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Characterization of N-nitrosodimethylamine formation from the ozonation of ranitidine

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ABSTRACT

N-nitrosodimethylamine (NDMA) is an emerging disinfection by-product which is formed during water disinfection in the presence of amine-based precursors. Ranitidine, as one kind of amine-based pharmaceuticals, has been identified as NDMA precursor with high NDMA molar conversion during chloramination. This study focused on the characterization of NDMA formation during ozonation of ranitidine. Influences of operational variables (ozone dose, pH value) and water matrix on NDMA generation as well as ranitidine degradation were evaluated. The results indicate high reactivity of ranitidine with ozone. Dimethylamine (DMA) and NDMA were generated due to ranitidine oxidation. High pH value caused more NDMA accumulation. NDMA formation was inhibited under acid conditions (pH ≤ 5) mainly due to the protonation of amines. Water matrix such as HCO_3^- and humic acid impacted NDMA generation due to .OH scavenging. Compared with .OH, ozone molecules dominated the productions of DMA and NDMA. However, .OH was a critical factor in NDMA degradation. Transformation products of ranitidine during ozonation were identified using gas chromatography–mass spectrometry. Among these products, just DMA and N,N-dimethylformamide could contribute to NDMA formation due to the DMA group in the molecular structures. The NDMA formation pathway from ranitidine ozonation was also proposed.

Introduction

N-nitrosodimethylamine (NDMA), as a disinfection by-product (DBP) associated with chloramination, has drawn the most attention due to its high lifetime cancer risk level and its frequent detection in the aquatic environment, especially in the drinking water (Choi and Valentine, 2001; US EPA, 2002; Mitch et al., 2003; Le et al., 2011). NDMA has been regulated in drinking water in US, Canada and EU due to its carcinogenicity (EU, 1998; US EPA, 1998; Health Canada, 2010).

Since the potential precursors of NDMA in wastewater are the main cause of NDMA formation, lots of efforts have been made on identification and characterization of NDMA precursors. In municipal wastewater, dimethylamine (DMA) was reported to be the primary NDMA precursor owing to the similar DMA function group. However, low DMA concentration present in wastewater and low NDMA molar conversion of DMA (0.082%–3%) (Lee et al., 2007) indicate that the contribution of DMA in NDMA formation is not as significant as expected. Subsequently, tertiary amines and quaternary amines with

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DMA function groups were verified to be associated with NDMA formation during disinfection (Gerecke and Sedlak, 2003; Chen and Valentine, 2007), including polyelectrolytes and anion exchange resins applied for wastewater treatment (Kohut and Andrews, 2003; Mitch and Sedlak, 2004; Padhye et al., 2011), fungicides and herbicides related with agriculture (Chen and Young, 2008; Schmidt and Brauch, 2008), and key components in consumer products (Kemper et al., 2010). Recently, there is an increasing focus on pharmaceuticals and personal care products (PPCPs) containing DMA groups, which were proved to be NDMA precursors with an exceptionally high NDMA molecular conversion during chloramine disinfection (Schmidt et al., 2006; Shen and Andrews, 2010; Selbes et al., 2013). Among these PPCPs, ranitidine is a much more potential precursor, with a very high NDMA molar conversion of 89.9%–94.2% (Shen and Andrews, 2010). Ranitidine, N-(2-[[5-dimethylamino-methyl]-2-furanil]-methylthioethyl)N-ethyl-nitro-1, 1-diamino ethane), is widely used in the treatment of peptic ulcer and gastroesophageal reflux diseases, which remains in the top 15 sold-list of prescribed drugs in European countries (Fent et al., 2006). As a histamine H_2-receptor antagonist, only 30% of a dose of ranitidine is metabolized by the human body, and up to 70% of the dose is excreted in urine as unchanged drug (Rivas et al., 2009). Ranitidine has been detected in the surface water and wastewater in US and Europe (Kolpin et al., 2002; Gros et al., 2007). It was found in the effluents of wastewater treatment plants in Greece at a median level of 1059 ng/L (Dasenaki and Thomaidis, 2015). As an emerging pollutant, the performance of ranitidine during disinfection needs to be traced.

NDMA formation from ranitidine during chloramination disinfection was first investigated, including kinetics of ranitidine decomposition and NDMA formation mechanism (Shen and Andrews, 2011; Roux et al., 2012). Then the subsequent studies revealed that ranitidine can also serve as an NDMA precursor during disinfection using free chlorine and chlorine dioxide (Zhang et al., 2014). Recently, pre-oxidation with ozone, chlorine and other oxidants has been tested to decrease the NDMA formation potential (NDMAFP) of ranitidine (Selbes et al., 2014; Wang et al., 2015; Jeon et al., 2016). The results of these studies confirmed that ozonation was effective in reducing the NDMA formation in the post-chloramination process by ranitidine oxidation, but the direct generation of NDMA by ranitidine ozonation was ignored. Since NDMA cannot be removed during chloramination process, NDMA produced by pre-oxidation may pose a direct threat to receiving water body whether it was disinfected by chloramines subsequently or not. On the other hand, ozonation has been proven to be an effective and widely accepted oxidation technique for drinking water and wastewater treatment, through direct oxidation by ozone molecules and indirect oxidation by ozone decay products (mainly hydroxyl radicals). It has been widely applied in drinking water and wastewater treatment plants. In fact, it has been demonstrated that ranitidine is highly reactive with molecular aqueous ozone (Rivas et al., 2009; Christophoridis et al., 2016). However, NDMA formation from the ozonation of ranitidine has not yet been clarified thoroughly. Especially, the intermediate products related to NDMA formation during ranitidine oxidation are not clearly known.

In this paper, the characteristics of NDMA formation during ranitidine ozonation were investigated. Focus was given on the effects of several operational parameters (pH value, ozone dose), and water matrix on ranitidine removal, especially on NDMA generation. In addition, the NDMA generation pathway is proposed based on identification of the degradation products during ranitidine ozonation.

1. Materials and methods

1.1. Chemicals

NDMA-d_6, NDMA, DMA, and N,N-dimethylformamide (DMF) were purchased from Chem Service Inc. (West Chester, PA, USA). Ranitidine, phenyl isothiocyanate and ammonium dihydrogen phosphate were obtained from Sigma-Aldrich (Milwaukee, WI, USA). Methanol, methylene dichloride, tert-butanol (TBA), acetonitrile and humic acid (HA) were obtained from Sigma Chemical Co. (St. Louis, MO, USA). All reagents used without further purification. Ultrapure (UP) water was prepared with a Gradient A10 water purification system (Millipore, Bedford, MA, USA).

1.2. Ozonation experiments procedure

Ozonation experiments were carried out in a sealed cylindrical reactor with a working volume of 5 L. The procedure for ozonation experiments was similar to that used in our previous study (Lv et al., 2015). Fresh ozone was produced from a laboratory ozone generator (JiuYu, Shanghai, China), which was connected to dry oxygen. Once the gas concentration remained stable, ozone was introduced to the reactor through a ceramic sparger. Considering the lower detection limit of NDMA, the initial ranitidine concentration of the solution was set in the range of 2–20 mg/L to investigate NDMA formation during ranitidine ozonation. The solution was continuously ozonated for 30 min. All water solutions were prepared using a buffer solution (5 mmol/L phosphate and 1 mmol/L carbonate prepared with UP water of pH 7.6) except stated. Water samples were withdrawn at predefined time points and quenched by addition of 1 mL Na_2SO_3 solution (0.1 mmol/L). All experiments were performed in triplicate.

To study the influence of ozone dose on ranitidine removal, experiments were conducted by bubbling gaseous ozone at different concentrations into the solution. The gas flow rate was kept constant at 3 L/min, four ozone doses (7.5, 12.4, 19.3, and 24.8 mg/L) were tested. The pH of the solution plays an important role in the ozone decomposition and hydroxyl radical (.OH) generation. Thus, the impact of pH was studied in the range of 5–9 in the presence of phosphate buffer. .OH inhibition experiments were performed to investigate the role of .OH and the pathway of NDMA formation during ranitidine ozonation. The experiments were carried out according to the same procedure used in the previous ozonation experiments (Lv et al., 2015).

Moreover, the influence of water matrix was also examined with the addition of HA and $NaHCO_3$ solution, respectively. Ozonation experiments were also conducted in natural water under the same conditions. The natural water was taken from Huangpu River (HPR water) which is located

in Shanghai, China. The HPR water was characterized by a pH of 7.45 ± 0.1, a dissolved organic carbon (DOC) concentration of 53.2 ± 0.1 mg/L, and an alkalinity (HCO_3^-) of 350 mg/L. HPR water was filtered (0.45 mm cellulose nitrate) within 24 hr after sampling and then used for the ozonation experiments.

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

$$Y_{NDNMA-m} = \frac{C_{NDMA_m}}{C_{M0}} \times 100\% \quad (1)$$

$$Y_{DMA-m} = \frac{C_{DMA_m}}{C_{M_0}} \times 100\% \quad (2)$$

where C_{NDMAm} (mmol/L) and C_{DMAm} (mmol/L) represent the maximum values of NDMA and DMA concentrations respectively formed during 30 min of ozonation. C_{M0} (mmol/L) is the initial concentration of the target compound.

1.3. Analytical methods

NDMA was quantified using solid-phase extraction (SPE) (Munch and Bassett, 2004) followed by ultra performance liquid chromatography/electrospray ionization tandem mass spectrometry (UPLC–ESI–MS) (Thermo, USA). The UPLC–ESI/MS methods have been described previously (Lv et al., 2013). An Eclipse XDB C18 column (150 mm × 2.1 mm, 3.5 μm; Agilent) was used for separation. The method detection limit (MDL) for NDMA was 4 ng/L, and the recovery of NDMA was 82% ± 5%.

DMA concentration was determined by high performance liquid chromatography (HPLC, Agilent 1200 Series) with ultraviolet (UV) detection at 240 nm after pre-column derivatization with phenyl isothiocyanate (Sahasrabuddhey et al., 1999). DMF and ranitidine concentrations were measured using HPLC with UV detection at 200 and 210 nm (Wang et al., 2014; Zhang et al., 2014), respectively. Separation was performed on a Kromasil C18 column (250 mm × 4.6 mm, 5 μm; Akzo Nobel Co., Sweden) with the injection volume of 50 μL and the flow rate of eluent at 1 mL/min at 30°C.

Degradation products of ranitidine were identified using a gas chromatography–mass spectrometry (GC/MS) system (Agilent 7890GC-5975 MS, USA). Samples (150 mL) were collected when ozonation was completed, then extracted and concentrated (Lv et al., 2013). The separation of the products was achieved using a fused-silica capillary column (WAX-17MS, 30.0 m × 0.25 mm × 0.25 μm). The column temperature was controlled as follows: kept at 50°C for 2 min, heated to 120°C in 40°C/min increments, heated to 300°C in 5°C/min increments, and maintained at 300°C for 8 min. Helium was used as the carrier gas. The MS ion source temperature was 250°C and the electron energy was 70 eV. The mass spectrometer was operated in total ion chromatogram mode for qualitative analysis from *m/z* 50 to 600. The mass spectral library database of National Institute of Standards and Technologies (NIST) was used to identify compounds from the GC/MS mass fragment pattern data.

Ozone concentration in gas phase was determined using the iodometric method (Rakness et al., 1996).

2. Results and discussion

2.1. Effect of initial ranitidine concentration

The assessment of ranitidine reactivity towards ozone was performed at different initial ranitidine concentrations. Obviously, the reaction of ranitidine with ozone was fast, and was affected by the initial ranitidine concentration (Fig. 1a). Ranitidine was completely removed in nearly 10 min when the initial ranitidine concentration was 2 mg/L. When the initial ranitidine concentration increased to 20 mg/L, the removal of ranitidine proceeded for 30 min. The pseudo first-order kinetic model described ranitidine degradation very well ($R^2 > 0.9$) (Appendix A Table S1). The rate constant (k) decreased from 0.459 to 0.0484 min^{-1} when the initial ranitidine concentration increased from 2 to 20 mg/L (Fig. 1a). This indicates that prolonged ozonation is necessary for high concentration of ranitidine.

DMA and NDMA formations were both observed due to ranitidine oxidation (Fig. 1b and c). DMA concentration increased along with more ranitidine presented (Fig. 1b). Since DMA can also be oxidized by ozone (Andrzejewski et al., 2008), the generation and degradation of DMA occurred concurrently during ranitidine ozonation. Thus, DMA concentration profiles rose at first and then descended. The peak value of DMA appeared later at higher initial ranitidine concentration. More ranitidine also resulted in more NDMA formation (Fig. 1c). Similar to DMA, NDMA can also be decomposed during ozonation (Lv et al., 2013), so the concentration of NDMA increased in the beginning of ozonation and then decreased. Compared with DMA, NDMA degradation was prone to occur, so the peak value of NDMA appeared earlier than DMA. The Y_{NDMA-m} of ranitidine was between 0.0069% and 0.0076%, which was much less than the yield (89.9%–94.2%) during chloramines disinfection (Shen and Andrews, 2010).

2.2. Effect of ozone dose

Obviously, both ranitidine decomposition rate and removal efficiency were significantly improved with ozone dose increase (Fig. 2a). The removal efficiency of ranitidine was only 62% after 30 min when the ozone gas dose was 7.5 mg/L. However, no ranitidine was detected after 20 min when ozone dose was increased to 19.3 mg/L. As shown in Fig. 2a and Appendix A Table S2, the removal rate constant (k) increased from 0.0377 to 0.2478 min^{-1} when the ozone dose increased from 7.5 to 24.8 mg/L.

Ozone dose also strongly influenced the concentration profiles of DMA. The concentration of DMA kept increasing slowly when limited ozone (7.5 mg/L) was provided. Due to the competition with ranitidine for ozone, DMA degradation was suppressed. When more ozone was supplied, DMA concentration increased firstly and then reduced. It indicated that DMA decomposition was enhanced when a high ozone dose was provided, resulting in a peak value of DMA. The peak value of DMA occurred earlier along with ozone dose increasing. Though the generation rate and amount of DMA were enhanced, the least accumulation of DMA was observed

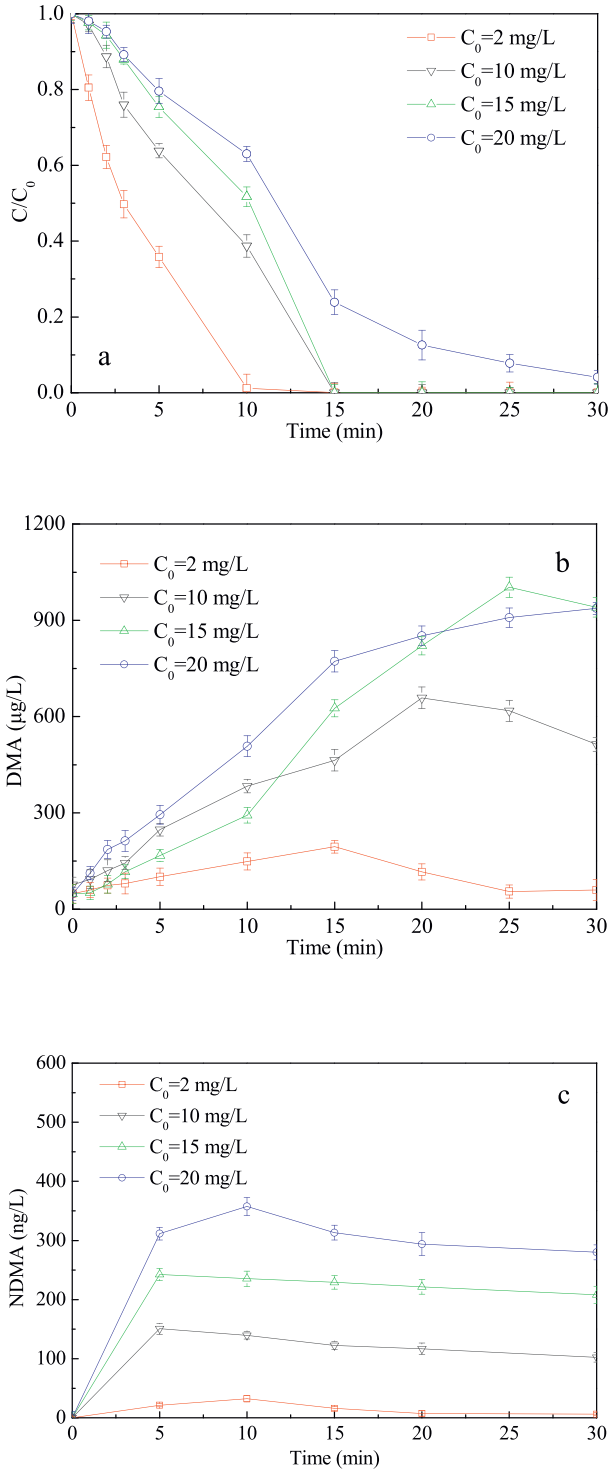


Fig. 1 – Ranitidine (a) decomposition as well as dimethylamine (DMA) (b) and N-nitrosodimethylamine (NDMA) (c) formation during ozonation at different initial ranitidine concentrations (Q_g = 3 L/min, O_{3g} = 12.4 mg/L, pH = 7.6).

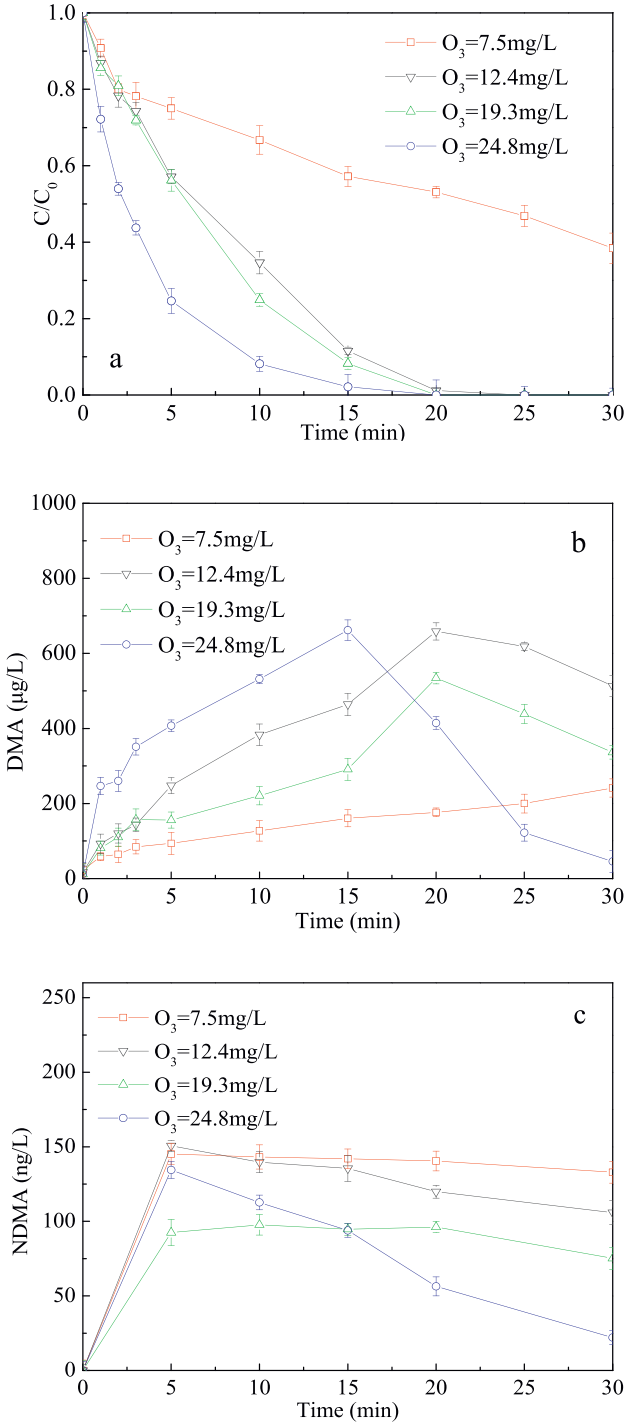


Fig. 2 – Effect of ozone dose on (a) ranitidine decomposition as well as (b) DMA and (c) NDMA formation (ranitidine$_0$ = 10 mg/L, Q_g = 3 L/min, pH = 7.6).

due to DMA oxidation by sufficient oxidant (ozone dose was 24.8 mg/L).

Rapid production of NDMA was observed in spite of different doses of ozone provided. The peak values of NDMA appeared in 5 min, and then NDMA concentration declined due to degradation by ozone. Higher ozone dose (24.8 mg/L) led to sharp decrease of NDMA. It means that high ozone dose is beneficial to reduce NDMA accumulation. Compared Fig. 2a with Fig. 2c, though ranitidine degradation lasted for 20 min, NDMA concentration began to decline in 5 min, even at low dose of ozone (7.5 mg/L). Since NDMA decline rate was very slow when ozone dose less than 19.3 mg/L, the accumulation of NDMA was higher than 100 ng/L even

after 30 min. It is obvious that higher dose of ozone is beneficial to both ranitidine removal and NDMA formation control.

2.3. Effect of pH

Ranitidine decomposition rate was enhanced when pH increased from 5 to 8, while there was only a slight difference in ranitidine degradation rates as the pH increased from 8 to 9 (Fig. 3a and Appendix A Table S3). The value of pH influences the charged state and ionic form of organic compounds. It has been known that ozone reacts with non-protonated amines readily (Von Gunten, 2003). Thus, higher reaction rate is expected under alkali conditions. Ranitidine's molecular structure incorporates one tertiary and two secondary amine groups. Under pH 8.2 (pKa 8.2), the tertiary amine functional group is gradually protonated (Dumanović et al., 1997). This may be the main reason for the relatively slow decomposition of ranitidine under acidic conditions. In addition, the stability of ozone largely depends on the water matrix, especially its pH, the type and content of organic matter and its alkalinity (Hoigné, 1998). As shown in Fig. 3a, the higher ranitidine degradation rate at pH 8 and 9 might also be due to more .OH release at higher pH (Von Gunten, 2003).

Both DMA and NDMA generations were greatly impacted by pH. DMA concentration kept at relatively low levels (10–40 μg/L) under acidic conditions (Fig. 3b). Since ozone reacts slowly with protonated DMA under acidic conditions (Von Gunten, 2003), no significant decline of DMA was observed at pH 5 and pH 6 (Fig. 3b). Increasing pH enhanced DMA formation and degradation simultaneously during ranitidine ozonation. The peak value of DMA was around 500 μg/L at pH 8. However, stronger DMA oxidation at pH 9 resulted in more DMA degradation, and in consequence less DMA accumulation was observed compared with that at pH 8. The different ranitidine and DMA profiles in Fig. 3a and b indicate that DMA formation was not directly correlated with ranitidine decomposition. As shown in Fig. 3c, no NDMA production was observed at pH 5. Since DMA ozonation was inhibited under acidic conditions due to the protonation of DMA (Von Gunten, 2003), it supposed that NDMA formation was related to DMA oxidation during ranitidine ozonation. NDMA generation was enhanced obviously at pH ≥ 6. Higher pH led to more .OH release, which resulted in higher peak value of NDMA. The highest NDMA accumulation (380 ng/L) was observed at pH 9. This indicates that higher pH enhanced ranitidine degradation, but resulted in more NDMA accumulation.

In order to identify the role of .OH in ranitidine degradation and NDMA generation, TBA was added during the ranitidine ozonation experiments as a radical scavenger. As expected, ranitidine removal was affected due to .OH consumption by TBA (Fig. 4a). It is noteworthy that the removal efficiency of ranitidine was still close to 100% in 30 min although 1000 mg/L TBA was injected. This indicates that the oxidation of ranitidine by ozone molecule may be dominant over .OH. TBA addition also influenced DMA formation (Fig. 4b). DMA concentration kept increasing when TBA was present. More TBA addition resulted in more DMA accumulation, indicating that DMA oxidation was inhibited due to TBA addition. This suggests

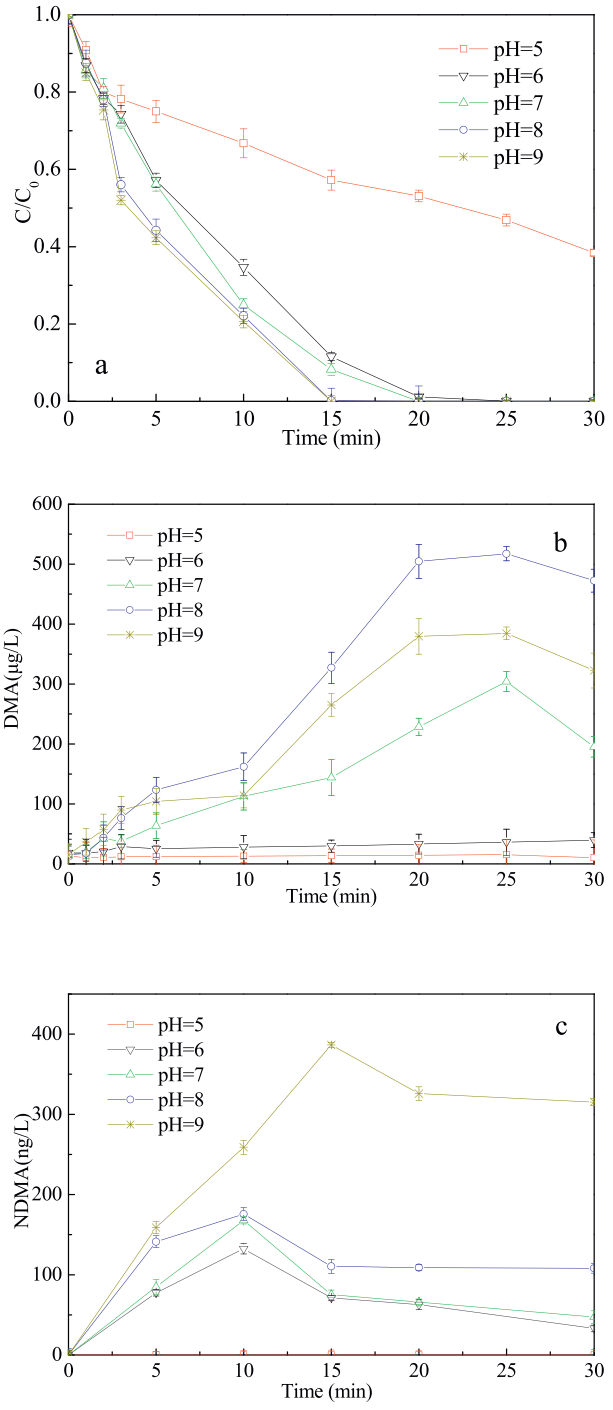


Fig. 3 – Effect of pH on (a) ranitidine decomposition as well as (b) DMA and (c) NDMA formation (ranitidine$_0$ = 10 mg/L, Q_g = 3 L/min, O_{3g} = 12.4 mg/L).

that .OH played a dominate role for DMA decomposition, but it was not critical for DMA generation by ranitidine oxidation. So ozone molecules should be directly related to DMA formation. As Fig. 4c shown, since .OH plays a critical role in NDMA ozonation (Lv et al., 2013), NDMA degradation was suppressed due to TBA addition. Thus, more NDMA accumulation was observed at higher TBA dose. When TBA addition was up to

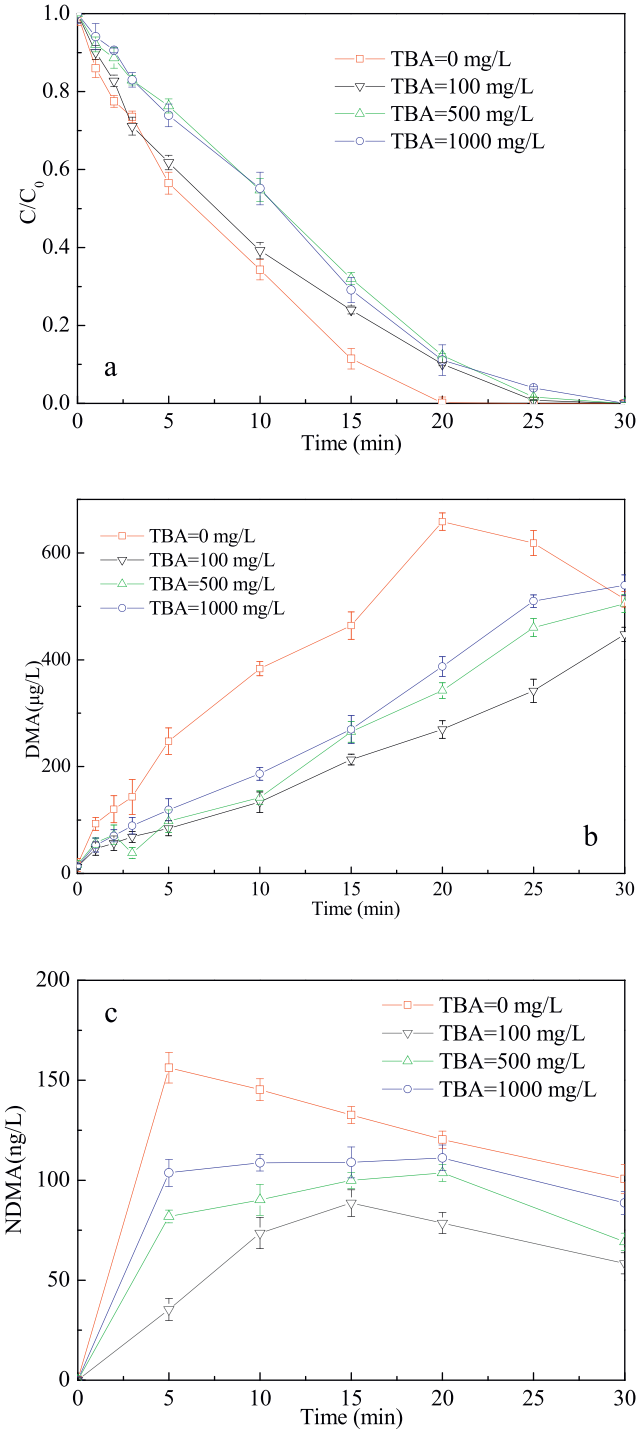


Fig. 4 – Effect of tert-butanol (TBA) on (a) ranitidine decomposition as well as (b) DMA and (c) NDMA formation (ranitidine$_0$ = 10 mg/L, Q_g = 3 L/min, O_{3g} = 12.4 mg/L, pH = 7.6).

1000 mg/L, NDMA generation was still observed although NDMA formation was also impacted due to .OH consumption by TBA. Therefore, ozone molecules were involved in NDMA formation during ranitidine ozonation.

2.4. Effect of water matrix

Ranitidine ozonation was performed in natural water (HPR water) to simulate ranitidine oxidation in water matrices under field conditions. As shown in Fig. 5a, ranitidine degradation rate was lower in natural water than in UP water. HCO_3^- and DOC in the HPR water might cause more ozone consumption, and thus suppress ranitidine decomposition.

DMA formation was also impacted by the water matrix. In UP water, DMA increased and reached the peak value after 20 min of ozonation, then decreased quickly due to DMA oxidation. In HPR water, although DMA concentration increased more slowly than that in UP water, no decline of DMA was observed (Fig. 5b). This means that both the generation and degradation of DMA were inhibited by the natural water matrix, and the inhibition of the later was much stronger than that of the former. As a result, the concentration of DMA in HPR water was much higher than that in UP water after 30 min of ozonation for ranitidine. As a typical NDMA precursor, more DMA accumulation means higher NDMAFP. Therefore, higher ozone dose or higher pH was needed to enhance DMA degradation when ranitidine ozonation was conducted in natural water.

NDMA concentration profiles presented similar trend in both UP water and HPR water (Fig. 5c). NDMA concentration increased at the beginning of ozonation and reached the peak value, then declined. The NDMA concentration increase rate in HPR water was much slower than that in UP water. The control experiment of HPR water without ranitidine was also performed under the same condition with ranitidine ozonation (Appendix A Fig. S1). The initial concentration of NDMA in HPR water was 4.3 ng/L (0 min), and it increased to 5.6 ng/L in 5 min. However, all NDMA was removed after 10 min due to the NDMA oxidation by ozone.

Besides pH, alkalinity and natural organic matters (NOM) in water also impact ozone stability (Hoigné, 1998). NOM may affect NDMA formation in two ways. Firstly, NOM may compete for oxidant through direct reaction with ozone and .OH, which in turn impressed both NDMA generation and oxidation. Secondly, NOM may interact with ranitidine, and thereby suppress NDMA formation through obstructing ranitidine decomposition. NOM is usually negatively charged due to the presence of abundant carboxyl groups, while ranitidine is positively charged at neutral pH. Therefore, the possible electrostatic attraction may take place between NOM and ranitidine, and then hinder the decomposition of ranitidine. Shen and Andrews also demonstrated a similar conclusion when investigating NDMA formation from three pharmaceuticals in four water matrices (Shen and Andrews, 2011). However, it's noted that a continuous increase of NDMA lasted for 15 min in HPR water, while it only lasted for 5 min in UP water (Fig. 5c). This suggests that NDMA degradation was inhibited in HPR water. The higher peak value of NDMA in HPR water also confirmed this deduction. Compared with NDMA generation, NDMA degradation was prone to be influenced by water matrix. Thus, more NDMA accumulation was observed during ranitidine ozonation in HPR water. To further investigate the role of alkalinity and NOM components in NDMA production during

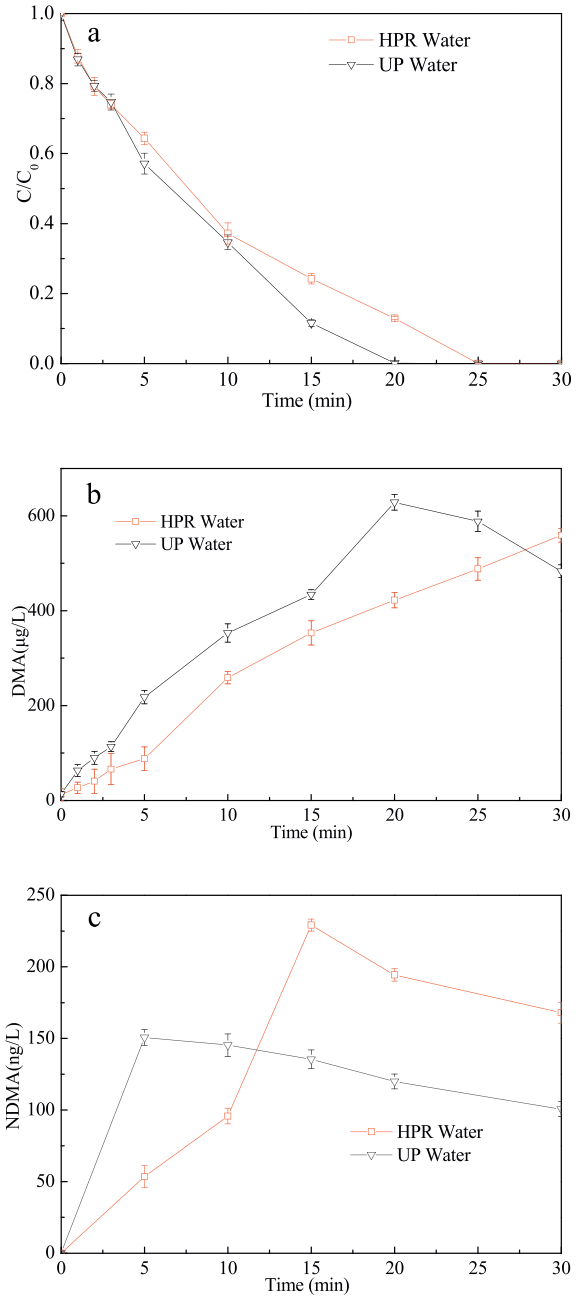


Fig. 5 – Comparison of (a) ranitidine decomposition as well as (b) DMA and (c) NDMA formation in natural water (Huangpu River (HPR) water) and in ultrapure water (UP water) during ozonation (ranitidine$_0$ = 10 mg/L, Q_g = 3 L/min, O_{3g} = 12.4 mg/L, pH = 7.6).

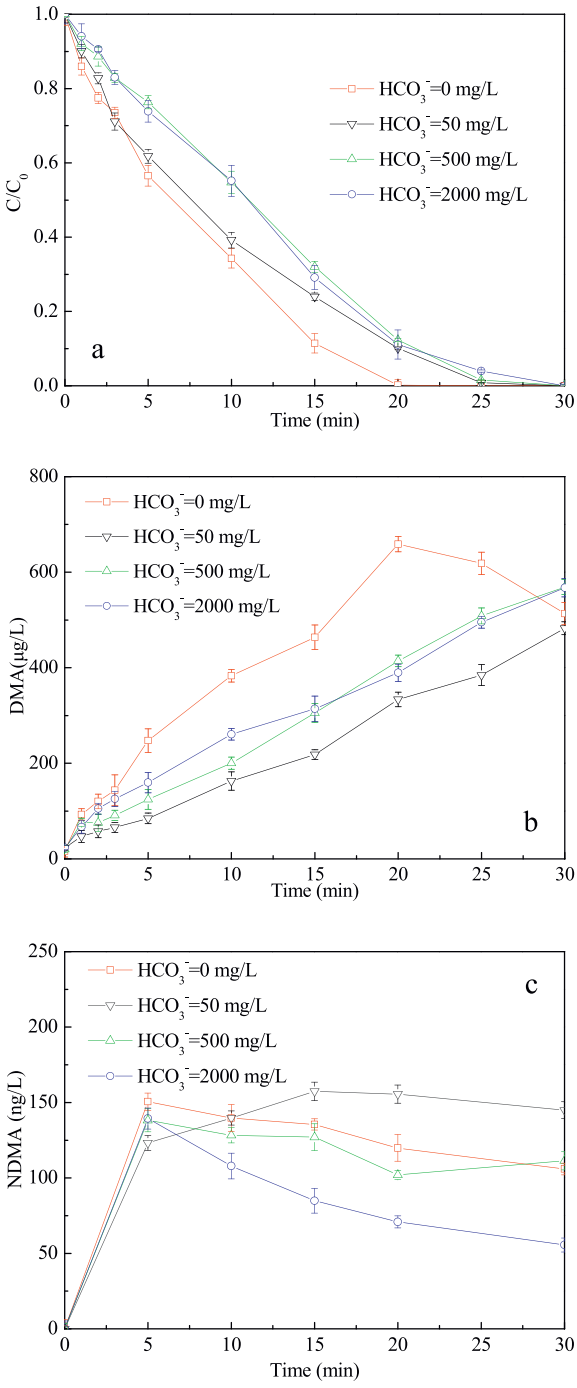


Fig. 6 – Effect of HCO_3^- on (a) ranitidine decomposition as well as (b) DMA and (c) NDMA formation (ranitidine$_0$ = 10 mg/L, Q_g = 3 L/min, O_{3g} = 12.4 mg/L, pH = 7.6).

ranitidine ozonation, we investigated the effects of HCO_3^- and HA.

As a common component in natural water, HCO_3^- is usually thought to be an .OH scavenger (Staehelin and Hoigné, 1985). Ranitidine decomposition was clearly suppressed by HCO_3^- addition, but ranitidine can still be removed completely in 30 min even the concentration of HCO_3^- was up to 2000 mg/L (Fig. 6a). It confirmed that the influence of .OH consumption was not significant for ranitidine degradation, and .OH and ozone molecules were both involved in ranitidine oxidation.

DMA concentration kept rising during the whole ozonation due to HCO_3^- addition, and DMA generation rate decreased compared with that without HCO_3^- addition (Fig. 6b). This means that both DMA generation and degradation were suppressed because of .OH consumption by HCO_3^-. It also verified that DMA degradation was more sensitive to .OH than DMA formation. The more HCO_3^- addition resulted in the stronger inhibition on DMA oxidation. Thus higher DMA concentration was observed when more HCO_3^- was added.

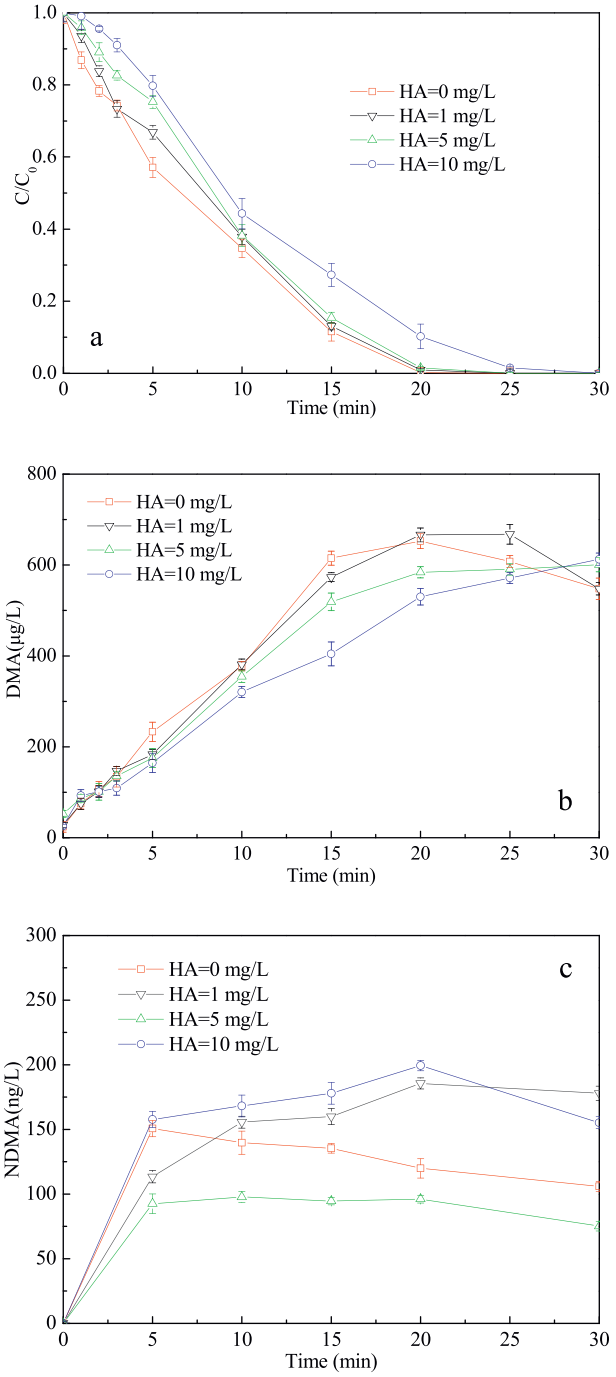


Fig. 7 – Effect of HA on ranitidine (a) decomposition as well as DMA (b) and NDMA (c) formation ([ranitidine]$_0$ = 10 mg/L, Q_g = 3 L/min, O_{3g} = 12.4 mg/L, pH = 7.6).

HCO_3^- addition had little influence on the NDMA concentration profiles. The concentration of NDMA increased rapidly in the first 5 min, and then declined due to NDMA oxidation by ozone (Fig. 6c). However, both the NDMA production rate and NDMA peak value were impacted by HCO_3^- addition. Combined with Fig. 6b, more HCO_3^- addition resulted in more DMA accumulation, while less NDMA formation was observed. This indicates that the inhibition of DMA degradation caused the suppression of NDMA formation, which also verified that NDMA generation was related to DMA oxidation during ranitidine ozonation.

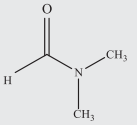
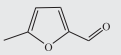
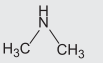
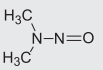
Similar to HCO_3^-, HA also had a negative effect on ranitidine decomposition (Fig. 7a). The more HA led to the slower ranitidine degradation. As a typical NOM, HA can compete with ranitidine for oxidant in directly and indirectly ways, such as reacting with ozone and scavenging of .OH (Staehelin and Hoigné, 1985). DMA and NDMA formations were also impacted. DMA formation and oxidation occurred concurrently during ranitidine ozonation as discussed earlier. Obviously, DMA degradation was suppressed due to HA addition. Consequently, the concentration of DMA kept increasing when more HA was present (HA = 10 mg/L), leading to DMA accumulation. NDMA generation and oxidation were also influenced by HA. However, the influence did not show any regularity. Further studies are needed to explore the role of HA in NDMA formation during the ozonation of ranitidine.

2.5. NDMA formation pathway during the ozonation of ranitidine

The major intermediates identified during ranitidine ozonation were summarized in Table 1, and all the compounds listed in Table 1 were unequivocally ascertained by comparison with their pure standards. Only a few organic intermediates were identified by GC/MS.

Based on the molecular structures of the intermediates, besides DMA, only DMF with a DMA functional group seems to be a potential precursor of NDMA. Compared with previous studies, because of the different conditions of ranitidine ozonation and detection methods, various transformation products were reported (Christophoridis et al., 2016). However, DMA and DMF have not been detected before. Actually, DMF has already been confirmed as a NDMA precursor during ozonation of chlorpheniramine in our previous studies (Lv et al., 2015). The calculated Y_{NDMAm} and Y_{DMAm} of DMF were 4.02×10^{-3}% and 1.3% when ozone dose was 37.2 mg/L, respectively (Lv et al., 2015). Compared with Fig. 2, since the initial concentration of ranitidine was 10 mg/L, 0.032 mmol/L of DMF should be generated theoretically during ranitidine

Table 1 – Intermediates identified by GC/MS during ranitidine ozonation.

Product	Molecular structure	MW (g/mol)	RT (min)
DMF		75.08	3.884
5-Methyl furfural		110.11	8.890
DMA *		45.08	/
NDMA *		74.08	/

* DMA and NDMA were identified by HPLC and UPLC–ESI/MS, respectively.

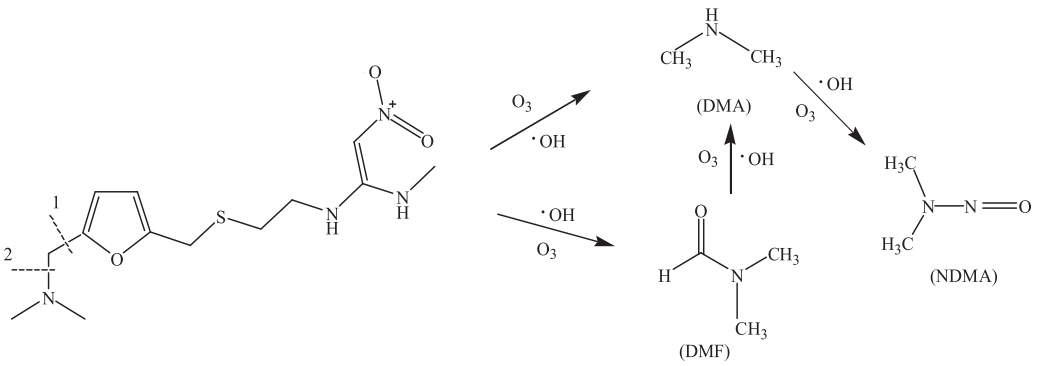


Fig. 8 – Proposed NDMA formation pathway from ranitidine ozonation.

ozonation. Under the same experimental conditions, the production of NDMA and DMA from DMF should be 1.29×10^{-6} mmol/L (95.56 ng/L) and 4.16×10^{-4} mmol/L (18.72 μg/L), respectively, according to the Y_{NDMAm} and Y_{DMAm} of DMF. As Fig. 2 shown, more DMA (513 μg/L) and NDMA (102 ng/L) were observed. This means that DMF may be not the only source for DMA formation. On the other hand, assuming all the DMA were generated directly from ranitidine decomposition, much more DMA (1.43 mg/L) should be observed. It appears that both the direct decomposition of ranitidine and oxidation of DMF contributed to DMA formation. According to the above analysis, both DMF and DMA generated from ranitidine ozonation resulted in NDMA formation.

Fig. 8 proposes a possible pathway of NDMA formation during ranitidine ozonation based on the identified intermediates as well as their performance during ozonation. Ranitidine decomposition was caused by the broken of the C–C bond linked to the furan ring (site 1) (Fig. 8), which was attacked by ozone molecule and .OH. It was also reported that in a first stage the $(CH_3)_2$–N–CH_2-moiety bonded to the furan ring could be separated from the rest of the ranitidine structure during ozonation (Rivas et al., 2009). However, the breakage on the site 1 with an addition of oxygen resulted in DMF generation. The further oxidation of DMF also caused DMA production. Jeon et al., (2016) also indicated that the reaction of ozone with the tertiary amine or furan moiety led to complete deactivation of the NDMAFP of ranitidine. Based on the discussion of DMA production above, it indicated the C–C bond broken on the site 2 led to DMA formation directly. Then NDMA was formed due to DMA ozonation. As discussed earlier, ozone molecule and .OH both contributed to DMA and NDMA generation.

3. Conclusions

Ozone was effective in ranitidine removal. Ranitidine degradation during ozonation fits the pseudo first-order kinetic model. Ranitidine ozonation resulted in DMA and NDMA formation, and the NDMA molar yield of ranitidine was between 0.0069% and 0.0076%. The impacts of pH and water matrix on ranitidine degradation were not significant, while productions of DMA and NDMA were both influenced. Especially, NDMA formation was inhibited under acidic conditions (pH ≤ 5) mainly due to the lack of non-protonated amines. Conversely, high pH of the solution caused more NDMA accumulation. Ozone molecules played a dominant role in the beginning of ranitidine degradation as well as the following productions of DMA and NDMA. However, .OH was a critical factor in NDMA degradation. Higher dose of ozone is beneficial to both ranitidine removal and NDMA formation control. The major transformation products during ranitidine ozonation were identified by GC/MS. Among the detected intermediates, DMF and DMA contributed to NDMA generation. A possible pathway for NDMA formation from ranitidine ozonation was proposed.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.jes.2017.05.028.

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