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NDMA FORMATION MECHANISM BY CHLORAMINATION OF TERTIARY AMINES

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Abstract

Chloramination is used to reduce the formation of regulated disinfection by-products (i.e. trihalomethanes and haloacetic acids), or to avoid biofouling of membranes during wastewater reclamation processes. However, chloramination favors the formation of N-nitrosodimethylamine (NDMA), a human carcinogen. Proposed NDMA formation mechanisms used dimethylamine as a model precursor, but some anthropogenic tertiary amines presenting dimethylamine (DMA) functional groups have been demonstrated to lead to important amounts of NDMA (e.g. the pharmaceutical ranitidine). In this study, the mechanisms of NDMA formation by chloramination of tertiary amines (including model compounds presenting aromatic or heterocyclic rings, e.g. (dimethylaminomethyl)furfuryl alcohol (DFUR) or ranitidine) were studied. Compounds presenting heterocyclic rings substituted with DMA functions (e.g. DFUR, ranitidine) show much higher conversion rates to NDMA than other tertiary amines or DMA. A mechanism is proposed to explain the high yields of NDMA obtained from the decomposition of these tertiary amines during chloramination. This mechanism is based on the production of a carbocation intermediate formed from the methylated aromatic moieties present in the compounds, favouring the release of NDMA.

Keywords

NDMA; Nitrosamines; Chloramination; Disinfection by-products; Ranitidine; Tertiary amines
**INTRODUCTION**

Monochloramine is used as disinfectant to reduce the formation of regulated disinfection by-products (DBPs) such as trihalomethanes (THMs) and haloacetic acids (HAAs). Monochloramine can also be used in reclaimed water treatment plants to avoid biofouling of membranes. However, chloramination favors the formation of N-nitrosamines, including N-nitrosodimethylamine (NDMA), a probable human carcinogen (U.S. Environmental Protection Agency, 1987).

Over the last decade, many formation mechanisms have been proposed to explain the formation of NDMA during chloramination (Choi and Valentine, 2002; Mitch and Sedlak, 2002; Schreiber and Mitch, 2006). Common mechanisms are based on a nucleophilic substitution between monochloramine (NH$_2$Cl) and dimethylamine (DMA), forming an Unsymmetrical Dimethylhydrazine (UDMH) intermediate (Choi and Valentine, 2002; Mitch and Sedlak, 2002). Monochloramine is then proposed to rapidly oxidize UDMH to form NDMA (< 3% molar yields). Schreiber and Mitch (2006) demonstrated that dichloramine (NHCl$_2$) and dissolved oxygen concentrations may enhance the formation of NDMA (Schreiber and Mitch, 2006). They proposed a mechanism based on the formation of a chlorinated UDMH (UDMH-Cl) rather than UDMH, followed by dissolved O$_2$ incorporation to form NDMA.

Some studies have indicated that the amounts of DMA present in surface waters or secondary municipal wastewaters cannot be sufficient to explain the amount of NDMA formed (Gerecke and Sedlak, 2003; Mitch and Sedlak, 2004). NDMA formation potentials of anthropogenic tertiary or quaternary amines such as pesticides, pharmaceuticals or personal care products have been pointed out to explain NDMA yields observed in water treatment plants using chloramination (Mitch and Sedlak, 2004; Schmidt et al., 2006; Kemper et al., 2010; Le Roux et al., 2011; Shen and Andrews, 2011).

It has been suggested that the formation of NDMA from tertiary amines occurs through the formation of an iminium intermediate followed by degradation into secondary amines (i.e. DMA) (Mitch and Sedlak, 2004). This supplementary step would explain the lower NDMA yields observed from trimethylamine (TMA) as compared to DMA (Mitch and Sedlak, 2002). This mechanism has been confirmed during chloramination of diuron (a phenylurea herbicide), leading to the formation of dichloroaniline and DMA and subsequent formation of NDMA (Chen and Young, 2008). However, some tertiary amines have been demonstrated to form more NDMA than DMA does. Especially, the pharmaceutical ranitidine (a histamine antagonist often used for peptic ulcer treatment) is of particular interest because of its high molar conversion rate into NDMA (> 60%) (Schmidt et al., 2006; Le Roux et al., 2011; Shen and Andrews, 2011). 5-(dimethylaminomethyl)furfuryl alcohol (one of the compounds used for the production of ranitidine) has been shown to form as much NDMA as ranitidine, indicating that this structure would be responsible for the high yields observed with ranitidine (Schmidt et al., 2006).

In this study, the NDMA formation potential of several nitrogen-containing organic compounds is investigated from the reaction with monochloramine. In order to better understand the role of molecular structures (especially aromatic rings or heterocyclic compounds) on the formation of NDMA, selected model compounds include various aromatic moieties substituted with DMA groups (Figure 1). We compare NDMA formation potentials with the formation of several halogenated DBPs such as trihalomethanes (THMs), haloacetonitriles (HANs), haloketones (HKs) or trichloronitromethane (TCNM, also known as chloropicrin). A mechanism is proposed to explain the high yields of NDMA obtained from the decomposition of some aromatic tertiary amines during chloramination.
Figure 1. Molecular structures of investigated compounds

MATERIALS AND METHODS

Materials
All experiments were conducted using deionized water (Milli Q, Millipore) buffered with sodium acetate (pH = 4.0 5.5), a mixture of sodium phosphate monobasic and sodium phosphate dibasic (pH = 7.0 8.5), or sodium carbonate (pH = 10). pH values were adjusted as needed using sodium hydroxide or sulfuric acid (0.1 N, Fisher Scientific). Fisher Scientific methylene chloride (GLC grade) and Carlo Erba methanol (>99.9 %) were used without further purification. Chemical structures of the investigated compounds are summarized in Figure 1. All of these compounds were used without further purification and were supplied through Sigma Aldrich. Sodium hypochlorite (NaOCl, 13 %, Acros Organics) and ammonium chloride (Fisher Scientific, 99.9 %) were used to prepare chloramines solutions. Anhydrous sodium thiosulfate (Fisher Scientific) was used to quench residual chloramines. Isotopically labeled standards, [6-2H] N-nitrosodimethylamine (NDMA-d6, 98 %, 1 mg.mL-1 in methylene chloride) and [14-2H] N-nitrosodi-n-propylamine (DPNA-d14, 98 %, 1 mg.mL-1 in methylene chloride) were obtained from Cambridge Isotope Laboratories (Andover, MA, USA). A standard solution containing seven N nitrosamines (2000 µg/mL each in methylene chloride) was purchased from Supelco (Sigma-Aldrich). The SPE materials used to
extract nitrosamines from aqueous solutions consisted in Supelclean™ prepacked coconut charcoal EPA 521 tubes, 2g/6ml, supplied through Supelco. Standards solutions of trihalomethanes (100 µg/mL each) and of haloacetonitriles (HANs), trichloronitromethane (TCNM) and haloketones (HKs) (EPA 551B Halogenated Volatiles Mix, 2000 µg/mL each) and internal standard 1,2-dibromopropane were supplied from Supelco.

Chloramination experiments
All glassware used during these experiments was washed with deionized water and baked at 500 °C for at least 5 hours prior to use. Monochloramine (NH₂Cl) stock solutions were prepared by dissolving ammonium chloride (NH₄Cl) in deionized water adjusted to pH = 8.5 with sodium hydroxide. Sodium hypochlorite (NaOCl) was then added slowly to the rapidly stirred solution, at a Cl:N molar ratio of at least 1:1.2 to avoid breakpoint chlorination resulting from local excess of hypochlorite (Mitch and Sedlak, 2002). Adjusting the pH at 8.5 minimizes the disproportionation of NH₂Cl to dichloramine (NHCl₂), since NHCl₂ forms at pH < 8 (U.S. Environmental Protection Agency, 1999).

Reactions were conducted in sealed 1 L amber glass bottles at room temperature, under dark conditions to avoid photolysis of NDMA. Chloramination experiments were conducted following the approach of Mitch et al. (Mitch et al., 2003), using high concentrations of monochloramine (2.5 mM) and a reaction time of 24 h for most of our experiments. Solutions were prepared by dissolving a pre-determined amount of compounds investigated in 1 L of 10 mM buffer. 100 mL of preformed monochloramine was then added to the working solution. Each series of experiments included a blank (deionized water buffered and chloraminated) and samples were conducted in triplicate. At given contact time, 850 mL of samples were processed for nitrosamines analyses, and 250 mL were transferred for residual chlorine analysis and other DBPs analyses. Percent molar yields were calculated using the initial molar concentration of the studied compounds, following equation 1.

\[
\text{DBP yield (\%)} = \frac{[\text{DBP}]\text{(nM)}}{[\text{Organic compound}]_0\text{(nM)}} \times 100
\]

Analytical methods
NH₂Cl and NHCl₂ were quantified by spectrophotometric measurement using their respective molar extinction coefficients at 245 nm and 295 nm. Residual chloramines were analyzed by iodometric titration (Eaton, 1995). Nitrosamines were analysed following the US EPA method 521 (U.S. Environmental Protection Agency, 2004), consisting in a solid-phase extraction (SPE) using coconut charcoal tubes followed by GC/MS analysis in EI mode. Analytical details are provided elsewhere (Le Roux et al., 2010) and are summarized below. Chloramination reactions were quenched using ~2 g sodium thiosulfate before SPE. Prior to the extraction, NDMA-d₆ was added to each sample as an internal standard. Each sample was passed through a SPE cartridge under slight vacuum. Analytes were then eluted from the SPE bed with 15 mL methylene chloride. Extracts were concentrated down to 1 mL under a stream of N₂, and DPNA-d₁₄ was added as a recovery standard. Samples extracts were analyzed after SPE using a HP 6890 series gas chromatograph system coupled with a HP 5973 mass selective detector (MSD) in electron ionization (EI) mode. Quantitative analyses were performed in selected-ion monitoring (SIM) mode. Quantitation ions were 74 m/z for NDMA, 80 m/z for NDMA-d₆, 78 and 144 m/z for DPNA-d₁₄, 70 and 130 m/z for DPNA. Full scan mode (40 - 240 m/z) analyses were also conducted for complementary spectral information. This method reached extraction efficiencies of
approximately 85 %, and the method detection limit (MDL) for NDMA at the 99 % confidence level was determined to be 33 ng/L. THMs, HANs, HKs and TCNM analysis was based on the US EPA 551.1 method, which consists in a liquid-liquid extraction (LLE) using MTBE followed by GC/MS analysis in EI mode (Munch and Hautman, 1995).

RESULTS AND DISCUSSION

Table 1 shows the formation of nitrosamines, DCAN, TCNM, 1,1-DCP and TCM by chloramination of selected compounds after 24 h of reaction at pH 8 (10 mM phosphate buffer). From the pool of compounds, 5-(dimethylaminomethyl)furfuryl alcohol (DFUR) exhibited the highest molar yield with 74.9% NDMA formed. DMP30 also formed important amounts of NDMA (59.9% yield), which can be partly related to the presence of three dimethylamine groups in its structure. TMA formed NDMA in similar amounts than DMA (i.e. 2.3%). These results are in accordance with NDMA formation potentials of DMA (2.6%) and TMA (2.0%) after 10 days reported by Mitch and Sedlak (Mitch and Sedlak, 2004). NDMA yields from other tertiary amines than DFUR and DMP30 were always lower than that from DMA.

Table 1. Formation of NDMA, TCNM, 1,1-DCP and TCM by chloramination (2.5 mM) of model compounds (500 nM) over 24 h at pH 8 with 10 mM phosphate buffer

<table>
<thead>
<tr>
<th>Compound investigated</th>
<th>Nitrosamine&lt;sup&gt;b&lt;/sup&gt;</th>
<th>DCAN</th>
<th>TCNM</th>
<th>1,1-DCP</th>
<th>TCM</th>
</tr>
</thead>
<tbody>
<tr>
<td>DFUR</td>
<td>74.9 (1.1)</td>
<td>0.7 (0.2)</td>
<td>-</td>
<td>0.2 (0.02)</td>
<td>-</td>
</tr>
<tr>
<td>DMP30</td>
<td>55.2 (5.4)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>DMA</td>
<td>2.3 (0.2)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1.4 (0.6)</td>
</tr>
<tr>
<td>TMA</td>
<td>2.3 (0.3)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1.1 (0.1)</td>
</tr>
<tr>
<td>CVL</td>
<td>1.8 (0.3)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>MB</td>
<td>1.6 (0.1)</td>
<td>5.8 (0.8)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>DPYR</td>
<td>1.6 (0.1)</td>
<td>1.2 (0.2)</td>
<td>0.3 (0.04)</td>
<td>0.2 (0.1)</td>
<td>-</td>
</tr>
<tr>
<td>DPD</td>
<td>1.4 (0.1)</td>
<td>0.7 (0.1)</td>
<td>0.1 (0.02)</td>
<td>-</td>
<td>2.1 (0.6)</td>
</tr>
<tr>
<td>DPHE</td>
<td>1.0 (0.1)</td>
<td>2.8 (0.1)</td>
<td>0.5 (0.03)</td>
<td>0.7 (0.07)</td>
<td>21.2 (3.8)</td>
</tr>
<tr>
<td>DMPD</td>
<td>0.9 (0.1)</td>
<td>0.5 (0.1)</td>
<td>-</td>
<td>-</td>
<td>2.3 (0.3)</td>
</tr>
<tr>
<td>DFUL</td>
<td>0.53 (0.07)</td>
<td>2.9 (0.6)</td>
<td>2.1 (0.5)</td>
<td>8.9 (0.7)</td>
<td>-</td>
</tr>
<tr>
<td>DPYRI</td>
<td>0.37 (0.01)</td>
<td>0.7 (0.1)</td>
<td>0.1 (0.02)</td>
<td>0.7 (0.02)</td>
<td>-</td>
</tr>
</tbody>
</table>

<sup>a</sup> SD = Standard Deviation on 3 replicates  
<sup>b</sup> Nitrosamine formed is NDMA except for DPD (DENA)

Weak precursors of NDMA produced higher amounts of halogenated DBPs (DCAN, TCNM, 1,1-DCP and TCM) than DFUR, DMP30 or DMA. DPHE led to important yields of chloroform (21.2%) (Table 1). The presence of a DMA substituent, an even stronger electron-donating group than hydroxyl (known to activate the benzene ring for electrophilic aromatic substitution) can explain the high yields of TCM observed. Although crystal violet lactone (CVL), DMP30 and methylene blue (MB) present benzene rings substituted with DMA groups, the absence of activating groups in meta position explains that no TCM was formed from these compounds.
Compounds presenting furan rings substituted with DMA functions (i.e. DFUR and ranitidine) form more NDMA than other compounds (especially DMA). Hence, current proposed mechanisms, based on DMA as a precursor, cannot explain these results.

**Effect of pH and chloramine speciation**

The formation of NDMA from DFUR and NH\(_2\)Cl exhibited a maximum at around pH 8 (Figure 2). This observation is similar to previous results obtained for ranitidine (Le Roux et al., 2011). Molar yields reached 84% at pH 8, while ranitidine formed only 60% of NDMA in the same conditions. The presence of this optimum was attributed to the pKa of ranitidine (pKa = 8.2). At pH < 8, NH\(_2\)Cl is decomposed into NHCl\(_2\), which would explain why NDMA formation decreases. At pH > 8, it was hypothesized that the lower concentration of the protonated form of ranitidine would lead to a decrease in NDMA formation.

![Figure 2](image)

Figure 2. Effect of pH on NDMA formation from 125 nM DFUR and 2 mM NH\(_2\)Cl or 1 mM NHCl\(_2\) over 48 h with 10 mM buffer (acetate for pH 4.0-5.5, phosphate for pH 7.0-8.5 and carbonate for pH 9.5-11).

The influence of pH on NDMA was also investigated by application of dichloramine (NHCl\(_2\)) on DFUR (Figure 2). Almost no NDMA was formed at pH 4, where NHCl\(_2\) is the major chloramine species. Therefore, NHCl\(_2\) does not seem to play a role in NDMA formation from DFUR. At pH < 7, NDMA formation increased with pH and exhibited similar yields with either NH\(_2\)Cl or NHCl\(_2\) as initial oxidant entity injected. At pH > 4, NHCl\(_2\) decomposition leads to the formation of NH\(_2\)Cl, according to equation 2.

\[
\text{NHCl}_2 + \text{NH}_4^+ + \text{OH}^- \rightarrow 2 \text{NH}_2\text{Cl} + \text{H}_2\text{O}
\]  

(2)

The amounts of NH\(_2\)Cl formed from NHCl\(_2\) decomposition could be responsible for NDMA formation at pH > 4. Hence, the influence of NHCl\(_2\) on NDMA formation (as proposed by Schreiber & Mitch, 2006) cannot be clearly established in the case of DFUR chloramination. At pH > 7, NDMA formation observed when injecting preformed NHCl\(_2\) was lower than with NH\(_2\)Cl (Figure 2). This could be related to the lower concentration of NH\(_2\)Cl formed (C.t value of ~14 mM.h) as compared to the initially pure solution of NH\(_2\)Cl (C.t value > 90 mM.h). Furthermore, chloramines decomposition at alkaline pH leads to the formation of compounds such as hydrazines (Yagil and Anbar, 1962) or other unidentified products (Valentine et al., 1986) that could interfere with the formation of NDMA.
**Effect of dissolved oxygen and potential role of UDMH**

Dissolved oxygen has already been demonstrated to play a major role in NDMA formation by chloramination of DMA (Schreiber and Mitch, 2006) and ranitidine (Le Roux et al., 2011). A similar impact was observed by chloramination of DFUR, which yielded 6.9% NDMA in the presence of only 0.3 mg O₂/L, while the formation of NDMA was 81% in saturated oxygen conditions (Figure 3).

![Figure 3. Effect of dissolved oxygen on NDMA formation from 250 nM DFUR and 2.5 mM, over 6 h at pH 8 with 10 mM phosphate buffer](image)

NDMA formation mechanisms proposed in the literature generally involve the formation of an Unsymmetrical Dimethylhydrazine (UDMH) intermediate from the nucleophilic substitution between dimethylamine and monochloramine. The potential role of UDMH in the formation of NDMA during chloramination of tertiary amines was evaluated. UDMH (500 nM) was chloraminated (2.5 mM NH₂Cl) at pH 8 during 24h in the presence of dissolved oxygen. Molar yields were very low (<0.01%), while the formation of NDMA from DFUR was maximized (>80% yields) in these conditions. Our results are in accordance with several studies that investigated UDMH oxidation by dissolved oxygen and/or NH₂Cl (Lunn and Sansone, 1994; Schreiber and Mitch, 2006). Hence, the formation of UDMH as an intermediate in the formation of NDMA from DFUR or ranitidine seems very unlikely to occur.

**Proposed mechanism for NDMA formation**

During chloramination of amines, either chlorine transfer or nucleophilic substitution can occur. Chlorine transfer from NH₂Cl to the nitrogen atom of the DMA group of ranitidine is unlikely to occur as a predominant pathway because it would only lead to the formation of DMA or dimethylchloramine (DMCA) that are minor precursors of NDMA (i.e., <3% molar yields) (Mitch and Sedlak, 2004; Choi and Valentine, 2002; Mitch and Sedlak, 2002). Several tertiary amines have been demonstrated to produce important yields of NDMA, especially ranitidine (>60% molar yield), and more recently dimethylbenzylamine (64% molar yield)(Kemper et al., 2010). As a result, a chlorine transfer (i.e., electrophilic substitution) cannot explain the high yields of NDMA obtained for those tertiary amines.

Based on these observations, we hypothesize that nucleophilic substitution rather than chlorine transfer is the main reaction occurring on the DMA moiety of ranitidine. Figure 4 summarizes pathways proposed to explain NDMA formation by chloramination of tertiary amines. We propose that DMA groups must be attached at the benzylic position of aromatic or heterocyclic rings in order to produce high yields of NDMA. Indeed, as proposed in Figure 4, the release of NDMA from the furan ring substituted with a DMA group leads to the formation of a stable carbocation at benzylic position of the furan ring that is favored thermodynamically. The formation of this carbocation was confirmed by HPLC-MS analyses of the
by-products formed during the chloramination of ranitidine (Le Roux et al., 2012).

The formation of NDMA by chloramination of DMA was previously proposed to occur via the formation of an UDMH or UDMH-Cl intermediate, followed by an oxidation in the presence of dissolved oxygen. However our results demonstrate that the formation UDMH is unlikely to be the main reaction occurring during chloramination of ranitidine or other highly reactive tertiary amines (e.g., DFUR or dimethylbenzylamine), because it would only lead to low NDMA yields (< 3%). Because the formation of UDMH and its oxidation by dissolved oxygen is not likely to occur, dissolved oxygen incorporation has to occur directly on the intermediate formed after the reaction between NH₂Cl and the DMA group of the tertiary amine.

Figure 4. Proposed NDMA formation pathways for the reactions between amines and monochloramine

Lower yields obtained for TMA and some other tertiary amines were previously attributed to the supplementary step leading first to the formation of DMA and then to NDMA (Mitch and Sedlak, 2004). During chlorination, chlorine transfer to the nitrogen atom of tertiary amines forms a chloroammonium ion (Ellis and Soper, 1954). Subsequent dehydrohalogenation and hydrolysis lead to the release of DMA and formaldehyde. A similar mechanism has been suggested during chloramination of tertiary amines (Mitch and Schreiber, 2008). However, during chloramination, either chlorine transfer or nucleophilic substitution can occur. Chlorine transfer from NH₂Cl to the nitrogen atom of tertiary amines is unlikely to occur because it would only lead to the formation of DMA or dimethylchloramine (DMCA), which are low precursors of NDMA. This cannot explain the high yields of NDMA obtained for several tertiary amines (e.g., ranitidine, DFUR, or dimethylbenzylamine). Only nucleophilic substitution (Reaction a in Figure 4), and stabilization of the resulting methylfuran carbocation can explain the observed high molar conversion rates. In contrast, when the DMA moiety is not placed at benzylie or methylfuran position, a nucleophilic substitution (Reaction b in Figure 4) leads to the release of DMA as shown in Figure 5, in a similar manner than through chlorine transfer during chlorination.
Subsequent chloramination of DMA (Reaction c in Figure 4) leads to the formation of NDMA in similar amounts than those observed from the secondary amine (i.e. < 3%). DMA reacts with NH₂Cl to form DMCA through chlorine transfer (Reaction d in Figure 4), thus limiting the amounts of DMA and NH₂Cl available for UDMH formation through nucleophilic substitution (Reaction c in Figure 4) (Choi and Valentine, 2002). UDMH can also be formed from the reaction between DMCA and NH₃ (Reaction e in Figure 4), but in smaller amounts than from DMA and NH₂Cl (Mitch and Sedlak, 2002).

The lower NDMA formation potentials observed for most of tertiary amines as compared to DMA can also be explained by competing reactions leading to the formation of other DBPs (e.g. DCAN, TCNM, 1,1-DCP or TCM) (Reaction f in Figure 4).

CONCLUSIONS

From the pool of compounds investigated, only a few compounds (i.e. DFUR and DMP30) exhibited important yields of NDMA following chloramination. All the other tertiary amines yielded less NDMA than DMA did (i.e. < 2.3%). This indicates that most aromatic structures are not important NDMA precursors. DMA groups must be attached at the benzylic position of aromatic or heterocyclic rings (e.g., benzylic or methylfuran moiety) to produce high yields of NDMA, because it enables the formation of a stable carbocation, favored thermodynamically.

We hypothesize that secondary and tertiary amines present a different reactivity towards NH₂Cl. Secondary amines (i.e. DMA) undergo electrophilic substitution to form DMCA, while tertiary amines would rather undergo nucleophilic substitution. As it was previously described for DMA and ranitidine (Schreiber and Mitch, 2006; Le Roux et al., 2011), the important role of dissolved oxygen was confirmed during chloramination of DFUR. The absence of dissolved O₂ significantly decreased the amount of NDMA formed, confirming that oxidation by O₂ is a key step in the formation mechanism of NDMA. However, UDMH is not likely to be a major intermediate involved in the formation of NDMA during chloramination of tertiary amines such as ranitidine or DFUR. Hence, we propose that dissolved oxygen incorporation occurs directly on the intermediate formed after the nucleophilic substitution between NH₂Cl and the DMA moiety.

Unlike previous studies, our results show that NHCl₂ would not be the main species involved in NDMA formation from DFUR. The influence of pH on NDMA formation remains unclear, especially at alkaline pH where chloramines decomposition can produce hydrazines and other unknown compounds that could contribute to reduce the formation of NDMA.
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