Free-Radical-Induced Oxidative and Reductive Degradation of Fluoroquinolone Pharmaceuticals: Kinetic Studies and Degradation Mechanism

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Fluoroquinolones, as a class of broad-spectrum antibiotics, have been detected in both surface and ground waters, and advanced oxidation/reduction processes (AO/RPs) are currently in development to remove these and other pharmaceuticals from wastewater because currently utilized treatment methods have proven to be ineffective. This article reports the reaction kinetics of six common fluoroquinolones with hydroxyl radicals and hydrated electrons, which are the major reactive species involved in AO/RPs. The bimolecular reaction rate constants (M^{-1} s^{-1}) for orbifloxacin, flumequine, marbofloxacin, danofloxacin, enrofloxacin, and the model compound, 6-fluoro-4-oxo-1,4-dihydro-3-quinoline carboxylic acid, with •OH are $(6.94 \pm 0.08) \times 10^9$, $(8.26 \pm 0.28) \times 10^9$, $(9.03 \pm 0.39) \times 10^9$, $(6.15 \pm 0.11) \times 10^9$, $(7.95 \pm 0.23) \times 10^9$, $(7.65 \pm 0.20) \times 10^9$, and with e_{aq}^-, $(2.25 \pm 0.02) \times 10^{10}$, $(1.83 \pm 0.01) \times 10^{10}$, $(2.41 \pm 0.02) \times 10^{10}$, $(1.68 \pm 0.02) \times 10^{10}$, $(1.89 \pm 0.02) \times 10^{10}$, and $(1.49 \pm 0.01) \times 10^{10}$. These rate constants are related to the functional groups attached to the quinolone core, particularly the steric hindrance of the piperazine ring, making it possible to obtain a preliminary estimate of the •OH rate constant of an arbitrary fluoroquinolone by observing the ring constituents. In addition, the products of gamma-irradiation degradation of fluoroquinolones were analyzed by LC-MS to elucidate the probable pathways of AO/RPs degradation. Results indicate that preliminary degradation pathways include hydroxyl radical attack on the aromatic ring with subsequent hydroxylation, the substitution of a fluorine atom with a hydroxyl group, and the removal of the piperazine-derived side chain.

Introduction

Pharmaceutical compounds have recently been classified as emerging pollutants of concern because of their detection in surface waters. High consumption of pharmaceuticals, $248 billion[1] in the United States in 2004, provides a steady stream of pharmaceutical compounds into the environment. Pharmaceutically active compounds can enter wastewater treatment plants as biologically active substances via excretion,[2] manufacturing facilities,[3] or even being dumped "down the drain" by consumers.[4,5] The removal efficiency of pharmaceutical compounds in treatment plants varies widely, often resulting in their discharge into natural bodies of water.[1,6−9]

Fluoroquinolones are a family of antibiotics used against a wide range of disease-causing bacteria. Excreted in the urine by human patients and livestock, mostly as the parent compound,[10] fluoroquinolones have been detected in treated wastewater at multiple locations around the world.[12−14] In a recent USGS study, fluoroquinolone levels up to 0.12 μg L^{-1} were detected in various streams throughout the United States.[6] The situation is worse in developing countries, as illustrated by the effluent from a drug manufacturing facility located in Patancheru, India, which had the highest concentration of pharmaceuticals ever reported in an effluent, with many individual compounds in the milligrams per liter range.[3] Six of the top eleven active pharmaceutical ingredients detected at this site were fluoroquinolones. Whereas the consequences of the presence of fluoroquinolones in the environment are not fully understood, it has been suggested that they are toxic to plants[15] and aquatic organisms.[16] Their widespread presence and potential toxicity necessitate a better understanding of their fates during water treatment processes to assess their risk properly.

Treatment processes such as biodegradation,[17] nanofiltration,[18−21] activated carbon adsorption,[22,23] and ozonation[24] have shown varying degrees of success in removing low concentrations of many organic compounds. Alternative processes, with the potential for generating drinking water and water for reuse, are advanced oxidation/reduction processes (AO/RPs) given that they are capable of efficient and thorough removal of anthropogenic pollutants, including pharmaceutical compounds.[25] AO/RPs typically involve the formation of hydroxyl radicals (•OH) as oxidizing species and either hydrated electrons (e_{aq}^-) or hydrogen atoms (H•) as reducing species, all of which can be utilized in the destruction of organic pollutants present in drinking or wastewater.

To provide a fundamental understanding of the applicability of these processes to the degradation of pharmaceutical compounds, it is necessary to determine the bimolecular reaction rate constants between the reactive species and the chemicals of interest. The purpose of this research, therefore, was to measure the absolute bimolecular reaction rate constants for the reaction of •OH and e_{aq}^- with five fluoroquinolones and with 6-fluoro-4-oxo-1,4-dihydro-3-quinoline carboxylic acid, which represents the skeleton of the fluoroquinolones in this research without added functional groups (referred to in this article as the "model compound"), and to attempt to correlate the rate constants to the structures of the compounds. Transient, free radical spectra produced by •OH reaction were obtained after

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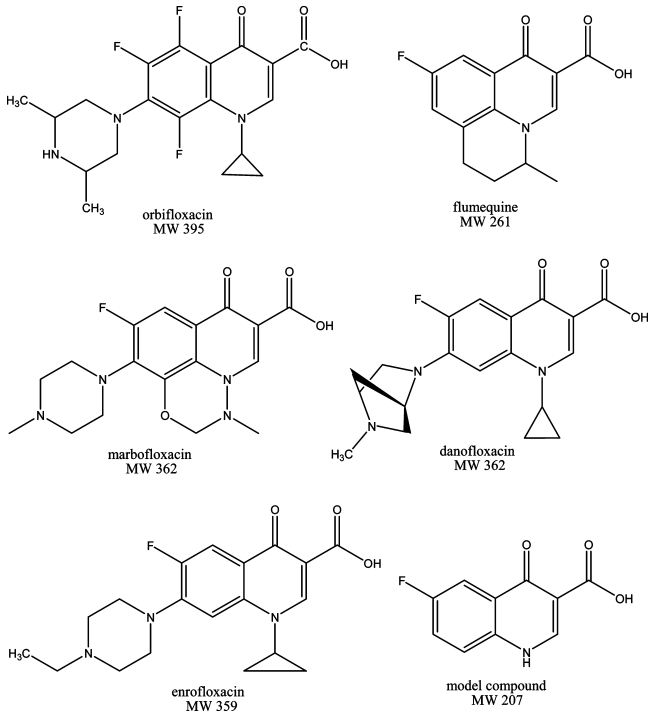


Figure 1. Chemical structures of the target compounds.

irradiation. Product studies were performed using gamma irradiation to elucidate the free radical-induced degradation mechanisms. These are likely to be similar to the degradation observed during advanced oxidation treatment.

Methods and Materials

Orbifloxacin, flumequine, marbofloxacin, danofloxacin, and enrofloxacin (Figure 1) were purchased from Sigma-Aldrich at >98% purity. The model compound, 6-fluoro-4-oxo-1,4-dihydro-3-quinolone carboxylic acid, was purchased from Ryan Scientific Products at 95% purity. All compounds, as received, were shown to be greater than 99% pure by HPLC. Solutions were prepared in a buffer solution consisting of 5 mM KH_2PO_4 and adjusted to pH 7.0.

Electron pulse radiolysis was performed with an 8 MeV Titan Beta model TBS-8/16-1S linear accelerator, which has been described in detail in the literature.[26] Dosimetry experiments used 2 ns pulses, which generated radical concentrations of 1−3 μM per pulse. For each experiment, 12 to 15 replicate trials were run, with sample introduction in continuous flow mode, and the results were averaged.

When aqueous solutions are irradiated with high-energy radiation, the water absorbs most of the radiation, producing several species,[27] as shown in eq 1. The numbers in brackets are *G* values, the yield of that particular species per unit of radiation, in micromoles per joule.[28,29]

$$H_2O \rightarrow e_{aq}^-(0.27) + H\cdot(0.06) + \cdot OH(0.28) + H_2(0.05) + H_2O_2(0.07) + H_3O^+(0.27) \quad (1)$$

As can be seen from the *G* values, about half of the radicals produced by this reaction are hydroxyl radicals. Understanding the reaction processes of each radical simplifies the degradation picture. Therefore, to isolate reactions of the ·OH, sample solutions were saturated with nitrous oxide, which converts electrons and hydrogen atoms to hydroxyl radicals[28] (eqs 2 and 3)

$$e_{aq}^- + N_2O + H_2O \rightarrow N_2 + HO^- + \cdot OH \qquad k_2 = 9.1 \times 10^9\ M^{-1}s^{-1} \quad (2)$$

$$H\cdot + N_2O \rightarrow \cdot OH + N_2 \qquad k_3 = 2.2 \times 10^6\ M^{-1}s^{-1} \quad (3)$$

Similarly, to isolate reactions of the compounds with e_{aq}^-, solutions of the pharmaceuticals were sparged with N_2 and mixed with 0.10 M isopropanol to remove the highly reactive ·OH and H· by forming the relatively inert isopropyl radical (eqs 4 and 5)[28]

$$(CH_3)_2CHOH + \cdot OH \rightarrow (CH_3)_2C\cdot OH + H_2O \qquad k_4 = 1.9 \times 10^9\ M^{-1}\ s^{-1} \quad (4)$$

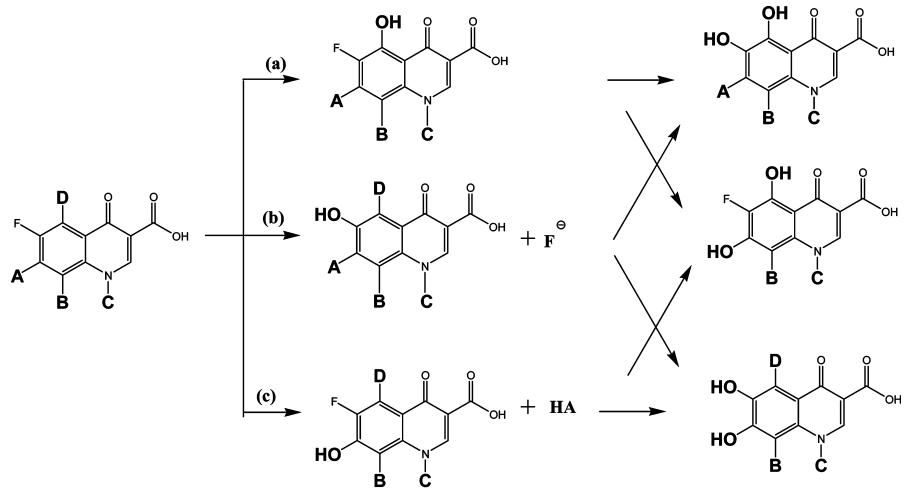
$$(CH_3)_2CHOH + H\cdot \rightarrow (CH_3)_2C\cdot OH + H_2 \qquad k_5 = 7.4 \times 10^7\ M^{-1}\ s^{-1} \quad (5)$$

Gamma radiolysis was performed in a J. L. Shepherd Mark I model A68 irradiator, which has a fixed central rod cesium-137 source in a cavity 30 cm in diameter and 33 cm high. Samples were saturated with air and irradiated in glass test tubes. The dosage varied as a function of time and distance from the radiation source and ranged from 0 to 7 kGy.

High-Performance Liquid Chromatography and Mass Spectometry Conditions. The fluoroquinolones and their degradation byproducts were analyzed by HPLC using a Phenomenex Gemini C_{18} column (4.6 × 250 mm) with an isocratic mobile phase consisting of various mixtures of methanol and water. The liquid chromatography/mass spectrometry system consisted of an Agilent 1100 HPLC pump and a Waters LCT Classic mass spectrometer with an electrospray ionization source. A 10 μL sample was injected onto a Phenomenex Luna C_{18} HPLC column (2.0 × 150 mm). The mobile phase consisted of (A) 98% H_2O + 2% CH_3CN + 0.2% formic acid and (B) CH_3CN + 0.2% formic acid. Gradient elution was 2% B for 1 min, followed by a linear increase to 95% B at 50 min, and then held constant for an additional 7 min. The mass spectral data were obtained in the positive and negative ion modes from m/z = 100 to 350, 200 to 1000, or both depending on the molecular weight of the compound.

Results and Discussion

·OH Transient Spectra. Transient spectra for the reaction of each compound with ·OH are shown in Figure 1S in the Supporting Information. All five fluoroquinolone pharmaceuticals show similar transient absorption spectra with strong absorbance in the 350 to 400 nm range. The λ_{max} of each intermediate was red shifted by around 100 nm compared with that of the parent compound. Such a shift is characteristic of ·OH addition to the aromatic ring to form the corresponding hydroxycyclohexadienyl radical.[30,31] The transient absorption spectra also show well-defined shoulders that are not present in the absorption spectra of the parent compounds. The model compound's transient spectra showed one rather sharp peak at 360 nm. Flumequine has the transient spectra most comparable to those of the model compound, suggesting that the substitutions at positions B and C (Figure 2) seen in flumequine when compared with the model compound have only minor effects on the transient spectrum. Compared with the spectra of the parent compound and the transients of the model compound,



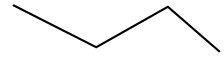
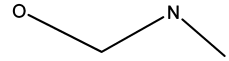
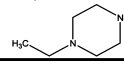
	A	B	C	D
Orbifloxacin		F	△	F
Flumequine	H			H
Marbofloxacin				H
Danofloxacin		H	△	H
Enrofloxacin		H	△	H

Figure 2. Degradation products and reaction pathways for fluoroquinolones.

the transient spectra of orbifloxacin, danofloxacin, enrofloxacin, and marbofloxacin showed stronger shoulder peaks in the 400−450 nm range, suggesting that the substituted piperazine moiety may be associated with the transient spectra peaks in this range.

Measurement of Rate Constants. Absolute bimolecular reaction rate constants were calculated from the rate of change of absorption with concentration at the wavelength of maximum absorption, using the procedure established by Mezyk, et al.,[11] which involves fitting exponential functions to growth curves at various concentrations to determine pseudo-first-order rate constants and plotting these as a function of concentration. The resulting linear curves indicated second-order reactions. Representative plots for danofloxacin are shown in Figure 3, and all •OH rate constants are summarized in Table 1. These rates were in the order: danofloxacin < orbifloxacin < model compound < enrofloxacin < flumequine < marbofloxacin.

In general, •OH reacts via two competing pathways: hydrogen abstraction or hydroxylation. The rates of reaction of •OH with different reaction sites present in fluoroquinolones are expected to vary significantly. However, the addition of •OH to an aromatic ring, such as the quinolone moiety present in the fluoroquinolones, is expected to be fast. All five of the fluoroquinolone reaction rate constants were on the order of 10^9 M^{-1} s^{-1}. The reaction rate for the model compound was also on the same order of magnitude, suggesting that the core aromatic ring structure rather than the substituent groups was responsible for the majority of the compounds' reactivity. Prior research by Zhang et al., determined that when oxidized by manganese oxide, the piperazine moiety is the predominant adsorptive and oxidative reaction site,[12] perhaps because of the formation of a surface complex and the reduction in the oxi-

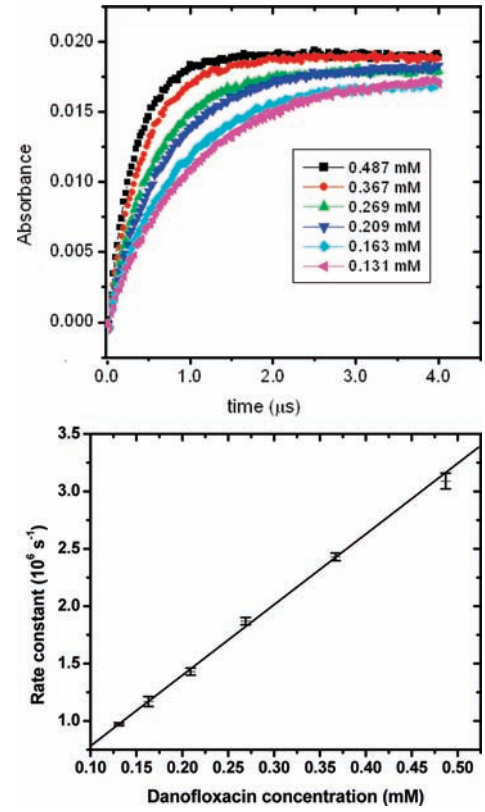


Figure 3. Growth kinetics for hydroxyl radical oxidation of danofloxacin at various concentrations (top) and pseudo-first-order rate constants as a function of concentration used to determine second-order bimolecular rate constant (bottom).

TABLE 1: Measured Spectral Parameters and Rate Constants for Reaction of Fluoroquinolones with Hydroxyl Radicals and Hydrated Electrons

compound	·OH λ_{max} (nm)	ε_{max} (M^{-1} cm^{-1})	k(·OH) (M^{-1} s^{-1})	$k(e_{aq}^-)$ (M^{-1} s^{-1})	γ-irradiation half-life (kGy)[a]
orbifloxacin	370	5200	$(6.94 \pm 0.08) \times 10^9$	$(2.25 \pm 0.02) \times 10^{10}$	1.56
flumequine	360	3500	$(8.26 \pm 0.28) \times 10^9$	$(1.83 \pm 0.01) \times 10^{10}$	1.64
marbofloxacin	400	4120	$(9.03 \pm 0.39) \times 10^9$	$(2.41 \pm 0.02) \times 10^{10}$	1.80
danofloxacin	440	5370	$(6.15 \pm 0.11) \times 10^9$	$(1.68 \pm 0.02) \times 10^{10}$	1.85
enrofloxacin	400	4610	$(7.95 \pm 0.23) \times 10^9$	$(1.89 \pm 0.02) \times 10^{10}$	1.38
model compound	350	5300	$(7.65 \pm 0.20) \times 10^9$	$(1.49 \pm 0.01) \times 10^{10}$	0.05

[a] Value is dose in kGy at which 50% of the parent compound was destroyed.

dation state of the manganese. This was not seen in the present work perhaps because of the lack of a metal atom.

Despite the general similarity, there are minor variations in the rates observed that may be explained by the structures of the compounds. It is proposed that this variation is partially due to the availability of hydrogen (abstraction) and fluorine (ipso hydroxylation) and partially due to steric hindrance from the constituents around the circumference of the ring preventing attack by ·OH. Danofloxacin, which contains a bridged piperazine ring at position A (Figure 2), has the lowest ·OH rate constant, perhaps because of steric effects from this relatively bulky functional group. Orbifloxacin, enrofloxacin, and marbofloxacin, which have nonbridged, planar piperazine rings at position A, react slightly faster, perhaps reflecting the reduction in the substitution of the piperazine ring, and in the case of marbofloxacin, which has the fastest ·OH reaction rate constant of the set, there is the presence of an electron-donating oxygen atom at position B. Bearing this trend in mind, it may be possible to estimate the ·OH adduction reaction rate constant for any fluoroquinolone by observing the "bulkiness" of the piperazine ring. The cyclopropane functional group, present on danofloxacin, orbifloxacin, and enrofloxacin, has been shown to have a relatively slow reaction rate constant with ·OH ($\sim 10^7$ M^{-1} s^{-1}),[32,33] and thus its contribution to the observed ·OH reaction rates for these compounds can be ignored. The reaction rate of flumequine is slightly faster than the model compound, perhaps because of the availability of additional bonding sites on the ring attached at positions B and C (Figure 2), which may also partially account for marbofloxacin's higher rate constant.

We measured rate constants for reaction with e_{aq}^- by monitoring the change in absorption of electrons in nitrogen-saturated solutions at pH 7.0. Calculations were carried out as described by Mezyk, et al.[11] in a manner entirely analogous to those for ·OH. Sample graphs for danofloxacin are shown in Figure 4. Exponential decay functions were fitted to the absorbance versus time data to determine pseudo-first-order rate constants. These were then plotted as a function of concentration, resulting in linear plots from which the second-order rate constant was obtained.

In the case of reaction with e_{aq}^-, the model compound had the lowest rate constant, indicating that the attached functional groups play a larger role in the compounds' reactivities than they did in the cases of the reactions with ·OH. However, once again, all of the constants are on the same order of magnitude and do not differ by a factor of more than two, highlighting the general similarity of the compounds. The bimolecular e_{aq}^- reaction rate constants are summarized in Table 1 and follow the order: model compound < danofloxacin < flumequine < enrofloxacin < orbifloxacin < marbofloxacin.

Degradation Mechanism. In addition to the reaction kinetics for the five fluoroquinolones, stable products formed in these reactions were studied in an attempt to elucidate the degradation mechanisms. These experiments were performed using ^{137}Cs steady-state radiolysis, with products assigned using LC-MS. The experiments were conducted using air-saturated solutions. In the presence of air, the hydrated electrons and hydrogen atoms produced in the radiolysis are expected to mostly react with dissolved oxygen to produce the relatively inert superoxide anion. Therefore, under these conditions, the chemistry will mostly be dominated by the ·OH reactions. All five fluoroquinolones degraded rapidly, with less than 50% of the initial concentration remaining after 2 kGy of radiation (Supporting Information, Figure 2S). Our structural assignments of the degradation products of fluoroquinolones were based on the analysis of the total ion chromatogram (TIC) and the corresponding mass spectra. The masses of the different products were determined from the peaks corresponding to the protonated or deprotonated molecule, $[M + H]^+$ and $[M - H]^-$ for positive and negative ionization, respectively. For the purposes of this article, the products are referred to by molecular weight (MW), and representative LC-MS charts showing decomposition products for each pathway are shown in the Supporting Information (Figure 3S).

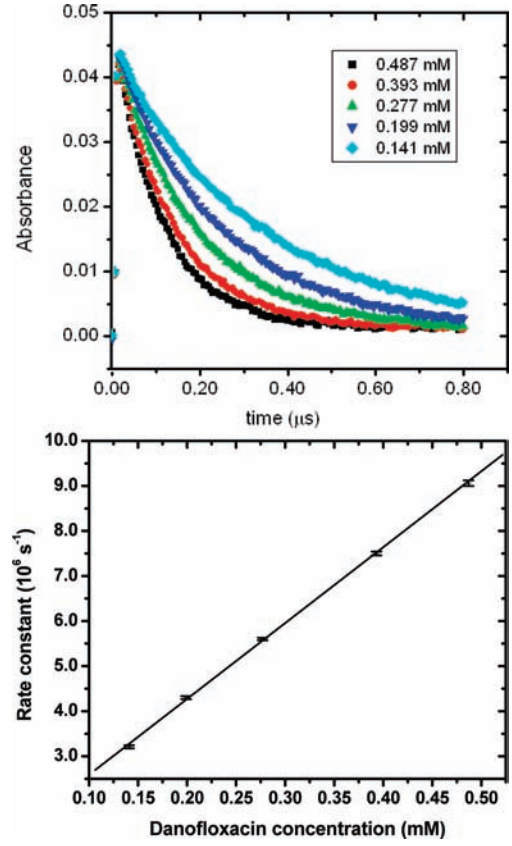


Figure 4. Decay kinetics for hydrated electron reduction of danofloxacin at various concentrations (top) and pseudo-first-order rate constants as a function of concentration used to determine second-order bimolecular rate constant (bottom).

The reaction of •OH with the aromatic group typically leads to hydroxylation yielding a phenol, as shown in Figure 2, pathway (a). The addition of the electrophilic •OH to the aromatic ring forms a resonance-stabilized carbon-centered radical, and subsequent addition of oxygen and elimination of a hydroperoxyl radical yields the phenolic product. This mechanism is described in detail by Song et al.[5]

Products were observed with molecular weights of 411, 277, 378, 373, and 375 Da for orbifloxacin, flumequine, marbofloxacin, danofloxacin, and enrofloxacin, respectively, corresponding to the addition of 16 Da to the parent compounds. This is consistent with hydroxylation of the aromatic ring as shown in Figure 2, pathway (a). This mechanism has been previously observed for various fluoroquinolones using different methods of oxidation.[12]

Defluorination, another main degradation pathway, is shown in Figure 2, pathway (b). The addition of •OH to the carbon−fluorine position (ipso attack) leads to a geminal fluorohydrin intermediate that undergoes rapid HF elimination to form phenoxy radicals. A similar degradation pathway has been observed for •OH oxidation of pentafluorophenol.[34] This degradation is seen in all members of the group and results in a net decrease of 2 Da in molecular weight, yielding products of molecular weight 393, 259, 360, 355, and 357 for orbifloxacin, flumequine, marbofloxacin, danofloxacin, and enrofloxacin, respectively. Whereas prior research on 2,4-dichlorophenoxyacetic acid, a chlorinated aromatic compound, indicates that reaction at ipso positions is preferred by a significant margin,[35] our results suggest that for fluorine-substituted compounds, •OH reacts significantly at both substituted and unsubstituted positions.

Orbifloxacin is unique in that it has three fluorine atoms attached to the benzene ring, any of which can potentially be substituted by a hydroxyl group. Two products of MW 393 were observed by LC-MS, indicating the importance of hydroxyl substitution of the fluorine moiety. We also observed a product with a decrease of 4 Da (MW 391), corresponding to the substitution of two of the three fluorine atoms. Previous studies have indicated that fluorine substitution improves the biological activity of quinolones while increasing their stability.[36] Our studies demonstrate that defluorination could be an important degradation pathway for wastewater, potentially associated with a loss of biological activity.

All of the target compounds, except flumequine, contain a substituted piperazine group attached at position A (Figure 2) that can also be substituted by •OH, as shown in pathway (c). This was observed in danofloxacin, orbifloxacin and marbofloxacin and results in the substitution of the piperazine ring with a hydroxyl group, yielding products of 263, 299, and 280, respectively. The fragments containing the piperazine ring are also relatively stable and were observed in the degradation of danofloxacin, orbifloxacin, marbofloxacin, and enrofloxacin at MW 112, 114, 100, and 114, respectively.

The replacement of hydrogen, fluorine, and piperazine groups also occurs in series in various combinations. For example, in orbifloxacin, flumequine, and enrofloxacin, we observe products with MW 409, 275, and 373, which result from the substitution of one fluorine atom and one hydrogen atom with hydroxyl groups for a net gain of 14 Da. For flumequine, marbofloxacin, and enrofloxacin, one fluorine and two hydrogen atoms may be replaced with hydroxyl groups, resulting in a net gain of 30 Da to MW 291, 392, and 389, respectively. These combinations are shown in the rightmost column of Figure 2. Finally, we observed the partial dealkylation of the piperazine ring in marbofloxacin, resulting in a net decrease of 26 Da (MW 336), analogous to a previously identified degradation pathway for ciprofloxacin.[12]

Conclusions

The absolute bimolecular reaction rate constants (M^{-1} s^{-1}) for •OH and e_{aq}^- with orbifloxacin, flumequine, marbofloxacin, danofloxacin, enrofloxacin, and the model compound, 6-fluoro-4-oxo-1,4-dihydro-3-quinolinecarboxylic acid, are shown in Table 1. The variation in these rate constants is roughly correlated to the composition of the constituent piperazine ring on each compound, with increased steric hindrance due to a bulkier functional group resulting in a lower •OH rate constant. Using this observation, it may be possible to estimate the rate constant for an unknown fluoroquinolone on the basis of the ring constituents.

Assuming an average •OH concentration at the surface of natural waters of 10^{-17} M,[37] half-lives for the fluoroquinolone compounds in the environment would be approximately 100 days. This suggests that oxidation of fluoroquinolones by indirect photolysis of dissolved organic matter in sunlight-generated •OH is relatively slow and that other factors are likely to have a larger contribution to their degradation. At a treatment facility utilizing AO/RPs, the •OH concentration would be much higher, and the compounds would be eliminated in seconds rather than days.

The major degradation pathway arising from γ-irradiation of fluoroquinolone antibiotics appears to involve •OH addition to the benzene ring to form mixtures of phenolic compounds. Hydroxyl radicals can replace hydrogen atoms, fluorine atoms, or entire substituted piperazine rings. These results indicate that advanced oxidation processes involving the production of •OH radicals are attractive treatment methods for the degradation of fluoroquinolone antibiotics in aqueous solution. To develop kinetic models that fully describe the destruction mechanism would involve isolating the major reaction byproduct and evaluating their absolute reaction rate constants. It will also be necessary to undertake a careful evaluation of the toxicity of the degradation products, and their related intermediate species, before there is any practical implementation of an AO/RP treatment method.

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Supporting Information Available: Transient absorption spectra for reaction of fluoroquinolones with hydroxyl radicals, degradation curves for each fluoroquinolone by γ-irradiation, and representative LC/MS data for marbofloxacin showing decomposition products for each pathway in Figure 2. This material is available free of charge via the Internet at http://pubs.acs.org.

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