation, (see Supporting Information, Figures S3 and S5) shows an increase in mass of 16 Da in its EI mass spectrum, which corresponds to ACIN with an additional oxygen atom. A search of the NIST library and a comparison with the authentic compound confirms this to be 9(10*H*)-acridinone (ACON, Table 2). During derivatization the ether forms on the 9-hydroxy group of the ACON "enol" tautomer, yielding a fragmentation pattern with the corresponding-type fragmentation as CBZ-MTBS. Complementarily, the ESI(+)TOF acquisition and collision-induced dissociation of the protonated ACON molecule at $[M + H]^+$ 196 were performed, where its elemental composition was confirmed with a mass error of 1.5 ppm.

The chemical structure of X1, another UV breakdown product eluting at 10.2 min, was resolved based on its EI-MS and EI-MS/MS fragmentation (see Supporting Information). X1 was identified as hydroxy-(9*H*,10*H*)-acridine-9-aldehyde, which confirms the existence of this TP, previously proposed to be a product of CBZ photocatalytic breakdown (*15*). Other structural isomers are also possible and further investigation is needed to confirm—with certainty—its structure.

The structural elucidation of X2 was, despite its relatively prominent chromatographic peak, unsuccessful. Since the highest ion fragment yielded an even mass (see Supporting Information, Figures S7 and S8), it is supposed that X2 was subjected to the loss of the molecular ion, which is not uncommon for a "hard" ionization method, such as EI. One solution would be to use chemical ionization (CI) to observe the molecular ion, which is enabled by modern GC-IT instruments. Another option would be to employ LC-MS using milder ionization techniques. Unfortunately, an inspection of the ESI(+) mass spectra revealed no compound having the related mass fragmentation pattern. Alternatively, NMR studies would be the way ahead, but this requires obtaining a sufficient amount of X2 by adapting the dosage of UV irradiation, optimizing the enrichment by solid phase extraction, and developing an appropriate purification method.

The fragmentation pattern of X3 resembles closely that of ACON, with the exception of the molecular ion at m/z 223. The molecular ion shows a mass increase of 28 Da, i.e., a carbonyl group, which is likely positioned on the heterocyclic nitrogen as the residual from the carbamyl side chain of CBZ (see Supporting Information, Figure S9). Thus, X3 is tentatively assigned as acridone-*N*-carbaldehyde, which to the authors' knowledge is the first identification of this TP.

The last UV-breakdown product, sufficiently volatile to be analyzed by GC-IT (Figures S3 and S10) was identified according to its EI-MS, EI-MS/MS, and EI-MS^3 fragmentation. McDowell et al. (*19*), who determined three TPs during the ozonation of CBZ all containing the quinazoline structural fragment, published an identical mass fragmentation pattern. Hence, based on a match to the mass spectra published by McDowell et al. (*19*) one can assume that this compound is 1-(2-benzaldehyde)-(1*H*,3*H*)-quinazoline-2,4-dione (BQD).

The inspection of the GC-IT extracted mass chromatogram of the ClO_2-treated sample (Supporting Information, Figures S3 and S11) yielded a new compound X4, the concentration of which increases with increasing ClO_2 dose. Its mass spectrum suggests it is an acridine structural fragment with the mass increased by 28 Da, which corresponds to a carbonyl-bearing compound, i.e., acridine-carbaldehyde.

X5 was identified during ClO_2 treatment of ACIN. The compound was highlighted by MetaboLynx and its mass spectra (ESI(+)TOF and ESI(+)TOF-MS/MS) matched that of ACON (see Figure S5). Taking into account the similar mass fragmentation and that oxidation at position 9 is favorable due to a low electron density at this carbon on the acridine ring (*24*), X5 is assigned as the 9-hydroxy-derivative of acridine.

Fate during UV, Chlorine Dioxide, and Biological Treatment. Based on the identified TPs, a possible degradation pathway is proposed (Figure 1). During UV degradation six TPs were detected and structures of five were tentatively assigned (ACIN, ACON, X1, X3, BQD), chlorine dioxide treatment produced three TPs (ACIN, X4, X5), and biodegradation produced two TPs (ACIN, ACON). One compound (IMS) was formed during sample analysis. The high number of TPs is indicative of the complexity of the reactions involved, however regardless of the nature of the transformation, i.e. abiotic or biological, ACIN is involved as an important intermediate.

In case of chlorine dioxide treatment, abiotic breakdown is the consequence of chemical oxidation, while during UV treatment an organic molecule may undergo structural alteration during the electronic transition from an excited state to the ground state (direct/primary photolysis) or by photolytic transformation induced by reactive oxygen species generated by the UV-photons (advanced oxidation/secondary photolysis) (*25*). As derived from Figure 1, the most reactive site on the CBZ molecule is at the 10,11-double bond, which is commonly attacked by hydroxyl radicals or oxidation reagents to yield an intermediate that evolves into 10,11-epoxycarbamazepine (*15*). Subsequent opening of the epoxide ring will give a labile species that forms a quinazoline derivative (BQD) (*19*) or suffers a facile ring contraction to give acridine-9-carbaldehyde (X4) (*14*) or acridone-*N*-carbaldehyde (X3). This ring contraction takes place via a pinacol-type rearrangement (*26*) and is reasoned by the tendency of an azepine ring to yield an aromatic structure. Further conversion of X4 leads to the cleavage of an aldehyde group to form ACIN and further ACON (Figure 1). This is supported by a rapid increase in X4 during the first phase of ClO_2 treatment and the fact that it reaches a peak concentration before the secondary breakdown product ACIN does (see Supporting Information). Another reactive site is the carbamyl side chain, the cleavage of which is possible by thermal degradation and by various oxidizing species.

To get an insight into the reaction mechanism, methanol was added to the test solution during the UV experiment to inhibit any radical mediated breakdown processes and enable the detection of short-lived intermediates. In contrast to expectations, no significant difference in the decay of CBZ was observed nor any additional intermediates detected in the presence of 1.2%, 2.5%, or 6.2% of methanol. However, increasing the content of methanol in the test solution did cause a notable decrease in the formation of ACON, suggesting that the predominant mechanism responsible for transformation of ACIN to ACON is indirect photolysis.

Under UV experimental conditions, CBZ shows a steady decrease following first order kinetics. This results in 99.8% elimination after 30 min of UV irradiation (Figure 2 left). The amount of TPs formed increases during the first 5 min, and then reaches a steady state before decreasing slowly after 15 min. The exception is X2 (see Supporting Information, Figure S12), which does not reach its maximum concentration within the 30 min. It is important to emphasize that the TPs (except for X1) are not eliminated within 30 min of irradiation, which supports the need for prolonged treatment to ensure their complete oxidation. During UV treatment of ACIN, the concentration of ACON steadily increases with the irradiation time. This confirms the transformation step from ACIN to ACON in the proposed breakdown pathway (Figure 1).

With increasing dosage of ClO_2 the decay of CBZ and, simultaneously, an exponential increase of ACIN are observed (Figure 2 right). The latter is thought to be a result of the

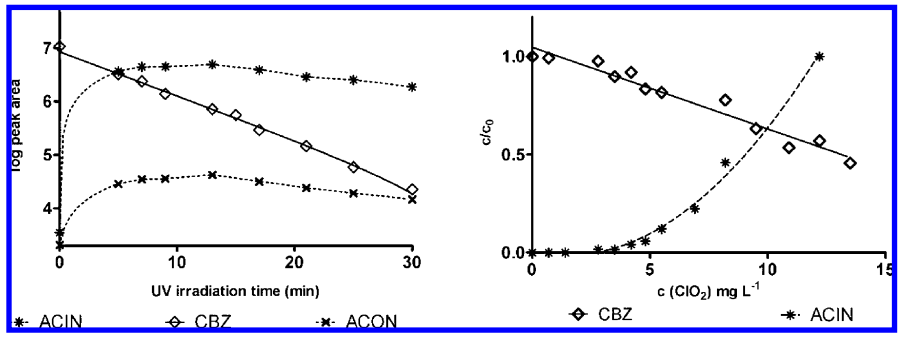

FIGURE 2. Left: the fate of carbamazepine during the UV treatment. Right: ClO_2 treatment of CBZ.

TABLE 3. Removal of CBZ, ACIN, and ACON during Biological, UV, and ClO_2 Treatment

	percent removal			
compound	aerobic	anoxic	UV treatment (10 min UV)	ClO_2 treatment (13.5 mg L^{-1} ClO_2)
CBZ	16%	16%	93%	54%
ACIN	92%	90%	76%	38%
ACON	40%	23%	<10%	not tested[a]

[a] ACON was not treated with ClO_2.

higher resilience of ACIN to oxidation by ClO_2. This hypothesis is confirmed by treating CBZ and ACIN individually, where at the highest concentration of ClO_2 (13.5 mg L^{-1}) 54% of CBZ was removed; whereas only 38% of ACIN was eliminated (Table 3). The ClO_2 oxidation tests were not made using ACON as the starting compound, since it is not a transformation product of CBZ when treated with ClO_2.

In general, ClO_2 treatment proved to be less efficient in comparison to UV for both CBZ and ACIN (Table 3). Also, the number of the TPs detected under ClO_2 oxidation of CBZ was lower, with only acridine-9-carbaldehyde (X4) and ACIN being detected (see Supporting Information, Figure S3). Further, the ClO_2 oxidation of ACIN alone resulted in the formation of a single TP, 9-hydroxy-acridine (X5).

As an alternative method of removing TPs, biological treatment was investigated. Table 3 shows the removal efficiencies of CBZ, ACIN, and ACON determined in the benchtop activated-sludge bioreactors under aerobic and anoxic conditions. The most important outcome of this experiment was the efficient removal of ACIN, which was 90% and 92% under anoxic and aerobic conditions, respectively. Further, the elimination of CBZ is poor with only 16% removal irrespective of the RedOx conditions (Table 3), while the removal of ACON is more efficient under aerobic conditions (40%) comparing to anoxic removal (23%). Biodegradation products were also screened for in the bioreactor outlets, where only trace levels of ACIN were found in the reactors fed with CBZ (Table 1: R1, R2, and R8). The absence of TPs in these reactors is attributed to the low biodegradability of CBZ, while, agreeing with expectations, substantial amounts of ACON were formed in the bioreactors fed with the readily biodegradable ACIN (R3, R4, and R9). According to Figure 1, the biological transformation reactions take place on a moiety with the most readily available electrons, which in the case of CBZ is the nonaromatic double bond and the nonbonded nitrogen electrons. Thus the 10,11-double bond is first transformed into the epoxide by a monooxygenase enzyme system (*25*). In addition, ring contraction and the cleavage of the carbamyl bond both occur in vivo to form X4 (*27*), which is further converted into ACIN and ACON. The latter did not show formation of any additional TPs.

Taking into account the poor biological removal efficiency of CBZ together with the enhanced biodegradability of carbamazepine residues by UV irradiation (Table 3), prolonging the treatment time to achieve complete mineralization may not be necessary. Instead, one could apply a combination of UV treatment with a second biological treatment step (sandfilter) for advanced water treatment. In this respect, the proposed coupled treatment technology for removing carbamazepine residues may be relevant for treating raw water for potable water production. Furthermore, the data presented in Table 3 show that the chlorine dioxide treatment of CBZ produces the readily biodegradable ACIN. The system involving ClO_2 oxidation with a subsequent biological treatment is then potentially useful for wastewater treatment, since together with an improved elimination of CBZ residues, there will be a decrease in the BOD (biological oxygen demand), which had been created from COD (chemical oxygen demand) during the ClO_2 oxidation. Naturally, the two systems proposed above will require scale-up and further evaluation, both from a scientific and economic perspective.

Most notably, the major intermediates arising from ClO_2, UV, and biological treatment of CBZ belong to the azaarenes, an established class of air and water pollutants, known for their photoenhanced toxicity, mutagenic, and carcinogenic activity (*16, 18, 28*). This raises an important issue concerning the possible environmental impact of pharmaceutical residues in either domestic wastewaters or drinking waters.

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Supporting Information Available

Mass spectra of the transformation products and a graph showing the behavior of carbamazepine and its transformation products during chlorine dioxide treatment. The information is available free of charge via the Internet at http://pubs.acs.org.

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