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CRITICAL REVIEW

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Halonitroalkanes, Halonitriles, Haloamides, and N-Nitrosamines: A Critical Review of Nitrogenous Disinfection Byproduct Formation Pathways

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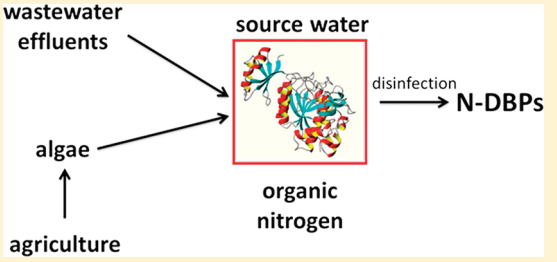
ABSTRACT: Interest in the formation of nitrogenous disinfection byproducts (N-DBPs) has increased because toxicological research has indicated that they are often more genotoxic, cytotoxic, or carcinogenic than many of the carbonaceous disinfection byproducts (C-DBPs) that have been a focus for previous research. Moreover, population growth has forced utilities to exploit source waters impaired by wastewater effluents or algal blooms. Both waters feature higher levels of organic nitrogen, that might serve as N-DBP precursors. Utilities are exploring new disinfectant combinations to reduce the formation of regulated trihalomethanes and haloacetic acids. As some of these new combinations may promote N-DBP formation, characterization of N-DBP formation pathways is needed. Formation pathways for halonitroalkanes, halonitriles, haloamides, and N-nitrosamines associated with chlorine, ozone, chlorine dioxide, UV, and chloramine disinfection are critically reviewed. Several important themes emerge from the review. First, the formation pathways of the N-DBP families are partially linked because most of the pathways involve similar amine precursors. Second, it is unlikely that a disinfection scheme that is free of byproduct formation will be discovered. Disinfectant combinations should be optimized to reduce the overall exposure to toxic byproducts. Third, the understanding of formation pathways should be employed to devise methods of applying disinfectants that minimize byproduct formation while accomplishing pathogen reduction goals. Fourth, the well-characterized nature of the monomers constituting the biopolymers that likely dominate the organic nitrogen precursor pool should be exploited to predict the formation of byproducts likely to form at high yields.



INTRODUCTION

Since the discovery of trihalomethanes (THMs) as disinfection byproducts (DBPs) in the 1970s,[1] research has focused on DBP formation from the reaction of free chlorine, the predominant disinfectant used in much of the world, with natural organic matter (NOM) constituents, such as humic and fulvic acids, in pristine source waters. These materials often arise from the prolonged degradation of nitrogen-poor plant-based structural polymers, such as lignin and cellulose. Because of the low organic-nitrogen content of NOM (generally <5% of DOC by weight),[2] DBP research has targeted *carbonaceous* disinfection byproducts (C-DBPs), particularly THMs and haloacetic acids (HAAs), rather than *nitrogenous* disinfection byproducts (N-DBPs).

Interest in N-DBPs has increased for several reasons. First, population growth has forced utilities to consider exploitation of source waters impaired by municipal wastewater effluents or algal blooms. Due to relatively fresh biopolymers associated with human waste or bacterial exudates in effluent organic matter (EfOM) or algal exudates in algal organic matter (AOM), these waters feature higher organic nitrogen content[2] that serves as a source for N-DBP precursors. Among N-DBP families of current interest are halonitroalkanes (e.g., chloropicrin), halonitriles (e.g., cyanogen chloride and dichloroacetonitrile), haloamides (e.g., dichloroacetamide), and N-nitrosamines (e.g., N-nitrosodimethylamine (NDMA)) (Figure 1). Unlike the other families, N-nitrosamines are not halogenated and so are not captured as part of the total organic halogen (TOX) analysis.

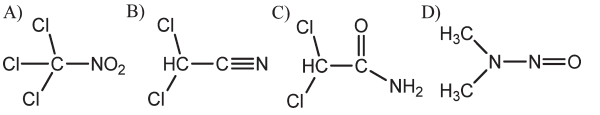


Figure 1. Structures of A) chloropicrin (trichloronitromethane), B) dichloroacetonitrile, C) dichloroacetamide, and D) N-nitrosodimethylamine (NDMA).

Second, to reduce the formation of THMs and HAAs, utilities are experimenting with alternatives to chlorine disinfection. Unfortunately, some of these emerging disinfectant combinations reduce THMs and HAAs at the expense of promoting N-DBPs. Lastly, *in vitro* geno- and cytotoxicity assays suggest that haloacetonitriles, haloacetamides, and halonitromethanes are significantly more toxic than their regulated THM and HAA

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analogues.[3−5] Information on the US EPA's Information Risk Information System (IRIS) database indicates that, for oral exposure, NDMA has a cancer potency ∼600 times greater than any of the regulated THMs and that a drinking water concentration as low as 0.7 ng/L would be associated with a 10^{-6} lifetime cancer risk.[6] Therefore, although N-DBPs often occur at lower concentrations than THMs and HAAs, their importance to the overall toxicity of a disinfected water may be significant.

The recent regulatory attention on N-nitrosamines has focused interest on this N-DBP family. The California Department of Health Services has established 10 ng/L Notification Levels for NDMA, N-nitrosodiethylamine, and N-nitrosodipropylamine,[7] and N-nitrosamines are currently under consideration for regulatory action by the US EPA. The formation, precursors, and removal of N-nitrosamines in drinking water have been reviewed.[8,9] However, it is helpful to consider the N-DBP families together, because the EfOM and AOM in impaired waters serves as a common precursor pool, while different disinfectants may promote one family at the expense of the other. The occurrence of these N-DBP families has recently been reviewed.[10] The purpose of this work is to review formation pathways for halonitroalkanes, halonitriles, haloamides, and N-nitrosamines from disinfectants. Important themes to be drawn from these pathways are discussed, along with their implications for fruitful research avenues.

Halonitroalkane Formation Pathways. Halonitroalkanes contain a nitro group and up to three halogens on the α-carbon (Figure 1). Among N-DBPs, their formation pathways have received the least attention. Chloropicrin formation has been the primary focus. Most pathways involve initial formation of a nitroalkane, followed by halogenation by chlorine or chloramines, which are used to maintain disinfectant residuals in distribution systems. Halogenation occurs on the α-carbon because the nitro group enhances the acidity of its C−H bonds.[11] Maximal halogenation is favored as increasing incorporation of electron-withdrawing halogens promotes deprotonation, the rate-limiting step for halogenation. Accordingly, halogenation of nitroalkane intermediates is promoted at high pH.[11,12]

The presence of bromide in source waters promotes the formation of hypobromous acid during chlorination or bromamines during chloramination. Compared to their chlorine-containing analogues, these bromine-containing disinfectants are more likely to engage in transfer of the halogen to the organic precursor.[13−15] Accordingly, the presence of bromide can promote the overall molar yield of halogenated byproducts, including N-DBPs. However, for halonitroalkanes, the presence of bromide promotes bromine incorporation to a greater extent than for other halogenated byproduct families.[16,17]

Three pathways relevant to disinfection have been characterized for the formation of the nitroalkane intermediate. First, disinfectants may oxidize the nitrogen in amine precursors from their −3 oxidation state to a +3 nitro group. Chlorination and chloramination of model primary amines (e.g., monomethylamine[18,19]), amino acids/dipeptides (e.g., glycine, glycylglycine, and tryptophan[12,19]), and nucleic acids (e.g., cytosine and adenine[19]) formed chloropicrin at 0.01−0.08% yields. While chloramines are a weaker oxidant than chlorine, chloropicrin decays faster in the presence of free chlorine;[18] the decay pathway is unclear. Chlorination of surface waters formed 0.27−0.62 μg chloropicrin/mg-DOC.[20,21] Chloropicrin formation after chlorination of NOM isolates correlated with DON content but not with specific UV absorbance at 254 nm ($SUVA_{254}$), a surrogate for aromatic content.[22] These results suggest the importance of nonaromatic amine precursors. Size fractionation using ultrafiltration membranes indicated that 90% of chloropicrin precursors were retained by 500 nominal molecular weight cutoff membranes.[23]

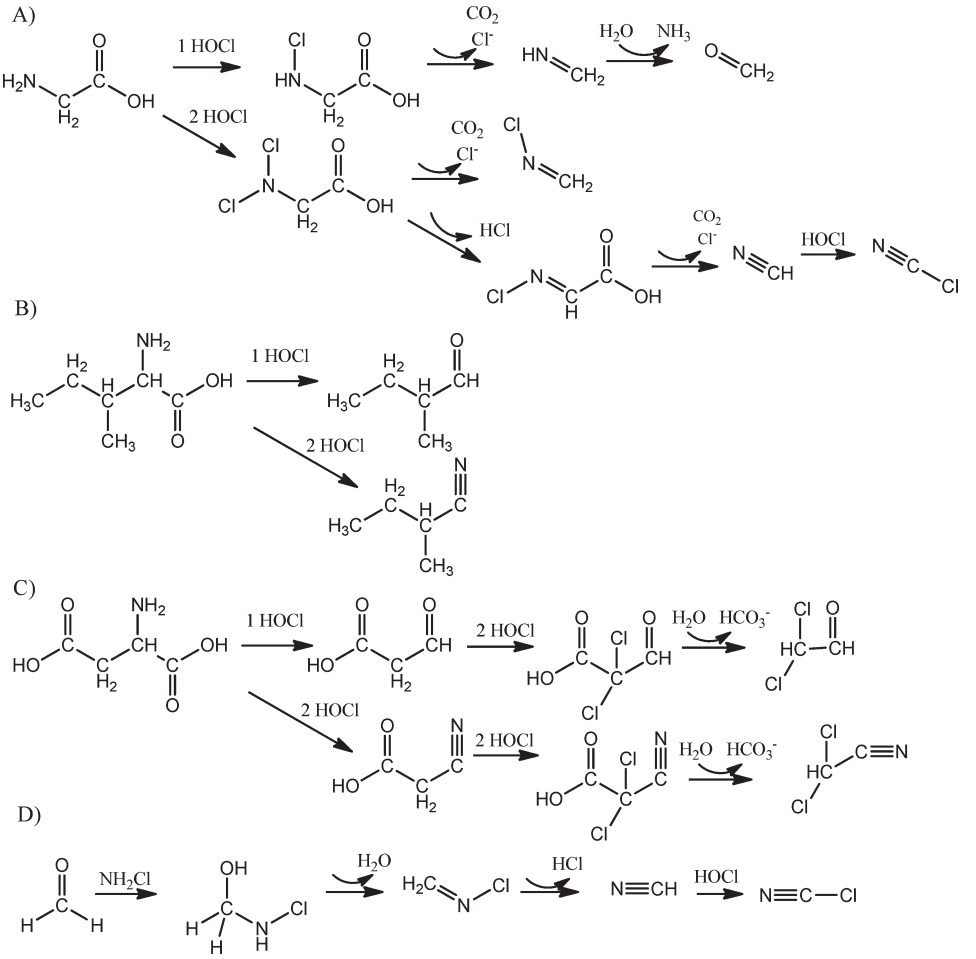
Ozone was potent at promoting chloropicrin formation upon postchlorination. Preozonation of raw and settled drinking waters increased halonitromethane formation by 160−380% compared to chlorination alone.[17,20,24] Whether direct ozone reactions or ozone-associated hydroxyl radicals are responsible for amine oxidation is unclear. Rate constants for direct reaction of ozone with primary amines are $\sim 10^3$ M^{-1} s^{-1},[25] while those for hydroxyl radical reactions are $\sim 10^9$ M^{-1} s^{-1}.[26] Because the ratios of hydroxyl radical and ozone exposures under typical disinfection conditions are $10^{-7}-10^{-9}$,[27] direct ozone reactions may be slightly more important. In the presence of bromide, preozonation promoted the formation of brominated halonitromethanes.[28]

The second relevant halonitroalkane formation pathway involves nitrite. Chlorination of nitrite forms the nitrating agent $ClNO_2$.[29] Further reaction with nitrite forms N_2O_4, another nitrating agent.[30,31] Most reaction pathway studies have focused on the nitration of aromatic structures.[24] Subsequent chlorination promotes ring cleavage. Chlorination of phenol, Sigma-Aldrich humic acid, or raw and partially treated drinking waters in the presence of 1−2 mg/L-N nitrite at circumneutral pH formed 1.3−3.1 μg/L chloropicrin.[17,24,32] Chloropicrin formation after postchlorination also increased with increasing doses of ozone or chlorine dioxide to phenol in the presence of 1.4 mg/L-N nitrite, although at the highest doses, chloropicrin formation declined.[24]

During water treatment, these pathways may co-occur. Ozonation followed by chlorination or chloramination of municipal wastewaters exhibiting <0.02−1.0 mg/L-N nitrite promoted chloropicrin formation compared to chlorination or chloramination alone.[33] Chloropicrin formation did not correlate with nitrite concentrations, suggesting that amine oxidation was the primary pathway governing chloropicrin formation.[33] However, another study with raw and treated drinking waters found that chloropicrin formation increased in the presence of nitrite during chlorination alone.[17] Even higher formation was observed when these waters were treated with ozone followed by chlorination in the absence of nitrite. Lastly, ozonation followed by chlorination in the presence of nitrite formed the most chloropicrin. These results indicate that these pathways can operate simultaneously.

Recently, a third pathway to chloropicrin formation has been characterized involving UV primary disinfection coupled with chlorination or chloramination. Both nitrite and nitrate exhibit absorbance bands <250 nm and ∼270−400 nm. Photolysis of nitrite forms nitric oxide ($NO^{\bullet}$) and the hydroxyl radical ($^{\bullet}OH$)[34]. Reaction of the hydroxyl radical with nitrite forms the nitrating agent, nitrogen dioxide ($NO_2^{\bullet}$).[34] Further reactions form other nitrating agents, including dinitrogen tetraoxide (N_2O_4) and peroxynitrous acid (ONOOH).[31,35] Photolysis of nitrate forms nitrite, $NO_2^{\bullet}$, and ONOOH.[34] Similar to chlorination of nitrite, nitration of NOM, particularly aromatic substituents,[36] would promote halonitroalkane formation upon postchlorination or chloramination. The type of UV lamp is important, because low-pressure UV lamps emit monochromatic light at 254 nm, where there is minimal overlap with nitrite or nitrate absorbance bands, while medium pressure lamps emit polychromatic light from ∼200−400 nm. Low pressure UV treatment of Sigma-Aldrich humic acid in the presence of 1 mg/L-N

Scheme 1



nitrite or 10 mg/L-N nitrate[32] or of authentic drinking waters[37] and wastewaters[33] did not promote chloropicrin formation upon postchlorination or postchloramination. Application of medium pressure UV to drinking waters containing ~1 mg/L-N nitrate followed by postchlorination increased halonitromethane formation by ~200% compared to chlorination alone at germicidal fluence relevant to drinking water disinfection (140−186 mJ/cm^2).[32,37] Promotion of chloropicrin formation occurred predominantly at low nitrate concentrations; further increases in nitrate concentrations up to 10 mg/L-N resulted in only modest further increases in chloropicrin formation.[32,37] Although several nitrating agents likely co-occur in this system, mechanistic experiments suggested that $NO_2^{\bullet}$ was the main nitrating agent.[32,37] In the presence of 2.7 mg/L-N nitrate, chlorination of a drinking water upstream of medium pressure UV treatment approximately doubled chloropicrin formation compared to medium pressure UV followed by chlorination.[32] Mechanistic experiments indicated that the increase was attributable to UV-promoted modification of chlorinated organic precursors.

Halonitrile and Haloamide Formation Pathways. Halonitriles and haloamides contain up to three halogens on the α-carbon bound to nitrile or amide groups, respectively (Figure 1). Two pathways have been characterized for nitrile formation. Via the first pathway, the "decarboxylation pathway", the nitrile nitrogen originates from primary amine constituents of DON. Researchers evaluated twelve free amino acids and two urine constituents of similar structures.[38−50] Free chlorine rapidly chlorinates the α-amine group (Scheme 1A). For monochlorinated amines, the proximate carboxylic acid group is prone to decarboxylation coupled with chloride elimination (i.e., concerted decarboxylation), yielding an imine. Imine hydrolysis releases ammonia and an aldehyde. During chlorination, this reaction is rapid, with half-lives of ~1−22 h for the free amino acids studied, and is promoted by electron-donating substituents.[51] Similar reactions are likely during chloramination but would be less rapid, due to the slower transfer of Cl[+1] from inorganic chloramines to the α-amine.

At free chlorine or chloramine to free amino acid ratios >1, formation of dichlorinated α-amine groups is favored. Concerted decarboxylation forms a chlorinated imine that can hydrolyze to release NH_2Cl and an aldehyde but is more stable than the imines formed from monochlorinated free amino acids.[44,48] Alternatively, the electron-withdrawing nature of the dichlorinated amine and carboxylic acid render the central carbon acidic, such that hydrochloric acid elimination may precede concerted decarboxylation to yield a nitrile. During chlorination, these reactions occur <1 h.[51] Low pH conditions promote nitrile formation.[42] Because nitrile formation is coupled with loss of two Cl[+1], chlorine titration curves similar to breakpoint chlorination are observed.[44,48,49]

The specific aldehydes and nitriles formed depend on the amino acid precursor structure. Free glycine forms cyanide that can be rapidly chlorinated to yield cyanogen chloride.[49] However, less-studied aldehydes and nitriles form from other amino acids. For example, Scheme 1B presents the aldehyde and nitrile formed from isoleucine.[44] Chlorination of free aspartic acid and the urine constituent, kynurenine, are somewhat unique.[40,47] The combined electron-withdrawing strength of the side chain carboxylic acid and the aldehyde or nitrile formed by concerted decarboxylation renders the intermediate carbon acidic (Scheme 1C for aspartic acid). Dichlorination of this carbon followed by decarboxylation forms either dichloroacetaldehyde or dichloroacetonitrile (DCAN).

Most work has focused on the α-amine terminus of free amino acids. Free amino acids constitute only 5−10% of total amino acids in source waters,[52,53] and so they can rarely account for the observed formation of halonitriles. An exception is free glycine, where the 25 nM detected in the Huron River accounted for ∼45% of cyanogen chloride formation.[54]

The other major pathway characterized for nitrile formation, the "aldehyde pathway", features inorganic chloramine reactions with aldehydes, where the inorganic chloramines serve as the source of the nitrile nitrogen.[55] The nucleophilic attack of inorganic monochloramine on formaldehyde forms chloroaminomethanol. Subsequent dehydration and hydrochloric acid elimination yields cyanide that is rapidly chlorinated to produce cyanogen chloride. With formaldehyde, this reaction was fast and nearly quantitative.[55] Formation by this pathway increases with pH.[19,55] Less work has focused on NH_2Cl reactions with other aldehydes to form analogous nitriles. Despite the formation of propionaldehyde during application of $^{15}NH_2Cl$ to n-propylamine, yields of ^{15}N-propionitrile were very low.[18] Aldehydes are byproducts of chlorination and particularly ozonation (e.g., ∼4 μg/L and ∼10 μg/L formaldehyde, respectively).[56−58] Accordingly, higher halonitrile formation is anticipated when ozonation is followed by chloramination, unless biofiltration removes the aldehydes.

During chloramination, the aldehyde and decarboxylation pathways may operate simultaneously. Application of ^{15}N-labeled NH_2Cl to a range of model nucleic and amino acids provided contradictory results regarding whether NH_2Cl (the aldehyde pathway) or the model organic (the decarboxylation pathway) served as the source of the cyanogen chloride nitrogen.[19,59,60] $^{15}NH_2Cl$ application to Suwannee River NOM indicated that 90% of the dichloroacetonitrile formation derived from $^{15}NH_2Cl$,[19] suggesting the importance of the aldehyde pathway to aldehydes other than formaldehyde in authentic waters.

Lastly, it has been noted that pretreatment with UV followed by chlorination can enhance the formation of cyanogen chloride, as well as THMs and HAAs.[61] The reasons for this increase are not clear, although fragmentation of natural organic matter constituents to lower molecular weight precursors is likely involved. Unlike UV-promoted halonitromethane formation during MP UV treatment of nitrite- or nitrate-containing waters, promotion of cyanogen chloride formation was observed during pretreatment with either LP or MP bulbs.

Nonhalogenated nitriles are resistant to hydrolysis over time scales of ∼2 d.[41] However, when the α-carbon is halogenated (e.g., cyanogen chloride and dichloroacetonitrile), hydrolysis by bases, including hydroxide and hypochlorite, becomes important. In the presence of hypochlorite, cyanogen chloride rapidly hydrolyzes to cyanate (half-lives ∼1 h [62]), such that cyanogen chloride is rarely detected in the presence of excess free chlorine.[62] The lack of hypochlorite-catalyzed hydrolysis, coupled with the operation of the aldehyde pathway, may explain why cyanogen chloride is associated with chloramination rather than chlorination. The sequential hydrolysis of DCAN forms dichloroacetamide and dichloroacetic acid, although hydrolysis rates are slower than for cyanogen chloride such that DCAN remains measurable in the presence of excess free chlorine.[63] Indeed, concentrations of dichloroacetamide were roughly 3% of those of dichloroacetonitrile during application of a free chlorine formation potential assay to a raw drinking water supply.[64] Hydrolysis of brominated acetonitriles is slower than for chlorinated analogues due to the larger radius (i.e., steric hindrance) and lower electronegativity of the bromine atoms.[63,65]

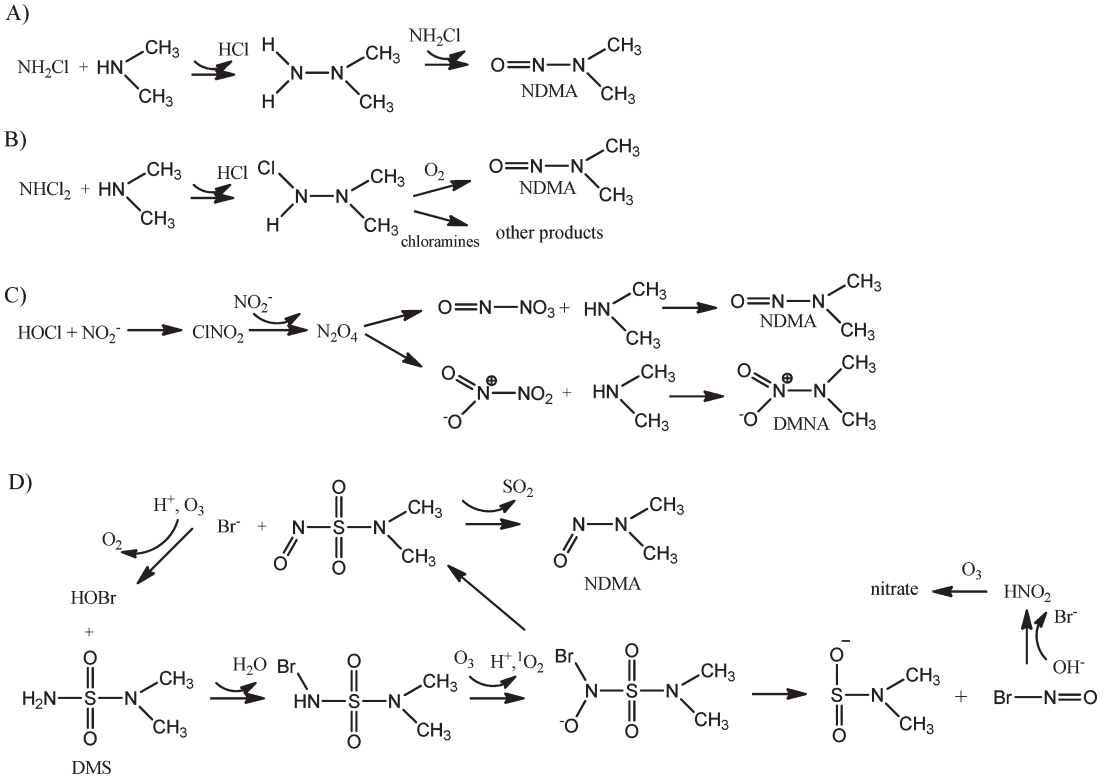
Further research with application of $^{15}NH_2Cl$ to authentic waters is needed to determine the relative importance of the decarboxylation and aldehyde pathways for halonitrile and haloamide formation during chloramination and to characterize precursors. Work with authentic drinking waters or NOM isolates indicated that DCAN formation was higher from chlorination than from chloramination, suggesting the importance of the decarboxylation pathway.[32,53,66] However, the opposite result has also been obtained with NOM isolates.[22] Reflecting that dichloroacetamide is a hydrolysis product of DCAN, DCAN and dichloroacetamide yields during chlorination both were highest from isolates that were likely enriched in protein.[22,64] The NOM fractions yielding the highest dichloroacetamide concentrations were enriched in hydrophilic aromatic nitrogen, not the hydrophobic aromatics associated with trihalomethane formation.[64] However, during chloramination, DCAN formation was not correlated with the nitrogen content of NOM isolates, suggesting a role for the aldehyde pathway.

Nitrosamine Formation Pathways. Prior to the discovery that N-nitrosamines form during disinfection, toxicological research focused on their formation in food preserved with nitrite.[67] Of particular concern was endogenous formation in the stomach. Catalyzed by stomach acid, ingested nitrite forms dinitrogen trioxide (N_2O_3), a potent agent for nitrosation of unprotonated amines. Attention was focused on nitrosation of secondary amines to form stable secondary N-nitrosamines (e.g., NDMA). The primary N-nitrosamines formed by nitrosation of primary amines decay nearly instantaneously to release nitrogen gas and a carbocation.[67]

Formation during Chloramination. Among nitrosamine formation pathways, this pathway is likely to be the most important. A California-wide drinking water survey conducted following the detection of NDMA in drinking water wells downgradient of facilities using unsymmetrical dimethylhydrazine (UDMH) rocket fuel found that NDMA also formed as a byproduct of chloramine disinfection; wastewater recycling operations were particularly at risk, likely due to higher amine precursor concentrations.[8] Early mechanistic research suggested this formation arose by a nucleophilic substitution reaction between unprotonated secondary amines and monochloramine, the predominant chloramine species under typical water chloramination conditions, to form UDMH (Scheme 2A).[68,69] UDMH oxidation by chloramines formed NDMA.

Chen and Valentine incorporated this mechanism into a broader model for monochloramine reactions with NOM to accurately predict NDMA formation in several natural waters.[70] The expanded model included an initial step involving the

Scheme 2



oxidation of NOM functional groups by monochloramine, or the lower free chlorine concentrations in equilibrium with monochloramine (i.e., $HOCl + NH_4^+ \leftrightarrow NH_2Cl + H_2O + H^+$), to release nitrosamine precursors (e.g., dimethylamine). NDMA formation was proportional to the degree of NOM oxidation.[71] With the initial step proposed to be rate-limiting, the succeeding steps involving reactions with dimethylamine could be lumped into a source-specific parameter denoting the yield of NDMA per oxidized NOM unit.

Further mechanistic research with dimethylamine as a model precursor pointed out several important flaws with the initial monochloramine hypothesis.[72] First, the proposed 6.4 M^{-1} s^{-1} rate constant for UDMH formation from the reaction of dimethylamine and monochloramine[68] is 2 orders of magnitude higher than the 0.08 M^{-1} s^{-1} literature value determined by direct measurement of UDMH.[73,74] Second, application of preformed monochloramine formed significant concentrations of NDMA from 10 μM of dimethylamine (up to 0.2% yields after 8 h), but no measurable NDMA when applied to 10 μM UDMH. Third, the monochloramine pathway did not explain the origin of the oxygen in NDMA.

The reaction pathway was revised based upon experiments indicating that application of preformed dichloramine ($NHCl_2$) to dimethylamine or wastewater effluents formed 2 orders of magnitude more NDMA than did application of an equivalent concentration of preformed monochloramine and that NDMA formation increased with dissolved oxygen concentration.[72,75] Although monochloramine is the dominant chloramine species under typical chloramination conditions, dichloramine always coexists according to eq 1

$$2NH_2Cl + H^+ \leftrightarrow NHCl_2 + NH_4^+ \quad (1)$$

The revised pathway proposed formation of a chlorinated unsymmetrical dimethylhydrazine intermediate (Cl-UDMH) from a nucleophilic substitution reaction between dimethylamine and $NHCl_2$ (Scheme 2B). Oxidation of Cl-UDMH by oxygen to form NDMA competes with its oxidation by chloramines to form other products. The pathway was demonstrated to accurately model NDMA formation over a wide range of conditions during application of preformed dichloramine to dimethylamine. Even during application of preformed monochloramine, the model was able to explain nearly all NDMA formation from reactions attributable to the traces of dichloramine forming in solution due to eq 1. The importance of bromamines formed in the presence of bromide toward promoting this reaction has not been adequately explored.

Formation during Breakpoint Chlorination. Utilities may address nitrification episodes in chloraminated distribution systems by increasing the chlorine dose to minimize the free ammonia residual, or by conducting breakpoint chlorination. The former strategy might exacerbate nitrosamine formation by promoting dichloramine formation. Evaluation of NDMA formation as a function of free chlorine dose to deionized water solutions containing ammonia and dimethylamine or to an ammonia-containing wastewater revealed that NDMA formation increased dramatically at a 1.7:1 free chlorine to ammonia molar ratio where breakpoint chlorination resulted in no measurable residual chlorine.[76] Use of scavengers indicated that the formation was associated with radicals generated during breakpoint reactions. The identity of the responsible agents is unclear but may involve some of the same inter-related reactive nitrogen species (RNS) involved in halonitromethane formation during medium pressure UV treatment of nitrite or nitrate-containing waters (e.g., $NO^{\bullet}$, $NO_2^{\bullet}$, N_2O_3, ONOOH). However, when the

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applied free chlorine dose was sufficient to ensure a measurable free chlorine residual, NDMA formation was less important than during chloramination.[76,77] Because sufficient chlorine residuals are generally present, nitrosamine formation by this pathway is likely to be of minor importance.

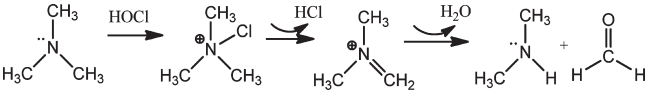
Formation during Chlorination of Nitrite-Containing Waters. Choi and Valentine[78] noted that NDMA also forms during chlorination of nitrite-containing waters. The formation was attributed to the production of dinitrogen tetraoxide (N_2O_4), whose two tautomeric forms can nitrosate or nitrate amines, respectively (Scheme 2C).[31] As the free chlorine to nitrite molar ratio increases, nitramine formation is favored over nitrosation,[76] possibly due to the promotion of $ClNO_2$, a nitrating agent, over N_2O_4, a nitrosating and nitrating agent. Under comparable conditions, NDMA yields over 1 h from dimethylamine by this pathway (~0.0007%) are significantly lower than from chloramination (~0.05%).[76] The importance of this pathway to drinking waters, where nitrite concentrations are generally <100 μg/L as N, and nitrite and chlorine rarely co-occur, requires clarification. This pathway may be important for wastewater recycling utilities when nitrified wastewater effluents are disinfected with free chlorine.

N-DBP formation in chlorinated pools is of interest due to high organic nitrogen precursor loadings from bathers (e.g., sweat and urine) and maintenance of chlorine residuals throughout the months-long typical residence times of water. Both NDMA and N-nitrodimethylamine were detected in chlorinated pools. Formation of both compounds was attributed to this pathway by correlation of N-nitrodimethylamine concentrations with residual nitrite concentrations.[79]

Formation during Ozonation. Ozonation of dimethylamine forms NDMA but yields generally are <0.02% at neutral pH.[80,81] Because dimethylamine concentrations in natural waters or wastewaters typically are <10 nM,[82,83] this formation may not be important. However, ozonation of a more limited array of precursor structures formed NDMA at high yield. Ozonation of UDMH itself, or the plant growth inhibitor daminozide (alar) and semicarbazide antiyellowing agents for polymer production, both of which have UDMH-like functional groups, formed NDMA at yields >50%.[84,85] Ozonation of N,N-dimethylsulfamide (DMS), a byproduct of the fungicide, tolylfluanide, formed NDMA at 52% yield.[84] NDMA formation from ozonation of DMS is particularly important, as DMS was detected in 94% of German groundwater samples; with half of DMS concentrations >100 ng/L, NDMA formation during ozonation would often exceed 10 ng/L.[84] HOBr formed by ozonation of bromide brominates the primary amine group of DMS (Scheme 2D). Ozonation of the bromamine group forms an ozonide intermediate, followed by elimination of singlet oxygen ($^1O_2$).[86] Elimination of bromide followed by extrusion of SO_2 forms NDMA and releases bromide, completing the catalytic cycle. Alternatively, elimination of Br−N═O leads to chain-terminating nitrate formation. Bromide catalysis of NDMA formation by this pathway was important at bromide concentrations as low as 15 μg/L.[86]

Formation during Sunlight Photolysis of Nitrite-Containing Waters. Sunlight photolysis of nitrite at λ < 400 nm forms $NO^{\bullet}$ and $^{\bullet}OH$. Formation of the same reactive nitrogen species (RNS) described in the halonitromethane formation section can occur following $^{\bullet}OH$ oxidation of $NO^{\bullet}$ to $NO_2^{\bullet}$, including the nitrosating species N_2O_3 and N_2O_4. Lee and Yoon[87] observed that NDMA yields leveled out at 0.015% during sunlight photolysis of 4 mM dimethylamine and 1 mM nitrite, as continued formation was balanced by sunlight photolysis of NDMA resulting from its 300−350 nm absorbance band. Due to the low concentrations of nitrite and dimethylamine[82] present in natural waters, this formation pathway is likely not important in practice.

Scheme 3



Precursors. Although the precursor for the amine moiety of nitrosamines should be a constituent of dissolved organic nitrogen (DON), application of a large monochloramine dose to organic matter isolates (i.e., a formation potential assay) indicated no clear correlation between NDMA formation and DON.[22] NDMA concentrations formed from chloramine formation potential analysis of secondary municipal wastewater effluents were 200−6,300 ng/L.[83] In contrast, a maximum of 58 ng/L NDMA formed when the assay was applied to relatively pristine natural waters, including eutrophic systems with up to 25 mg/L dissolved organic carbon.[82] Similarly, < 167 ng/L NDMA formed when the assay was applied to whole cell bacterial cultures of Gram-positive *Gordona amarae*, Gram-negative *Escherichia coli*, a lysed culture of *Escherichia coli,* or a whole cell yeast culture of *Saccharomyces cerevisiae* (total suspended solids concentrations 340−490 mg/L).[83] These results suggest two important conclusions. First, a subset of DON constituents in effluent organic matter (EfOM) is likely to account for the majority of NDMA formation in source waters. Reflecting the particular risks of NDMA formation observed during wastewater recycling operations,[8] wastewater-impacted source waters, rather than algal-impaired waters, are prone to NDMA formation. Application of a chloramine formation potential assay to samples collected upstream and downstream of wastewater outfalls along a river demonstrated a steady accumulation of NDMA precursors attributable to municipal wastewater inputs, with little loss of precursors between outfalls.[88] Similarly, for two Alberta utilities, higher NDMA formation was observed at the utility subject to wastewater impacts from the town upstream.[77]

Second, although municipal wastewater effluents are likely to contain biomolecules from eukaryotes (humans) and prokaryotes (bacterial exudates) the lack of significant NDMA formation from chloramination of these cultures indicates that common biomolecules are not significant NDMA precursors. Although both dimethylamine and trimethylamine are human waste constituents and NDMA precursors, concentrations in municipal wastewater effluents were insufficient to account for NDMA formation.[83,89] These results point to the potential importance of anthropogenic chemicals in wastewater as the responsible NDMA precursors.

Although the specific precursors have not yet been identified, work with model precursors has suggested potential candidates. Tertiary amines with dimethylamine functional groups (e.g., trimethylamine) form NDMA at ~2.5% yields, far higher than the ~0.3% yields from amides with dimethylamine functional groups (e.g., dimethylformamide and diuron).[83,90] During chlorination or chloramination, chlorine transfer to the tertiary amine rapidly releases a secondary amine and an aldehyde with minimal regioselectivity (Scheme 3), such that yields from dimethylamine and tertiary amines are comparable. However, for tertiary amines where dimethylamine is associated with benzyl-like functional

groups, NDMA yields from chloramination are significantly higher.[27,91] For example, the antacid ranitidine (Zantac) formed NDMA at ~90% yield. These high yields suggest that an alternative pathway pertains which avoids a dimethylamine intermediate but which has not yet been characterized. These high yields may offset the low concentrations expected for these micropollutants in municipal wastewater effluents to render these compounds significant precursors.

In addition to wastewater-impacted source waters, NDMA formation has also been associated with quaternary amine-based treatment polymers used as coagulants in drinking water and wastewater treatment and as the active groups in anion exchange resins.[83,92−94] For anion exchange resins, resins shed precursors, including dimethylamine and trimethylamine, that could form nitrosamines upon postchloramination.[93] Significant NDMA concentrations were observed when exposed to disinfection-relevant chlorine or chloramine doses, particularly for Type II resins exhibiting dimethylethanolamine functional groups, where concentrations of ~400 ng/L were observed;[93] these results suggest a risk associated with incorporation of anion exchange resins in point-of-use treatment devices exposed to chlorinated or chloraminated tap water. For coagulant polymers, NDMA formation was correlated to dimethylamine released during chloramination, rather than dimethylamine impurities in the initial polymer stocks.[94] Poly(epichlorohydrin dimethylamine)-based polymers (polyamines) formed more NDMA than poly(diallyldimethylammonium chloride)-based coagulants (polyDADMAC),[94] potentially due to the occurrence of dimethylamine-based tertiary amine groups at the polymer chain ends.

Although reaction of chloramine oxidants with quaternary amines is not expected due to the positive charge on quaternary amines, purification experiments demonstrated that quaternary amine functional groups could serve as NDMA precursors.[94,95] Unfortunately, these results suggest that nitrosamine formation cannot be avoided completely by improvements in polymer purity. Further work suggested that the liberation of NDMA precursors from these quaternary amines was due to the action of radicals, potentially amidogen or chloramino radicals formed during chloramine decay.[95] Similarly, ozonation of polyDADMAC formed low yields of NDMA, as hydroxyl radicals formed during ozonation liberated dimethylamine.[96] NDMA yields from chloramination of quaternary amines with dimethylamine functional groups were 0.1−0.2%, about an order of magnitude lower than from dimethylamine. However, in contrast to tertiary amine-based microconstituents, quaternary amine-based coagulants are applied at mg/L concentrations, and quaternary amines are employed as major ingredients in a range of consumer products likely to enter sewage, including shampoos and detergents. These higher loadings may offset the low NDMA yields to render these compounds important precursors in wastewater-impacted waters.[95]

In drinking water practice in the U.S., chloramination is usually preceded by application of strong preoxidants. A notable exception is chlorination of non-nitrified municipal wastewater effluents during wastewater recycling, where the presence of ammonia results in chloramine formation. A range of preoxidants have been noted to deactivate NDMA precursors. Increasing free chlorine exposure generally reduced NDMA formation during subsequent chloramination.[77,97] However, short free chlorine exposures actually increased NDMA formation during postchlorination in some cases.[97] These results suggest that oxidants first convert higher order amines (i.e., tertiary or quaternary amines) to lower order precursors but that extended oxidant exposures may deactivate these precursors.[70,97] Preoxidation with ozone, chlorine dioxide, ferrate, hydrogen peroxide, permanganate, and sunlight were also noted to deactivate NDMA precursors.[27,97,98] Ozone and free chlorine were the most effective at precursor deactivation at doses relevant to drinking water treatment. Application of 1−2 mg/L ozone to natural waters deactivated NDMA precursors by 23−94%.[27] Evaluation of model tertiary amine-based precursors indicated that all but the most recalcitrant precursors should be deactivated under these conditions, suggesting that a fraction of precursors in natural waters may be less reactive tertiary amines or quaternary amines. Direct reactions of ozone, rather than hydroxyl radical, appeared to be responsible for precursor deactivation.

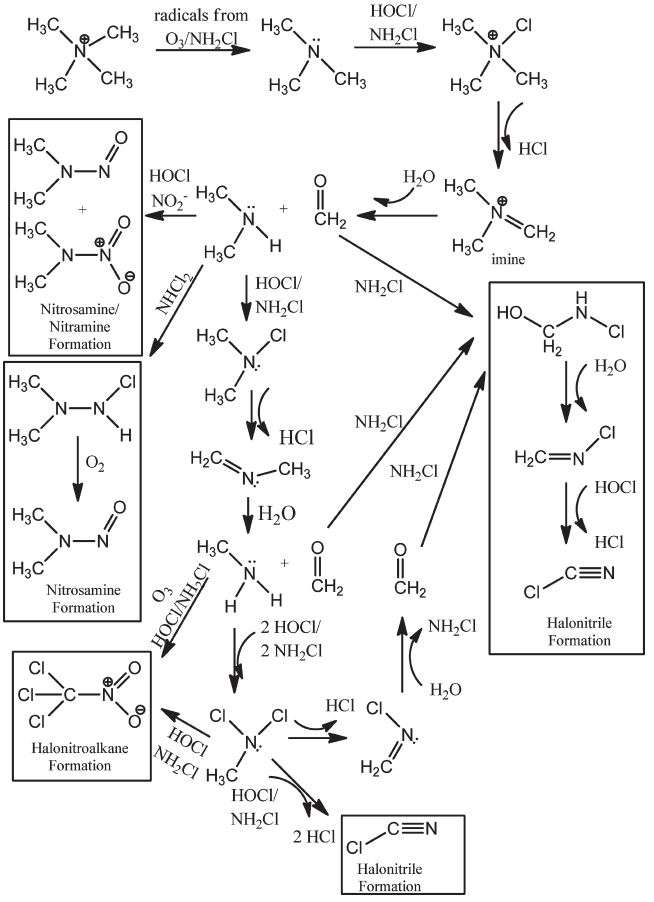
DISCUSSION

The reaction pathway review suggests several important themes pertinent to future N-DBP research.

Theme 1 − Linkages between Amine Precursors. First, with the exception of some pathways where inorganic nitrogen served as the nitrogen source for N-DBPs, most formation pathway studies have focused on amine precursors (primary amines for precursors for halonitriles, haloamides, and halonitroalkanes and secondary, tertiary, and quaternary amines for precursors of nitrosamines). These amine-based N-DBP precursors tend to be found in hydrophilic neutral or base fractions of source water organics that are poorly removed during conventional drinking water treatment processes (e.g., coagulation) compared to the hydrophobic fractions harboring trihalomethane precursors.[53] The focus on amines is reasonable because the other major nitrogenous functional group in organic molecules, amides ($R\text{-}C(=O)\text{-}N\text{-}R_2$; e.g., peptide bonds and the side chains of glutamine and asparagine) are orders of magnitude less reactive than amines with oxidants, such as free chlorine,[99] due to the adjacent electron-withdrawing carbonyl group. An exception is quaternary amines, where, as discussed above, the permanent positive charge on the nitrogen reduces reactivity with oxidants, but where the high mass loadings of quaternary amines from treatment polymers and consumer products may counterbalance the low yields to render these compounds significant nitrosamine precursors.

It is important to note likely linkages between N-DBP families resulting from the conversion of amines from higher to lower orders during disinfection, such that higher order amine precursors may ultimately serve as precursors for all of these N-DBP varieties. For example, Scheme 4 summarizes pathways relevant to chlorine or chloramine-associated conversion of methylamines to some N-DBPs of current interest. In low yield reactions (<5%), chloramines and ozone convert quaternary amines to secondary amines, likely due to reactions involving radicals (e.g., chloramino or hydroxyl radicals).[95,96] Tertiary amines are rapidly and quantitatively converted to secondary amines by free chlorine, ozone, chlorine dioxide, and chloramines.[27,89] For chlorination and chloramination, initial Cl[+1] transfer to the amine is rapid for chlorine but slower for chloramines. In either case, decay of the chlorinated amine intermediate to produce a secondary amine and an aldehyde via an imine intermediate is rapid, such that the conversion of tertiary amines was complete within 10 min during chlorination.[89] The rapidity of tertiary amine degradation inhibits the ability to detect potential tertiary amine intermediates during quaternary amine conversion to

Scheme 4[a]



[a] Source: Mitch, W. A.; Krasner, S. W.; Westerhoff, P.; Dotson, A. Occurrence and Formation of Nitrogenous Disinfection Byproducts. ©2009. Water Research Foundation. Reprinted with permission.

secondary amines. The secondary amine products can participate in formation of stable secondary nitrosamine products at yields <5% over time scales of several days. Alternatively, chlorination and chloramination converts them to primary amines and aldehydes by a similar pathway to that observed for tertiary amines. However, although high yields are expected, their conversion is likely slower, as the lack of a positively charged nitrogen in the secondary chloramine intermediates renders them more stable. The primary amine products can participate in formation of halonitriles (yields up to 40%) and halonitroalkanes (yields <1%). When amines with alkyl chains longer than methyl groups are employed, hydrolysis of the halonitrile products can form haloamides. Formation of a dichlorinated amine intermediate also yields an aldehyde (yields up to 30%) and inorganic monochloramine by a chlorinated imine intermediate, in a fashion similar to that described for tertiary and secondary amines.[18] Like secondary amines, the lack of a positive charge on the dichlorinated amine intermediate renders it more stable than chlorinated tertiary amine intermediates (i.e., primary amine half-lives during chlorination on the order of days[18]).

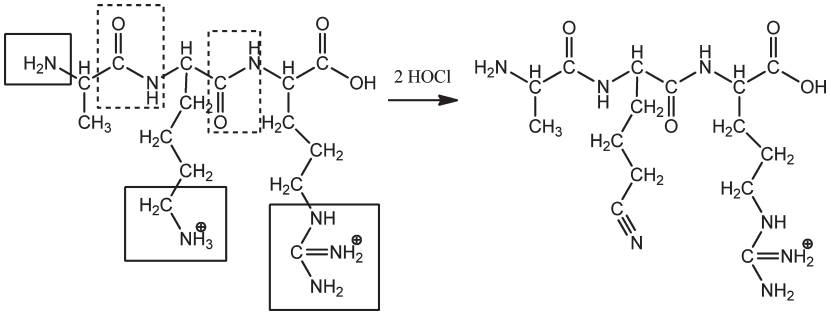
Theme 2 – Byproduct-Free Disinfectants Are Unlikely. A second theme is that it is unlikely that a disinfectant will be identified that will avoid DBP formation. Each of the major disinfectants are associated with the formation of particular DBPs. Free chlorine forms regulated trihalomethanes and haloacetic acids, along with a wide range of unregulated halogenated DBPs. Ozonation promotes the formation of bromate in bromide-containing waters and promotes the formation of halonitroalkanes during postchlorination or chloramination. Chloride dioxide is associated with chlorite, a regulated DBP. The lack of chemical application during UV treatment raised some hope that DBP formation could be avoided. However, UV treatment with medium pressure UV bulbs promoted halonitromethane formation during postchlorination/chloramination due to photolysis of nitrate and nitrite.[32,37]

Rather than searching for a DBP-free disinfectant, it may be more fruitful to optimize disinfection to reduce overall exposure to potentially harmful DBPs. Utilities are exploring combinations of disinfectants. Such combinations may reduce the final concentrations of the specific DBPs associated with each individual disinfectant, but optimization of the disinfectant exposures in these combinations likely will involve characterization of the trade-offs in formation of their relevant DBPs. For example, free chlorine, ozone, and chlorine dioxide have been noted to deactivate precursors for nitrosamine formation during subsequent chloramination.[27,77] However, the CT for these preoxidants should be optimized to balance the reduction in nitrosamine formation against the formation of DBPs associated with each preoxidant.

Theme 3 – Reaction Pathways Can Be Used to Design Disinfection Systems That Minimize Byproduct Formation. A third theme is that knowledge of N-DBP formation pathways can be applied to modify disinfection systems to minimize N-DBP formation while still meeting pathogen reduction goals. A facile example regards halonitroalkane formation during UV disinfection, where use of low pressure mercury lamps reduces formation due to the minimal overlap between the lamp emission band and the absorption bands of nitrate and nitrite.[32,37]

A more complex example regards nitrosamine formation, where dichloramine and dissolved oxygen have been identified as key reagents.[72] One option to minimize nitrosamine formation is to reduce dichloramine concentrations in the applied chloramines. Ammonia is generally applied at a slight molar excess compared to chlorine, favoring monochloramine formation. The ammonia and chlorine reagents for chloramine formation can be added in any order. Their reaction to form inorganic chloramines is very rapid. If chlorine is injected downstream of ammonia, the molar ratio of free chlorine to ammonia at the point of chlorine injection may be >1 prior to complete mixing, promoting dichloramine formation to a greater extent than anticipated.[75] Application of chlorine upstream of ammonia would prevent this effect by promoting monochloramine formation. When chloramines are combined with ozone, chlorine dioxide, or UV for drinking water treatment, chlorine should be applied prior to ammonia for chloramine formation. During wastewater recycling, where chlorine may be applied to disinfect non-nitrified secondary effluents, which contain ammonia, chloramines would form under conditions promoting dichloramine formation. As an alternative, chloramines could be preformed by application of chlorine followed by ammonia to an ammonia-free water (e.g., tap water) and then applied to the wastewater. This strategy was successfully pilot-tested at a wastewater recycling facility.[100] Over a ~4 min contact time upstream of membrane treatment, the application of chlorine directly to the non-nitrified wastewater resulted in a ~150% increase in NDMA, while NDMA formation from application of preformed monochloramine was negligible. Application of preformed monochloramine also reduced

Scheme 5



dichloroacetonitrile formation compared to addition of free chlorine followed by ammonia.[101] In this case, Cl[+1] transfer from free chlorine to the primary amine precursors for dichloroacetonitrile can occur in <1 min but is much slower from chloramines. Since chlorine transfer initiates dichloroacetonitrile formation, application of preformed monochloramine prevents exposure of dichloroacetonitrile precursors to free chlorine.

Theme 4 – Important N-DBPs Are Predictable. A final theme is whether we can apply the reaction pathways to precursor structures likely to be important in algal- or wastewater-impaired waters to predict specific N-DBPs likely to form at high concentrations. Attempts to predict specific DBPs in pristine waters have been hampered by the uncharacterized nature of the humic substance precursors. These highly degraded materials are likely fragmented into a wide array of structures. Accordingly, DBP research has relied upon analytical chemists to identify DBPs, yet the importance of those identified remains unclear since ~70% of total organic halogen (TOX) remains uncharacterized.[102]

The organic matter contributed by algal exudates in algal-impacted waters, or human waste and bacterial exudates in waters impacted by biologically treated wastewater are comparatively fresh, such that the structures of the biomolecules likely remain relatively intact. Knowledge of the limited array of monomers constituting biopolymers enables the prediction of N-DBP structures likely to form in high yield. However, current research continues to dwell on low molecular weight members of N-DBP families identified by analytical chemists. For example, US Method EPA 521 quantifies N-nitrosodimethylamine, N-nitrosomethylethylamine, N-nitrosodiethylamine, N-nitrosodipropylamine, N-nitrosodibutylamine, and the cyclic N-nitrosopiperidine and N-nitrosopyrrolidine. While many of these nitrosamines were popular targets for research into nitrosamine concentrations in food, there is little justification for targeting these nitrosamines based upon the likely occurrence of their precursors in source waters. Indeed, N-nitrosodimethylamine was found to be a disinfection byproduct during a California utility survey partially by accident.[8] The compounds included suggest a systematic search for nitrosamines of longer alkyl chain length. Results from a nationwide survey conducted as part of the US EPA's Unregulated Contaminant Monitoring Rule 2 indicated that NDMA dominated the EPA Method 521 nitrosamines in terms of detections and concentrations.[103] Similar results were found in other studies.[104] As the US EPA evaluates potential nitrosamine regulations, a key question is whether NDMA is the only nitrosamine of concern, or whether other nitrosamines should be targeted for analysis. To answer this question, a total nitrosamine assay was developed, akin to total organic halogen.[105] Application of the method to chlorinated recreational waters in combination with EPA Method 521 suggested that NDMA accounted for only ~10% of the total nitrosamine pool, while the other EPA Method 521 nitrosamines were rarely detected.

Combined amino acid-derived byproducts exemplify a new approach. Amino acids are of interest, as they constitute a significant fraction of the organic nitrogen in cells. Effort has focused on the formation of the low molecular weight halonitriles, cyanogen chloride and dichloroacetonitrile, during chlorination or chloramination of free amino acids.[19,50] With the exception of the high yields from chloramination of free glycine,[50] yields from other amino acids were ~0.01% for dichloroacetonitrile and ~2% for cyanogen chloride.[19] These low yields result from the need to break carbon−carbon bonds in free amino acids to liberate the one or two carbons required for these specific N-DBPs. Other research demonstrated that each free amino acid is transformed at relatively high yield to specific nitriles relevant to the structures of the amino acid (e.g., 2-methylbutyronitrile from chlorination of free isoleucine[44]) (Scheme 1B).

In a survey of wastewater- and algal-impacted raw drinking water supplies, amino acids constituted 15% of dissolved organic nitrogen, but only ~6% of total amino acids were free amino acids.[53] Amino sugars accounted for roughly an order of magnitude less total organic nitrogen than combined amino acids.[53] The identity of other dissolved organic constituents is unclear. However, as protein and polysaccharides constitute the bulk of organic matter in cells, it is possible that a significant fraction of the unidentified organic nitrogen consists of constituent combinations (e.g., glycoproteins) that may not be amenable to analysis according to existing combined amino acid analytical techniques. In this case, the importance of amino acid side chain-based byproducts would still hold. Accordingly, research regarding protein-derived DBPs should focus on combined amino acids.

Research has begun to target functional groups in combined amino acids. Work remains focused on amine functional groups (boxed nitrogens for the tripeptide in Scheme 5), which are orders of magnitude more reactive with disinfectants than amide nitrogens (dashed boxes in Scheme 5) due to their adjacent electron-withdrawing carbonyl groups.[99] Accordingly, within peptides, chlorine will react first with amine sites (e.g., within side chains), while reactions with amides, such as peptide bonds, occur only at 70−200 molar excess of chlorine to peptide reactive sites. During disinfection, molar ratios or chlorine or chloramines to organic nitrogen are closer to one (e.g., 0.03 mM Cl[+1] to ~0.03 mM organic nitrogen for drinking water).

Two articles evaluated chlorination of the α-amino terminus of dipeptides.[51,106] In peptides, the carboxylic acid associated with the α-terminal amino acid is locked in a peptide bond, preventing concerted decarboxylation. In this case, imine production

following monochlorination of the α-terminal amine proceeded by hydrochloric acid elimination over time scales of several days. Less work has focused on the reactivity of amines in amino acid side chains, although side chains outnumber α-terminal amines in peptides (e.g., the tripeptide alanine-lysine-arginine in Scheme 5). One work evaluated chlorination of n-propylamine, as a model for primary amines in amino acid side chains (e.g., lysine). With free chlorine in excess, rapid dichlorinated propylamine formation was followed by the slow elimination of hydrochloric acid to form propionaldehyde (yields ∼10−30%) and propane nitrile (yields up to 40%) over ∼3 d.[18] These results suggest that yields of the associated aldehyde and nitrile products from lysine monomers in combined amino acids should be significant. Quantification of byproducts resulting from disinfectant reactions with side chains in peptides is difficult, because there can be a wide array of peptides due to the variation in the number and order of the amino acid monomers. However, unlike humic substances, there is a limited array of amino acid monomers, and their structures are known. If these disinfectant-modified monomers could be liberated from the peptides, their total concentrations could be quantified. An enzyme-based digestion technique was developed to accomplish this liberation.[107] Application to a relatively pristine disinfected tap water detected 105 ng/L of lysine nitrile, the nitrile predicted to form from chlorine reactions with the lysine side chain (Scheme 5). Lysine constituted one of the lowest proportions of total amino acids detected in peptides from raw or partially treated treated drinking waters (<5%).[53] However, the same approach could be applied to predict and quantify the byproducts of other combined amino acids likely to form at high yield.

Although N-DBPs are an emerging field of study, there has been some ambivalence among the research community borne from the frustrations arising from the more traditional field of C-DBPs. Further progress in the C-DBP field has been hampered by the inability to fully characterize the natural organic matter precursors. To a first approximation, the result has been a reduced ability to predict byproducts likely to form at high yield or to redesign disinfection methods to minimize byproduct formation, other than precursor removal techniques (e.g., enhanced coagulation). There may be a tendency to feel that N-DBPs are simply the latest "Flavors of the Month" within the overall DBP field. However, there are some exciting opportunities in this field associated both with experimentation with new disinfectant combinations and the better-characterized nature of the organic nitrogen precursors in algal- and wastewater-impacted waters. In particular, these trends offer the potential to apply disinfectant reaction pathways to precursor structures to predict trends in byproduct formation.

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