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Ozonation of ranitidine: Effect of experimental parameters and identification of transformation products

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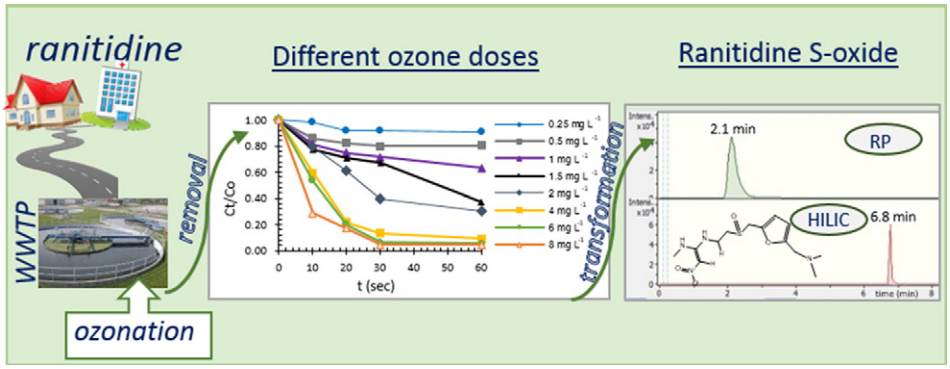
HIGHLIGHTS

- O_3 initial concentration is the most critical parameter for ranitidine removal.
- Alkaline pH of the solution promotes removal and overall mineralization.
- 11 TPs of ranitidine were detected and structurally elucidated by LC-Q-ToF-MS.
- Both HILIC and RPLC were used as a holistic approach for TPs identification.
- Retention time prediction was used as a supporting tool for TPs identification.

GRAPHICAL ABSTRACT



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ABSTRACT

This study focuses on the effect of experimental parameters on the removal of ranitidine (RAN) during ozonation and the identification of the formed transformation products (TPs). The influence of pH value, the initial concentrations, the inorganic and the organic matter on RAN's removal were evaluated. Results indicated high reactivity of RAN with molecular aqueous ozone. Initial ozone concentration and pH were proven the major process parameters. Alkaline pH values promoted degradation and overall mineralization. Dissolved organic matter reacts competitively to RAN with the oxidants (ozone and/or radicals), influencing the target compound's removal. The presence of inorganic ions in the matrix did not seem to affect RAN ozonation. A total of eleven TPs were identified and structurally elucidated, with the complementary use of both Reversed Phase (RP) and Hydrophilic Interaction Liquid Chromatography (HILIC) quadrupole time of flight tandem mass spectrometry (Q-ToF-MS/MS). Most of the TPs (TP-304, TP-315b, TP-299b, TP-333, TP-283) were generated by the attack of ozone at the double bond or the adjacent secondary amine, with the abstraction of NO_2 moiety, forming TPs with an aldehyde group and an imine bond. Oxidized derivatives with a carboxylic group (TP-315a, TP-331a, TP-331b, TP-299a) were also formed. RAN S-oxide was identified as an ozonation TP (TP-330) and its structure was confirmed through the analysis of a reference standard. TP-214 was also produced during ozonation, through the C—N bond rupture adjacent to the NO_2 moiety. HILIC was used complementary to RP, either for the separation and identification of TPs with isomeric structures that may have been co-eluted in RPLC or for the detection of new TPs that were not eluted in the RP chromatographic system. Retention time prediction was used as a supporting tool for the identification of TPs and results were in accordance with the experimental ones in both RP and HILIC.

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1. Introduction

Recent studies have shown that numerous pharmaceuticals have been introduced into the environment, mainly through anthropogenic sources of pollution (Huerta-Fontela et al., 2011). These compounds, after being discharged from wastewater treatment plants (WWTPs), are detected in the environment at various concentration levels (from ng to μg per liter) depending on their water solubility, physicochemical characteristics, local consumption rates and biodegradability (Borova et al., 2014; Thomaidi et al., 2015; Vieno et al., 2007; Ziylan and Ince, 2011). Many micropollutants are not entirely removed even through wastewater or drinking water treatment processes, thus they are consequently detected at various concentrations in drinking water supplies (Kumar and Xagoraraki, 2010; Zuccato et al., 2005).

Various oxidation processes have been proposed, studied and applied for the removal of emerging pollutants and they have shown increased ability to significantly degrade or transform selected micropollutants (Ikehata et al., 2006). Ozonation has been proven to be an effective, robust and widely accepted oxidation technique (Gerrity and Snyder, 2011; Hey et al., 2014), where oxidative degradation occurs mainly through direct reaction with aqueous ozone or through indirect reaction with ozone decay products (mainly hydroxyl radicals). Ozonation has been also applied for the disinfection of drinking water (Ternes et al., 2002), wastewater (Ternes et al., 2003; Yargeau and Leclair, 2007) and hospital effluents (Vasconcelos et al., 2009).

Although the degradation or removal of many pollutants may be significant, often total mineralization is not achieved. As a consequence, transformation products (TPs), which may be more toxic than their parent compounds, may be produced. So, over the last decade, the detection, identification and toxicity assessment of the produced TPs is a field of growing interest. The development of high resolution mass spectrometers and sophisticated computer tools, have enabled this achievement (Bletsou et al., 2015).

Molecular ozone selectively attacks organic compounds with high electron density functional groups, such as double bonds, activated aromatic rings, amines and thioethers. Hydroxyl radicals, produced during the decomposition of ozone in water, could lead to further oxidative non-selective reactions (von Gunten, 2003). For an overall study of the degradation caused by ozonation processes, a kinetic study is useful, since it offers a time-dependent view of the pollutants' remediation.

Ranitidine (RAN) is commonly used in the treatment of ulcer, gastrointestinal hypersecretory conditions and gastroesophageal refluxes (common trade names: Zantac, Taladine, Nu-Ranit, Raniplex), pKa values 8.13 and 1.95 (Dumanović et al., 1997; Rivas et al., 2009) and log K_{ow} 0.27 (Dasenaki and Thomaidis, 2015a). RAN acts as a histamine H_2-receptor antagonist due to the furan ring present in its structure (Chung et al., 2000; Henry et al., 1980). The occurrence of RAN in surface waters and wastewaters has already been reported in several studies (Castiglioni et al., 2005; Conley et al., 2008; Fent et al., 2006). RAN was found in the effluents of STPs in Greece at a median level of 1059 ng L^{-1} (Dasenaki and Thomaidis, 2015b) and in river waters of Spain at a median concentration of 396.5 ng L^{-1} (Valcárcel et al., 2011). It is excreted partly as an untransformed (30–70%) compound in urine and partly as its main metabolites, RAN *N*-oxide, *N*-desmethyl RAN and RAN S-oxide (Carey et al., 1981; Martin et al., 1981), in urine and feces.

The removal of RAN in ultrapure water and wastewater samples has already been studied through the application of electrochemical processes (Carlesi Jara et al., 2007), ozonation competitive kinetics (Rivas et al., 2009), photochemical oxidation (Latch et al., 2003), photolysis (Jamrógiewicz and Wielgomas, 2013) and solar photocatalysis (Radjenović et al., 2010). RAN structure encompasses multiple reactive sites that are labile to ozone oxidation (*e.g.* amine, conjugated diene, sulfide and electron-rich alkene group) (Radjenović et al., 2010). However, the degradation and TP formation of RAN through an ozonation process has not been extensively studied. Furthermore, the identification of TPs is crucial for the determination of the removal pathway.

The objective of this study was the systematic investigation of RAN removal in water, using a lab-scale ozonation apparatus. Focus was given on the effect of various operational parameters (pH value, initial concentration of oxidant and analyte, matrix effect as well as the presence of organic matter) on the removal of the compound. Furthermore, the main TPs were detected, identified and structurally elucidated, using liquid chromatography coupled with quadrupole-time-of-flight tandem mass spectrometry (LC-Q-ToF/MS). Two complementary chromatographic systems were used for the analysis, RPLC and HILIC, in order to investigate their complementarity for the detection of additional compounds. The hierarching hypothesis behind the use of HILIC is that polar TPs are well-retained in HILIC with higher sensitivity, additional retention mechanisms may lead to the separation of isomeric TPs, thus increased selectivity is achieved (better and clearer MS/MS information and higher confidence in identification). In-house developed Quantitative Structure–Retention Relationship (QSRR) prediction models were also used to support identification.

2. Materials and methods

2.1. Standards and reagents

Ranitidine hydrochloride (CAS 66357-59-3), (≥98% HPLC) was purchased by Sigma-Aldrich, Germany. The reference standards of Ranitidine S-oxide and Ranitidine N-oxide solutions (1000 mg L^{-1} in methanol) were donated by the Swiss Federal Institute of Aquatic Science and Technology (Eawag, Department of Environmental Chemistry). Hydrochloric acid (37.0–38.0 wt%, ACS grade) and sodium hydroxide (>99%, ACS grade) were supplied by Merck, Germany. K_2SO_4 (>99%), Na_2SO_4 (>99%), $NaHCO_3$ (>99%), $CaCl_2 \cdot 2H_2O$ (>99%) and $MgCl_2 \cdot 6H_2O$ (>99%) were supplied by Fluka, Germany. Formic acid (LC-MS Ultra) was provided by Fluka Analytical, Sigma-Aldrich, Germany. LC-MS ultrapure water was produced on site using a Milli-Q water purification system (18.2 μΩ/cm, Millipore Direct-Q UV, Bedford, MA, USA). Methanol (MeOH for HPLC, M/4056/17) was provided by Fisher Scientific, Germany. MeOH LC-MS grade was purchased from Merck (Darmstadt, Germany). Acetonitrile (ACN, LC-MS grade) for LC-Q-ToFMS analysis was provided by Merck. Ammonium formate and ammonium acetate were purchased from Fluka (Buchs, Switzerland). For the experiments including DOM, humic acid (CAS 0001415936 (technical grade) was used, which was purchased by Sigma-Aldrich (Germany).

2.2. Experimental setup

The ozonation experiments were carried out as follows. Ozone was produced from industrial/biomedical grade oxygen (99.5%, Revival Bottled Gas, Athens, Greece) using AZCOZON VMUS-2 ozone generator, by AZCO Industries Ltd (Canada). The gas flow rate was kept constant at 40 L h^{-1} and dosed through a sintered sparger at the bottom of a 1 L glass reactor, which was placed in a bucket filled with ice. A saturated ozone stock solution (20–25 mg L^{-1}) was prepared daily. The concentration of dissolved ozone in stock solution was determined by direct absorption determination at 258 nm ($\varepsilon = 2700$ cm^{-1} mol^{-1} L) (Bader and Hoigne, 1981).

Ozonation experiments were conducted in sealed bottles by mixing a predefined amount of the ozone saturated solution with an aqueous solution of RAN, in order to obtain the desirable aqueous ozone concentration. An aliquot was taken before the addition of ozone, representing the zero-time sample. During the course of experiments, samples were withdrawn at predefined time points and were added into vials containing KI for the immediate quenching of the reaction. Initial experiments, which lasted 30 min, showed that RAN ozonation reaction is very fast,