The effects of competing precursors and pre-oxidation on N-Nitrosodimethylamine formation from ranitidine upon chloramination

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Abstract. N-nitrosodimethylamine (NDMA) is a potent carcinogen and frequently detected nitrosamine from water chloramination. This study investigated the effects of pre-oxidation on the reduction of NDMA formation potential (FP) from ranitidine (RNT) upon subsequent chloramination. Reactive chlorine species (RCS) were generated by employing a coated titanium anode with IrO₂-Ta₂O₅ and a titanium plate as a cathode material. The TiO₂ photocatalyst was immobilized by electrospraying TiO₂ dispersion on stainless-steel mesh. In addition, the effects of competing NDMA precursors on the NDMA FP of RNT was examined. Reduced NDMA FP values of RNT in the presence of co-existing compounds might be ascribed to competing reactions and NH₂Cl demand. In the presence of N,N-diethyldihydroxylamine, complete inhibition of NDMA FP resulted from the depletion of dissolved oxygen. Pre-chlorination was found to effectively mitigate NDMA FP, depending on the applied [RCS], duration, and pH. The NDMA FP of RNT decreased approximately 95–99.3% with an increase in the pre-oxidation time and applied [RCS], dose. The optimal pH with a contact time of 30 min and [RCS], of 0.15 mM to achieve an insignificant level of NDMA FP ranged from 6.5 to 7.0. However, using ultraviolet (UV) photolysis alone, the NDMA FP of RNT was reduced by ca. 50%, while 30 min of irradiation with TiO₂ significantly reduced the NDMA FP up to 84%. These results demonstrated that both UV/TiO₂ and RCS were effective in minimizing the NDMA FP.

Keywords: Chloramination; competing precursor; N-nitrosodimethylamine; (photo)electrocatalytic oxidation; ranitidine

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1. Introduction

Emerging organic micropollutants, i.e. pharmaceuticals and personal care products (PPCPs), are of growing environmental concern because of their frequent occurrence and transformation products exhibit high toxicity (Kasprzyk-Hordern et al., 2008). PPCPs and their metabolites can be transformed to more toxic and carcinogenic byproducts during water and waste water treatment processes. Among them, N-nitrosodimethylamine (NDMA), is a potent carcinogen and nitrosamine is frequently nitrosamine from water chloramination (Sharma, 2012). An H$_2$-receptor antagonist, ranitidine (RNT), was characterized by molar yields of NDMA up to 90% upon chloramination (Shen and Andrews, 2010). Such an unusually high yield of NDMA from RNT is a result of its molecular structure, i.e. a furan ring and a stable carbocation (Selbes et al., 2012). RNT contains multiple moieties that are susceptible to the attacks of reactive oxygen and chlorine species during chloramination (Le Roux et al., 2012), photo-Fenton or photocatalytic oxidation (Radjenović et al., 2010), ozonation (Christophoridis et al., 2016), electrochemical oxidation (Jasper et al., 2016), and chemical oxidation (Wang et al., 2015). The NDMA formation potential (FP) of a given precursor could be defined as the maximum yield of NDMA via electrophilic or nucleophilic substitution in the presence or absence of ammonium ions (Andrzejewski and Nawrocki, 2007; Wang et al., 2015). Thus far, NDMA FP values have been observed upon chloramination among many types of advanced oxidation processes.

Early studies of NDMA mitigation strategies showed that pre-oxidation of the precursor before chloramination could reduce the NDMA FP (Selbes et al., 2014). The key structural groups of the NDMA precursors could be transformed or deactivated by strong oxidants such as ozone, chlorine, ferrate, and potassium permanganate (Selbes et al., 2014; Shen and Andrews, 2013; Wang et al., 2015). However, in some cases, specific pre-oxidants could promote the formation of NDMA or regulated disinfection by-products (DBPs), including trihalomethanes (Wang et al., 2015). While the efficiency of pre-oxidation to reduce the NDMA FP primarily depends on the intrinsic chemical structure of the precursors and the water matrix, such as pH (Selbes et al., 2014), the array of precursors competing for the oxidants might be another consideration. To this end, the present study addresses the NDMA FP during chloramination of RNT for variable mixtures of potential NDMA precursors. Twelve compounds (Fig. 1) were selected as model compounds based on either detection frequency in aquatic environments or NDMA FP value. In addition, semiconductor photocatalysis (UV/TiO$_2$) and electrochemically generated reactive chlorine species (RCS) were evaluated as novel peroxidation methods for NDMA FP reduction.

2. Materials and methods

2.1. Reagent and chemicals

All selected model compounds were obtained from Sigma Aldrich. Sodium chloride, sodium hypochlorite (12.5%), ammonium chloride, sodium hydroxide, and sodium thiosulfate were purchased from Showa and Junsei chemicals. Unless described, all experiments were conducted using distilled water (ultrapure, conductivity 0.3 μs/cm, Humas). Phosphate buffer (pH 7) was prepared from potassium monobasic and potassium dibasic salts (from Sigma Aldrich). pH values were adjusted as needed using 5 N sodium hydroxide (Showa) and sulfuric acid (95%, Samchun chemicals). Reverse osmosis (RO) concentrate was obtained from a pilot plant near Pohang (Republic of Korea). Methanol, acetonitrile (both from Avantor), phosphoric acid, and trifluoroacetic acid (both from Sigma Aldrich) were used to prepare the eluent for high-performance liquid chromatography analysis. All experiments were performed in duplicate.

2.2. Pre-oxidation and chloramination of NDMA precursors

2.2.1 Chloramination of precursor mixtures

Chloramination experiments were conducted in 0.1-L amber bottles by the addition of 10 µM of RNT, 5 mM preformed NH$_2$Cl, and 10 µM of another precursor at pH 7.8 (10 mM phosphate
buffer) for 24 h of contact time. Samples were periodically withdrawn, quenched with excess sodium thiosulfate, and filtered through a polytetrafluoroethylene Whatman membrane filter before further analysis. Control experiments were examined in two trial setups (i) chloramination of RNT alone and (ii) chloramination of each co-existing compound without the addition of RNT.

2.2.2. Pre-oxidation followed by chloramination

Pre-oxidation experiments were conducted using RCS (0–0.2 mM) and immobilized TiO$_2$ (2.5 cm × 2.5 cm; 1.10 mg of TiO$_2$) under ultraviolet A (UVA) irradiation. A precisely given amount of RCS and 10 µM RNT (buffered with 2 mM phosphate solution) were reacted under variable pH (5.7–8.6) for 0–120 min. Unless specified otherwise, the pre-oxidation experiments were conducted using a 0.15 mM RCS concentration and a pH of 7.1 for 30 min of oxidation time. A 30-min ultraviolet (UV) photolysis or UV/TiO$_2$ oxidation was conducted inside a black box equipped with six 4-W black light blue lamps (λ = 350–400 nM, F10T8, Sankyo Denki, Japan) and a quartz reactor, in which an immobilized TiO$_2$ photocatalyst was hung inside a reactor containing a given amount of phosphate-buffered RNT solution. The procedures for immobilization of TiO$_2$ and RCS generation have been reported in our previous studies (Chung et al., 2018; Ramasundaram et al., 2017). Post-chloramination experiments were conducted in a similar manner as previously mentioned in section 2.1.1 except the samples were buffered with 10 mM phosphate at pH 7.1 for 6 h of chloramination time.

2.3. Analysis

Total chlorine and NH$_2$Cl were quantified using an ultraviolet-visible (UV-Vis) spectrophotometer (Scinco 3100, Korea or Hach DR 2700, USA) according to the $N,N$ diethyl-p-phenylenediamine /KI and indophenol methods, respectively. A high-performance liquid chromatography system (1260 infinity Quaternary LC VL, Agilent, USA) equipped with a UV-Vis detector and C18 column was used to monitor the concentrations of NDMA and RNT.

3. Results and discussion

3.1. Effect of co-existing compounds

As compared to other pharmaceuticals and amine-based substances, RNT has an unusually high NDMA yield upon chloramination. Despite diverse experimental protocols (Table 1), previous studies have reported 40–97% of molar yield during chloramination (Farré et al., 2016; Gan et al., 2015; Le Roux et al., 2011; Seid et al., 2018; Selbes et al., 2012; Shen and Andrews, 2010; Spahr et al., 2017a, 2017b). The RNT has a structure liable to chloramine while the carbon between the furan ring and DMA moiety of RNT with an electron donating heteroatoms plays a critical role during stabilization of the carbocation intermediates (Bond et al., 2017; Selbes et al., 2012). However, a previous study (Liu et al., 2014) has demonstrated that nitrosating agents could be generated during chloramination of tertiary amines. In this mechanistic view, the molecular structure of RNT might favor a self-catalytic generation of nitrosating agents and stable carbocation (i.e. NDMA generation). In this regard, it can be hypothesized that the nitrosating agents might enhance the formation of NDMA from other amine-containing compounds.

The NDMA formation was evaluated in batch experiments by chloramination of model compounds in various categories; (i) DMA, (ii) thioether compounds without a DMA moiety (SMX, CMT, and FMT), (iii) compounds with a tertiary amine at the center of the structure (MCP, TEA, DEHA, and TEAO), and (iv) a branched amine with Alkyl-R group (NZT, VLX, TMB, and PMZ). Fig. 2a shows the wide variability in NDMA FP during the chloramination of a single compound. A group of histamine H$_2$-receptors (CMT and FMT) and SMX without a DMA moiety showed negligible NDMA FP, as readily expected. Even with a tertiary amine moiety at the center, marginal NDMA FP was observed for TEA, TEAO, and DEHA under our experimental conditions, consistent with a previous study (Chen et al., 2011). In addition, for RNT, the highest NDMA yield was observed for NZT (7.0%), followed by TMP (3.2 %), PMZ (2.8 %), MCP (1.2 %), DMA (1.13 %), and VLX (0.8). To the best of our
knowledge, NDMA generation upon chloramination of TMP and MCP has not been previously reported, whereas the others have already been identified as NDMA precursors (Bond et al., 2017; Shen and Andrews, 2010).

Fig. 2b shows the ultimate concentration of NDMA for the chloramination of RNT in the presence of another precursor compound (10 μM each). As a reference, chloramination of 20 μM RNT produced 12.8 μM. The results showed that the effects of the coexisting precursor on the NDMA FP of RNT has a negligible correlation with the NDMA FP of the precursor itself. SMX, TEOA, and TEA resulted in significant reductions in the NDMA FP of RNT, while less pronounced decreases occurred via the addition of NZT, CMT, and FMT. The NDMA FP values with and without the addition of VLX, PMZ, and DMA were superimposable. In addition, a complete inhibition on NDMA formation was observed in the presence of DEHA, whereas the ultimate NDMA concentrations were elevated under simultaneous addition of MCP or TMP.

The reduced NDMA FP by a subset of co-existing precursors might be ascribed to competing reactions consuming NH₂Cl, dissolved oxygen, and reaction intermediates. For instance, upon chloramination, SMX can yield an N-centered adduct or reaction intermediates as a result of bond rapture on the isoxazole ring, aromatic amine, and sulfonamide moiety (Gao et al., 2014). A fast chlorine transfer to a group of H₂ blockers could generate sulfoxide and/or imidazole-containing compounds (Buth et al., 2007). Considering the excess amount of NH₂Cl, however, scavenging reactions either for dissolved oxygen or principal reaction intermediates would account for the inhibition on NDMA formation. The well-known oxygen scavenger DEHA would deplete a source for nitroso functionality or N-peroxyl radicals, which has been suggested to be a principal intermediate for NDMA formation during chloramination of RNT (Spahr et al., 2017a). The compounds with diethylamine moiety (TEOA and TEA) might compete with the terminal amines for N-peroxyl radicals to generate N-nitrosodiethylamine (Chen et al., 2010). The present results showed that self-catalytically generated nitrating agents play a limited role in NDMA formation, given the limited enhancement of NDMA FP from the co-existing tertiary amines.

However, it cannot be ruled out that amine-enhanced chloramination or self-catalytic nitrosation by RNT might lead to the transformation of co-existing compounds to other types of nitrosamines and DBPs.

3.2. Effects of pre-oxidation on the NDMA FP

3.2.1. Pre-oxidation by RCS

The degree of RNT degradation by chlorination was observed to increase with initial oxidant dose and pre-oxidation time. Approximately 90.2% of the RNT was removed within 30 min of oxidation duration and an [RCS]₀ of 50 μM. These results are in accordance with previous studies on chemical (Jeon et al., 2016; Zhang et al., 2014) and electrochemical (Jasper et al., 2016) chlorination of RNT. The chlorinated samples were analyzed after the pretreatment was exposed to the subsequent chloramination (5 mM preformed NH₂Cl) to assess the variations in NDMA FP. Fig. 3 illustrates the ultimate NDMA concentration from the chloramination of RNT in response to initial [RCS]₀, pre-oxidation time, and pH. At a fixed pre-chlorination duration of 30 min, an increasing [RCS]₀ up to 0.2 mM showed a significant decrease in the final NDMA concentration, from 8.8 to 0.06 μM (Fig. 3a). At a fixed [RCS]₀ of 0.15 mM, the NDMA formation monotonically and nearly exponentially decreased with the contact time up to 30 min (Fig. 3b). The reduction in NDMA FP was maximized at [RCS]₀/[RNT]₀ of approximately 15 to 20, in accordance with the earlier studies on pre-chlorination of RNT (Jeon et al., 2016).

At the given contact time (30 min) and [RCS]₀ (0.15 mM), the efficacy of the pre-chlorination was also significantly affected by pH (Fig. 3c). The reduction in NDMA FP during the pre-oxidation would be associated with removal or deactivation of core moieties, i.e. DMA and the furan ring of RNT (Jeon et al., 2016; Wang et al., 2015). The pH value would primarily affect such chlorine-moiety reactivity, which in-turn would influence the generation of radical intermediates, stability of leaving group, and ultimately NDMA FP during subsequent chloramination. Without pre-chlorination, NDMA formation was significantly retarded at a pH ~ 6 because of the dominance of dichloramine. At this pH value, there was an unapparent change in the NDMA FP due to the pre-
chlorination. It is known that chlorine reaction rate constants with neutral (deprotonated) primary or secondary amines are generally much greater than those with tertiary amines (Deborde and von Gunten, 2008). Therefore, at a low pH value, chlorine transfer on thioether or acetamidine moiety would be favorable to that on the protonated DMA moiety. The chlorine transfer to the acetamidine moiety would not significantly contribute to the NDMA FP reduction (Jeon et al., 2016). In addition, a chlorine attack on the thioether moiety would form more reactive daughter analogs such as 5-(dimethyl-aminoethyl)furfuryl alcohol, a potent NDMA precursor upon chloramination (Le Roux et al., 2012).

In contrast, virtually complete destruction of the NDMA FP was obtained at a circum-neutral pH (6.5 and 7.1), whereas limited (approximately 68.5%) reduction was observed at a pH of 8.6. At a circum-neutral pH, electrophilic substitution of free chlorine on the furan ring and DMA moiety of RNT is expected to be significant (Jeon et al., 2016). A chlorine transfer on the furan moiety could affect the stability of carbocation and favor N-dealkylation, decreasing the NDMA FP during chloramination (Wang et al., 2015). In addition, reaction of free chlorine species with the deprotonated amine moiety of RNT would yield chlorammonium intermediates (Abia et al., 1998), hampering further interaction with monochloramine (amination) and the NDMA formation. However, at a pH > 8, the free chlorine should be dominated by hypochlorite ions with lower reactivity with the terminal amine than that of the HOCl. A limited reduction in NDMA FP under basic conditions has also been reported, specifically for the pre-chlorination of RNT (Selbes et al., 2014). Consequently, the optimal pH for an insignificant level of NDMA FP was found to range from 6.5 to 7.

The impacts of the water matrix on NDMA FP removal (Shen and Andrews, 2013) was further investigated in reverse osmosis (RO) brine water, considering that chloramine-based cleaning of membranes may potentially generate NDMA. A part of the dissolved precursors would be present in the concentrate (Farré et al., 2011), leading to NDMA formation during chloramination. As shown in Fig. 4, spiking 10 µM RNT in RO concentrate resulted in an NDMA FP comparable to the value in DI water within 6 h of chloramination ([NH₂Cl]₀ = 5 mM, pH = 7.1). As a control, chloramination of the RO concentrate without spiking generated marginal (0.5 µM) NDMA. However, pre-oxidation with RCS showed only a 43% reduction in the NDMA FP (Fig. 4) in the brine water. A substantial fraction of RCS could be quenched by dissolved organic compounds, intervening with the removal or deactivation of core moieties in RNT. Nevertheless, a prolonged oxidation with RCS up to 24 h led to a more significant reduction in NDMA FP (data not shown).

The effects of UV/TiO₂ treatment on the NDMA FP were assessed based on a substrate-immobilized TiO₂ nanofiber photocatalyst, whose preparation procedure and activity for degradation of model organic pollutants are reported elsewhere (Ramasundaram et al., 2017). RNT was completely degraded within 40 min of irradiation. Using UV photolysis alone, as shown in Fig. 5, the NDMA FP of RNT was reduced by ca. 50%, in agreement with the previous report (Farré et al., 2012). Analogous irradiation with TiO₂ further reduced the NDMA FP up to 84.0%. A longer irradiation resulted in a complete deactivation of NDMA FP from RNT (data not shown). During the photocatalytic oxidation of RNT, reactive oxygen species including OH radicals would rapidly attack the photo-labile moieties of RNT, leading to N-oxides, S-oxides, and N-dealkylated products (Loddo et al., 2005; Radjenović et al., 2010). An oxygen transfer to DMA moiety and N-dealkylation was reported to inhibit a nucleophilic initiation and remove NDMA FP during subsequent chloramination (Wang et al., 2015).

4. Conclusion

This study investigated the effects of the water matrix and competing precursor compounds on NDMA formation during chloramination of RNT. In addition, RCS and UV/TiO₂ were evaluated as potential pre-oxidation methods to reduce the NDMA FP. The NDMA FP of RNT in a mixture with a competing precursor showed a
negligible correlation with that of the co-existing compound itself. The observed variations in the NDMA FP were attributed to competitive reactions demanding NH$_2$Cl, dissolved oxygen, and radical intermediates. TMP and MCP were first identified as potential NDMA precursors upon chloramination, with their NDMA FP values being approximately twice that of DMA and similar to that of DMA, respectively. The reduction in NDMA FP was influenced by pre-oxidation dose, time, and pH. The NDMA FP decreased with increasing pre-oxidation time and RCS dose, while the optimal pH with the highest reduction in NDMA FP was 6.5–7. The pre-oxidation with RCS showed only a 43% reduction in the NDMA FP in the RO concentrate when compared to that of the distilled water. Pre-oxidation with UV/TiO$_2$ resulted in an 84% reduction in the NDMA FP.

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References

Table 1 NDMA formation potential from RNT during chloramination

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<tr>
<th>[RNT]₀ (µM)</th>
<th>[NH₂Cl]₀ (mM)</th>
<th>pH</th>
<th>Contact time (hours)</th>
<th>*Molar yield (%)</th>
<th>Reference</th>
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<td>0.2</td>
<td>1.4</td>
<td>7.5</td>
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<td>80.5</td>
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</tr>
<tr>
<td>3</td>
<td>0.045</td>
<td>7.0–8.0</td>
<td>Over 11</td>
<td>84–97</td>
<td>(Spahr et al., 2017a, 2017b)</td>
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<tr>
<td>14.8</td>
<td>4</td>
<td>8.5</td>
<td>120</td>
<td>40.2</td>
<td>(Le Roux et al., 2011)</td>
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<tr>
<td>0.025</td>
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<td>7.0</td>
<td>24</td>
<td>89.9</td>
<td>(Shen and Andrews, 2010)</td>
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<tr>
<td>20</td>
<td>5</td>
<td>7.0</td>
<td>6</td>
<td>77.7</td>
<td>(Seid et al., 2018)</td>
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<tr>
<td>2</td>
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<td>7.0</td>
<td>120</td>
<td>65.7</td>
<td>(Gan et al., 2015)</td>
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<tr>
<td>6.5</td>
<td>2</td>
<td>6.8</td>
<td>168</td>
<td>50</td>
<td>(Farré et al., 2016)</td>
</tr>
<tr>
<td>10</td>
<td>5</td>
<td>7.8</td>
<td>24</td>
<td>67.4–89.9</td>
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* Observed molar yield based on initial RNT concentration in DI water matrix.
Fig. 1 Structures of model compounds
Fig. 2 NDMA formation from selected precursors (a) and the effect of co-exiting compounds (b) on NDMA FP during RNT chloramination (b). ([NH2Cl]0 = 5 mM, pH = 7.8, [precursors]0 = 10 μM, and 24 h).
Fig. 3. NDMA formation from RNT upon pre-oxidation with RCS: effect of (a) RCS dose, (b) pre-oxidation time, and (c) pre-oxidation pH. (Post-chloramination, [NH₂Cl]₀ = 5 mM, pH = 7.1, and 6 h).
Fig. 4 Formation of NDMA during chloramination of RNT (10 µM) spiking in DI water and RO concentrate with or without pre-oxidation ([RCS]₀ = 0.15 mM, pH = 7.1, and pre-oxidation = 30 min).
Fig. 5 Effect of pre-oxidation by UV and UV/TiO$_2$ on NDMA FP, after post-chloramination ($[\text{NH}_2\text{Cl}]_0 = 5$ mM, pH = 7.1, and 6 h). Light intensity = $3.33 \times 10^{-4}$ E min$^{-1}$L$^{-1}$ and pre-oxidation = 30 min.