



New insights into the aquatic photochemistry of fluoroquinolone antibiotics: Direct photodegradation, hydroxyl-radical oxidation, and antibacterial activity changes



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HIGHLIGHTS

- It is first reported on hydroxyl-radical oxidation of 6 fluoroquinolone antibiotics.
- Methods were developed to assess photolysis and oxidation fate in surface waters.
- The neutral form reacted faster with hydroxyl radical than protonated forms.
- The main oxidation intermediates and transformation pathways were clarified.
- The antibacterial activity changes depend on dominant photolysis pathways.

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ABSTRACT

The ubiquity and photoreactivity of fluoroquinolone antibiotics (FQs) in surface waters urge new insights into their aqueous photochemical behavior. This study concerns the photochemistry of 6 FQs: ciprofloxacin, danofloxacin, levofloxacin, sarafloxacin, difloxacin and enrofloxacin. Methods were developed to calculate their solar direct photodegradation half-lives ($t_{d,E}$) and hydroxyl-radical oxidation half-lives ($t_{OH,E}$) in sunlit surface waters. The $t_{d,E}$ values range from 0.56 min to 28.8 min at 45° N latitude, whereas $t_{OH,E}$ ranges from 3.24 h to 33.6 h, suggesting that most FQs tend to undergo fast direct photolysis rather than hydroxyl-radical oxidation in surface waters. However, a case study for levofloxacin and sarafloxacin indicated that the hydroxyl-radical oxidation induced risky photochlorination and resulted in multi-degradation pathways, such as piperazinyl hydroxylation and cleavage. Changes in the antibacterial activity of FQs caused by photodegradation in various waters were further examined using *Escherichia coli*, and it was found that the activity evolution depended on primary photodegradation pathways and products. Primary intermediates with intact FQ nuclei retained significant antibacterial activity. These results are important for assessing the fate and risk of FQs in surface waters.

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1. Introduction

Fluoroquinolone antibiotics (FQs) are important aqueous micropollutants that are not effectively removed by wastewater treatment plants (Chen et al., 2013) and are confirmed to be ubiquitous in surface waters (Schwarzenbach et al., 2006; Luo et al., 2011; Chen and Zhou, 2014; Liang et al., 2013). This large class of pollutants can promote bacterial resistance and photomodified toxicities, making them an emerging concern (Ge et al., 2010; Li et al., 2011). In aquatic systems, FQs show resistance to hydrolysis and biodegradation (Ge et al., 2010; Knapp et al., 2005). However, exposure to sunlight will weaken the

persistence of FQs in the aqueous euphotic zone (Ge et al., 2010). Thus, new insights into their environmental photochemical behavior and associated risk are required to assess the fate and effects of FQs in sunlit surface waters.

FQs can undergo not only direct or indirect photodegradation but also self-sensitized photo-oxidation via reactive oxygen species (ROS, such as hydroxyl radicals, $\bullet\text{OH}$) (Ge et al., 2010; Li et al., 2011; Sturini et al., 2010; Wei et al., 2013). Many other antibiotics, such as tetracycline (Werner et al., 2006; Chen et al., 2008), and phenicols (Ge et al., 2009), are also self-sensitized photodegradable. Werner et al. (2006) investigated the photochemical kinetics of tetracycline and found that the pseudo-first-order rate constants (k) increased with the increasing initial concentration (C_0), likely because of the self-sensitization effect. Because FQs can self-sensitize, their photolytic k might be affected by C_0 .

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To verify the hypothesis, it is necessary to examine the C_0 -affected kinetics and to weigh the contribution of self-sensitized photolysis to total FQ elimination.

Many previous studies have calculated the environmental direct photolytic half-lives ($t_{d,E}$) for various micropollutants in surface waters based on the method of Leifer (1988) (Boreen et al., 2004, 2005; Edhlund et al., 2006). However, the FQ $t_{d,E}$ values reported by different investigators differ at orders of magnitude. For example, Burhenne et al. (1997) calculated $t_{d,E} = 1.6$ h (summer)–55.4 h (winter) for the direct photolysis of enrofloxacin (ENR) in surface waters at 30°–60° N latitude, whereas Ge et al. (2010) reported the $t_{d,E} = 1.25$ min (summer)–6.11 min (winter) at 45° N latitude. Therefore, it is necessary to examine the distinct difference of $t_{d,E}$, and develop a calculation method for evaluating $t_{d,E}$ might be beneficial to better understand this behavior.

Some previous studies that reported the phototransformation pathways of FQs in water mainly focused on their direct photolysis (Ge et al., 2010; Sturini et al., 2010; Babić et al., 2013; Sturini et al., 2012a). Ge et al. (2010) found that photoinduced decarboxylation, defluorination, or piperazinyl N^4 -dealkylation occurred effectively depending on the structures of the FQs, whereas Sturini et al. (2010) identified a completely different path, i.e., photopolymerization for marbofloxacin. Additionally, FQs might undergo indirect photodegradation or sensitized photooxidation mediated by the photogenerated \bullet OH from dissolved organic matter, Fe(III) and nitrate (Mack and Bolton, 1999; Grannas et al., 2014; Fisher et al., 2006; Walse et al., 2004). The hydroxyl-radical oxidation is also common in advanced oxidation (Keen and Linden, 2013; DeWitte et al., 2008) and self-sensitization processes (Ge et al., 2010), which indicate that the bimolecular reactions between \bullet OH and FQs might be the relevant mechanisms in these processes. However, information regarding the \bullet OH-initiated kinetics and associated photoproducts of FQs remains limited.

Because \bullet OH is ubiquitous in sunlit surface waters and shows less selectivity to oxidize most organic chemicals (Keen and Linden, 2013; Mill, 1999; Li et al., 2014), the \bullet OH oxidation reaction of FQs may result in more degradation pathways than direct photolysis. Moreover, the different FQ protonation states are supposed to react with \bullet OH at different reactivities. Therefore, the environmentally apparent \bullet OH-oxidation half-lives ($t_{\bullet\text{OH},E}$) for FQs in surface water will depend on the ambient pH value. Previously, photooxidation reactivities toward \bullet OH were reported for each protonated state of a few chemicals, such as hydroxylated polybrominated diphenyl ethers (Xie et al., 2013). For antibiotics, they can react with \bullet OH at mean rate constants of $5.3 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$, $5.0 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$ and $3.8 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$ for sulfa drugs (Boreen et al., 2004, 2005), nitrofurans (Edhlund et al., 2006) and ionophores (Yao et al., 2013), respectively. However, their reactivities toward \bullet OH of different protonated states are still largely unknown.

Because photodegradation is an important transformation pathway for FQs in surface waters, it is of great significance to investigate their antibacterial activity changes caused by photodegradation. For ciprofloxacin (CIP), Paul et al. (2010) found that the antibacterial potency to *Escherichia coli* (*E. coli*) of irradiated solutions decreased and that the photolytic products retained negligible antibacterial activity relative to the parent compound. However, Sturini et al. (2012b) showed notable antimicrobial activity of *E. coli* to the ciprofloxacin photoproducts. Furthermore, norfloxacin and ofloxacin photoproducts were found to be inactive to *E. coli*, whereas ENR photoproducts retained significant activity (Wammer et al., 2013). These results appear to be inconsistent, suggesting that antibacterial activity changes of FQs because of their photodegradation need to be further explored. For other classes of antibiotics, such as tetracycline, triclosan and sulfa drugs, changes in antibacterial activity caused by photochemical transformations have been studied previously (Wammer et al., 2011; Wammer et al., 2006).

This study seeks new insights into the aquatic photochemical behavior of 6 FQs: CIP, danofloxacin (DAN), levofloxacin (LEV), sarafloxacin (SAR), difloxacin (DIF), and ENR. The objectives are to develop methods to calculate the environmental half-lives ($t_{d,E}$ and $t_{\bullet\text{OH},E}$), investigate

\bullet OH-oxidation kinetics and pathways of selected FQs, and examine changes in antibacterial activity because of photodegradation. To the best of our knowledge, this is the first comprehensive report on the kinetics and mechanisms for \bullet OH-mediated photodegradation of FQs.

2. Materials and methods

2.1. Reagents and materials

The 6 FQs and other reagents were provided by different suppliers, and surface waters were collected and filtered as described in our previous study (Ge et al., 2010). The FQ chemical structures are given in Table S1. A freeze-dried wild-type *E. coli* K12 (ATCC 23716) culture was obtained from Nissu Biotechnologies Co., Ltd. (Qingdao, China). Broth cultures were prepared under sterile conditions by transferring *E. coli* colonies sampled from the agar cultures into 5–6 mL of Mueller-Hinton broth and incubating overnight at 37 °C on a shaker plate rotating at 200 rpm.

2.2. Photodegradation experiments

A merry-go-round photochemical reactor was employed, and a Pyrex-well cooled and filtered xenon lamp (1000 W) was used to simulate sunlight ($\lambda > 290$ nm). The light intensity and spectrum were reported previously (Ge et al., 2010). To test whether FQ photolytic kinetics were affected by initial concentration (C_0), pseudo-first-order rate constants (k) were determined with $C_0 = 1$ –30 μM in pure water. To examine the changes in antibacterial activity because of photodegradation, 6 individual FQs dissolved in water ($C_0 = 10 \mu\text{M}$) were irradiated and sampled before the antibacterial test.

Competition kinetics were used to determine the bimolecular rate constants ($k_{S,\bullet\text{OH}}$) for the reaction between FQs and \bullet OH according to Eq. (1):

$$k_{S,\bullet\text{OH}} = \frac{\ln([S_t]/[S_0])}{\ln([R_t]/[R_0])} k_{R,\bullet\text{OH}} \quad (1)$$

in which S is the substrate FQ, and R is the reference compound acetophenone with $k_{R,\bullet\text{OH}} = 5.9 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$ (Edhlund et al., 2006). Hydroxyl radicals were generated by H_2O_2 with irradiation of light at $\lambda > 380$ nm. Initial concentrations of H_2O_2 were adjusted with pH values, as described previously (Xie et al., 2013). To investigate photooxidation products, the irradiated reaction solutions of LEV and SAR were sampled and analyzed by LC–MS/MS.

2.3. Analytical determinations

A Waters UPLC with a fluorescence detector was employed to analyze the FQs. The intermediates were enriched by solid phase extraction and then analyzed by an Agilent 1100 HPLC coupled to a triple quadrupole mass spectrometer in both positive and negative modes. Ions were analyzed with a Shimadzu Class-VP ion chromatogram. Detailed descriptions of sample pretreatment and instrumental analysis are provided in the Supplementary material.

2.4. Antibacterial activity screening

The in vitro antimicrobial activities of the samples were tested to examine the changes in antibacterial activity of FQs because of their simulated solar photodegradation in various waters. The assay was performed by following the China standard method QB/T 2738-2012, with *E. coli* as the tested species. The inhibition zone diameters were measured to the nearest millimeter and recorded as antibacterial activity indexes (Tao et al., 2010). All tests were performed in triplicate, and one-way analysis of variance (SPSS version 19.0) was utilized to assess the changes in antibacterial activity of FQs caused by photodegradation.

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