Unveiling formation mechanism of carcinogenic N-nitrosodimethylamine in ozonation of dimethylamine: A density functional theoretical investigation

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HIGHLIGHTS

- Formation mechanism of NDMA in ozonation of dimethylamine is revealed based on DFT.
- NDMA is found to be formed through a hydroxylamine mechanism.
- HO
- oxidizing dimethylamine produces hydroxylamine.
- O_3 or HO
- oxidizing unsymmetrical dimethylhydrazine produces NDMA.
- NDMA yield is related with dissociation states of dimethylamine and hydroxylamine.

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ABSTRACT

Recent studies found that ozonation of organic pollutants with dimethylamino groups produces N-nitrosodimethylamine (NDMA) that is highly carcinogenic to humans. However, the formation mechanism of NDMA remains inexplicit, and previously proposed mechanisms are inconsistent with experimental observations. In this study, the formation mechanism of NDMA in ozonation was explored by density functional theory (DFT) calculations, with dimethylamine (DMA) as a model compound. By calculating Gibbs energies and energy barriers, formation of NDMA in ozonation of DMA was observed to proceed through a hydroxylamine mechanism. The calculation results show that hydroxylamine is generated through DMA reacting with hydroxyl radicals (HO•) formed from hydrolysis of ozone. DMA reacting with hydroxylamine can produce unsymmetrical dimethylhydrazine (UDMH), a well-known NDMA precursor. Transformation of UDMH to NDMA is mainly induced by ozone or HO• rather than dissolved oxygen proposed previously. The reaction of DMA and hydroxylamine is pH dependent, with energy barriers increasing from neutral pH to the second pK_a of hydroxylamine and then decreasing. This is in accordance with the experimentally observed pH dependence of NDMA yield in ozonation, indicating that the hydroxylamine mechanism is responsible for the NDMA formation in ozonation.

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1. Introduction

N-nitrosodimethylamine (NDMA) has drawn considerable concerns as a disinfection byproduct possessing highly mutagenic and carcinogenic effects [1–3]. The compound is classified as a probable human carcinogen by US EPA and the carcinogenic risk from oral exposure is estimated as 10^{-6} at $0.7\,\mathrm{ng\,L^{-1}}$ NDMA in water (US EPA) [4]. Since the detection of NDMA in wastewater [5], its precursors and formation mechanism in wastewater treatment
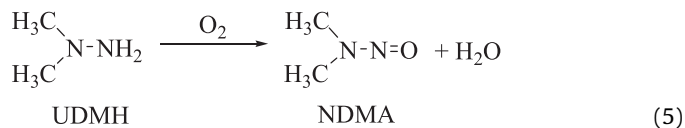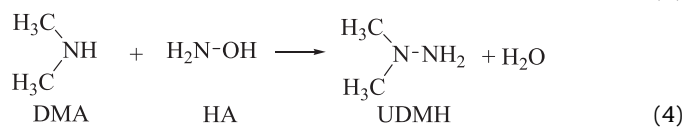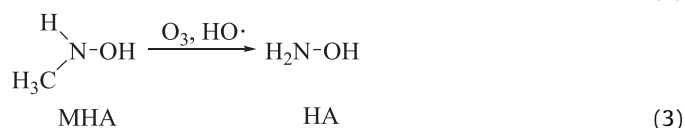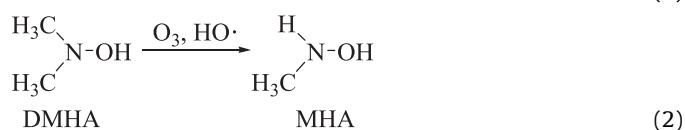
plants have received extensive attentions due to the concern that NDMA in wastewater effluents may eventually reach drinking water resources [6–8]. Recent observations indicate that ozonation of some organic pollutants with dimethylamino groups can produce NDMA [9–11]. As ozonation is widely used in wastewater and drinking water treatments, the observations triggered increasing research interests on NDMA formation mechanisms [9,12].

Dimethylamine (DMA), which was detected at submicrograms to $20\,\mu g\,L^{-1}$ in surface waters [13,14], was observed to be an efficient NDMA precursor in ozonation [9]. Moreover, DMA was suspected to be related with NDMA formation in ozonation of quaternary amines [11]. Andrzejewski et al. [9] speculated that DMA transforms to NDMA through a HCHO catalyzed nitrosation mechanism, as NO_2^- and HCHO were detected after ozonation of DMA. However, the NDMA yield with the catalyzed nitrosation mechanism decreases with pH increasing [15,16], which is opposite to the experimental observations on amines that the NDMA yield increases with pH increasing [9–11]. Accordingly, there should be other mechanisms responsible for the formation of NDMA in ozonation of amines.

Yang et al. [12] proposed that hydroxylamine might play an important role in the formation of NDMA in ozonation of DMA. According to their speculations, DMA reacting with ozone produces hydroxylamine (reactions (1)–(3)), with *N*-dimethylhydroxylamine (DMHA) and *N*-methylhydroxylamine (MHA) as intermediates. Hydroxylamine reacting with DMA produces a well-known NMDA precursor, unsymmetrical dimethylhydrazine (UDMH) [8,17], which is then oxidized by dissolved oxygen to produce NDMA (reactions (4) and (5)). Their experiments show that hydroxylamine reacting with DMA can produce UDMH and NDMA, with the NDMA yield increased from neutral to alkaline pH. This increase is consistent with the increased NDMA yield with increasing of pH in ozonation of DMA observed by Andrzejewski et al. [9]

$$\begin{array}{c}H_3C\\ \hphantom{H_3C}\diagdown\\ \hphantom{H_3C}\diagup NH\\ H_3C\end{array} \xrightarrow{\text{O}_3} \begin{array}{c}H_3C\\ \diagdown\\ \diagup N\text{-OH}\\ H_3C\end{array}$$
$$\text{DMA} \qquad\qquad \text{DMHA} \qquad\qquad (1)$$

$$\begin{array}{c}H_3C\\ \diagdown\\ \diagup N\text{-OH}\\ H_3C\end{array} \xrightarrow{\text{O}_3,\ \text{HO}\cdot} \begin{array}{c}H\\ \diagdown\\ \diagup N\text{-OH}\\ H_3C\end{array}$$
$$\text{DMHA} \qquad\qquad \text{MHA} \qquad\qquad (2)$$

$$\begin{array}{c}H\\ \diagdown\\ \diagup N\text{-OH}\\ H_3C\end{array} \xrightarrow{\text{O}_3,\ \text{HO}\cdot} H_2N\text{-OH}$$
$$\text{MHA} \qquad\qquad \text{HA} \qquad\qquad (3)$$

$$\begin{array}{c}H_3C\\ \diagdown\\ \diagup NH\\ H_3C\end{array} + H_2N\text{-OH} \longrightarrow \begin{array}{c}H_3C\\ \diagdown\\ \diagup N\text{-NH}_2\\ H_3C\end{array} + H_2O$$
$$\text{DMA} \qquad \text{HA} \qquad\qquad \text{UDMH} \qquad (4)$$

$$\begin{array}{c}H_3C\\ \diagdown\\ \diagup N\text{-NH}_2\\ H_3C\end{array} \xrightarrow{\text{O}_2} \begin{array}{c}H_3C\\ \diagdown\\ \diagup N\text{-N=O}\\ H_3C\end{array} + H_2O$$
$$\text{UDMH} \qquad\qquad \text{NDMA} \qquad\qquad (5)$$
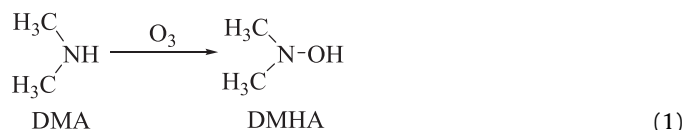
However, Andrzejewski et al. [18] recently performed an experimental work and found that only addition of hydroxylamine to the DMA solution increases the yield of NDMA after ozonation, but addition of DMHA or MHA shows no enhancement in the NDMA yield. This is opposite to the hypothetical formation pathway of hydroxylamine (reactions (1)–(3)), as DMHA and MHA were supposed to produce HA after ozonation. Moreover, the oxidation mechanism of UDMH proposed as reaction (5) is inconsistent with

experimental results that the oxidation of UDMH by O_2 (in aerated solution) hardly occurs in the absence of catalysis [19]. Additionally, the influence of pH on the formation of NDMA in the reaction of DMA and hydroxylamine is still elusive. The NDMA yield was assumed to reach a maximum at strong alkaline pH due to dissociation of the reactants [12]. However, the experimental results show that the yield of NDMA generated from DMA reacting with hydroxylamine increases continuously from pH 6.79 to 11.27 [12]. Accordingly, the role of hydroxylamine and formation mechanism of NDMA in ozonation remains inexplicit.

In this work, the formation mechanism of NDMA in the ozonation of DMA was investigated by density functional theory (DFT) calculations. In comparison with experimental studies, quantum chemical calculations have advantages in exploring reaction mechanisms by identifying transient species and providing thermodynamic data. The formation pathway of hydroxylamine and oxidation pathway of UDMH were calculated. The pH dependence of NDMA formation was evaluated by calculating reactions of DMA and HA of different protonated states. Finally, a hydroxylamine mechanism for explaining NDMA formation in ozonation of DMA was proposed.

2. Computational methods

DFT calculations were performed with Gaussian 09 software package [20]. Geometry optimizations were performed at the B3LYP/6-311 + G(d,p) level. For transition states (TS), geometries were optimized to saddle points. Frequency analysis was performed at the same level to characterize the stationary points and to obtain Gibbs energy corrections (298 K, 1 atm). A broken symmetry (BS) approach incorporated with approximate spin-projection (ASP) correction [21] was employed for calculating energies of singlet biradicals. Details on correction process are described in Supporting information. Intrinsic reaction coordinate (IRC) calculations starting with optimized geometries of TSs were performed to confirm that TSs connect designated reactants. In order to consider solvent effects on reactions, the integral equation formalism polarized continuum model (IEFPCM) based on the self-consistent-reaction-field (SCRF) [22] was employed for all calculations including geometry optimizations. Gibbs free energy of reactions (ΔG_r) was calculated as $\Delta G_{\text{products}} - \Delta G_{\text{reactants}}$. Energy barriers ($\Delta G^{\ddagger}$) were calculated as $\Delta G_{\text{TS}} - \Delta G_{\text{reactants}}$.

3. Results and discussion

3.1. Formation pathway of hydroxylamine

DMA exists as cationic form (DMA^+) and/or neutral form (DMA^0) at non-acidic pH (Fig. 1). The rate constant (k) for reacting with O_3 is lower than $(0.13 \pm 0.2)\,M^{-1}\,s^{-1}$ for DMA^+ or $(19 \pm 4) \times 10^6\,M^{-1}\,s^{-1}$ for DMA^0 [23]. Considering the low reaction rate and the protonated nitrogen of DMA^+, its reaction with O_3 can be neglected. Although DMA^0 reacts fast with O_3, the reaction won't be significant at neutral pH, as the acid dissociation constant (pK_a) value of DMA is 10.7 [12], which means that DMA^0 is scarce at a neutral pH (e.g. pH = 7, $DMA^0/DMA = 0.2\%$, Fig. 1). When DMA^0 becomes dominant with pH increasing, the importance of hydroxyl radicals (HO•) in DMA degradation will increase due to rapid decomposes of O_3 [24] and moreover the rate constant for reacting with HO• is generally several orders higher than that for reacting with O_3. Therefore, the kinetic data imply that HO• plays a non-ignorable at neutral pH to an essential role at alkaline pH in the transformation of DMA, with the importance dependent on water matrix components, which heavily impact the half-life of O_3 and steady-state concentration of HO• [24].