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Transformation of ranitidine during water chlorination and ozonation: Moiety-specific reaction kinetics and elimination efficiency of NDMA formation potential

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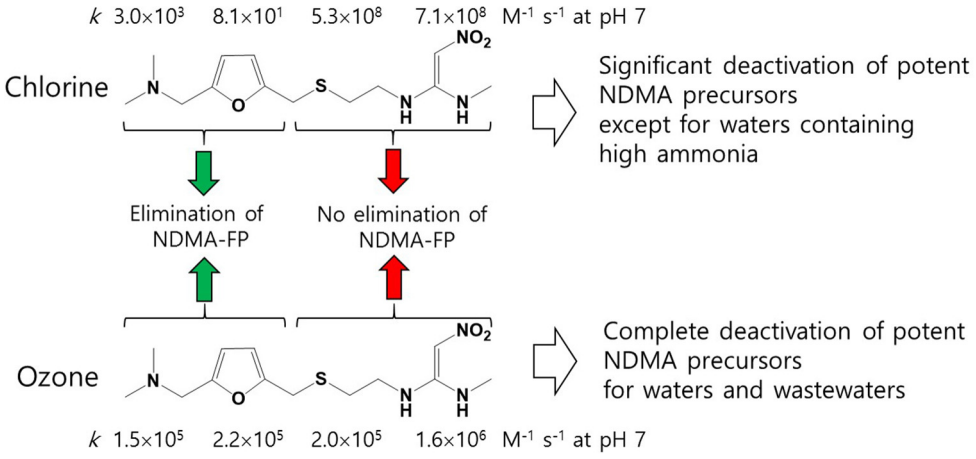
GRAPHICAL ABSTRACT



HIGHLIGHTS

- Moiety-specific reaction kinetics were determined for chlorine/ozone with ranitidine.
- NDMA-FP of ranitidine decreases when chlorine reacts with the tertiary amine moiety.
- Ozone reacts rapidly with the tertiary amine and furan moieties of ranitidine.
- Chlorine can deactivate potent NDMA precursors except for water with high ammonia.

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ABSTRACT

Ranitidine can produce high yields of *N*-nitrosodimethylamine (NDMA) upon chloramination and its presence in water resources is a concern for water utilities using chloramine disinfection. This study assessed the efficiency of water chlorination and ozonation in transforming ranitidine and eliminating its NDMA formation potential (NDMA-FP) by determining moiety-specific reaction kinetics, stoichiometric factors, and elimination levels in real water matrices. Despite the fact that chlorine reacts rapidly with the acetamidine and thioether moieties of ranitidine ($k > 10^8$ M^{-1} s^{-1} at pH 7), the NDMA-FP decreases

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significantly only when chlorine reacts with the less reactive tertiary amine ($k = 3 \times 10^3\ M^{-1}\ s^{-1}$ at pH 7) or furan moiety ($k = 81\ M^{-1}\ s^{-1}$ at pH 7). Ozone reacts rapidly with all four moieties of ranitidine ($k = 1.5 \times 10^5 - 1.6 \times 10^6\ M^{-1}\ s^{-1}$ at pH 7) and its reaction with the tertiary amine or furan moiety leads to complete elimination of the NDMA-FP. Treatments of ranitidine-spiked real water samples have shown that ozonation can efficiently deactivate ranitidine in water and wastewater treatment, while chlorination can be efficient for water containing low concentration of ammonia. This result can be applied to the other structurally similar, potent NDMA precursors.

1. Introduction

To cope with the stringent regulations governing disinfection by-products (DBPs), such as trihalomethanes (THMs) and haloacetic acids (HAAs), in chlorinated drinking water, chloramines have been increasingly used as an alternative disinfectant in the distribution systems of some countries [1]. Although chloramine disinfection is effective in minimizing the formation of regulated DBPs (e.g., THMs and HAAs), it is associated with the formation of *N*-nitrosamines [2,3]. Among the *N*-nitrosamine family, *N*-nitrosodimethylamine (NDMA) has received the most attention due to its frequent occurrence and high carcinogenic potency [2,3]. Even though NDMA is not regulated yet, guideline values or notification levels are set at low ng/L ranges in some countries [4,5].

Dimethylamine and tertiary amines containing *N*,*N*-dimethylamine moiety are known to produce NDMA during chloramination [2,3]. While the molar yields of NDMA formation from dimethylamine and most tertiary amines are less than 3%, a subset of tertiary amines, however, have been shown to form NDMA at considerably higher yields (e.g., 20%–90%) [2,3]. Ranitidine, a common anti-acid drug, is a representative example and has a tertiary amine with *N*,*N*-dimethyl and *N*-methylfuran groups (Fig. 1). The molar NDMA yield of ranitidine ranges from 60%–90% upon chloramination [6–8]. A molar NDMA yield of 78% and 84% was also reported for *N*,*N*-dimethyl-thiophene-2-methylamine and *N*,*N*-dimethyl-benzylamine, respectively [7]. Tertiary amines with *N*,*N*-dimethyl and *N*-isopropyl groups also form high NDMA (23%–84%), such as pharmaceutical methadone [9] and *N*,*N*-dimethyl-isopropylamine [7] (see Fig. S1 for the structures). Studies have shown that the β aromatic or isopropyl groups can easily leave from the key reaction intermediate of the reaction between the tertiary amines and monochloramine, leading to a higher NDMA yield [6,10]. In this study, the term "potent NDMA precursor" will be used to refer to the precursors with activated tertiary amine moieties forming >20% molar NDMA compared to the "regular NDMA precursors" having <3% molar NDMA.

Due to population growth and urbanization, drinking water resources worldwide are increasingly affected by the discharge of municipal or industrial wastewaters. Studies have shown that municipal wastewater effluents contain much higher concentrations of NDMA precursors compared to pristine natural waters [2,3]. While the exact sources and structural identities of the NDMA precursors are still unclear [11], potent NDMA precursors from tertiary amine-based pharmaceuticals, such as ranitidine [12–14] and methadone [9], or other structurally related compounds are likely to constitute a significant fraction of the total NDMA precursor pool of municipal wastewater effluents.

Pre-oxidation with chlorine, ozone, and some other oxidants has been tested to decrease the NDMA formation in the post chloramination process by transforming the key structural moieties of NDMA precursors. The pre-oxidation of natural waters affected by wastewater discharge showed significant decreases in the NDMA formation potential (NDMA-FP), especially for ozonation and chlorination [15–18]. Even though the results of these studies are valuable for assessing pre-oxidation efficiency for NDMA formation control, their generalized applications to other waters can sometimes be limited due to the complex, uncharacterized nature of the NDMA precursors. In addition, the previous studies mainly focused on drinking water matrices, and the pre-oxidation efficiency for wastewater effluent matrices is currently poorly understood.

Pre-oxidation has also been tested for deactivating various specific NDMA precursors, such as amine-based pharmaceuticals and water treatment polymers. After the oxidation, the NDMA-FP decreased significantly for several compounds [15,19,20]. However, the NDMA-FP sometimes did not decrease or even increase, depending on the type of precursors/oxidants or treatment conditions [19–23], which requires further investigations. Reductions in the NDMA-FP after ozonation or chlorination have been reported for some potent NDMA precursors, including ranitidine [19,20,24]. Nevertheless, it is still difficult to design oxidation processes that are generally applicable to various NDMA precursors or water matrices due to the lack of principle-based reaction kinetics and stoichiometric information. This is critical in determining optimal oxidant dose and contact time (i.e., oxidation exposure) to maximize NDMA precursor mitigation with the formation of the regulated DBPs under control.

This study aims to assess the efficiency of pre-chlorination and pre-ozonation to deactivate potent NDMA precursors using ranitidine as a representative compound. Reaction kinetics and stoichiometric factors were determined for each structural moiety of ranitidine (Fig. 1) and the corresponding NDMA-FP elimination. The elimination of ranitidine and the deactivation of its NDMA-FP were determined in simulated water treatment conditions using natural water and wastewater effluent samples and discussed with the chemical kinetics models.

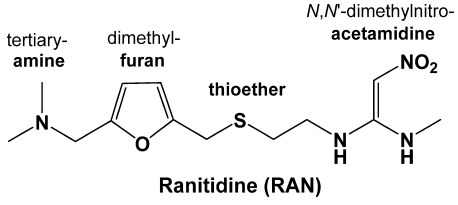

Fig. 1. Ranitidine and its sub-structural moieties.

2. Materials and methods

2.1. Standards and reagents

All chemicals and solvents were purchased from various commercial suppliers and used as received. The details regarding the preparation of the oxidants are provided in SI-Text-1.

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