Mechanistic Considerations for the Advanced Oxidation Treatment of Fluoroquinolone Pharmaceutical Compounds using TiO₂ Heterogeneous Catalysis

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Pharmaceutical compounds and metabolites are being found in surface and ground waters which is indicative of inefficient removal by conventional wastewater treatment technologies. Advanced oxidation processes (AOPs), which utilize free-radical reactions to degrade chemical contaminates, are an alternative to traditional water treatment. Three fluoroquinolone pharmaceutical compounds were studied and the absolute rate constants for hydroxyl radical (•OH) and hydrated electron (e⁻ₐq) are reported. For norfloxacin, levofloxacin, and lomefloxacin, the bimolecular reaction rate constants with •OH were determined as $(6.18 \pm 0.18) \times 10^9$, $(7.59 \pm 0.16) \times 10^9$ and $(8.04 \pm 0.62) \times 10^9$ M⁻¹ s⁻¹, and with e⁻ₐq were $(1.18 \pm 0.10) \times 10^{10}$, $(2.46 \pm 0.05) \times 10^{10}$ and $(2.79 \pm 0.05) \times 10^{10}$ M⁻¹ s⁻¹, respectively. To provide insights into the chemistry of destruction of these three target pharmaceuticals, transient spectra were obtained for the reaction of hydroxyl radicals with the three compounds. Photocatalysis was chosen as a representative advanced oxidation technology to degrade these three fluoroquinolones and their degradation pathways were proposed. Elimination of piperazynilic ring in fluoroquinolone molecules, addition of hydroxyl radical to quinolone ring, and ipso attack at the F atoms on the aromatic ring by hydroxyl radicals occurred. These results indicate that AOPs involving production of •OH radicals are efficiently alternative treatment technologies for degradation of fluoroquinolones in aqueous solution.

Introduction

The treatment or removal of trace amounts of active pharmaceutical ingredients (APIs) from aquatic environments has received increased attention in recent years.[1,2] Although no formal regulations exist, their presence, even at trace levels, may adversely affect aquatic ecosystems and human health.[1] However, no definitive results have appeared. As a precautionary measure it is prudent to develop alternatives for the removal of these pharmaceuticals in water use or reuse applications.[3]

Fluoroquinolone antibiotics are among the many groups of these chemicals that have been detected. They are used as antimicrobial compounds because of their pharmacological action, specifically, inhibition of subunit-A of the bacterial topoisomerase DNA gyrase, which controls the shape of DNA.[4–6] However, most fluoroquinolones are not fully metabolized in the body and may be excreted. In some cases, they are poorly biodegraded and end up in wastewater treatment effluent.[7,8] Several recent studies have demonstrated that fluoroquinolones are found in waters and wastewater treatments in many countries, for example, Switzerland, The United States, Australia, and China, to name a few.[7,9–11] Moreover, fluoroquinolones have significant genetoxicity,[12] and it has also been verified that they are toxic to plants[13] and aquatic organisms.[14]

Thus, their environmental fate, transfer, effect, and potential risk during water treatment are of concern.

Although partial removal of APIs can be achieved through conventional water treatment processes, recent studies have demonstrated that the effectiveness of the processes are variable.[15] In addition, these technologies require the postdisposal of wastes such as membrane retentate or residuals formed during the wastewater treatment.[16] Advanced oxidation/reduction processes (AO/RPs) are alternatives to traditional treatment and have recently received considerable attention for APIs removal.[2,10] AO/RPs with the highly reactive hydroxyl radical (•OH) as the main oxidative species and either hydrated electrons (e⁻ₐq) or hydrogen atoms (H•) as reducing species can degrade these soluble biorefractory antibiotics effectively.[2,17,18] However, to ensure that the AOP treatment process occurs efficiently and quantitatively, a full understanding of the reaction kinetics and destruction mechanisms involved under various conditions is necessary.

The objective of this study was to evaluate the oxidative and reductive behavior of three representative fluoroquinolones in aqueous solution. Specifically, we have determined absolute rate constants for the reactions of oxidizing hydroxyl radicals (•OH) and reducing hydrated electrons (e⁻ₐq) with norfloxacin, levofloxacin and lomefloxacin. In this research, heterogeneous photocatalysis using TiO₂, was selected as the AO/RP to evaluate the initial reactions leading to either biodegradable chemicals or possibly to mineralization.

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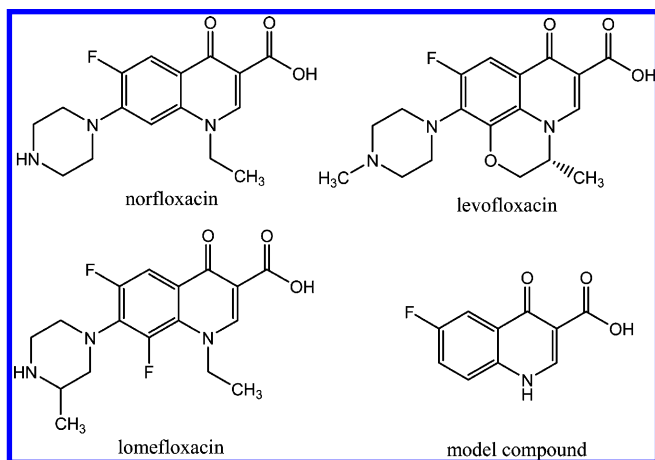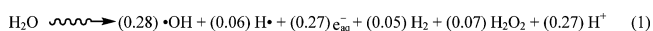‡ Graduate School of Chinese Academy of Sciences.
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Figure 1. The chemical structure of three fluoroquinolones and the model compound.
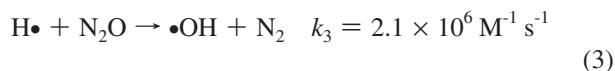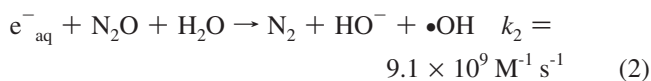
Methods and Materials

Materials. The fluoroquinolone pharmaceuticals, norfloxacin, levofloxacin and lomefloxacin hydrochloride, were purchased from Sigma-Aldrich (≥99% purity). Their chemical structures are shown in Figure 1. Solutions were prepared using water filtered with a Millipore Milli-Q system, which included constant illumination by a Xe arc lamp at 172 nm to keep total organic carbon concentrations below 13 μg L^{-1}. All solutions in electron pulse radiolysis experiments were buffered with 5.0 mM phosphate adjusted to pH 7.0 and sparged with high purity N$_2$O (for hydroxyl radical experiments) or N$_2$ (hydrated electron experiments) to remove dissolved oxygen.
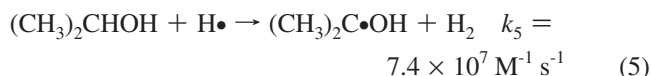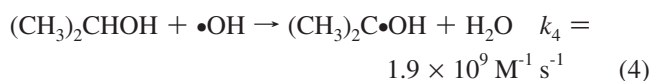
Pulse Radiolysis. Electron pulse radiolysis experiments were performed at the Notre Dame Radiation Laboratory with the 8-MeV Titan Beta model TBS-8/16−1S linear accelerator. This irradiation and transient absorption detection system has been described in detail previously.[18] Dosimetry was performed using N$_2$O-saturated, 1.00×10^{-2} M KSCN as described elsewhere.[19] All experimental data were determined by averaging 8−12 replicate pulses using the continuous flow mode of the instrument. The radiolysis of water is described in eq 2, where the numbers in parentheses are the G-values in μmol J^{-1}.[20]

$$H_2O \rightsquigarrow (0.28) \cdot OH + (0.06) H\bullet + (0.27) e^-_{aq} + (0.05) H_2 + (0.07) H_2O_2 + (0.27) H^+ \quad (1)$$

To isolate reactions of the hydroxyl radical, solutions were presaturated with nitrous oxide (N$_2$O), which quantitatively converts the hydrated electrons and hydrogen atoms to hydroxyl radicals via the following two reactions

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

$$H\bullet + N_2O \rightarrow \cdot OH + N_2 \quad k_3 = 2.1 \times 10^6 \text{ M}^{-1} \text{ s}^{-1} \quad (3)$$

The hydrated electron reaction solutions were presaturated with nitrogen in the presence of 0.10 M isopropanol to scavenge the hydroxyl radicals and hydrogen atoms[20]

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

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

Photocatalytic Experiments. The adsorption and photocatalytic degradation of fluoroquinolones were carried out in a Pyrex tube (150 mL) with a double-walled cooling water jacket to keep the temperature constant at 25 ± 1 °C throughout all experiments. The light source, which was a high-pressure mercury lamp (GGZ-125, Shanghai Yaming Lighting, $E_{max} =$ 365 nm, the light intensity at the surface of Pyrex tube was achieved at the average of 0.38 mW cm^{-2}), was housed in one side of the photocatalytic reactor to provide the irradiation. Prior to illumination, 150 mL of 0.3 g (2 g L^{-1}) photocatalyst (TiO$_2$, Degussa P25) and fluoroquinolones (100 μM) were stirred in the dark for 30 min to achieve the adsorption−desorption equilibrium. Then the UV light was turned on and 3 mL of solution was removed at predetermined time intervals and passed through a 0.2 μm Millipore filter immediately prior to HPLC and LC/MS/MS analysis.

HPLC and LC/MS/MS Analysis. The fluoroquinolones were analyzed by Agilent 1200 series HPLC under the following conditions: Kromasil C18 column, 250 × 4.6 mm i.d., at 30 °C. The mobile phase consisted of 70% CH$_3$CN, 30% formic acid solution (0.3% HCOOH), filtered with a Water Associates (Milford, MA, USA) filtering kit, $\varphi = 0.45 \mu$M. The mobile phase flow rate was 1 mL min^{-1}. For LC-MS/MS, a Shimadazu high-performance liquid chromatography (HPLC) system with the same HPLC column, SIL-HTa autosampler, LC-10 ATvp pumps, and API 3000 mass analyzer was used. LC separations were performed at the flow rate at 0.5 mL min^{-1} with injection volumes of 20 μL. The linear gradient elution was selected as the following: from 90% A (0.3% formic acid solution) and 10% B (CH$_3$CN) to 10% A and 90% B within 30 min and then reverse to the initial conditions within 10 min. An electrospray interface (ESI) was used for the MS and MS−MS measurements in positive ionization mode at the full scan acquisition between m/z 100−500. The collision energy varied according to the requirement of the different measurements, and the other parameters were set as the following: the ESI was set as 5.5 kV, and the source block and desolvation temperatures were 130 and 400 °C, respectively. The desolvation and nebulizer gas (N$_2$) flow rate were 6 L min^{-1}, and argon was used as a collision gas at 2500 mbar.

Ion Chromatography (IC) and Total Organic Carbon (TOC). A Dionex IC, ISC-900 model, fitted with a conductivity detector was employed to analyze the concentration of ions. The determination of ammonium ion was performed by adopting a column CS12A and 25 mM H$_2$SO$_4$ as eluent with flow rate of 1 mL min^{-1}. The retention time for ammonium ions was 5.2 min. The anions were analyzed by using AS9HC anionic column. A mixture of NaHCO$_3$ (4.5 mM) and K$_2$CO$_3$ (0.8 mM) was used as eluent at a flow rate of 1 mL min^{-1}. The retention times obtained were 4.23 and 11.7 min for fluoride and nitrate ions, respectively. TOC was measured after the suspensions were filtered as above, using a Shimadzu TOC-5000 analyzer.

Results and Discussion

Hydroxyl Radical Transient Spectra and Reaction Rates. The fluoroquinolones studied have an aromatic ring and are N-heterocyclic compounds. The absorption spectra from the reaction of the hydroxyl radical with norfloxacin, levofloxacin, and lomefloxacin are shown in Figure 2. Under the experimental conditions the absorption coefficients were calculated using a
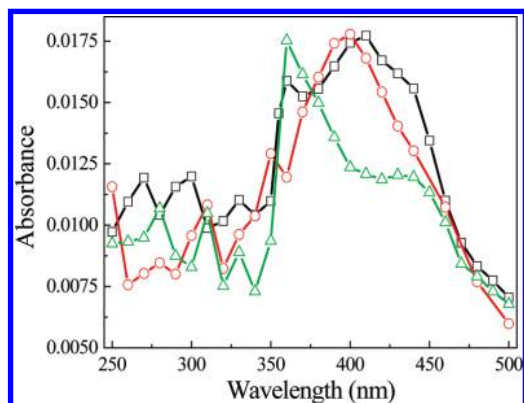
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Figure 2. The absorption spectrum obtained from the reaction of the hydroxyl radical with 0.50 mM norfloxacin (□), 1.00 mM levofloxacin (○) and 0.82 mM lomefloxacin (△) at 5 μs in N$_2$O-saturated pH value 7.0 solutions at room temperature.
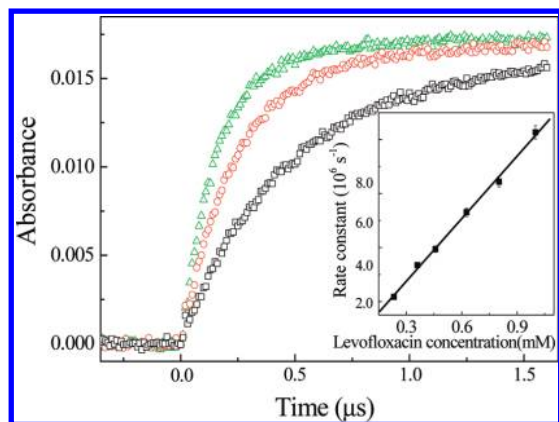

Figure 3. Growth kinetics observed for the hydroxyl radical oxidation at 400 nm for 0.49 mM (□), 0.63 mM (○), and 0.80 mM (△) levofloxacin at pH value 7.0 and at room temperature. Inset: Second-order rate constant determination for the reaction of hydroxyl radicals with levofloxacin. The straight line is the weighted linear plot with a slope 7.59 ± 0.34.

TABLE 1: Bimolecular Reaction Rate Constants (M^{-1} s^{-1}) with Fluoroquinolone Pharmaceuticals and the Hydroxyl Radical and Hydrated Electron, and Transient Spectral Parameters for Reaction with the Hydroxyl Radical[a]

compound	norfloxacin	levofloxacin	lomefloxacin	model compound[26]
•OH λ_{max}/nm	410	400	360	350
ε_{max}/M^{-1} cm^{-1}	5010	5030	4960	5300
10^9 k$_{•OH}$/M^{-1} s^{-1}	6.18 ± 0.18	7.59 ± 0.16	8.04 ± 0.62	7.65 ± 0.20
10^{10} k$_{e\text{-aq}}$/M^{-1} s^{-1}	1.18 ± 0.10	2.46 ± 0.05	2.79 ± 0.05	1.49 ± 0.01

[a] Model compound = 6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid.

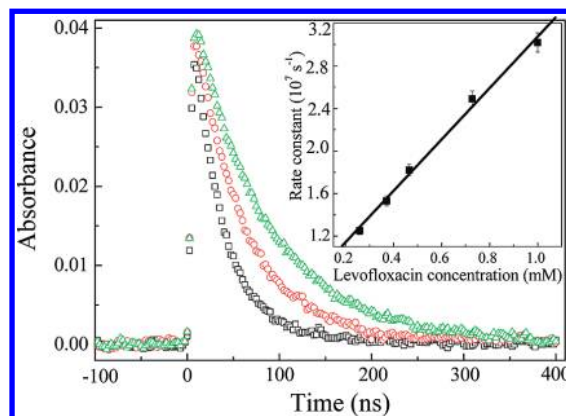**Figure 4.** Typical decay kinetics for hydrated electron reduction at 700 nm for 0.73 mM (□), 0.47 mM (○), and 0.37 mM (△) levofloxacin at pH value 7.0 and at room temperature. Inset: Second-order rate constant determination for the reaction of the hydrated electron with levofloxacin. The straight line is the weighted linear plot with a slope of 2.46 ± 0.25.

hydroxyl radical *G*-value of 0.59 mol J^{-1}.[21] The hydroxyl radical is highly reactive toward aromatic and heterocyclic compounds and typically adds to the aromatic ring to form the hydroxy-cyclohexadienyl radical with a characteristic absorption in the 310−350 nm range.[22–24] However, the transients of the three fluoroquinolones showed complex spectra, exhibiting weak absorption peaks in the region 250−350 nm but two stronger absorption peaks in the 350 to 450 nm regions. The λ_{max} for all three intermediates was red shifted by 80−120 nm compared to that of the parent compounds. The peaks around 350 nm were usually assigned to the aromatic moieties.[25] However, the peaks around 400 nm in the transient spectra may be associated with the substituted piperazine moieties.[26]

The absolute bimolecular reaction rates were determined using absorption-time profiles and a typical result levofloxacin at 400 nm is shown in Figure 3. The rates were plotted as a function of the concentrations, and the rate constants of levofloxacin was determined to be (7.59 ± 0.16) × 10^9 M^{-1} s^{-1} (inset of Figure 3 and Table 1). The rate constants of norfloxacin and lom-efloxacin were evaluated as (6.18 ± 0.18) × 10^9 M^{-1} s^{-1} and (8.04 ± 0.62) × 10^9 M^{-1} s^{-1}, respectively.

The rate constant of 6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (the model compound, chemical structure in Figure 1) with the hydroxyl radical, (7.65 ± 0.20) × 10^9 M^{-1} s^{-1},[26] was comparable to the fluoroquinolone pharmaceutical

compounds. Moreover, these rate constants show the following order: norfloxacin < model compound < levofloxacin < lom-efloxacin. The rate constant of norfloxacin is less than the model compound. This indicated that the predominant reaction occurred at the quinolone ring rather than the piperazynilic ring and the other substituted groups. This is because the substituted groups on quinolone ring retard hydroxyl radical attack. The slight increase in the rate constant for levofloxacin is due to the electron-donating effect of −OCH$_2$CH(CH$_3$)− side chain group, which activate the quinolone ring toward hydroxyl radical attack. The highest value for lomefloxacin is attributed to the inductive electron-withdrawing effect and electron-donating conjugative effect of the two F atoms on the quinolone ring. Halogen atoms on aromatic and heterocyclic ring structures are replaced by ipso attack of the hydroxyl radical.[27,28]

Reaction Kinetics with Hydrated Electron. The rate constants of three fluoroquinolones with the hydrated electron were measured by directly monitoring the change in the absorption of e$^-_{aq}$ at 700 nm in nitrogen-saturated solutions at pH 7.0, as reported previously.[16,18] The results for levofloxacin are shown in Figure 4. The bimolecular reaction rate constants were evaluated for levofloxacin (2.46 ± 0.05) × 10^{10} M^{-1} s^{-1} and the other two fluoroquinolones (1.18 ± 0.10) × 10^{10} M^{-1} s^{-1} and (2.79 ± 0.05) × 10^{10} M^{-1} s^{-1} for norfloxacin and lomefloxacin, respectively. For the model compound, the rate constant was (1.49 ± 0.01) × 10^{10} M^{-1} s^{-1}.[26] Constants of three fluoroquinolones and the model compound with the hydrated electron also show the following order: norfloxacin < model compound < levofloxacin < lomefloxacin. These results suggest that the solvated electron reacted with the quinolone rings predominantly rather than the piperazynilic ring.
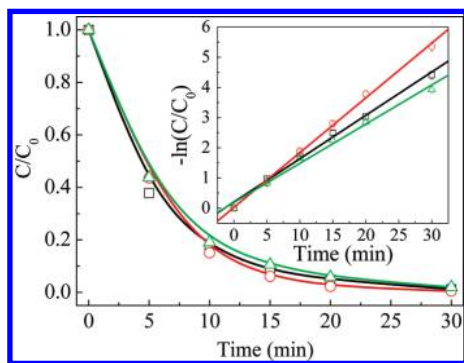
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Figure 5. Heterogeneous photocatalyzed disappearances of C/C_0 profiles for norfloxacin (□), levofloxacin (○), and lomefloxacin (△) with 100 μM and 2 g L^{-1} TiO$_2$ concentration. Inset: The linear transformation of $-\ln(C/C_0)$ versus time, pseudo-first-order rate constants, for the photocatalytic degradations of norfloxacin (□), levofloxacin (○), and lomefloxacin (△).

Photocatalytic Degradation Kinetics for Fluoroquinolones. The photocatalytic degradation kinetics of fluoroquinolones, using TiO$_2$ heterogeneous catalysis, was investigated (Figure 5). From the data, the residual for norfloxacin, levofloxacin, and lomefloxacin were obtained as 0.2, 0.5, and 2.0%, respectively, within 30 min UV irradiation. The photocatalytic degradation of three fluoroquinolones can be described by pseudofirst-order kinetic law, $-dc/dt = k_6C$ eq (6), where k_6 is the pseudo-first-order rate constant. The linear plots of $-\ln(C/C_0)$ versus time are shown in the inset of Figure 5. The rate constants were calculated as the slope of the curves as 0.14 min^{-1} (norfloxacin), 0.18 min^{-1} (levofloxacin), and 0.13 min^{-1} (lomefloxacin), respectively. Compared to the reaction with individual species (•OH) or (e$^-_{aq}$), the photocatalytic degradation rate constants show a different order, lomefloxacin < norfloxacin < levofloxacin. This suggests that the TiO$_2$ process is different than simply examining the •OH and e$^-_{aq}$ reaction rates and likely includes other processes, such as adsorption/desorption on the surface.

Photocatalytic Degradation Intermediates and Destruction Pathways for Fluoroquinolones. During photocatalysis the degradation products were separated and the intermediates identified by HPLC (Supporting Information, Figure 1S) and HPLC/MS/MS. The structural assignments of the breakdown byproduct of fluoroquinolones were based on the analysis of the molecular ion peaks and corresponding mass spectral cleavage patterns. The ion assignments/mass characteristic of norfloxacin and its degradation intermediates (NO1−NO7) are shown in Table 2. For norfloxacin, several cleaved fragments with m/z [M + H −18]$^+$, [M + H − 44]$^+$, [M + H − 42]$^+$ and [M + H − 86]$^+$ were found. The former two fragments correspond to the loss of H$_2$O and CO$_2$ from the carboxylic group, and the latter two are the characteristic fragments of the piperazynilic ring in the fluoroquinolone molecule.[29] Thus the intermediates NO1, NO2, and NO3 with mass units of 251, 294, and 322 may correspond to the partial and complete elimination of the piperazynilic ring from norfloxacin molecule, respectively. In the MS−MS fragments of these three products, [M + H − 18]$^+$ was found in each, indicating the loss of H$_2$O from the carboxylate group of the quinolone ring. This finding confirmed that the carboxyl group was intact in the quinolone ring of all of these three degradation intermediates; however no piperazynilic ring signal was found. Furthermore, the fragments of [M + H − 17]$^+$ and [M + H − 43]$^+$, corresponding to [M + H − NH$_3$]$^+$ and [M + H − C$_2$H$_5$N]$^+$, were also obtained in MS spectra of intermediates NO2 and NO3, respectively. Thus,

the intermediate NO4 with mass units of 239 may result from the cleavage of N−CH$_2$CH$_3$ on quinolone ring from intermediate NO1, followed by oxidation by the hydroxyl radical. At the same time, two separate intermediates NO5 with m/z of 336 and three separate intermediates NO6 with m/z of 352 corresponded to the addition of 16 and 32 mass units to the parent compound, indicating the formation of monohydroxy and dihydroxy derivatives. In their MS fragments, the presence of fragments [M + H − 42]$^+$ and [M + H − 86]$^+$, corresponded to the elimination of −C$_2$H$_4$N and −CO$_2$−C$_2$H$_4$N fragments from the piperazynilic ring, respectively. That suggests that the piperazynilic side chain is still intact and the hydroxylation reaction occurred predominantly on the quinolone rings. Further, the intermediates NO7 with mass 318, having similar fragments with norfloxacin, may be attributed to loss of the F atom by ipso attack of the hydroxyl radical. (All of the proposed chemical structures of intermediates for norfloxacin are shown in Table 1S, Supporting Information.)

The intermediates from the photocatalytic degradation of levofloxacin (LE1-LE9) were also separated and their MS−MS fragments summarized in Table 3. It can be seen from the table that nine major byproduct with different mass units were found. Similar to norfloxacin, the presence of fragments [M + H − 18]$^+$ and [M + H − 44]$^+$ also suggest the loss of H$_2$O and CO$_2$ from the carboxylic group, and the fragments [M + H − 57]$^+$ and [M + H − 101]$^+$ correspond to the fragments of [M − C$_3$H$_7$N] and [M − C$_3$H$_7$N − CO$_2$] cleaved from the piperazynilic ring. The intermediates LE1 and LE2 with mass units of 336 and 278 correspond to the partial and complete elimination of the piperazynilic ring from levofloxacin molecule, respectively. In the MS−MS fragments, there were no signals for the [M − C$_3$H$_6$N] and [M − C$_3$H$_6$N − CO$_2$] fragments, but the carboxylic acid group was still present. The intermediate LE3 with mass units of 294, owning the similar fragments with the intermediate LE2 with mass units of 278, may be the oxidant's intermediate by hydroxyl radicals from the intermediate LE2. However, the intermediates LE4 and LE5 with mass units 364 and 354 may be produced by the ring-opening of morpholine moiety, followed by further oxidization via the hydroxyl radicals. The carboxylate moiety and piperazynilic ring were intact, based on the MS−MS fragments. Additionally, two separate intermediates LE6 with mass units 322 were also observed, and these two intermediates may be attributed to partial elimination of piperazynilic ring and morpholine ring. That was suggested by the absences of fragments [M − C$_3$H$_6$N] and [M − C$_3$H$_6$N − CO$_2$] which were found in the former LE6 compound (corresponding to partial elimination of piperazynilic ring) but not in the latter LE6 intermediate (corresponding to partial elimination of morpholine ring). Moreover, the signal for fragment [M + H − 17]$^+$, corresponding to the [M + H − NH$_3$]$^+$, was found in the former intermediate of 322. At the same time, the monohydroxy and dihydroxy derivatives LE7 and LE8 with mass units 378 and 394, respectively, were also found. Compared to parent compound, the MS fragments [M + H − H$_2$O]$^+$, [M + H − CO$_2$]$^+$, [M + H − C$_3$H$_7$N]$^+$ and [M + H − C$_3$H$_7$N−CO$_2$]$^+$ were also detected, indicating the quinolone ring as the main position attacked by hydroxyl radicals. However, no more fragments were observed in the degradation intermediates LE9 with mass units of 360. This compound may be result from replacement of F atoms with hydroxyl radicals at the same position. (The proposed structures for photocatalytic degradation of levofloxacin were also summarized in Table 2S, Supporting Information.)

TABLE 2: Summary of Fragmentation of Parent Ions for Norfloxacin and Photocatalytic Products

| compounds | retention time (min) | m/z | MS−MS (relative intensity) | | | | | |
			[M + H]$^+$	[M + H − H$_2$O]$^+$	[M − C$_2$H$_4$N]	[M + H − CO$_2$]$^+$	[M − CO$_2$ − C$_2$H$_4$N]	others
norfloxacin	11.5	320	320(100)	302(8)	277(45)	276(56)	233(72)	205(45)
NO1	18.52	251	251(74)	233(100)				
NO2	4.39	294	294(100)	276(11)		250(42)		277(81),264(34),251(25), 227(17),204(44),190(27)
NO3	16.68	322	322(100)	304(10)		278(42)		305(42),279(23),259(11), 231(17), 205(41)
NO4	1.38	239	239(81)	221(100)				
NO5	3.81	336	336(100)	318(16)	293(41)	292(77)	249(25)	275(12),244(25),229(20)
	18.00		336(100)	318(19)	293(30)	292(25)	249(30)	245(22)
NO6	1.33	352		334(33)	309(40)	308(8)	265(100)	219(40),200(25)
	4.33		352(8)	334(100)	309(13)	308(24)	265(41)	275(33),262(61),240(11), 235(23),235(31)
	6.43		352(12)	334(100)	309(40)	308(20)	265(18)	290(13),262(22)
NO7	5.30	318	318(100)	300(15)	275(33)	274(62)	231(11)	

TABLE 3: Summary of Fragmentation of Parent Ions for Levofloxacin and Photocatalytic Products

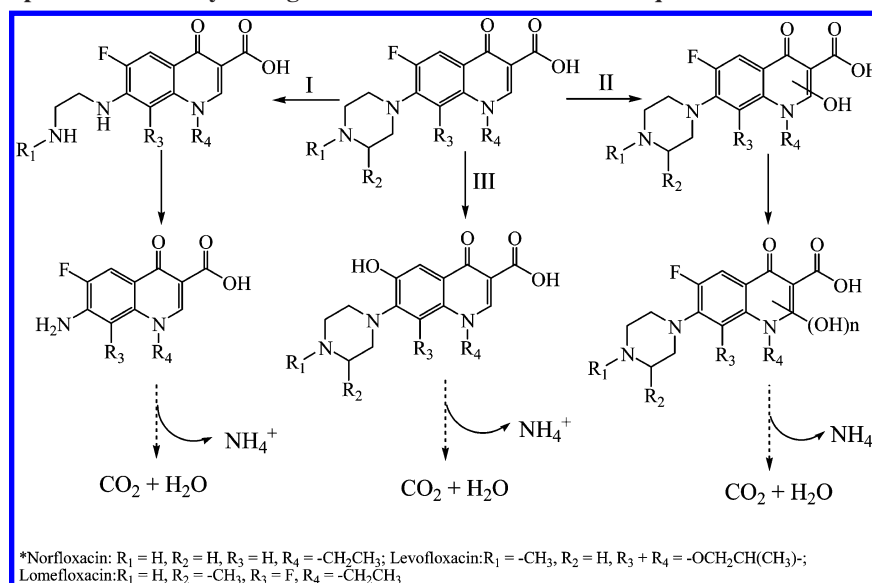| compounds | retention time (min) | m/z | MS−MS (relative intensity) | | | | | |
			[M + H]$^+$	[M + H − H$_2$O]$^+$	[M + H − CO$_2$]$^+$	[M − C$_3$H$_7$N]	[M − C$_3$H$_7$N − CO$_2$]	others
levofloxacin	17.77	362	362(100)	344(7)	318(42)	304(66)	260(17)	284(86)
LE1	4.54	336	336(100)	318(12)	292(71)			298(23),258(10),245(63), 233(50)
LE2	18.04	278	278(17)	260(100)				232(45),205(22),201(31), 165(40), 149(35)
LE3	18.18	294	294(8)	276(100)				221(41),193(32),177(16), 165(34)
LE4	18.31	364	364(100)	346(50)	320(22)	306(75)	262(50)	321(10),318(8),274(24), 264(20),248(55),241(25)
LE5	17.71	354	354(21)	336(100)	310(8)	296(77)	252(6)	316(32),293(11),266(24), 254(45), 245(20)
LE6	17.64	322	322(100)	304(18)	278(74)			305(57),212(25),193(81), 149(10), 122(33)
	16.44		322(100)	304(42)	278(51)	264(54)	220(12)	233(14),217(22)
LE7	4.42	378	378(15)	360(100)	334(23)	320(34)	276(10)	205(50)
LE8	18.96	394	394(11)	376(100)	350(10)	336(8)	292(87)	206(43),189(17),127(20)
LE9	11.04	360	360(100)	342(13)				

TABLE 4: Summary of Fragmentation of Parent Ions for Lomefloxacin and Photocatalytic Products

| compounds | retention time (min) | m/z | MS−MS (relative intensity) | | | | | | |
			[M + H]$^+$	[M + H − H$_2$O]$^+$	[M + H − CO$_2$]$^+$	[M + H − C$_2$H$_4$N − H$_2$O]$^+$	[M − C$_2$H$_4$N − CO$_2$]	[M − C$_3$H$_6$N − CO$_2$]	others
lomefloxacin	15.71	352	352(100)	334(8)	308(4)	292(10)	265(47)	251(36)	288(8), 236(8), 225(8)
LO1	4.42	326	326(100)	308(5)	282(10)				309(43),280(23),261(32), 251(11),237(13),223(20)
LO2	16.44	269	269(77)	251(100)					
LO3	4.54	241	241(81)	223(100)					
LO4	3.67	257	257(67)	239(100)					
LO5	17.71	368	368(8)	350(100)	324(44)	308(62)	281(44)	267(77)	248(23),230(17),228(23)
LO6	18.96	348	348(100)	330(22)	304(33)	288(45)	261(35)	247(78)	
LO7	18.31	350	350(100)	332(15)	306(31)	290(55)	263(42)	249(35)	
LO8	18.04	307	307(100)	289(5)	263(10)				278(41)
	18.18		307(54)	289(100)	263(13)				251(22),244(18),233(24), 207(66),194(10)

The photocatalytic degradation intermediates of lomefloxacin (LO1−LO8) were also studied and their MS−MS fragments shown in Table 4. In the MS fragments of lomefloxacin, the fragments [M + H − 18]$^+$ and [M + H − 44]$^+$ indicated the presence of carboxylic groups. The fragments [M+H −60]$^+$, [M+H −86]$^+$ and [M+H −101]$^+$, corresponding to [M + H − C$_2$H$_4$N − H$_2$O], [M − C$_2$H$_4$N − CO$_2$] and [M − C$_3$H$_6$N − CO$_2$], were the results of fragmentation from the piperazynilic ring (shown in Table 4). The intermediates LO1 and LO2 with

mass units 326 and 269 are due to the partial and complete elimination of the piperazynilic ring from lomefloxacin. The loss of −CH$_2$CH$_3$ from the N in the quinolone ring leads to the formation of the intermediate fragment with mass units 241, LO3. This intermediate was further oxidized to the intermediate LO4 with mass units 257 by addition of hydroxyl group from the radical attack. For these four compounds, there is no signal of piperazynilic ring in their MS−MS fragments, but the carboxylate fragments are still present (all chemical structure

SCHEME 1: The Proposed Photocatalytic Degradation Mechanism for Fluoroquinolones

*Norfloxacin: $R_1 = H$, $R_2 = H$, $R_3 = H$, $R_4 = -CH_2CH_3$; Levofloxacin: $R_1 = -CH_3$, $R_2 = H$, $R_3 + R_4 = -OCH_2CH(CH_3)-$;
Lomefloxacin: $R_1 = H$, $R_2 = -CH_3$, $R_3 = F$, $R_4 = -CH_2CH_3$

are shown in Table 3S, Supporting Information). On the other hand, the hydroxylation intermediates were also found. The intermediate LO5 with mass units 368 corresponded to the monohydroxy derivatives with the addition of 16 mass units to the parent compound. The F atom substituted intermediates with hydroxyl radicals were also found. For the intermediates LO6 and LO7 with mass units 350 and 348, their MS fragments are very similar with the MS fragments of lomefloxacin obtained, and the fragments signals for carboxylic group and piperazynilic ring are still present. So these two compounds may be intermediates from substitution of one and two F atoms with hydroxyl radicals on quinolone ring. Additionally, two separate intermediates LO8 with *m/z* of 307 were also observed. According to MS fragments, these two compounds may be corresponding to the opening of piperazynilic ring and further elimination from the intermediate LO6.

In summary, the photocatalytic degradation pathways of three fluoroquinolones were compared in Scheme 1. It appears that the elimination of piperazynilic ring was the first degradation pathway (I). In this degradation pathway, the partial and complete elimination of piperazynilic ring was observed for all three fluoroquinolones. Then, several hydroxylation intermediates were also observed after cleavage of the N−R₄ bound to quinolone ring (shown in Scheme 1). The hydroxylation reaction with the parent compound was considered the second degradation pathway (II). The monohydroxy and polyhydroxy intermediates were also found during the photocatalytic degradation of all these three fluoroquinolones. The monohydroxy intermediates with mass units 336, 378, and 368 were found for norfloxacin, levofloxacin, and lomefloxacin, respectively. Furthermore, the dihydroxy intermediates with mass units 352 and 394 were also observed in photocatalytic degradation of norfloxacin and levofloxacin, respectively. The F atom loss due to ipso attack of the hydroxyl radical is proposed as the third degradation pathway (III). The F atoms substituted intermediates with mass units 318, 360, and 350 are all found for norfloxacin, levofloxacin, and lomefloxacin, respectively.

To further evaluate the environmental fate of three fluoroquinolones and their intermediates, TOC and evolution of inorganic ions were also measured during the photocatalytic degradation (shown in Figure 6). After 180 min degradation, only 4.8, 5.2, and 6.2% of the TOC remained for norfloxacin,

levofloxacin and lomefloxacin, respectively. At the same time, nitrogen moieties in organic compounds were transformed into either NH_3 (NH_4^+ in acidic media) or nitrate ions by photocatalytical oxidation. For these compounds, 98.3, 95.1, and 97.3% of the nitrogen was released as NH_4^+ ions, while only 1.7, 1.2, and 1.4% were NO_3^- ions for norfloxacin, levofloxacin, and lomefloxacin, respectively. These results are consistent with other studies.[30] In additional, within the 180 min reaction time, 96.1, 94.3, and 97.4% of F atoms were released as F^- ion for
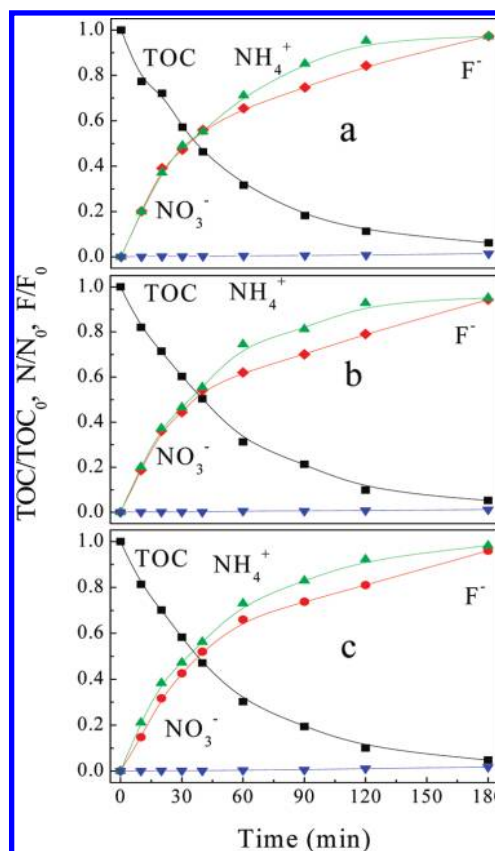

Figure 6. Disappearance of TOC and evolution of ammonium, nitrate and fluoride ions for (a) norfloxacin, (b) levofloxacin, and (c) lomefloxacin.

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norfloxacin, levofloxacin, and lomefloxacin, respectively. These results indicate that most of fluoroquinolones and their daughter products could be mineralized at the final stage of photocatalytic process.

Conclusions

The absolute bimolecular reaction rate constants for reaction of •OH and e$^-_{aq}$ with norfloxacin, levofloxacin, and lomefloxacin were measured and they are all very similar. The rate of destruction was shown to be similar for all three compounds. The photocatalytic degradation mechanisms proposed for three fluoroquinolones, and three pathways, including the elimination of piperazynilic ring, the addition of hydroxyl radical to quinolone ring, and the substitution of F atoms with hydroxyl radicals were also shown to be similar for all three compounds. The loss of fluoride ion suggests that the compounds will be more susceptible to biodegradation if mineralization is not achieved. These results indicate that AO/RPs are an attractive treatment technologies for the degradation of fluoroquinolones in aqueous solution because under photocatalytic degradation process most of produced intermediates can be finally mineralized into CO$_2$, water, and mineral species within 180 min.

Supporting Information Available: Includes one figure showing HPLC chromatograms of the photocatalytic degradation of norfloxacin, levofloxacin, and lomefloxacin, respectively, and three tables for the proposed intermediates during photocatalytic degradation of norfloxacin, levofloxacin and lomefloxacin, respectively. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Kummerer, K. *Pharmaceuticals in the Environment: Sources, Fate, Effects and Risks*, 3rd ed.; Springer, New York, 2008.

(2) Ikehata, K.; Naghashkar, N. J.; Ei-Din, M. G. *Ozone: Sci. Eng.* **2006**, *28*, 353.

(3) Santos, J. L.; Aparicio, I.; Alonso, E. *Environ. Int.* **2007**, *33*, 596.

(4) Domagala, J. M.; Hanna, L. D.; Heifetz, C. L.; Hutt, M. P.; Mich, T. F.; Sanchez, J. P.; Solomon, M. *J. Med. Chem.* **1986**, *29*, 394.

(5) Lorenzo, F.; Navaratnam, S.; Edge, R.; Allen, N. S. *Photochem. Photobiol.* **2008**, *84*, 1118.

(6) Navaratnam, S.; Claridge, S. *J. Photochem. Photobiol., A* **2000**, *72*, 283.

(7) Watkinson, A. J.; Murby, E. J.; Costanzo, S. D. *Water Res.* **2007**, *41*, 4164.

(8) Kummerer, K.; Al-Ahmad, A.; Mersch-Sundermann, V. *Chemosphere* **2000**, *40*, 701.

(9) Zhang, H. C.; Huang, C. H. *Environ. Sci. Technol.* **2005**, *39*, 4474.

(10) Ikehata, K.; Gamal El-Din, M.; Snyder, S. A. *Ozone: Sci. Eng.* **2008**, *30*, 21.

(11) Xu, W. H.; Zhang, G.; Li, X. D.; Zou, S. C.; Li, P.; Hu, Z. H.; Li, J. *Water Res.* **2007**, *41*, 4526.

(12) Hartmann, A.; Alder, A. C.; Koller, T.; Widmer, R. M. *Environ. Toxicol. Chem.* **1998**, *17*, 377.

(13) Brain, R. A.; Johnson, D. J.; Richards, S. M.; Sanderson, H.; Sibley, P. K.; Solomon, K. R. *Environ. Toxicol. Chem.* **2004**, *23*, 371.

(14) Robinson, A. A.; Belden, J. B.; Lydy, M. J. *Environ. Toxicol. Chem.* **2005**, *24*, 423.

(15) Westerhoff, P.; Yoon, Y.; Snyder, S.; Wert, E. *Environ. Sci. Technol.* **2005**, *39*, 6649.

(16) Song, W.; Cooper, W. J.; Mezyk, S. P.; Greaves, J.; Peake, B. M. *Environ. Sci. Technol.* **2008**, *42*, 1256.

(17) Antoniou, M. G.; Nicolaou, P. A.; Shoemaker, J. A.; Cruz, A. A.; Dionysiou, D. D. *Appl. Catal., B* **2009**, *91*, 165.

(18) An, T. C.; Yang, H.; Li, G. Y.; Song, W. H.; Cooper, W. J.; Nie, X. P. *Appl. Catal., B* **2010**, *94*, 288.

(19) Buxton, G. V.; Stuart, C. R. *J. Chem. Soc., Faraday Trans.* **1995**, *91*, 279.

(20) Buxton, G. V.; Greenstock, C. L.; Helman, W. P.; Ross, A. B. *J. Phys. Chem. Ref. Data* **1988**, *17*, 513.

(21) Laverne, J. A.; Pimblott, S. M. *Radiat. Res.* **1993**, *135*, 16.

(22) Merga, G.; Schuchmann, H. P.; Rao, B. S. M.; vonSonntag, C. *J. Chem. Soc., Perkin Trans.* **1996**, *2*, 1097.

(23) Merga, G.; Rao, B. S. M.; Mohan, H.; Mittal, J. P. *J. Phys. Chem.* **1994**, *98*, 9158.

(24) Peller, J.; Kamat, P. V. *J. Phys. Chem. A* **2005**, *109*, 9528.

(25) Sharma, S. B.; Mudaliar, M.; Rao, B. S. M.; Mohan, H.; Mittal, J. P. *J. Phys. Chem. A* **1997**, *101*, 8402.

(26) Santoke, H.; Song, W.; Cooper, W. J.; Greaves, J.; Miller, G. E. *J. Phys. Chem. A* **2009**, *113*, 7846.

(27) An, T. C.; Chen, J. X.; Li, G. Y.; Ding, X. J.; Sheng, G. Y.; Fu, J. M.; Mai, B. X.; O'Shea, K. E. *Catal. Today* **2008**, *139*, 69.

(28) Subramanian, B.; Yang, Q. L.; Yang, Q. J.; Khodadoust, A.; Dionysiou, D. D. *J. Photochem. Photobiol., A* **2007**, *192*, 114.

(29) Torniainen, K.; Mattinen, J.; Askolin, C. P.; Tammilehto, S. *J. Pharm. Biomed. Anal.* **1997**, *15*, 887.

(30) Calza, P.; Medana, C.; Pazzi, M.; Baiocchi, C.; Pelizzetti, E. *Appl. Catal., B* **2004**, *53*, 63.