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Photocatalytic degradation of three amantadine antiviral drugs as well as their eco-toxicity evolution

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ABSTRACT

Advanced oxidation processes (AOPs) relying on in situ generated highly reactive •OH are successfully applied to water purification. The absolute reaction rate constants for •OH with three antiviral drugs were first reported through pulsed radiolysis experiments. Results found that •OH reacted quickly with these substrates, with bimolecular reaction rate constants of 6.31×10^9, 5.13×10^9, and 7.05×10^9 $M^{-1}s^{-1}$ for 1-amantadine, 2-amantadine, and rimantadine, respectively. The photocatalytic degradation kinetics of substrates were followed pseudo-first-order kinetics according to Langmuir–Hinshelwood model in TiO_2 suspensions, and the apparent rate constants were obtained as 0.076, 0.084, and 0.102 min^{-1} for three antiviral drugs, respectively. Scavenger experiments revealed that •OH was the major reactive species involved in antiviral drugs degradation. To probe the photocatalytic degradation mechanism, the fate of nitrogen elements and the change of total organic carbon were also examined, and the data showed that all three drugs could be completely mineralized into CO_2, H_2O, and inorganic ions (NO_3^- and NH_4^+) without generating any detectable products with enough degradation time. To further insight into the potential adverse effect of three antiviral drugs and their degradation products, the acute aquatic toxicity of degradation solutions were evaluated at three different trophic levels, and the toxicities first increased slightly and then decreased rapidly as the total organic carbon decreased.

1. Introduction

Pharmaceuticals and personal care products (PPCPs) are emerging organic contaminates (EOCs) that have attracted extensive attention recently due to their occurrence in waters [1,2]. Personal care products are washed directly into the wastewater streams, while a significant portion of pharmaceuticals also enter aquatic environments as both the original forms and metabolized products after use and excretion. Although PPCPs are commonly presented at low concentration (typically ng–μg L^{-1}), they constitute an important concern due to their potential risks to aquatic ecological systems and human health even at trace levels [3–5].

Amantadine and its associated drug, rimantadine, have been approved to protect and treat influenza and Parkinsonism for several decades [6,7]. Both of them are primarily used as therapeutic influenza drugs of people and used as additive drugs for various livestock [8,9]. Both drugs have been widely used in the developing countries, because they are the cheapest ones against flu and affordable drugs. The extensive usage provides a continuous release of them to the water environment, but it is difficult to eliminate these EOCs by traditional wastewater treatment technologies [10,11]. Furthermore, their degradation as well as their potential risk to aquatic ecological systems have never been attempted, although amantadine was known to cause several pharmacologic effects on the central nervous system stimulation at relatively high dose [12].

Advanced oxidation processes (AOPs), based on the production of hydroxyl radical (•OH) as the main oxidative species, can successfully degrade most organic contaminants. Among various AOPs, TiO_2 heterogeneous photocatalysis has been proved to be a promising destructive technology to decontaminate water-soluble refractory pharmaceuticals efficiently and cost-effectively [13,14], due to the process can be carried out under mild condition [15]. The possibilities as well as the mechanisms of the photocatalytic degradation of some pharmaceuticals have been reported [16,17].

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However, most studies were mainly focused on the elimination of parental compounds [17–19], although some degradation products were identified to be more toxicity to the aquatic ecosystems and the public health [20]. Thus, the assessments of possible adverse effects of degradation products on environment are very essential. To our knowledge, the works concerning the photocatalytic decomposition of amantadine and rimantadine in water was never attempted until now. Therefore, their photocatalytic transformation kinetics and mechanism in AOPs, as well as the risk assessment of degradation products are of great concern during the photocatalytic process.

With these backgrounds, the photocatalytic degradation kinetics of three antiviral drugs with the protonation and neutral forms are systematically studied under UV irradiation. In addition, the contribution of different reactive oxygen species to the photocatalytic degradation of substrates is also examined to properly understand its environmental fate and transformation mechanism using different scavengers' addition. Finally, the ecotoxicity risks of three antiviral drugs as well as its degradation products were assessed at three different tropic levels as the total organic carbon decreased slowly.

2. Materials and methods

2.1. Materials

1-Amantadine, 2-amantadine, rimantadine (the structure as shown in Scheme S1) and dansyl chloride (≥99% purity) were purchased from Tokyo Chemical Industry Co., Ltd. Titanium dioxide (TiO_2, P25, Degussa AG, Germany) was used as the photocatalyst. Luminescent bacterium *Ptotobacterium phosphoreum* (*P. phosphoreum*) was purchased from the Institute of Soil Science, Chinese Academy of Sciences (CAS), China. *Selenastrum capricornutum* (*S. capricornutum*) and monoclonal *Daphnia magna* (*D. magna*) were kindly provided by Prof. Xiangping Nie, Institute of Hydrobiology, Jinan University, China. All the solutions were prepared using HPLC grade water, which was obtained by the Milli-Q system by constant illumination with a xenon arc lamp at 172 nm to keep total organic carbon concentration below 13 $\mu g\,L^{-1}$. Methanol and acetonitrile (HPLC grade) obtained from Sigma were used as solvent, and all other chemicals used were of at least analytical-reagent grade.

2.2. Determination of •OH reaction rates

Bimolecular rate constants of •OH reaction with three antiviral drugs were determined using pulse radiolysis with competition kinetic model at Notre Dame Radiation Laboratory (NDRL), with the 8-Mev Titan Beta model TBS-8/16-1S linear accelerator. Dosimetry was performed using N_2O-saturated 0.87 mM KSCN solutions at $\lambda = 472$ nm, with average doses of 3–5 Gy per 2–3 ns pulse. The radiolysis of water is described in Eq. (1), where the numbers in the parentheses are the G-values in $\mu M\,J^{-1}$. All the experimental data were determined by averaging 8–12 replicate pulses using the continuous flow mode of the instrument.

$$H_2O \rightarrow e^-_{aq}[2.7] + {}^{\bullet}H[0.55] + {}^{\bullet}OH[2.7] + H_2[0.45] + H_2O_2[0.71] + H^+[2.7] \quad (1)$$

2.3. Photocatalytic degradation experiments and toxicity assays

The photocatalytic degradation was carried out in an open Pyrex reactor (150 mL, Fig. S1) with a double-walled cooling-water jacket to maintain the constant temperature of the solution ($25 \pm 1\,^{\circ}C$) throughout the experiment. The light source was a high-pressure mercury lamp (GGZ-125, Shanghai Yaming Lighting, $E_{max} = 365$ nm) with a power consumption 125 W, which paralleled to the photocatalytic reactor. The UV light intensity at the surface of the reactor was controlled at 0.36 mW/cm^2, measured with an UV-irradiance meter (UV-A, Beijing Normal University). A 150 mL solution (100 μM) of substrate and certain amount of TiO_2 was added into the reactor according to the experimental designed values. Prior to illumination, the suspension was stirred in the dark for 30 min to achieve the adsorption equilibrium. Then the light was turned on, signaling the start of photocatalysis. At given time intervals, 3 mL treated solution was sampled, and filtered through 0.22 μm Millipore filters to remove TiO_2 particles for further analysis.

The ecotoxicities of treated drug solution were evaluated at three trophic levels: *P. phosphoreum*, *S. capricornutum* and *D. magna*. The detailed procedure can refer to our previous publications [21,22]. For the toxicity bioassay with *P. phosphoreum*, the luminescence was determined with Dxy-3 analyzer (Nanjing Kuake, China), and the toxicity was determined after 15 min incubation. *S. capricornutum* bioassay was carried out according to the Organization for Economic Co-operation and Development (OECD) guideline for alga growth inhibition test No. 201, and the measurement of algal biomass at different exposure times was done by manual cell counting under microscope. *D. magna* bioassay was carried out according to the OECD guideline for *D. magna* acute immobilization test No. 202. The neonates (<24 h hold) of *D. magna* were used in all toxicity assay and 10 animals were used at each treatment in Pyrex beakers containing 50 mL of the test solution. Toxicological endpoint was the immobilization after 24 and 48 h exposure to the treated drug solutions and the definition of immobilization is that daphnia are not able to swim within 15 s after gentle agitation of the test vessel. All the degradation and toxicity assessment experiments were replicated in triplicate.

2.4. Analysis procedure

The analysis of three antiviral drugs was performed with Agilent 1200 series high-performance liquid chromatography (HPLC) equipped with a florescent detector after they were derived with dansyl chloride as shown in Scheme S2. Derivation procedure is shown as follows: The 500 μL dansyl chloride solution was added to 500 μL aliquot of 1-amantadine, 2-amantadine or rimantadine solution and optimized to pH 9.0 as shown in Fig. S2, with sodium bicarbonate–sodium hydroxide buffer solution. The mixture was vortexed and incubated in air bath at 50 °C for 60 min. After the derivation, conditions optimized and shown in Fig. S3, the solution was subjected to HPLC analysis.

HPLC analysis: The concentrations of derivatives were analyzed by Agilent 1200 series HPLC system under the following conditions: Agilent XDB-C18 Eclipse (4.6 × 150, 5 μm particle size) performed at 30 °C. The mobile phases used were water (A) and acetonitrile (B) at flow rate of 1 mL min^{-1}, with the linear gradient elution set as following: 0 min 20% B, 3 min 40% B, 4 min 70% B, 5 min 90% B, 11 min 90% B and 12 min 20% B. The fluorescence detection was setup as excitation at 320 nm and emission at 523 nm.

Ion chromatography (IC): A Dionex ion chromatograph (ICS-900) equipped with a conductivity detector was used for determination of NH_4^+ and NO_3^-. For NH_4^+, the separation was performed on an Ion Pac CS12A (4 × 250 mm, Dionex) column, and 11 mM H_2SO_4 was used as eluent at flow rate of 1.0 mL min^{-1}. For NO_3^-, the separation was performed on an Ion-Pac AS23 anion column (4 × 250 mm, Dionex), and a mixture of sodium carbonate (4.5 mM)/sodium bicarbonate (0.8 mM) was used as eluent at a flow rate of 1.0 mL min^{-1}.

Total organic carbon (TOC): TOC contents of samples were measured with a Shimadzu TOC-5000 analyzer (catalytic oxidation