Effect of oxidation on amine-based pharmaceutical degradation and N-Nitrosodimethylamine formation

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Article info
Article history:
Received 17 May 2015
Received in revised form 24 July 2015
Accepted 27 July 2015
Available online 29 July 2015

Keywords:
NDMA
PPCPs
Ozone
Chlorine
Chlorine dioxide
Potassium permanganate

Abstract
Four pharmaceuticals (ranitidine, nizatidine, doxylamine, and carbinoxamine) were selected as model compounds to assess the efficiency of four oxidants (ozone (O₃), chlorine (Cl₂), chlorine dioxide (ClO₂) and potassium permanganate (KMnO₄)) on the removal of amine-based pharmaceutical and personal care products (PPCPs), as well as the reduction of their N-Nitrosodimethylamine formation potentials (NDMAFPs). The changes in PPCPs and their NDMAFPs during oxidation were quantified using various oxidants and dosages. The relationship between oxidation product structures and NDMAFP changes was also analyzed. The results showed that oxidation with O₃, Cl₂ and ClO₂ were effective in removing the selected PPCPs. However, only ozonation was effective in reducing their NDMAFPs. Ozonation at 6 mg/L removed approximately 90% PPCPs and 90% NDMAFPs for all PPCPs. In addition, the results indicated that ozonation products made little contribution to NDMAFPs. In contrast, some PPCP products had higher NDMAFPs than PPCPs after oxidation with Cl₂, ClO₂ and KMnO₄. There were two possible reaction pathways that led to decrease in NDMAFPs after oxidation. One was oxygen transfer to nitrogen at the tertiary amine site and the other was N-dealkylation from the tertiary amine site.

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1. Introduction

N-Nitrosodimethylamine (NDMA), one of the disinfection byproducts (DBPs) is of emerging concern due to its extremely high toxicity. The United States Environmental Protection Agency (USEPA) (1993) has issued a cleanup level of 0.7 ng/L for NDMA based on an increased lifetime cancer risk of 10⁻⁶ in drinking water. The USEPA (2009) also placed six nitrosamines on the Unregulated Contaminant Monitoring Rule List 3. The Ontario Ministry of the Environment (MOE) (2003) in Canada established an interim maximum acceptable concentration of 9 ng/L for NDMA in drinking water. The Canadian Office of Environmental Health Hazard Assessment (OEHHA) (2006) also implemented a public health goal of 3 ng/L for NDMA. Although the typical NDMA concentration is about 10 ng/L (Mitch et al., 2003), NDMA was detected in drinking water at concentrations as high as 100 ng/L (Boyd et al., 2011). The higher NDMA concentration usually occurred in the water that was disinfected by chloramines (Zhao et al., 2008; Krasner et al., 2013). Chloramine is commonly used as a continuous disinfectant in pipe network system. It also served as an alternative disinfectant (Guay et al., 2005) to reduce the formation of trihalomethanes, haloacetic acids and other regulated DBPs.

Initial studies on NDMA precursors mainly focused on dimethylamine (DMA) (Choi and Valentine, 2002; Mitch and Sedlak, 2002; Schreiber and Mitch, 2005, 2006). Nevertheless, the contribution of DMA is not significant because DMA concentrations in wastewaters were generally lower than 200 ng/L and the NDMA molecular conversion of DMA was low (0.082–3%) (Lee et al., 2007). Some researchers subsequently focused their attention on other precursors such as quaternary amines and tertiary amines (Kemper et al., 2010; Mitch and Schreiber, 2008). Model quaternary amines formed NDMA at yields of about 0.2%. This was likely via a pathway involving the degradation of quaternary amines to secondary amines. In contrast, some tertiary amines, which have aromatic group at the β-position to nitrogen, had higher NDMA formation potential (NDMAFP) during chloramination (Roux et al., 2011). Many amine-based pharmaceuticals and personal care products (PPCPs) have the special tertiary amine structure. For example,
ranitidine, which is often used to prevent gastritis, can form NDMA at yields up to 90%. Andrews’s group (2011) found that NDMA could be formed through reaction between all the 20 amine-based PPCPs and monochloramine, and that most of these PPCPs had higher NDMAFPs than DMA. Previous surveys also showed widespread occurrence of ng/L–mg/L of PPCPs in an aquatic environment (Liu and Wong, 2013; Loos and Carvalho, 2013; Ying et al., 2004; Snyder et al., 2003). Ranitidine was detected ranging from 70 to 540 ng/L in primary effluents of wastewater treatment plants in Spain and at 10 ng/L in several surface waters (Radjenovic et al., 2009; Kolpin et al., 2002). Around 300 ng/L doxylamine was reported in a reclamation plant effluent (Farré et al., 2011). In addition, many PPCPs were hardly removed by the conventional coagulation/ sedimentation/ filtration process in drinking water treatment plant (Farré et al., 2011; Westerhoff et al., 2005). Therefore, PPCPs containing DMA groups are an important group of NDMA precursors.

Over the last few decades, oxidation has been widely used for drinking water treatment. The most commonly used oxidants include ozone (O3), chlorine (Cl2), chlorine dioxide (ClO2), ferrate (Fe(VI) and potassium permanganate (KMnO4)(Lee and von Gunten, 2010). Oxidation is very effective in controlling taste and odor as well as for the removal of precursors (Liu et al., 2013; Ellis et al., 2000). It is also very effective in aiding coagulation and in removing DBP precursors (Ma and Liu, 2002; Shah et al., 2012). Recently, researches were conducted to study PPCP degradation during oxidation processes (Westerhoff et al., 2005; Lee and von Gunten, 2010). The results showed that O3 was the optimal oxidant for PPCP degradation. Oxidation was also used to minimize NDMA formation by oxidizing the amine-based precursors upstream of chlorination. Among all the oxidants, O3 and Cl2 were found to be most effective in reducing NDMA formation. More than 50% NDMA precursors were deactivated by 140 mg/L × min for Cl2 and 2 mg/L × min for O3 (dosage for Giardia control) in river water and wastewater (Shah et al., 2012). However, an increase in NDMAFPs was observed in some samples after Cl2 and ClO2 oxidation (Shah et al., 2012; Shen and Andrews, 2011). This could indicate that some oxidation products had high contributions to NDMAFPs because of the incomplete mineralization at common oxidant dosages.

Some oxidation products of tertiary amines by O3 (Lange et al., 2006; Khan et al., 2010; Muñoz et al., 2001), Cl2 (Deborde and Von Gunten, 2008) and Fe(VI) (Zimmermann et al., 2012) have been reported. Degradation pathways of amine-based PPCPs by O3 and Fe(VI) were discussed in particular. A primary ozonation pathway was oxygen transfer to the lone electron pair at nitrogen, yielding N-oxide (Muñoz et al., 2001). A primary ferrate oxidation pathway was N-dealkylation at the tertiary amine site (Zimmermann et al., 2012). However, little was found on amine-based PPCP degradation by other traditional oxidants such as Cl2, ClO2 and KMnO4. In addition, a relationship between the degradation products and NDMAFP changes needs to be better understood.

The first aim of this study is to evaluate the potential of four oxidants (O3, Cl2, ClO2 and KMnO4) to remove PPCPs containing the DMA group, and the second is to better understand oxidation products and their NDMAFPs. Four common PPCPs were selected as model compounds because of their high NDMAFPs (89.5–94.2%) for ranitidine, 4.5–4.8% for nizatidine, 8.0–9.7% for doxylamine, and 1.0–1.4% for carbinoxamine (Shen and Andrews, 2011). As shown in Fig. 1, the structures of ranitidine and nizatidine were similar, except for the difference in the five-member rings. The structures of doxylamine and carbinoxamine were similar except for the two aromatic rings. Selection of target compounds was also based on their prevalence in Chinese pharmaceutical markets and their frequent presence in the water environment.

2. Material and methods

2.1. Chemicals

PPCPs (HPLC grade), NDMA (HPLC grade), formic acid (LC-MS grade), sodium hypochlorite (NaClO) solution (reagent grade) and sodium chloride (NaClO2) powder (80%) were purchased from Sigma–Aldrich in US. Methanol (HPLC grade) and acetonitrile (HPLC grade) were obtained from Fisher Scientific in US. KMnO4, ammonium chloride, disodium hydrogen phosphate, sodium dihydrogen phosphate, sodium chloride, sodium thiosulfate (all in AR grade) were purchased from Xilong Chemical Industry in China. Indigo carmine (AR grade), phosphoric acid (85%, AR grade) and sulfuric acid (98%, AR grade) were purchased from Sinopharm in China. Ultrapure water (18 MΩ) was produced with a Millipore system.

2.2. Natural water systems

To simulate real treatment conditions, experiments were performed using source water from a drinking water treatment plant in Jinan, Shandong Province, China. The basic quality parameters of the natural water are summarized in the Supporting Information Table S1. The natural water were filtered through a 0.45 μm membrane filter (Millipore, HAWP04700, USA) within 48 h after sampling and stored at 4 °C until use.

2.3. Oxidants preparation

A saturated O3 solution (40 mg/L) was prepared by bubbling gaseous O3 into ultrapure water in a 2 L airtight glass container in an ice bath. The gaseous O3 was prepared from extra dry grade (minimum purity of 99.99%) oxygen using an O3 generator (Newland, NLO-A-10, China). Aqueous O3 concentration was determined by the modified indigo colorimetric method with a UV-VIS spectrophotometer (Meipuda, UV-1800, China). ClO2 stock solution (300 mg/L as ClO2) was prepared by adding sulfuric acid to NaClO2 solution (Jin et al., 2006). The final yellow ClO2 solution was stored in an amber glass bottle and refrigerated. The concentration of ClO2 was determined by the DPD colorimetry (Hach, PCl 58700-51, USA). Cl2 stock solution (1500 mg/L as Cl2) was prepared by diluting a commercial NaClO solution and the concentration determined by the DPD colorimetry (Hach, PCl 58700-00, USA). KMnO4 stock solution (2000 mg/L) was prepared by dissolving 1 g KMnO4 in 500 mL of ultrapure water. Monochloramine (NH2Cl) solution was prepared freshly (1600 mg/L as Cl2) by slow addition of 5% NaClO solution with continuous stirring. After being stirred for 30 min, the solution was aged in the dark for 1 h and used within 1 d (Padhye et al., 2013). NH2Cl concentrations were determined prior to each experiment using the DPD colorimetry (Hach, PCl 58700-26, USA).

2.4. Experimental procedure

In order to better understand oxidation reaction pathways, each PPCP was studied individually. The initial PPCP water solution containing one PPCP, phosphate buffer and sodium chloride was prepared in a 500 mL volumetric flask.

All oxidation experiments were carried out at 20 °C, pH 7.0 using a 10 mM phosphate buffer and a certain ionic strength using a 5 mM sodium chloride was maintained. The initial concentration of the PPCP in the reaction solution was 25 μM. Each oxidation dosage was conducted at three concentration levels [e.g., [O3] = 1, 3, 6 mg/L].
For each concentration level, the four oxidant dosages were expressed by equal electron accepting ability. The oxidant dosages are shown in Table 1. 

For the samples that were treated with O3, 200 mL initial PPCP solution was poured into a reactor (250 mL Erlenmeyer flask) which has a true volume of 290 mL. Then, X mL ultrapure water was added. Finally, Y mL \(X + Y = 90\) mL saturated O3 solution was injected into the reactor (Kuang et al., 2013). For samples treated with the other three oxidants, oxidant stock solution was added directly into 40 mL amber vials containing sample solution, using oxidant dosages shown in Table 1. After 2 h oxidation reaction, a calculated sodium thiosulfate powder (at approximately 1 g/L). Then a part of the sample was prepared for residual PPCP and transformation product detection. The other part of the sample was prepared for NDMAFP tests. The MnO2 suspension, generated as a result of KMnO4, was removed by 0.45 μm syringe filter. 

NDMAFP tests were conducted in 20 mL amber vials with Teflon caps. 140 mg/L of monochloramine was added to ensure that there was enough residual monochloramine to predict the ultimate formation potential (Lee et al., 2007). The chloramination was carried out at 20 °C. Reactions were halted after 10 d by the addition of excess sodium thiosulfate powder (at approximately 1 g/L). Then the samples were prepared for NDMA detection. 

Oxidation of natural water was performed with 62.5 μM O3 (3 mg/L), 93.5 μM Cl2 (6.7 mg/L), 75 μM ClO2 (5 mg/L) and 75 μM KMnO4 (11.8 mg/L) in 1 L amber vials with Teflon caps. After filter with 0.45 μm membrane, the pH of the natural waters was adjusted to 7.0 using H2SO4 prior to treatment. 25 nM PPCP was added to the natural water to achieve enough NDMA precursors. Oxidation with different oxidants and NDMA incubation tests were similar to those in ultrapure water system. All experiments were conducted in duplicates.

2.5. PPCPs and NDMA analysis

NDMA, PPCPs and oxidation products were analyzed using liquid chromatography tandem mass spectrometry (LC-MS/MS) (Agilent 1290 LC coupled with 6460 MS/MS). The HPLC columns used were Agilent Poroshell 120, SB-C18 (2.1 mm × 100 mm, 2.7 μm) for NDMA and Agilent Zorbax SB-C18 (2.1 mm × 100 mm, 1.8 μm) for PPCPs and oxidation products. The mobile phase was composed of acetonitrile (solvent A) and 0.1% formic acid in ultrapure water (v/v, solvent B). The flow rate was 0.3 mL/min. The sample injection volume was 10 μL. The multiple reaction monitoring (MRM) MS detection mode was used to quantify NDMA and PPCPs. The MS detection modes for product identification were MS2 scan and MS2 product ion scan. The detailed instrument parameters for the compounds detected using LC-MS/MS were shown in Table S2. PPCPs and NDMA in natural water were enriched by solid phase extraction. The extraction programs were shown in Text S2 and Text S3.

3. Results and discussion

3.1. Degradation of PPCPs

Doxylamine and carbinoxamine seemed to be more sensitive to O3 than ranitidine and nizatidine (Fig. 2). When the O3 dosage was as low as 1.0 mg/L, 50% of doxylamine and carbinoxamine were removed while only 25% of ranitidine and nizatidine were removed. When the O3 dosage was increased to 3.0 mg/L, doxylamine and carbinoxamine were completely removed, while only about 50% of ranitidine and nizatidine were removed. All PPCPs were removed by almost 90% when the O3 dosage was increased to 6.0 mg/L.

In contrast, oxidation of PPCPs with Cl2 showed an opposite degradation pattern. Ranitidine and nizatidine were more sensitive to Cl2 than carbinoxamine and doxylamine. When the Cl2 dosage was as low as 2.2 mg/L, 50% of ranitidine and nizatidine were removed while only 30% of carbinoxamine and doxylamine were removed. When the Cl2 dosage was increased to 6.7 mg/L, 90% of ranitidine and nizatidine were removed while only 70% of doxylamine and carbinoxamine were removed. Almost 10% of carbinoxamine and doxylamine remained at 13.3 mg/L Cl2.

Degradation curves of four PPCPs paralleled with each other along with increasing dosage of ClO2, which indicated that they likely degraded through the same pathway. When the ClO2 dosage was as low as 1.7 mg/L, they were removed about 30%. When the ClO2 dosage was increased to 5 mg/L, they were completely removed, proving ClO2 to be an ideal oxidant for PPCP degradation.

Similar to oxidation with Cl2, ranitidine and nizatidine were more sensitive to KMnO4 than carbinoxamine and doxylamine. At 12 mg/L KMnO4, 90% of ranitidine and nizatidine were removed.

![Fig. 1. Structures of the selected PPCPs.](image-url)
However, only 10% of carbinoxamine and doxylamine were removed. A possible reason was low reaction activity between KMnO₄ and the two PPCPs. Similar experimental results have been reported with low reactivity of KMnO₄ (Rodríguez et al., 2007) for uracil \( (k_{\text{app}} = 1.00 \text{ M}^{-1} \text{ s}^{-1}) \) and cylindrospermopsin \( (k_{\text{app}} = 0.3 \text{ M}^{-1} \text{ s}^{-1}) \).

### 3.2. Effects of oxidation on NDMAFPs

The maximum NDMAFPs of the PPCPs without oxidation ranged from 0.1 to 17.5 \( \text{mM} \), and the molar conversion rate was 0.5%–80% (carbinoxamine < nizatidine < doxylamine < ranitidine), which are consistent with the value found in previous studies (Shen and Andrews, 2011). These oxidants could affect NDMAFPs of PPCPs to varying degrees (Fig. 3). Only ozonation was effective in removing NDMAFPs of the PPCPs.

The NDMAFP of doxylamine was completely (>95%) removed with 3 mg/L O₃. When the O₃ dosage was doubled from 3 mg/L to 6 mg/L, approximately 90% NDMAFPs were removed for all PPCPs. Even though the product, DMA, was considered as a residual NDMA precursor after complete ozonation (Lee et al., 2007), less than 5% DMA formed after ozonation of several tertiary amines and NDMAFP of DMA was 0.082% – 3%. The product DMA made little contribution to NDMAFP.

Cl₂ had a weak ability in removing NDMAFPs. NDMAFP of nizatidine increased with increasing Cl₂ dosage. When the Cl₂ dosage was as low as 2.2 mg/L, NDMAFPs of doxylamine, carbinoxamine and ranitidine were removed by 22%, 5% and 3% while NDMAFP of nizatidine increased 21%. When the Cl₂ dosage was increased to 6.7 mg/L, NDMAFPs of doxylamine, carbinoxamine and ranitidine were removed by 68%, 24% and 18% while NDMAFP of nizatidine increased 47%. Almost 98% of NDMAFP of nizatidine remained with 13.3 mg/L Cl₂. It was demonstrated that the products from nizatidine had a higher NDMAFP. Be different from ranitidine, a sulfur was contained in the five-membered heterocycle of nizatidine. Sulfur was an active site that is easy to be attacked by Cl₂. The products that chlorine transferred to the five-membered heterocycle may made a larger contribution to NDMAFP than nizatidine itself.

For ClO₂ oxidation, the higher the NDMAFP of the PPCP, the higher the NDMAFP removal was observed. NDMAFPs of ranitidine, nizatidine and doxylamine decreased while an increase was observed in samples containing carbinoxamine with increasing ClO₂ dosage. Shah et al. (2012) reported both reduced and enhanced NDMAFPs in natural water samples after oxidation with ClO₂. Product of DMA (Lee et al., 2007) was treated as the main residual NDMA precursor after complete ClO₂ oxidation. NDMAFP increased in the cabinoxamine solution was because NDMAFP of carbinoxamine was lower than DMA and more than 90% carbinoxamine transformed into DMA after ClO₂ oxidation.

The reaction between KMnO₄ and precursors was too slow to reduce NDMAFP significantly at limited reaction time. Even though it had some advantages as it formed particles that can be easily removed by flocculation and did not formed disinfection byproducts during KMnO₄ oxidation (Andrzejewski and Nawrocki, 2009). Using KMnO₄ for oxidation and disinfection would be difficult because of its long contact time requirement and low effectiveness in NDMAFP removal and pathogen inactivation.

In order to understand the relationships between the degradation products and NDAMFPs, the measured NDMA were compared with the calculated NDMA from residual PPCPs under various oxidant dosages. The latter was calculated through the following formula.

\[
[\text{NDMA}]_i = [\text{PPCP}]_i \times \frac{[\text{NDMA}]_0}{[\text{PPCP}]_0}
\]
[NDMA]₀ and [PPCP]₀ were the measured results without oxidation, [PPCP]ᵢ was the measured result after i mg/L oxidant oxidation, [NDMA]ᵢ was the calculated result with residual PPCP after i mg/L oxidant oxidation.

The results demonstrated that ozonation products from all PPCPs made little contribution to NDMAFPs (Fig. 4). Products from nizatidine and ranitidine made a large contribution to NDMAFPs while products from doxylamine and carbinoxamine made a small contribution to NDMAFPs after Cl₂ oxidation. In comparison to ozonation products, products after ClO₂ oxidation made higher contribution to NDMAFPs.

3.3. Relationship between oxidation product structure and NDMAFP

To further explore the mechanisms of PPCP degradation with oxidation and the relationships between oxidation products and NDMAFPs, the products were characterized by LC-MS/MS. The MS2 scan mode and MS2 product ion scan mode were used to obtain the mass spectrums. The products were named as m/z M + 1. Similar products were detected from doxylamine and carbinoxamine, as well as ranitidine and nizatidine (Fig. S1–S16). Only doxylamine and ranitidine were discussed in this chapter.

Oxygen transfer product m/z 287 [271 + O] from doxylamine was observed after ozonation (Fig. 5). Previous studies suggested that oxygen was transferred to the lone pair electrons on the nitrogen thereby forming an ozonide ammonium zwitterion after tertiary amines ozonation. The ozonide ammonium zwitterion later lost the dioxygen yielding the N-oxide (Lange et al., 2006; Muñoz et al., 2001). Oxygen transfer destroyed DMA structure in tertiary amines leading to NDMAFP decrease after ozonation. Meanwhile, m/z 106 [90 + O] was found in samples containing doxylamine. In Farré’s study, (2012) doxylamine also degraded to m/z 106 [90 + O] by UV treatment. Our results indicated that the production of m/z 106 [90 + O] came from the oxidation of hydroxyl radical existing in both O₃ and UV treatment.

N-dealkylation product m/z 257 [271-CH₂] and N–C bond cleavage product m/z 200 [271-NC₆H₅-C₂H₅] were detected in the doxylamine solution after Cl₂ oxidation. Under weak oxidant conditions, it was difficult to open the two aromatic rings. Therefore, for doxylamine, N-dealkylation took place in the DMA functional group where two branched chain methyl existed. Zimmermann’s group (2012) found that an N-centered radical cation was an intermediate in the oxidation of amines by ferrate, and the N-centered radical cation intermediate could lead to N-dealkylation. N-dealkylation destroyed DMA structure that was necessary for NDMA formation. This might be the main reason for NDMAFP decrease after Cl₂ oxidation. In addition, the odd molecular mass of this product m/z 200 [271-NC₆H₅-C₂H₅] indicated an odd number of nitrogen atoms (Ning, 2000), reflecting the loss of the DMA group. Product m/z 257 [271-CH₂] was also detected in doxylamine solution after ClO₂ degradation and after KMnO₄ oxidation. The yields of product m/z 200 [271-NC₆H₅-C₂H₅] were higher than m/z 257 [271-CH₂] after ClO₂ oxidation, whereas product m/z 200 [271-NC₆H₅-C₂H₅] was not detected due to low reactivity of KMnO₄ with doxylamine.

Ranitidine with long chain structure might be easier to be destroyed than doxylamine with steady ring structures after ozonation. Oxygen transfer product m/z 331 [315 + O] was not observed after ozonation (Fig. 5). Previous studies suggested that oxygen was transferred to the lone pair electrons on the nitrogen thereby forming an ozonide ammonium zwitterion after tertiary amines ozonation. The ozonide ammonium zwitterion later lost the dioxygen yielding the N-oxide (Lange et al., 2006; Muñoz et al., 2001). Oxygen transfer destroyed DMA structure in tertiary amines leading to NDMAFP decrease after ozonation. Meanwhile, oxygen transfer product m/z 172 [156 + O] from a fragment m/z 156 was detected. Roux et al. found that the rupture of C–S bond in ranitidine generated the product m/z 156 (Roux et al., 2012). MS2 product ion scan mode was used to characterize the structures of m/z 156 and

**Fig. 3.** Changes of NDMAFPs with increasing oxidant dosage (● ranitidine, ○ nizatidine, ▼ doxylamine, △ carbinoxamine, [PPCP]₀ = 25 μM, oxidation contact time = 2 h, NDMA incubation time = 10 d).
m/z 172 for confirming whether m/z 172 came from the fragment m/z 156. The mass spectrums showed that m/z 156 and m/z 172 had uniform product fragments m/z 111, m/z 83 and m/z 55. This result reflected the loss of the DMA m/z 45 and DMA + O m/z 61 [45 + O] from m/z 156 and m/z 172. The result also demonstrated that oxygen was added to the lone pair electrons on nitrogen in DMA groups. We could conclude that oxygen transfer reaction at the tertiary amine site caused NDMAFP decrease after ozonation.

Oxygen and chlorine transfer products m/z 365 [+OCl–H], m/z 399 [+OCl2–H2] were detected from ranitidine after Cl₂ oxidation. The amount of chlorine in the products was confirmed according to the special ratio of isotope abundance (m/z 35:37 = 3:1) (Pretsch et al., 2009). Unlike O₃, Cl₂ oxidation tended to add chlorine and oxygen to sulfur, primary and secondary amines, not tertiary amine (Debordea and Von Gunten, 2008). Generally, rate constants for the reaction Cl₂ with sulfur are typically 1–2 orders of magnitude higher than amines. The Cl₂ attack on sulfur ether would form a chlorosulphonium cation intermediate. After hydrolysis, sulfoxide compounds were formed. For primary and secondary amines, Cl₂ reactivity constants are in the range 10⁷–10⁸ M⁻¹ s⁻¹; for tertiary amines, lower rate constants of about 10⁵ M⁻¹ s⁻¹. It indicated that DMA structure in ranitidine had not been destroyed after Cl₂ oxidation. Some of these products still had high NDMAFPs. It is known that chlorine transfer occur in both Cl₂ and NH₂Cl oxidation. If sulfur, primary and secondary site were occupied firstly by chlorine from Cl₂, it would be easy that NH₂Cl attack tertiary amine site in ranitidine. Maybe this is a reason for chlorine transfer products still had a high NDMAFP after Cl₂ oxidation.

Oxygen transfer products m/z 331 [315 + O] and m/z 286 [315 + OH-NC₂H₆] were detected after ClO₂ oxidation in ranitidine solution. However, the yields of m/z 331 [315 + O] were much lower, but the yields of m/z 286 [315 + OH-NC₂H₆] were much higher with increasing ClO₂ dosage. The change of m/z odd–even parity suggested the cleavage of DMA functional groups. This result indicated ranitidine and doxylamine had a common N–C bond cleavage reaction pathway under ClO₂ oxidation. With ClO₂ pretreatment, an unbroken DMA group would drop off from the PPCP, while it was still acting as a NDMA precursor. The change of NDMAFP before and after ClO₂ pretreatment was determined by which had a higher NDMAFP, PPCP or DMA.

Oxygen transfer product m/z 347 [315 + O2] was detected in the ranitidine solution after KMnO₄ oxidation. Reduced sulfur was the most probable oxygen transfer site. Sulfur ether was very easy to be oxidized to sulfone or sulfoxide by KMnO₄ (Cremlyn, 1996). There was a symmetry-adapted configuration between empty 3d orbital in sulfur and 2p orbital in oxygen. A feedback coordination bond was formed when the sulfur accepted lone pair electrons of oxygen. DMA structures and neighboring aromatic rings in ranitidine had not been destroyed after KMnO₄ oxidation. These products still had high NDMAFPs.

![Fig. 4.](image_url) Comparison between measured NDMAFPs (white bar) and calculated NDMAFPs (striped bar) from residual PPCPs ([PPCPs]₀ = 25 μM, NDMA incubation time = 10 d).
3.4. The changes of PPCPs and NDMAFPs in natural water

To investigate the effect of oxidation with \( \text{O}_3 \), \( \text{Cl}_2 \), \( \text{ClO}_2 \) and \( \text{KMnO}_4 \) on the PPCP degradation and NDMA formation in natural water, experiments were performed using source water from a drinking water treatment plant with spiking of 25 nM model PPCP. The results of PPCP degradation and NDMA formation in natural water with oxidation treatment were shown in Fig. 6. As expected from the results with model PPCP in ultrapure water, nizatidine in natural water could be removed by four oxidants, and doxylamine could be removed by three oxidants except \( \text{KMnO}_4 \). Comparing to the other three oxidants, \( \text{O}_3 \) was the most effective in reducing NDMAFPs. And increasing NDMAFP was also observed in natural water with nizatidine after oxidation of \( \text{Cl}_2 \). The results were similar to those in ultrapure water with nizatidine after oxidation of \( \text{Cl}_2 \). The results were similar to those in ultrapure waters indicating that the selected PPCP had similar reactivity during oxidation in natural water and in ultrapure water. A result worth noting was that the change of NDMAFP in natural water was lower than in ultrapure water. One possible explanation is that the natural waters contained a significant amount of compounds, which may produce tertiary amine NDMA precursors by reaction with oxidation. In fact, it is very difficult to trace the definite origin of this behavior due to the complex matrix of the natural waters.

4. Conclusions

The results suggest that utilities employing chloramination can effectively minimize NDMA formation by incorporating a pretreatment with oxidation. \( \text{O}_3 \), \( \text{Cl}_2 \) and \( \text{ClO}_2 \) were effective in removing the selected amine-based PPCPs in aqueous solution. However, only \( \text{O}_3 \) was effective in reducing NDMAFPs from the selected PPCPs. Enhanced NDMAFPs were observed in some samples after \( \text{Cl}_2 \) and \( \text{ClO}_2 \) oxidation. It was notable that almost all NDMAFPs of the PPCPs decreased to 1% after \( \text{ClO}_2 \) oxidation. DMA is the main NDMA precursor produced from oxidation of \( \text{ClO}_2 \) and DMA is degradable. \( \text{ClO}_2 \) combined biologically activated carbon would be an ideal technology for both PPCPs degradation and NDMA formation.

NDMAFP could be controlled significantly if only the DMA structures of PPCP parents were destroyed. It was proposed that oxygen adds to the lone pair electrons in nitrogen through an ozonation pathway, thereby forming an ozonide ammonium zwitterion after tertiary amines ozonation. Then it loses dioxygen yielding the N-oxide. Methyl was cleaved from tertiary amine after \( \text{Cl}_2 \) and \( \text{KMnO}_4 \) oxidation. However, oxygen or chlorine transferred to the reduced sulfur, primary and secondary amines after \( \text{Cl}_2 \) and \( \text{KMnO}_4 \) oxidation. A whole DMA group dropped off from the PPCP.
and the DMA was the final NDMA precursor after ClO2 pretreatment.

Acknowledgments

This work was supported by National Natural Science Foundation of China (No. 51278268 and No. 51290284).

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.watres.2015.07.045.

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