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Kinetics, Mechanism, and Toxicity of Amlodipine Degradation by the UV/Chlorine Process

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Abstract: The UV/chlorine process, as a new type of AOP (Advanced Oxidation Process), was utilized to treat amlodipine (AML)-containing water. The influencing factors, including chlorine dose, UV intensity, solution initial pH value, and ammonia concentration, were investigated. The degradation of AML in real water and the relative contributions of OH• and Cl• were also studied. Finally, high-resolution mass spectrometry (HRMS) and GC-MS were used to identify the possible degradation products. The results demonstrated that the AML degradation process was fitted with apparent first-order kinetics. AML degradation had a positive correlation with UV intensity and chlorine dose, and a negative correlation with ammonia concentration. In the presence of ammonia nitrogen and DOM, the removal of AML from real water was reduced. OH• made a dominant percentage contribution of 55.7% to the degradation of AML. Sixteen intermediates were detected and identified. A possible degradation mechanism was also proposed. Acute toxicity tests and risk prediction both illustrated that the complete removal of AML does not guarantee the reduction of acute toxicity, but a prolonged degradation promoted the detoxification of toxic intermediates. The UV/chlorine process can be regarded to be an effective method to remove AML and reduce ecological risk.

Keywords: Amlodipine; UV/chlorine; influencing factors; degradation products; ecological risk

1. Introduction

It is well known that pharmaceutically active compounds (PhACs) are emerging trace organic contaminants, that are mainly used to diagnose, treat, or prevent diseases in humans and animals [1]. There are approximately 4000 active PhACs, such as sleeping drugs, antibiotics, antidiabetics, painkillers, and anti-inflammatory agents [2,3]. PhACs have entered the environment through human health care and animal disease treatment, and have attracted widespread attention [4]. Due to their widespread use and improper handling, a large amount of drugs can remain in the water environment. A wide variety of PhACs (up to mg·L⁻¹) have been found in soil [5,6], surface water [7], drinking water sources [8], and aquatic organisms [9] all over the world, including Asia, Europe, and USA [10–13]. Many studies have shown that PhACs can lead to numerous undesirable symptoms, such as developmental, endocrine, and reproductive disorders [14]. Therefore, the determination and regulation of PhACs in water has become a pressing problem to be resolved in many countries and regions.

As a chlorine-derivate treatment technology, the UV/chlorine process can inactivate water-borne pathogens, and degrade trace organic contaminants, thereby achieving multiple-barrier disinfection

and reducing secondary pollution [15]. UV light has been used to irradiate free chlorine to generate two types of active radicals with high oxidation potential, including chlorine radicals ($\text{Cl}\bullet$) and hydroxyl radicals ($\text{OH}\bullet$) [16]. The UV/chlorine process has been shown to be able to remove typical PhAC pollutants such as ibuprofen, carbamazepine, and atrazine [15,17,18]. The UV/chlorine process has potential application prospects for water treatment.

Amlodipine (AML) is a kind of calcium channel blocker (CCB) that can inhibit the flow of calcium ions into cardiac muscles and vascular smooth muscles [19]. AML is widely utilized to treat angina, arrhythmias, high blood pressure, and other heart diseases [20]. Due to its incomplete removal by wastewater treatment plants (WWTPs) and final discharge, AML has been found in drinking water sources and WWTPs in recent years, with concentrations up to $510.0 \text{ ng}\cdot\text{L}^{-1}$ [21–23]. Research has illustrated that excessive AML in aqueous environments can cause ecological damage [24]. For example, AML in recycled water can be absorbed by aquatic organisms and gather in their bodies with a half-life of more than 117 h and a bioconcentration factor of over 16 [25], which means that AML has poses a potential ecological risk to the humans. However, few studies have investigated AML control and removal in water bodies; therefore, they need to be further investigated.

The objective of this study was to investigate the influencing parameters and mechanism of AML degradation by the UV/chlorine process. The main reaction parameters were evaluated, including chlorine dose, UV light intensity, solution initial pH value, and ammonia concentration. The degradation effect of AML in real water and the relative contributions of $\text{OH}\bullet$ and $\text{Cl}\bullet$ were also explored. The degradation products were analyzed using an HRMS Q-E Plus Orbitrap and GC-MS. Risk assessment during AML degradation was also performed.

2. Materials and Methods

2.1. Chemicals

Sodium hypochlorite solution (NaClO), nitrobenzene (NB), formic acid (HPLC grade), and derivative agent (BSTFA/TMCS, 99:1) were purchased from Aladdin Reagent Co, Ltd. (Shanghai, China). AML was purchased from Energy Chemical Reagent (Shanghai, China). Hydrogen peroxide (H_2O_2 , 30%) was purchased from Lingfeng Reagent Co, Ltd. (Shanghai, China). Dichloromethane (DCM) was purchased from Yonghua Reagent Co, Ltd. (Suzhou, China). Analytical reagents, including Na_2SO_3 , $\text{NaH}_2\text{PO}_4\cdot 2\text{H}_2\text{O}$, $\text{Na}_2\text{HPO}_4\cdot 12\text{H}_2\text{O}$, HCl , NaOH , were obtained from Sinopharm Reagent (Shanghai, China). Methanol (HPLC grade) was acquired from Sigma-Aldrich Corp (St. Louis, MO, USA). Enrichment and desalination of water samples were performed by solid phase extraction (SPE) using a Generik H2P cartridge (200 mg/6 cc, Sepax Technologies, China). The available chlorine content ($620 \text{ mg}\cdot\text{L}^{-1}$ as Cl_2) was detected according to the DPD/FAS test method [16]. The NaClO solution was kept away from light at 4°C . The Na_2SO_3 solution (40 mM) was prepared periodically. The water for the reagent preparation was ultrapure Ultrapure water using a Milli-Q purifier (resistivity of $18.3 \text{ m}\Omega\cdot\text{cm}$).

2.2. UV Irradiation

A low-pressure mercury lamp (Philips, China, 75 W) was used in a photochemical device, which applied monochromatic UV radiation at 254 nm. The lamp was placed in the centerline of circular glassware containing reaction solutions (50 mL). A magnetic stirrer was used to ensure the homogeneity of the reaction. The UV intensity was controlled by changing the distance between the solution surface and the low-pressure mercury lamp. The light from the lamp could be viewed as parallel light. Each time the distance was changed, a UV radiometer (PIFBNU, Beijing, China) was used to determine at least 9 positions on the surface of the glass container. The final UV intensity was the average intensity of 9 positions. To stabilize the UV intensity, the UV lamp was turned on for at least 30 min before the experiment.

2.3. Kinetic Studies

Kinetic tests were carried out in the photoreactor described above. HCl, NaOH, and 10 mM phosphate buffer were used to maintain or adjust the pH value of the solution. A PHS-3C acidometer (REX, Shanghai, China) was used to determine the pH value.

A certain volume of the NaClO solution was added to AML water samples; then, the mercury lamp to start the experiments. At the different time intervals, one milliliter of an AML sample was collected, and immediately after collection, excessive Na₂SO₃ was added to quench the residual chlorine. Control tests of AML degradation by UV alone and dark chlorination were performed using a similar approach without chlorine and UV irradiation, respectively. Other tests, including NB degradation via the UV/chlorine process or the UV/H₂O₂ process, and AML degradation in real water, were also performed using the same procedure. Then, HPLC-MS/MS was used to determine the sample concentration. The experiment was repeated three times to obtain the average value.

AML water samples were determined by HPLC-MS/MS (Thermo UltiMate 3000, TSQ QuantumTM Access MAX) coupled to an RP column (Accucore C18, 3.0 × 50 mm). The following parameters were used: mobile phase of H₂O (A) and methanol (B), column temperature of 25 °C, gradient elution, flow rate of 0.6 mL·min⁻¹, precursor/product ion pairs 408.9/237.7 *m/z*, positive scan mode, and CE of 28 eV. The gradient profile is as follows: linear gradient 10% of B in 0–2 min, 95% B in 6 min, 95% B in 8 min, and re-equilibration of the column from 8 to 13 min with 10% of B.

Nitrobenzene water samples were detected using an Agilent 1260 HPLC equipped with a diode array detector at 262 nm. A Waters C18 column (4.6 mm × 100 mm) was used for separation at a flow rate of 0.4 mL·min⁻¹. The mobile phase was a mixture of methanol/water at a 70/30 (*v/v*) ratio.

2.4. Identification of Intermediates (IMs)

AML degradation samples were prepared under the typical conditions of UV/chlorine process given in Section 3.1. The samples were collected in different degradation times, including 10, 20, 30, 40, 50, and 60 min to get all the products in the whole process. The collection was repeated for several times to obtain higher quantities of the products. Enrichment and desalination of degradation samples for LC-MS analysis were performed according to an SPE procedure based on the US EPA standard method 1694 [26]. AML degradation samples were collected at intervals and brought to a volume of 1.5 mL for MS analysis.

Meanwhile, 1.2 L treated water samples were collected and mixed together. The samples were pretreated for GC-MS analysis according to a rotary evaporation procedure. After silylation by BSTFA/TMCS, the AML degradation samples was concentrated to 1.5 mL for analysis of small-molecule acid intermediates.

HRMS Q ExactiveTM Plus OrbitrapTM mass spectrometry (Thermo Scientific, USA) was performed to explain the unknown structure of degradation products. A RP column (Waters T3, 2.1 × 50 mm) was used to separate the relevant components. MS analysis was performed in both positive and negative modes. The parameters for heating electrospray ionization (HESI) were as follows: sheath gas rate of 12 mL·min⁻¹, capillary heat of 320 °C, and spray voltage of 4 kV. The other MS conditions included: a scan range of 70–600 *m/z*, dynamic exclusion of 5 s, HCD collision energy settings (CE%) 35, and a mass resolution of 70,000. Xcalibur 4.1 software was used for data analysis.

Small-molecule intermediates were identified using a GC-MS instrument (Thermo Trace 1300-ISQ LT) equipped with a C18 column (Thermo TG-624, 30 m × 0.25 mm × 1.4 µm). The helium flow rate was 1.0 mL·min⁻¹, the injection volume was 1 µL, and the inlet temperature was set to 280 °C. The full scan mode was used with a scan range of 30–600 *m/z*. The following gradient was applied: hold the temperature for 5 min at 50 °C, increase the temperature from 50–180 °C (at a rate of 5 °C·min⁻¹), 180–260 °C (slope of 15 °C·min⁻¹), and finally hold the temperature for 8 min at 260 °C.

2.5. Toxicity Tests and Assessment

The acute toxicity tests were performed using *Vibrio fischeri* luminescent bacteria. Bioluminescence was detected and recorded to investigate toxicity changes in the AML water samples [27]. The luminescent intensity of *Vibrio fischeri* was detected using a biotoxicity analyzer (ATD-P1, J&Q Environmental Technologies, Beijing, China). Freeze-dried bacteria were also provided by the same company. The Na₂SO₃ solution was used as a blank sample. The inhibition rate of bioluminescence could be determined by Equation (1):

$$I = \frac{L_0 - L_t}{L_0} \times 100\%, \quad (1)$$

where I represents the inhibition rate (100%) and L_0 and L_t represent the luminescence intensity of the blank, and AML samples, respectively.

ECOSAR (v1.1, EPA) software [28,29] is usually applied to assess the acute toxicity of a target substance. Therefore, the acute toxicity of AML and its degradation products during the process was achieved.

3. Results and Discussion

3.1. AML Degradation by the UV/Chlorine Process

The degradation of AML under three process conditions was compared, including UV irradiation alone (254 nm), dark chlorination, and the UV/chlorine process. As shown in Figure 1, only 8.8% of AML was removed by UV irradiation alone and 41.2% AML was removed by dark chlorination. However, the removal of AML reached 96.8% by the UV/chlorine process after 38 min. It is obvious that the UV/chlorine process evidently improved AML degradation efficiency compared with UV alone and dark chlorination. All the fitted curves between $\ln(c_t/c_0)$ and time retained linear relationship which means that these degradation reactions are suitable for pseudo-first-order kinetics (Equations (2) and (3)), with degradation rate constants (k'_{app}) of 0.0159, 0.0207, and 0.0680 min^{−1}, respectively:

$$\frac{d[AML]_t}{dt} = -k'_{app}[AML]_t, \quad (2)$$

$$k'_{app} = -\frac{\ln\left(\frac{[AML]_t}{[AML]_0}\right)}{t}, \quad (3)$$

where $[AML]_0$ and $[AML]_t$ stand for the AML concentration at 0 s and t s, respectively, μM. k'_{app} is the pseudo-first-order apparent rate constant, min^{−1}:

As mentioned above, it was difficult for AML to be directly photolyzed by UV irradiation alone. During chlorination, moderate degradation of AML occurred mainly because HOCl/OCl[−] can partially react with AML (Equations (4) and (5)). However, during the UV/chlorine process, in addition to direct photolysis and the slight effects of HOCl/OCl[−], the degradation of AML was significantly increased mainly due to the generation of active species, such as OH• and Cl• (Equation (6)). Among them, OH• is a non-selective radical that can react rapidly with various trace organic contaminants. Cl• is a strong oxidation radical, that has high reactivity with electrophilic functional groups. Therefore, the UV/chlorine process can promote the degradation of AML more effectively than the other processes,

due to attributed to the action of $\text{OH}\bullet$ and $\text{Cl}\bullet$ [15]. The superior degradation of carbamazepine [18] and atrazine [17] in the UV/chlorine process was also based on the same principle.

Figure 1. Amlodipine (AML) removal by UV alone, dark chlorination, and the UV/chlorine process ($[\text{AML}]_0 = 10 \mu\text{M}$, $[\text{chlorine}]_0 = 20 \mu\text{M}$, UV intensity = $1000 \mu\text{W}\cdot\text{cm}^{-2}$, pH = 7).

3.2. Effect of Chlorine Dose

The influences of different chlorine doses on AML degradation via the UV/chlorine process were investigated. As shown in Figure 2, the removal of AML increased from 47.5% to 97.5%; and the corresponding k'_{app} increased from 0.0155 to 0.0821 min^{-1} as the chlorine dose increased from 5 to $40 \mu\text{M}$ in 38 min. This result indicates that both the removal and the degradation rate constant of AML increased with increasing chlorine dose. With increasing chlorine dose, more radicals (such as $\text{OH}\bullet$ and $\text{Cl}\bullet$) were generated under UV irradiation, thereby accelerating the reaction with contaminants [30]. Thus, the degradation of AML was improved.

Figure 2. Effect of residual free chlorine on AML degradation by the UV/chlorine process ($[\text{AML}]_0 = 10 \mu\text{M}$, UV intensity = $500 \mu\text{W}\cdot\text{cm}^{-2}$, pH = 7).

Furthermore, Figure 2 shows that the chlorine dose and the degradation rate constant exhibited a significant linear relationship ($k'_{\text{app}} = 1.9 \times 10^{-3} \cdot [\text{oxidant}]$, $R^2 = 0.9668$). The effect of the chlorine dose was also similarly observed in diuron degradation by the UV/chlorine process [30].

3.3. Effect of UV Intensity

UV intensity is an essential factor in the UV/chlorine process [31]. At a pH value of 7, the influences of varying UV intensities on AML degradation were investigated with a 10 μM initial AML concentration and a 30 μM chlorine dose.

All the test results were successfully fitted with pseudo-first-order reaction kinetics ($R^2 > 0.93$). As shown in Figure 3, as the UV intensity increased from 0 to 2000 $\mu\text{W}\cdot\text{cm}^{-2}$, k'_{app} apparently improved from 0.0205 to 0.0973 min^{-1} . According to Equation (7) [32,33], k'_{app} is related to the UV intensity (I) and quantum yields of AML, HOCl and OCl^- . However, AML was barely degraded by UV photolysis, so the quantum yield of AML was negligible. In addition, the quantum yields of HOCl and OCl^- remain constant under different UV intensities [17]. Therefore, AML degradation was directly affected by the UV intensity, and the degradation of AML was enhanced with increasing of UV intensity.

Figure 3. Effect of UV light intensity on AML degradation by the UV/chlorine process ($[\text{AML}]_0 = 10 \mu\text{M}$, $[\text{chlorine}]_0 = 20 \mu\text{M}$, $\text{pH} = 7$).

Figure 3 also illustrates the linear regression relationship of k'_{app} versus UV intensity ($k'_{\text{app}} = 4.0 \times 10^{-5} \cdot I$, $R^2 = 0.9419$), which can be expressed in Equation (8) [34,35]. A similar relationship between the increase in the k'_{app} and UV light intensity was also observed in a study of atrazine degradation [17,36]. Therefore, the UV/chlorine process shows a superior degradation capability at a higher UV intensity:

$$k'_{\text{app}} = \frac{I}{n} \cdot (\Phi_{\text{AML}} + \Phi_{\text{HOCl}} + \Phi_{\text{OCl}^-}), \quad (7)$$

$$k'_{\text{app}} = k'_F \cdot I, \quad (8)$$

where I stands for the UV intensity, $\text{mol photon min}^{-1}$; Φ_{AML} , Φ_{HOCl} and Φ_{OCl^-} are the quantum yields of AML, HOCl and OCl^- , respectively, mol photon^{-1} ; n is the number of photons, mol ; and k'_F stands for the fluence based kinetic constant.

3.4. Effect of pH Value

The pH value of the AML solution is another important factor in the degradation process [37]. AML removal was investigated with pH values ranging from 3 to 11. The other conditions were as follows: 10 μM initial AML concentration, 30 μM chlorine dose, and 500 $\mu\text{W}\cdot\text{cm}^{-2}$ UV intensity.

As shown in Figure 4, the removal of AML over 38 min decreased from 95.2% to 76.6% while the pH value increased from 3 to 11. The reaction rate was high of 0.0723 min^{-1} at a pH value of 3, and low of 0.0378 min^{-1} at a pH value of 11. This phenomenon indicated that the degradation of AML was largely enhanced under acidic conditions and inhibited under alkaline conditions. The effect of

the pH value was similar to those observed in earlier studies of trichloroethylene, 2-methylisoborneol and benzoic acid [16,38,39]. The different degradations at different pH values were ascribed to the effect of pH on the dissociation of HOCl/OCl[−] [40,41]. HOCl became the dominant oxidant with the decreasing pH. HOCl oxidized AML more quickly than OCl[−] due to its higher oxidation reduction potential. Furthermore, unlike chlorination, HOCl/OCl[−] can generate active radicals under photolysis, and the quantum yield of OH• from HOCl photolysis (1.40) was much higher than that from ClO[−] (0.28). In the present study, OH• is considered to play the most important role among all the radicals in AML degradation. As shown in Equations (11) and (12), the reaction between OCl[−] and OH• was faster than that between HOCl, which indicates a higher radical scavenging effect of OCl[−] [16,42]. Moreover, the whole degradation rate was also affected by the form of contaminants. The amino group in the AML structure has a pKa of 8.6, which means that dissociated amlodipine will be dominant in an acidic solution. Researches showed that higher reaction rate constants can be observed for dissociated species than those for non-dissociated species [14,18,43]. Therefore, acidic conditions will benefit AML degradation:

Figure 4. Effect of the pH value on AML degradation by the UV/chlorine process ($[\text{AML}]_0 = 10 \mu\text{M}$, $[\text{chlorine}]_0 = 30 \mu\text{M}$, UV intensity = $500 \mu\text{W}\cdot\text{cm}^{-2}$).

3.5. Effect of Ammonia Concentration

Ammonia (NH_4^+) is an important parameter that affects the water environment, so the effect of the ammonia concentration on AML degradation was also studied. The other conditions were as follows: $10 \mu\text{M}$ initial AML concentration, $30 \mu\text{M}$ chlorine dose, $500 \mu\text{W}\cdot\text{cm}^{-2}$ UV light intensity, and a pH value of 7.

The reaction results were also in accordance with pseudo-first-order kinetics (Figure 5). However, ammonia in water samples has an unfavorable effect on AML degradation. The removal of AML was 94.7% without ammonia in solution. However, AML removal was reduced to 60.1% when the concentration of ammonia was increased to $100 \mu\text{M}$. As the ammonia concentration increased from 0 to $100 \mu\text{M}$, the k'_{app} decreased from 0.0652 to 0.0202 min^{-1} . Ammonia rapidly reacted with chlorine to form two kinds of inorganic chloramines during the UV/chlorine process, monochloramine (NH_2Cl), and dichloramine (NHCl_2) [44]. Under neutral conditions, NHCl_2 was mainly generated at molar

ratios of Cl and N less than 1, which significantly affected the generation of radicals. In addition, compared with radicals, inorganic chloramines have a lower redox potential, which inhibits the degradation of AML [45,46].

Figure 5. Effect of the ammonia concentration on AML degradation by the UV/chlorine process ($[\text{AML}]_0 = 10 \mu\text{M}$, $[\text{chlorine}]_0 = 30 \mu\text{M}$, UV intensity = $500 \mu\text{W}\cdot\text{cm}^{-2}$, pH = 7).

3.6. AML Degradation in Real Water by the UV/Chlorine Process

AML degradation in real water was studied and compared with that in ultrapure water to evaluate the effect of background matter. The total phosphorus, COD, ammonia nitrogen and dissolved oxygen of real water were 0.39, 8.07, 0.62 and $5.89 \text{ mg}\cdot\text{L}^{-1}$, respectively (Table A1). The initial concentration of AML was $10 \mu\text{M}$ under both conditions.

As shown in Figure 6, the removal of AML was 85.0% in real water and 97.9% in ultrapure water within 38 min. Combined with the main characteristics of the above-mentioned real water (Table A1) and the effects of the water quality parameters on AML degradation, the relatively high ammonia nitrogen and dissolved organic matter (DOM) in real water were considered to be the main factors leading to the slight decreases in AML degradation and k'_{app} in comparison with those in the ultrapure water tests. Ammonia nitrogen increased the consumption of free residual chlorine, while DOM, as a radical scavenger, could consume large amounts of $\text{OH}\cdot$ and $\text{Cl}\cdot$ [16]. Therefore, the removal of AML was affected by the presence of ammonia nitrogen and DOM. The UV/chlorine process can be considered a better option for removing AML from real water than the other process, especially from water with lower DOM and ammonia nitrogen contents [15,47].

Figure 6. AML degradation by the UV/chlorine process ($[\text{AML}]_0 = 10 \mu\text{M}$, $[\text{chlorine}]_0 = 30 \mu\text{M}$, UV intensity = $500 \mu\text{W}\cdot\text{cm}^{-2}$, pH = 7).

3.7. Relative Contributions of Active Ingredients

To evaluate the relative contributions of different radicals in the UV/chlorine process, under the same reaction conditions, the degradation of AML was investigated using nitrobenzene (NB) as the radical probe [15]. Figure 7 showed the degradation process of AML and NB with the same reaction parameters, respectively. As a selective scavenger of $\text{OH}\cdot$, NB selectively reacted with $\text{OH}\cdot$ ($k''_{\text{OH}\cdot-\text{NB}} = 3.90 \times 10^9 \text{ M}^{-1}\text{s}^{-1}$), and the reaction with $\text{Cl}\cdot$ was insignificant. In addition, NB can easily absorb UV light in water. This could further weaken the UV light and result in a decrease in the radical production [30,48]. Based on the steady-state variation in the radical concentrations, the contributions of $\text{OH}\cdot$ ($k'_{\text{OH}\cdot-\text{AML}}$) and $\text{Cl}\cdot$ ($k'_{\text{Cl}\cdot-\text{AML}}$) can be calculated according to Equations (13)–(15):

$$k'_{\text{NB}} = k''_{\text{OH}\cdot-\text{NB}} \cdot [\text{OH}\cdot]_{\text{ss}}, \quad (13)$$

$$k'_{\text{OH}\cdot-\text{AML}} = k''_{\text{OH}\cdot-\text{AML}} \cdot [\text{OH}\cdot]_{\text{ss}}, \quad (14)$$

$$k'_{\text{Cl}\cdot-\text{AML}} = k'_{\text{AML}} - k'_{\text{OH}\cdot-\text{AML}} - k'_{\text{UV-AML}} - k'_{\text{chlorine-AML}} - k'_{\text{other radicals-AML}}, \quad (15)$$

where $[\text{OH}\cdot]_{\text{ss}}$ represents the steady-state concentrations of $\text{OH}\cdot$, k'_{NB} and k'_{AML} represent the pseudo-first-order rate constant of AML and NB in the UV/chlorine process, respectively. $k''_{\text{OH}\cdot-\text{AML}}$ ($10.05 \times 10^9 \text{ M}^{-1}\text{s}^{-1}$) represents the second-order rate constant for the reaction of $\text{OH}\cdot$ with AML, which was obtained by competition kinetics (Figure A1). $k'_{\text{UV-AML}}$ and $k'_{\text{other radicals-AML}}$ are the corresponding pseudo first-order rate constants of AML degradation via UV irradiation and other radicals, respectively, which can be ignored in this study due to less effect on AML [33]. $k'_{\text{chlorine-AML}}$ represents the pseudo first-order rate constants of AML degradation by chlorination ($k'_{\text{chlorine-AML}} = 0.0152 \text{ min}^{-1}$). Consequently, the calculated relative contributions of $\text{Cl}\cdot$, $\text{OH}\cdot$ and chlorine to AML degradation were 27.4%, 55.7%, and 16.9%, respectively. These results illustrated that $\text{OH}\cdot$ makes a greater contribution to AML degradation than $\text{Cl}\cdot$. Therefore, $\text{OH}\cdot$ plays the dominant role in the degradation of AML among all the radicals in the UV/chlorine process.

Figure 7. AML and NB degradation in the UV/chlorine process ($[\text{AML}]_0 = [\text{NB}]_0 = 10 \text{ }\mu\text{M}$, $[\text{chlorine}]_0 = 30 \text{ }\mu\text{M}$, UV intensity = $500 \text{ }\mu\text{W}\cdot\text{cm}^{-2}$, pH = 7).

3.8. Intermediates Identification and Degradation Mechanism

The degradation intermediates of AML in the UV/chlorine process were analyzed by HRMS Q-E Plus Orbitrap LC-MS. Based on the MS and MS² spectra, twelve degradation intermediates were obtained in both the positive and negative ion modes. The isomeric structures were also determined under different retention times with the same m/z . In addition, four small-molecule acid intermediates in the late stage of AML degradation were also identified by GC-MS. The retention time, molecular formula, and other characteristics of the identified intermediates were summarized in Tables 1–3.

Table 1. Molecular formula, retention time, high-resolution accurate masses ($[M+H]^+$) with errors (Δ), and molecular structures of AML and its degradation products detected by HRMS.

No.	Compounds	LC Retention Time (min)	Molecular Formula	$[M+H]^+$			Molecular Structures
				Theoretical m/z	Measured m/z	Δ (ppm)	
1	AML	17.73	$C_{20}H_{25}ClN_2O_5$	409.1525	409.1522	0.73
2	AML-Cl-a	11.02	$C_{20}H_{24}Cl_2N_2O_5$	443.1135	443.1135	0.01
3	AML-Cl-b	17.50	$C_{20}H_{24}Cl_2N_2O_5$	443.1135	443.1131	0.90
4	AML-OH	12.67	$C_{20}H_{25}ClN_2O_6$	425.1474	425.1472	0.47
5	IM395	11.97	$C_{19}H_{23}ClN_2O_5$	395.1368	395.1368	0.01
6	IM288	14.97	$C_{16}H_{17}NO_4$	288.1230	288.1228	0.69
7	IM102	1.15	$C_4H_7NO_2$	102.0550	102.0550	0.01
8	IM240	10.30	$C_{12}H_{14}ClNO_2$	240.0786	240.0786	0.01
9	IM117	6.60	$C_6H_{12}O_2$	117.0910	117.0910	-0.01

Different from UV alone and dark chlorine disinfection, AML degradation in the UV/chlorine process was mainly motivated by active species ($OH\bullet$ and $Cl\bullet$) [34]. Chlorine substitution reactions always lead to the occurrence of mono-chlorine or bi-chlorine substitution product. The formation of these transformation products may be due to the structural dependence of the reaction of $Cl\bullet$ with compounds (electron transfer and hydrogen atom abstraction). Extracted ion chromatograms (EICs) of AML and AML-Cl obtained by HRMS and the corresponding MS^2 spectra were shown in Figure 8. The characteristic ion peak of AML at 409.1522 m/z was detected at a retention time of 17.73 min (Figure 8a). Based on the MS^2 spectrum analysis of AML (Figure 8c), the product ion at 206.0367 m/z ($C_{11}H_8ClNO$, 0.01 ppm) was produced due to aromatization of the dihydropyridine moiety and the loss of $C_9H_{17}NO_4$ from the side chain of AML [49]. With the attack of $Cl\bullet$, two mono-chlorine substitution products were produced with responsive characteristic peaks at retention times of 11.02 min (AML-Cl-a) and 17.50 min (AML-Cl-b) (Figure 8b). The fragment ion at 128.9535 m/z was observed in MS^2 spectra of AML-Cl-a (Figure 8d) and was attributed to the cleavage of the phenyl ring ($C_{18}H_{22}N_2O_3$, -314 Da). However, the fragment ion at 286.0264 m/z observed in the MS^2 spectrum of AML-Cl-b (Figure 8e) was produced in the same way as the product ion of AML.

Table 2. Molecular formula, retention time, high-resolution accurate masses ($[M-H]^-$) with errors (Δ), and molecular structures of AML and its degradation products detected by HRMS.

No.	Compounds	LC Retention Time (min)	Molecular Formula	$[M-H]^-$			Molecular Structures
				Theoretical m/z	Measured m/z	Δ (ppm)	
1	AML	17.73	$C_{20}H_{25}ClN_2O_5$	407.1379	407.1380	−0.25
10	AML-2OH	11.71	$C_{20}H_{25}ClN_2O_7$	439.1278	439.1281	−0.68
11	IM364	13.78	$C_{18}H_{20}ClNO_5$	364.0957	364.0961	−1.09
12	IM350	12.49	$C_{17}H_{18}ClNO_5$	350.0801	350.0804	−0.86
13	IM334	13.33	$C_{17}H_{18}ClNO_4$	334.0852	334.0855	−0.89

Table 3. Intermediates of AML degradation detected by GC-MS.

No.	Products	Molecular Weight	CAS Number	GC Retention Time (min)	Molecular Structures
14	Acetic acid	60.0211	64-19-7	8.2587
15	Oxalic acid	89.9953	144-62-7	17.6322
16	Glycolic acid	76.0160	79-14-1	17.9978
17	Lactic acid	90.0316	50-21-5	20.5232

Moreover, the bi-chlorine substitution product is also a common intermediate in the UV/chlorine process [50]. However, this product was not observed in the current study. the hydroxylation reaction of AML with $OH\bullet$ could generate direct OH-adding products (AML-OH) (Table 1, Figure A2). In addition, $OH\bullet$ may further attack the benzene ring to produce dihydroxy addition product. As shown in Table 2 and Figure A2, the dihydroxy addition product at 439.1281 m/z was observed at 11.71 min (AML-2OH). Through the continuous reaction initiated by reactive species, AML and AML-Cl can further produce IM395 through de-chlorination and demethylation reactions (Table 1, Figure A2). The product of 395.1368 m/z was found at 11.97 min. Subsequently, the terminal methenamine entity on the side chain of IM395 was attacked and produced IM364 with the formula $C_{18}H_{20}ClNO_5$ at 364.0961 m/z . IM364 possibly generated IM350 with the formula $C_{17}H_{18}ClNO_5$ at 350.0804 m/z by O-demethylation of the side chain. Then, IM350 could produce IM334 with the formula $C_{17}H_{18}ClNO_4$ at 334.0855 m/z by losing a hydroxyl group. After de-chlorination and demethylation reactions, IM334 could further produce IM288 with the formula $C_{16}H_{17}NO_4$ at 288.1228 m/z . These intermediates were also detected in

two AML degradation processes of UV photolysis and UV/H₂O₂, indicating that AML was transformed in different processes with similar degradation pathways [19,51].

Figure 8. Total ion chromatogram (TIC), extracted ion chromatogram (EIC) and MS² spectra of AML and AML-Cl obtained by HRMS. (a) TIC spectrum, (b) EIC spectrum of AML at 409.1525 m/z, (c) EIC spectrum of AML-Cl at 443.1135 m/z, (d) MS² spectrum of AML, (e) MS² spectrum of AML-Cl-a, and (f) MS² spectrum of AML-Cl-b.

During the later stage of the reaction process, the benzene ring was broken by active species to generate small molecular products, such as like IM102, IM117, and IM240. GC-MS analysis also showed that small-molecule acid intermediates existed, including acetic acid, oxalic acid, glycolic acid and lactic acid (Table 3). Based on the above analysis, the reaction pathways of AML degradation by the UV/chlorine process were posed, as shown in Figure 9.

Figure 9. Reaction pathway of AML degradation by the UV/chlorine process.

3.9. Toxicity Assessment

The degradation of AML was investigated under the typical conditions of a 10 μM initial AML concentration, 500 $\mu\text{W}\cdot\text{cm}^{-2}$ UV intensity, 30 μM chlorine dose, and a pH value of 7. Toxicity analysis of the AML water samples after the UV/chlorine process was performed using *Vibrio fischeri*. Acute toxicity was evaluated by the inhibitory effects on the bioluminescence intensity of the *Vibrio fischeri*. Figure 10 shows that the inhibition rate of the initial AML water sample was 36.0%. The inhibition rate gradually increased from 36.0% to 88.4% while AML removal reached 84.7% in 50 min, implying that the removal of AML does not guarantee the reduction in ecological risk [52]. Thereafter, the inhibition rate gradually decreased and eventually dropped to 15.8% at 120 min, which indicates that the toxicity of intermediates produced in the later stage was less than that of AML. The similar conclusion was also found in the degradation of dodecyl-benzyl-dimethyl-ammonium chloride (DDBAC) [14] and carbamazepine (CBZ) [18] by the UV/chlorine process. Toxicity tests indicate that prolonged degradation would promote the detoxification of toxic intermediates. The UV/chlorine process was taken as an effective method to remove AML and reduce ecological risk [14].

Figure 10. Inhibition rate of AML degradation by the UV/chlorine process on luminescent bacteria.

The ECOSAR program (EPA, USA) was used to predict the acute toxicity (LC_{50} or EC_{50}) of organic compounds to fish, *Daphnia* and green algae (Table 4) [28,29]. The LC_{50} and EC_{50} values of the degradation intermediates AML-Cl, IM240 and IM334 were all smaller than those of AML. For example, the LC_{50} (fish, 96 h) values of AML-Cl, IM240, and IM334 were only 82.9, 19.9, and 60.7 $mg \cdot L^{-1}$, respectively, which were obviously less than that of AML (290.0 $mg \cdot L^{-1}$). These results illustrated that the degradation intermediates had greater acute toxicity than their parent AML. In addition, the LC_{50} values of other intermediates were much higher than that of AML. Among them, the LC_{50} values of IM102, acetic acid and oxalic acid were 2 orders of magnitude higher than that of AML. In accordance with the luminescence test, intermediates with lower acute toxicity than AML were formed in the later stage of AML degradation.

Table 4. Estimated acute toxicity of AML and its intermediates by ECOSAR software.

Compounds	Fish	<i>Daphnid</i>	Green Algae
	96 h- LC_{50} ($mg \cdot L^{-1}$)	48 h- LC_{50} ($mg \cdot L^{-1}$)	96 h- EC_{50} ($mg \cdot L^{-1}$)
AML	290.0	155.5	144.3
AML-Cl	82.9	50.3	46.8
AML-OH	813.5	398.3	368.5
AML-2OH	2278.7	1018.4	939.7
IM395	868.6	419.8	388.3
IM288	201.2	107.9	100.2
IM102	28,420.7	8802.8	8032.8
IM240	60.7	35.8	33.3
IM117	131.1	67.4	62.4
IM364	106.1	61.7	57.4
IM350	433.2	220.8	204.6
IM334	19.9	13.5	12.6
Acetic acid	25,785.7	12,302.4	8704.6
Oxalic acid	168,000.0	67,876.8	39,658.6
Glycolic acid	355,000.0	152,000.0	95,559.1
Lactic acid	177,000.0	79,065.5	51,783.7

Therefore, it is of great significance to further evaluate the environmental risks caused by AML degradation in the UV/chlorine process for water environmental safety in the future.

4. Conclusions

Degradation of AML in water by the UV/chlorine process was studied. The AML degradation reactions were all successfully fitted with pseudo-first-order kinetics. The combination of UV and chlorination processes significantly accelerated AML degradation compared to UV alone or dark chlorination. In addition, several factors could affect the degradation efficiency, including chlorine

dose, UV light intensity, solution initial pH value, and ammonia concentration. Chlorine dose and UV intensity positively promoted AML degradation, whereas ammonia concentration had a negative effect. Strong acidic conditions were favorable for AML degradation. AML degradation was inhibited in real water and the inhibitory effect was correlated with the presence of ammonia nitrogen and DOM. Both $\text{OH}\bullet$ and $\text{Cl}\bullet$ contributed to the degradation of AML, while $\text{OH}\bullet$ was the dominant contributor. The calculated relative contribution of $\text{OH}\bullet$ to AML degradation was 55.7%.

Twelve AML degradation products in the process were detected by HRMS Q-E Plus Orbitrap LC-MS, including a chlorine substitution product (AML-Cl) and OH-adding products (AML-OH). Four small-molecule acid intermediates were also identified by GC-MS. Serial reactions initiated by active radicals, including chlorination, hydroxylation, demethylation, and ring breaking, led to the formation of intermediates.

Luminescent tests and ECOSAR prediction revealed that complete removal of AML does not guarantee a reduction in acute toxicity, but prolonged degradation promoted the detoxification of toxic products. It can be seen that the removal of the target substance does not represent an ecological risk reduction. However, longer treatment time will increase disposal costs. If the main goal of the pilot project is to control the ecological risk of the water, process parameters enhancement must be taken in consideration. The UV/chlorine process can be regarded as a promising method to remove AML and reduce ecological risk.

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Appendix A

Table A1. General water quality parameters of the real water.

Total Phosphorus (mg·L ⁻¹)	COD (mg·L ⁻¹)	Ammonia Nitrogen (mg·L ⁻¹)	Dissolve Oxygen (mg·L ⁻¹)	Oxidation-Reduction Potential (mV)	PH Value
0.39	8.07	0.62	5.89	−27	7.2

Figure A1. AML and NB degradation in the UV/H₂O₂ process ([AML]₀ = [NB]₀ = 10 μM, [H₂O₂]₀ = 30 μM, UV intensity = 500 μW·cm⁻², pH = 7).

Figure A2. MS² spectra of intermediates obtained by HRMS. (a) MS² spectrum of AML-OH, (b) MS² spectrum of IM395, (c) MS² spectrum of IM288, (d) MS² spectrum of IM102, (e) MS² spectrum of IM240, (f) MS² spectrum of IM117, (g) MS² spectrum of AML-2OH, (h) MS² spectrum of IM364, (i) MS² spectrum of IM350, and (j) MS² spectrum of IM334.

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