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N-nitrosodimethylamine formation from ozonation of chlorpheniramine: Influencing factors and transformation mechanism

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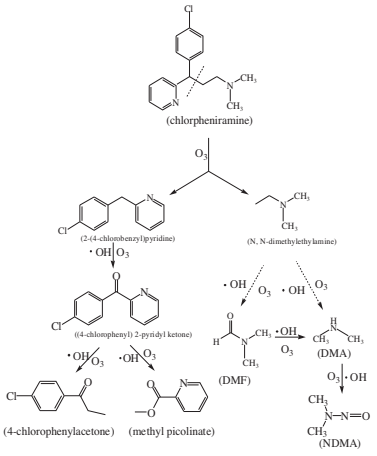
HIGHLIGHTS

- Ozone is effective for chlorpheniramine removal but NDMA is formed.
- DMA and DMF generated from chlorpheniramine ozonation contribute to NDMA formation.
- Ozone plays a dominant role in the initial decomposition of chlorpheniramine.
- •OH plays a critical role in NDMA formation and degradation.
- NDMA formation pathway from chlorpheniramine ozonation is proposed.

GRAPHICAL ABSTRACT



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ABSTRACT

As a disinfection byproduct, the detection of *N*-nitrosodimethylamine (NDMA) in aquatic environments across the globe has caused widespread concern due to its potential carcinogenicity. In this study, the possibility of NDMA formation from chlorpheniramine ozonation was investigated. The influencing factors including the initial chlorpheniramine concentration, ozone dose, pH, and water matrix were quantified. Furthermore, the mechanisms for chlorpheniramine transformation and NDMA formation were explored. Our results demonstrate that ozonation is effective in removing chlorpheniramine. Generation of dimethylamine (DMA) and NDMA was observed during chlorpheniramine ozonation. Higher initial chlorpheniramine concentration and ozone dose resulted in higher production of NDMA. Acidic conditions ($pH \leq 5$) did not facilitate the production of NDMA. Ozone molecules played a dominant role in chlorpheniramine degradation, and influenced DMA release and NDMA formation. DMA and NDMA generations as well as their degradations were mainly attributed to hydroxyl radicals (•OH) produced by ozone decomposition. Water matrix properties such as HCO_3^- and humic acid affected DMA and NDMA generation due to •OH competition. The degradation intermediates of chlorpheniramine were identified, among which only the intermediates with a DMA group were attributable to NDMA formation. A possible pathway for NDMA formation from chlorpheniramine ozonation is proposed.

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1. Introduction

Over the last decade, *N*-nitrosodimethylamine (NDMA) has caused widespread concern as a disinfection byproduct (DBP) associated with the practice of chloramination [1–3]. NDMA has been detected in surface and ground waters, in wastewater, as well as in drinking water [4]. As a suspected carcinogen, NDMA is regulated in drinking water by the US and EU [2,5,6]. The Drinking Water Inspectorate of England and Wales mandates that NDMA cannot exceed 1 ng/L [7]. The state of California has established a drinking water notification level of 10 ng/L for NDMA [8]. Health Canada has proposed a maximum acceptable concentration of 40 ng/L for NDMA in drinking water [9].

Besides chloramination, other chemical disinfection techniques such as chlorination have been reported to cause NDMA formation [10,11]. Several studies also revealed NDMA formation during ozonation treatment of water [12–14]. Andrzejewski et al. [13] reported that NDMA was formed during ozonation of DMA-containing waters. Oya et al. [14] demonstrated the formation of NDMA by ozonation of dyes. However, the mechanism of NDMA formation by ozonation has not been well identified.

Regardless of the disinfectant used, potential precursors play a key role in NDMA formation. Dimethylamine (DMA) was thought to be the dominant precursor of NDMA owing to the similar dimethylamine function group. Tertiary amines and quaternary amines with dimethylamine function groups have also been implicated with NDMA formation during disinfection [15,16]. These include fungicides and herbicides [12,17], polyelectrolytes and anion exchange resins [18–20], and key components in consumer products [21]. Recently, pharmaceuticals and personal care products (PPCPs) containing dimethylamine groups have been found to produce an exceptionally high yield of NDMA during chloramine disinfection [22–24]. Krasner [25] reported that amine-based pharmaceuticals might be components of the NDMA precursors. Shen and Andrews [23] also demonstrated the transformation of 20 selected PPCPs to nitrosamines during chloramination. However, few studies have been conducted to investigate the performance of pharmaceuticals during other disinfection processes. On the other hand, PPCPs as emerging contaminants have gained significant attention in recent years with their frequent detection in the aquatic environment [26,27]. Advanced oxidation processes (AOP) have been applied in the removal of PPCPs due to their strong oxidation abilities [28–31]. Nevertheless, little information was reported regarding the NDMA formation potential of the amine-based pharmaceuticals under ozone treatment.

Chlorpheniramine, 3-(4-chlorophenyl)-*N*,*N*-dimethyl-3-pyridin-2-yl-propan-1-amine, is a first-generation alkylamine antihistamine widely used for preventing the symptoms of allergic conditions [32]. Although reports of chlorpheniramine identification in wastewater treatment plants (WWTPs) have been rare, its qualitative identification was confirmed in a WWTP in New York [33]. Chlorpheniramine was also targeted as one of the priority pharmaceuticals for future study [34]. Furthermore, chlorpheniramine has been demonstrated to be a potential NDMA precursor with higher than 1% molar conversion during chloramination [23]. However, the behavior of chlorpheniramine during ozonation has not yet been reported.

In this study, the possibility of NDMA formation during ozone treatment of chlorpheniramine was investigated. The research focused on the effects of ozone dose, pH, and water matrix. Efforts were also made to identify the degradation products during ozonation of chlorpheniramine, and a transformation pathway for NDMA formation is proposed.

2. Materials and methods

2.1. Chemicals

NDMA, NDMA-d6, DMA, and *N*-dimethylformamide (DMF) were obtained from Chem Service Inc. (West Chester, PA, USA). Chlorpheniramine maleate, and phenyl isothiocyanate were obtained from Sigma–Aldrich (Milwaukee, WI, USA). Tert-Butanol (TBA) and humic acid (HA) were obtained from Sigma Chemical Co. (St. Louis, MO, USA). Ultrapure water prepared with a Gradient A10 water purification system was used (Millipore, Bedford, MA, USA). All other reagents were of analytical grade.

2.2. Ozonation experiments

Ozonation experiments were performed in a sealed cylindrical reactor with a working volume of 5 L. The reactor was stirred mildly and set in the dark at room temperature ($24 \pm 1\,^{\circ}C$). Fresh ozone was produced by a laboratory ozonizer (JiuYu, Shanghai, China) connected to dry oxygen. Once the gas concentration reached steady-state, ozone was introduced to the reactor through a ceramic sparger. In order to investigate NDMA formation during the ozonation of chlorpheniramine, the initial chlorpheniramine concentration was set in the range of 2–20 mg/L. Water solution containing the target compound was continuously ozonated for 30 min. All water solutions, unless otherwise specified, were prepared using a buffer solution with a pH of 7.6 (5 mM phosphate and 1 mM carbonate). The gas flow rate and the concentration of ozone in the outgoing gas were monitored during ozonation. Solution samples were collected at different reaction time intervals and quenched by addition of 1 mL Na_2SO_3 solution (0.1 mM). All experiments were performed in triplicate.

The experiments evaluating the effect of ozone dose on chlorpheniramine degradation were conducted by bubbling gaseous ozone at different concentrations into the chlorpheniramine solution. Five ozone doses were examined:16, 22.5, 37.2, 58.0, and 74.4 mg/min. Tests for the impact of pH levels of 5, 6, 7, 8, and 9 were carried out by altering the solution pH value with phosphate buffer. The influence of water matrix including HCO_3^- and HA was studied with the addition of $NaHCO_3$ and HA solution, respectively. Ozonation with natural water was also carried out under the same conditions. The natural water was taken from Huangpu River (HPR water) which is located in Shanghai, China. The characteristics of HPR water quality are listed in Table S1. The HPR water was filtered (0.45 mm cellulose nitrate) within 24 h after sampling and stored at 4 °C until use.

In order to investigate the role of hydroxyl radicals (•OH) during chlorpheniramine ozonation, •OH inhibition experiments were carried out with the same procedure as the other treatments except that TBA was added to consume •OH.

The maximum yields of NDMA and DMA during 30 min of ozonation were calculated using Eqs. (1) and (2), respectively.

$$Y_{NDMA-m}(\%) = \frac{[NDMA]_m}{[M]_0} \times 100\% \quad (1)$$

$Y_{DMA}(\%) = \frac{[DMA]_m}{[M]_0} \times 100\%$(2)where $[NDMA]_m$ (mmol/L) and $[DMA]_m$ (mmol/L) are the maximum values of NDMA and DMA concentrations respectively formed during 30 min of ozonation. $[M]_0$ (mmol/L) represents the initial concentration of the target compound that can result in NDMA or DMA formation during ozonation.

2.3. Analytical methods

Chlorpheniramine and DMF concentrations were measured using high performance liquid chromatography (HPLC) with