Assessing the *N*-Nitrosamine Formation Potential of Selected Ionic Liquids, 1-Ethyl-3-Methylimidazolium Bromide and 1-Ethyl-1-Methylpyrrolidinium Bromide, Treated With the Drinking Water Disinfectant Monochloramine

by

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Abstract

Ionic liquids (ILs) are increasingly used in industrial processes as "green chemicals" because of unique properties of low volatility and customizability. ILs can be used to enable novel processes and/or replace conventional organic solvents in a wide variety of applications. Widespread use may increase the risk of accidental release of IL-containing industrial wastes into environmental waters. Most ILs are highly water soluble, and have estimated environmental half-lives of several days to a month. IL cations often consist of aromatic or alkyl quaternary amines that resemble previously confirmed *N*-nitrosamine (NAs) precursors. NAs are confirmed animal carcinogens and classified as probable human carcinogens. NAs are also potent, estimated to have negative health effects at ng/L concentrations. Therefore, this study sought to evaluate two representative ILs, 1-ethyl-1-methylpyrroldinium bromide (EMPyrBr) and 1-ethyl-3-methylimidazolium bromide (EMImBr), for their nitrosamine formation potential. Each IL species was reacted with pre-formed monochloramine under varied reaction conditions. After 24h, samples were extracted from water by liquid-liquid extraction using dichloromethane. The extracts were analyzed to determine the produced nitrosamines using HPLC-MS/MS with multiple reaction monitoring mode. Quantification of NAs was achieved using a deuterated surrogate standard, and deuterated internal standard. Both EMImBr and EMPyrBr produced NAs during reactions with monochloramine: EMImBr acted as a precursor to *N*-nitrosomethylethylamine (NMEA), and EMPyrBr acted as a precursor to NMEA and *N*-nitrosopyrrolidine. EMPyrBr was a more productive precursor under all conditions evaluated, with a yield on the same order of magnitude as polydiallydimethylammonium

chloride, a confirmed *N*-nitrosodimethylamine precursor. This study emphasizes the importance of prevention of environmental discharge of ILs to water bodies, but also highlights a need for further evaluation of potential lifecycle impacts of ILs prior to their wide ranging applications.

Attempts were made to quantify EMImBr by LC-UV before and after treatment with NH_2Cl to measure degradation during reactions. Results of LC-UV were indicative of alternate product formation. This initial study suggests future studies on identification of major product(s) of this reaction and to elucidate reaction mechanism(s).

These results suggest that disposal of ILs should be carefully considered so as to prevent contamination of drinking water sources. IL-based drinking water treatment technologies should also attempt to minimize IL contamination of finished drinking water.

Preface

This is an original work by Ian Vander Meulen. No part of this thesis has been previously published

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List of symbols, terminology, and abbreviations

$(mg/kg/d)^{-1}$	Oral dose cancer slope factor (estimated increase in population lifetime rates of cancer, per dose of agent [milligram per kilogram per day])
µg/kg	Microgram per kilogram
µg/L	Microgram per litre
µM	Micromolar
mM	Millimolar
BASIL	Biphasic acid scavenging using ionic liquids
BMImCl	1-butyl-3-methylimidazolium chloride
DBP(s)	Disinfection by-product(s)
DOM	Dissolved organic matter
DWTP	Drinking water treatment plant
EC_{50}	Median (50%) Effective concentration
EMImBr	1-ethyl-3-methylimidazolium bromide
EMPyrBr	1-ethyl-1-methylpyrrolidinium bromide
FP	Formation potential
HAAs	Haloacetic acids
IL(s)	Ionic liquid(s)
LC	Liquid chromatography
LC_{50}	Median (50%) Lethal concentration
LC-MS/MS	Liquid chromatography tandem-mass spectrometry
LC-UV	Liquid chromatography with UV detector

LD_{50}	Median (50%) Lethal dose
MAC	Maximum acceptable concentration
mg	Milligram
mg/kg	Milligram per kilogram
mg/kg/d	Milligram per kilogram per day
mM	Millimolar
NH_2Cl	Monochloramine
$NHCl_2$	Dichloramine
MRM	Multiple reaction monitoring mode
MS/MS	Tandem mass spectrometry
NA(s)	*N*-nitrosamine(s)
NDMA	*N*-nitrosodimethylamine
NDMA-D_6	Deuterated *N*-nitrosodimethylamine
NDEA	*N*-nitrosodiethylamine
NDPhA	*N*-nitrosodiphenylamine
ng	Nanogram
NMEA	*N*-nitrosomethylethylamine
NMEA-D_3	Deuterated *N*-nitrosomethylethylamine
NMor	N-nitrosomorpholine
NPip	*N*-nitrosopiperidine
ng/L	Nanogram per litre
NMEA	*N*-nitrosomethylethylamine
PAHs	Polyaromatic hydrocarbons

PHG	Public health goal
polyDADMAC	Polydiallyldimethylammonium chloride
TD_{50}	Median lifetime tumour-inducing dose
THMs	Trihalomethanes
TSNA(s)	Tobacco-specific nitrosamine(s)
USEPA	United States Environmental Protection Agency
WHO	World Health Organization

1 Potential impacts of ionic liquids on drinking water as precursors to *N*-nitrosamines

1.1 Safe drinking water

There are few resources as absolutely necessary as clean drinking water. In 2010, the United Nations General Assembly affirmed this need by ratifying a document that describes and defines the importance of drinking water for all people. [1] The General Assembly's exact phrasing was that "[the General Assembly] recognizes the right to safe and clean drinking water and sanitation as a human right that is essential for the full enjoyment of life and all human rights."[1] This strong language clearly frames the need for water as a necessity for all people and societies. In this statement, there is a strong implied imperative for societies and/or governments to provide access to clean and safe drinking water. It can be difficult to provide populations with access to "safe and clean drinking water," but this is an absolutely necessary task. Without treatment, freshwater can and will act as a medium of disease transmission.

The risks associated with consumption of unsafe water have been historically significant. Waterborne disease transmission was recognized as early as 1854, when the source of a cholera outbreak was attributed to sewage-contaminated drinking water.[2] Although diseases like cholera, typhoid, and dysentery are no longer common in developed societies, modern drinking water disinfection systems are critically important to preventing the spread of these same waterborne diseases.

Waterborne pathogens are dangerous, and waterborne disease outbreaks continue to happen, even in developed nations.[3] An example of modern treatment system failure occurred in the town of Walkerton, Ontario, Canada in 2000.[4] Because of incomplete

chlorination of raw water after heavy rain, a population of ~4800 were exposed to *Escherichia coli* O157:H7 and *Campylobacter jejuni* through their drinking water. Around 2300 people fell ill from this exposure, of which 65 were hospitalized, 27 experienced life-threatening symptoms, and 7 people died.[4] Therefore it is important to prevent complacency and maintain vigilance in order to prevent future outbreaks, even in industrially developed countries.[5]

The World Health Organization (WHO) estimates that 663 million people still lack access to safe drinking water globally. This lack of access contributes to over 842,000 deaths annually from waterborne diseases.[6] Therefore it is imperative that disinfection efforts continue and expand to make drinking water safer for all. Drinking water disinfection is now conducted, mostly within municipalities of developed countries, to prevent the spread of waterborne illnesses.[7] Drinking water disinfection measurably contributes to significantly longer lifespans, preventing unnecessary illnesses and death.[8,9]

As an unintended consequence of disinfection, disinfectants react with the natural organic matter (NOM) present in source water, generating disinfection by-products (DBPs)[10]. While it is important to be aware of the potential public health impacts of DBPs, the public health benefits of disinfection clearly outweigh the risks of consuming disinfected water.[8,9] Disinfection of drinking water has been recognized as one of the most successful public health measures taken in the last century. Therefore the practice of drinking water disinfection should continue and expand to ensure continued safety of drinking water.

1.1.1 Disinfection by-products

In 1974 it was suggested that chemical contamination of drinking water from the Mississippi river was contributing to adverse health outcomes, as compared to those who drew their water from groundwater.[11] This led to a suspicion that people were being exposed to environmental contaminants through their drinking water. On December 16, 1974, the United States House of Representatives passed the "Safe Drinking Water Act," which mandated that the United States Environmental Protection Agency (USEPA) monitor for some chemical contaminants in drinking water.[12] This was followed by an investigation by the USEPA in 1975, which found that Mississippi drinking water contained some trace organic compounds that were suspected carcinogens.[13]

Around the same time in 1974, a Dutch chemist named Johannes Rook demonstrated that water disinfected with chlorine contained trihalomethanes (THMs), whereas raw water did not.[14] Rook proved that these THMs were generated by the combination of chlorine with dissolved organic matter, implicating disinfection as a novel source of THMs in drinking water.[14] Researchers at the USEPA replicated these results shortly after, strengthening this conclusion.[15] This was a landmark discovery, inspiring an entire field of research encompassing the characterization, generation, detection, and assessment of public health relevance of disinfection by-products (DBPs).[7,16]

Disinfection of water is absolutely necessary for the prevention of waterborne diseases. However it is also important to minimize risks associated with the consumption of DBPs. Assessments of the risks associated with consumption of DBPs and/or disinfected water have since been carried out, but it remains unclear to what degree the consumption of water containing DBPs does/does not contribute to an elevated lifetime risk of bladder

and/or other cancer(s). Epidemiological studies have assessed the association between DBP exposure and bladder cancer risk, and have found a potential association between the consumption of chlorinated water and increased risk of developing bladder cancer.[17,18] This is also the case in case-control studies attempting to correlate lifetime bladder cancer risk with exposure to well-known regulated DBP species such as chloroform, trihalomethanes (THMs), and haloacetic acids (HAAs).[19,20] These common DBP classes are now thought to be insufficiently potent to be the cause of significant deleterious public health effects.[19,20] However some DBPs have demonstrated greater toxicity and/or mutagenicity than classic chlorinated DBPs like THMs and HAAs, and so may be more public health relevant.[21]

1.2 *N*-nitrosamines

Under some circumstances *N*-nitrosamines (NAs) can be formed during disinfection of drinking water, particularly during chloramination. NAs are a class of DBPs that are relevant to public health.[22] NAs are notably carcinogenic,[23,24] and so it is important to minimize/eliminate nitrosamine formation during drinking water disinfection.

Since the 1900s, NAs have been noted for their tendency to cause adverse effects. This was highlighted in 1954, when *N*-nitrosodimethylamine (NDMA) was introduced as a new solvent for use in a laboratory.[25] Soon after the introduction of NDMA as a solvent, researchers making regular use of NDMA thereby experienced a high level of exposure, and began to experience severe adverse effects. After 10 months of NDMA use in the laboratory, one lab member passed away from pneumonia. This individual's autopsy revealed significant amounts of damage to the liver tissue.[25] Two cases of liver cirrhosis followed in

fellow researchers as they continued to make use of NDMA in their procedures.[25] Ceasing NDMA use/exposure allowed liver function to return to normal in these individuals, implicating NDMA as a common agent likely to be causing liver damage.[25] Therefore it is sensible to prevent large acute doses of NAs.

1.2.1 Toxicity of *N*-nitrosamines

NAs can also cause adverse effects at lower concentrations, as has been demonstrated in *in vivo* studies. NA toxicity studies have been conducted with *in vivo* animal models. NDMA toxicity has been evaluated in rats,[25,26] minks,[27] mice, rabbits, guinea pigs, and dogs[25] to confirm and quantify NA toxicity. Animal toxicity studies have consistently highlighted acute and sub-acute toxic effects to the livers of these animals.[25-28] Carcinogenesis is observed as the primary adverse health outcome of NDMA exposure across all mammalian animal models tested, primarily in the liver.[24] NDMA requires metabolic activation in the liver to cause toxic effects,[29-31] which may intuitively help explain why the liver is a common target organ in *in vivo* studies. However the liver is not the only organ adversely affected by NDMA. NDMA toxicity studies have also noted the induction of lung, kidney, testicular, and vascular cancers in male rats, and observations of liver and vascular cancers in female rats, as well as lung, and cancers of the nervous system in mice.[32] The mean reported values for 50% lifetime tumour induction (TD_{50}) in mice (106 week lifetime) from NDMA exposure for rats and mice are 95.9 µg/kg/day and 189 µg/kg/day respectively.[32]

There is a strong consensus that NAs, and NDMA in particular, are carcinogenic. The United States Environmental Protection Agency (USEPA) classifies NDMA as a "B2

(probable human) carcinogen based on the induction of tumors at multiple sites in different mammal species exposed to NDMA by various routes.[33] The U.S. Department of Health and Human Services (DHHS) states that NDMA is reasonably anticipated to be a human carcinogen (NTP 2014).[34] The American Conference of Governmental Industrial Hygienists (ACGIH) has classified NDMA as a Group A3 confirmed animal carcinogen with unknown relevance to humans (HSDB 2013)."[35]

Although NDMA is typically the most discussed/publicized NA, structurally similar NAs are estimated to be similarly toxic. These structurally similar NAs are estimated to be nearly as carcinogenic as NDMA, as the EPA's estimates of their oral cancer slope factors are on the same order of magnitude.[36] Estimates of oral dose cancer slope factors, as well as target organs observed from toxicity evaluations of each compound are listed in **Table 1.1**. The larger the slope factor, the more potent the estimated carcinogenicity.

Although NAs with larger alkyl substituents tend to be less toxic than less bulky NAs,[28] NAs with bulkier side-chain functional groups may still be health relevant. For example, *N*-nitrosodiphenylamine (NDPhA) has bulky substituent side-chains, and was previously understood to be one of the least toxic nitrosamines.[47] NDPhA is remarkably less carcinogenic than other NA species (as per the oral dose cancer slope factor in **Table 1.1**),[36] but results from *in vitro* studies have suggested that NDPhA may be more cytotoxic than other NAs. NDPhA was shown cause consistent cytotoxicity across a variety of cell lines, despite being much less mutagenic than other NAs.[48]

Table 1.1 – A selection of NAs commonly detected in drinking water. NA species are listed with associated carcinogenicity slope factors values as estimated by the United States Environmental Protection Agency. [36] The higher the slope factor, the more carcinogenic the toxicant. Target organs listed correspond to sites of carcinogenic toxicity endpoints observed during *in vivo* mammal toxicity studies.

Nitrosamine	Abbreviation	Oral dose cancer slope factor[36] ($[mg/kg/d]^{-1}$)	Target organ(s)
N-nitrosodimethylamine	NDMA	51	Liver, bile duct, nasal mucosa [25,27,37]
N -nitrosodiethylamine	NDEA	150	Liver, esophagus[37,38]
N-nitrosomethylethylamine	NMEA	22	Liver, bile duct, nasal mucosa[39]
N-nitrosopyrrolidine	NPyr	2.1	Liver, lung, nasal mucosa[40]
N-nitrosomorpholine	NMor	Not available	Liver, lung[41,42]
N-nitrosopiperidine	NPip	Not available	Liver, larynx, trachea[37,43]
N-nitrosodipropylamine	NDPA	7	Liver, esophagus, stomach[44]
N-nitrosodibutylamine	NDBA	Not available	Liver, stomach, bladder[45]
N-nitrosodiphenylamine	NDPhA	0.0049	Bladder[46]

1.2.2 Sources of *N*-nitrosamine exposure

NAs can be detected in a variety of products, including processed and/or cured meats[49], liquor,[50] tobacco,[50,51] and drinking water.[52-55] The presence of NAs in foodstuffs are largely attributable to nitrosation reactions that occur during the processing, curing, and/or cooking of preserved foods[50]. Nitrosation is responsible for generating NAs during the curing, smoking, and/or cooking of meats such as sausages and deli meats.[49,56] NDMA content in sausages can be as high as 2 μg/kg after cooking, while total NAs can be as high

as 200 μg/kg.[49] To prevent the generation of NAs in preserved foods, the FDA now limits the use of nitrates and nitrites.[57] Manufacturers must submit applications to be allowed to use nitrates and nitrites in new products, and these applications must be accompanied by sufficient data to demonstrate that the use of these preservatives does not promote the generation of NAs.[57] However, this does not necessarily prevent NA exposure, as NAs may still be generated endogenously after consuming nitrite-containing foods by acid-catalyzed nitrosation in the gastrointestinal tract.[58]

Individuals may also be exposed NAs through consumption of alcoholic beverages.[50] Beer has been found to contain 0 – 7.1 μg/kg (0 - 7.2 μg/L) of NDMA, depending on the brand and batch.[59] In whiskeys, NDMA content is typically 0.1 ± 0.09 μg/kg (~ 0.09 ± 0.08 μg/L).[59]

NAs are also detectable in tobacco smoke, with a few varieties that are tobacco-specific nitrosamines (TSNAs).[51] TSNAs have also been detected as drinking water contaminants.[55]

1.2.3 *N*-nitrosamines in drinking water

NAs are also detectable in some drinking water sources.[55,60,61] NDMA was first detected in drinking water in 1989 on the Ohsweken First Nations reserve in Ontario.[52] This finding constituted a new source of exposure to these previously identified toxic agents. Other extensive surveys have since followed, demonstrating that nitrosamines are a widely occurring class of disinfection by-products (DBPs) in drinking water.[54,55,60,62] Total NA concentrations in municipal drinking water systems are range from concentrations below detection limits, up to 100 ng/L.[54,55,60,62]

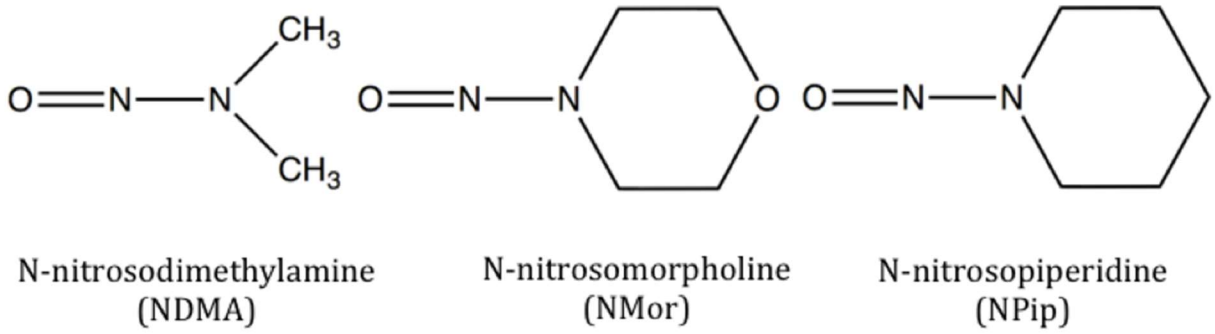

Figure 1.1 – Structures of a few *N*-nitrosamines commonly detected in drinking water

NA exposure through drinking water is relatively minor when compared to other sources of exposure. Endogenous acid-catalyzed nitrosation of nitrite-containing foods is estimated to contribute far more to lifetime NA exposures than drinking water.[58,63] Drinking water is estimated to contribute between 0.0002 - 0.001% of total lifetime exposure to NDMA.[63] Although this constitutes relatively minor NA exposure, some jurisdictions have nonetheless implemented standards (Ontario),[64] and guidelines (Canada, California, Massachusetts, and Australia)[65-68] to limit NDMA to ng/L concentrations in finished drinking water to minimize risk of adverse health outcomes.

1.2.4 Guidelines and regulations to limit *N*-nitrosamine exposure in drinking water

Because NAs are widely detected, and are relevant to public health, some jurisdictions have guidelines or regulations limiting NDMA concentrations in drinking water. Guidelines for a maximum acceptable concentration (MAC) of NDMA exist in Canada (40 ng/L NDMA),[65] Ontario (9 ng/L NDMA),[64] Australia,[68] Massachusetts,[67] and California.[66]

California has implemented warnings levels for NDMA, NDEA, and *N*-nitrosodipropylamine (NDPA), where notification levels of each are 10 ng/L, and the response levels are 300 ng/L, 100 ng/L, and 500 ng/L in drinking water respectively. At the notification level, water suppliers are notified, and recommendations are made to decrease contaminant levels; at the response level, the state authority recommends the drinking water source be removed from service. Both Australia and Massachusetts set guidelines for NDMA to an MAC of 100 ng/L.[67,68] While there are no federal regulations limiting NDMA concentrations in the United States, from 2007 - 2010 the USEPA required public utility providers to report NDMA, *N*-nitrosodiethylamine, *N*-nitrosomethylethylamine, *N*-nitrosodipropylamine, *N*-nitrosodibutylamine, and *N*-nitrosopyrrolidine for monitoring purposes, with minimum reporting concentrations of 2 ng/L, 5 ng/L, 2 ng/L, 7 ng/L, 4 ng/L, and 2 ng/L respectively under the second unregulated contaminant monitoring rule program in order to establish a database from which it might be possible to justify regulations for NA concentrations.[69] However, no regulations resulted from the Second Unregulated Contaminant Monitoring Rule Program, as national NA concentrations were insufficient to justify national regulation under the Safe Drinking Water Act.[70]

1.2.5 Factors affecting *N*-nitrosamine formation during water treatment

Total NA concentrations depend heavily on a number of factors.[71] One such factor is the choice of drinking water disinfectant. Many drinking water providers, including municipal utilities, have moved from traditional chlorine disinfection to alternative disinfectant systems, such as ozone or chloramine. This switch is often driven by the need to comply with legislated maximum concentrations of other DBPs particularly THMs and

HAAs.[72,73] One alternative approach is to use ozone, although ozonation can also generate nitrosamines.[74,75]. Chloramines may in some cases be an advantageous choice as an alternative disinfectant because chloramines are also effective for residual (secondary) disinfection, maintaining the safety of drinking water in distribution systems with long residence times.[73,76] However, the use of chloramines in municipal disinfection systems has a strong association with elevated concentrations of NAs in finished water.[23,62,77,78] Distribution systems that make use of chloramine as a residual disinfectant may also generate higher NA concentrations over time due to the accumulation of biofilm within the system, and biofilms in turn contribute DOM that may act as precursors to NAs.[79]

Source water affected by wastewater effluent generally has higher NA formation potential (FP).[78,80] NA FP is strongly associated with anthropogenic compounds such as over-the-counter pharmaceuticals.[78,81] This indicates a general need to prevent the release of anthropogenic compounds to the environment wherever possible.

1.2.5.1 Common structural features of identified *N*-nitrosamine precursors

Drinking water providers must be continually aware of and seek to control for the many of the factors affecting NA concentrations in drinking water. NA precursors vary by location, season, and according to sources of anthropogenic waste outputs. Some specific precursors have been demonstrated to promote the generation of NAs in drinking water. Although this section cannot be comprehensive, here general groups of compounds that may contribute to elevated total NA concentrations of finished drinking water are discussed.

Polymers such as polydiallyldimethylammonium chloride (polyDADMAC) or polyamine are often used to remove organics in source water during drinking water treatment to reduce DBP formation. However these polymers have been implicated to increase concentrations of NAs in finished water to varying degrees.[82-84] PolyDADMAC may act as an NA precursor by two possible routes. PolyDADMAC polymers can degrade to form 3° amines that further react to form NAs,[85] but polyDADMAC also contains some 3° amine impurities that contribute to NA formation potential.[85] Polyamine polymers act more directly as precursors, as they contain 3° amine moieties by design.[85]

Other precursors found in source water are present as the result of anthropogenic impact, as they include compounds such as ranitidine (an over-the-counter heartburn medication), [86] caffeine, and other pharmaceutically active compounds such as methadone,[87] primidone, and carbamezipine[88]. General classes of NA precursors can be categorized into 2° amines,[89-91] 3° amines,[85,86,92,93] and 4° amines.[83-85]

As the structural components of NA precursors are relatively common, drinking water providers must continually seek to be aware of and control for precursors affecting NA formation wherever possible. Novel precursors to NAs should be identified and managed effectively to prevent their release in environmental water bodies used for drinking water to thereby minimize NA formation.[92] Ionic liquids are one such class of compounds that resemble previously identified NA precursors and which represent an emerging class of industrial chemicals. These compounds are anticipated to become environmental water contaminants, and so warrant further study.

1.3 Ionic liquids

A recent theme in "green chemistry" research is an interest in ionic liquids (ILs) for use in commercial and industrial applications.[94] Although ILs were first described in 1914,[95] research on potential uses for ILs did not begin until 1992.[96] Since then, it has become clear that ILs are likely useful in a variety of applications, as some may be used as reaction solvents, catalysts, and/or electrolytes across a variety of industries and processes.[94,96] ILs are low melting temperature (<100 °C) organic salts[97], composed of a bulky organic cation and a bulky organic/inorganic anion.[98]

ILs generally have a reputation as "green chemicals," because they are regarded as benign when compared to conventional organic solvents.[99] This is due in large part to their general lack of volatility,[100,101] and their relative thermal stability,[94] as these are major advantages over conventional organic solvents. These properties lead to secondary benefits, including safer working conditions from lack of airborne exposure, lower flammability[102,103], and lesser atmospheric impact.[104,105]

ILs may also be referred to as "designer solvents," because it is possible to design ILs with custom ILs.[94] When designing an IL for use in a particular process, one can choose an ideal anion-cation pairing for a particular application. A few example blueprint cations and anions are displayed in **Figure 1.2**. There is a wide range of possible "blueprint" cation moieties on which to base an IL beyond what is listed in **Figure 1.2**. The choice of blueprint moieties is based on factors including the melting point, whether cations/anions are aromatic or aliphatic, or the inclusion of H-bond donors and/or acceptors. To tailor ILs to the specific needs of a particular process, it is possible to add specific functional groups to the cation/anion moieties to modify their physical properties by the addition of functional

groups[106,107]. Custom functionalization reactions usually only require the addition of a requisite alkyl-halide to a blueprint molecule.[108] This allows for versatile customization by many possible functional groups, which effectively tunes physicochemical parameters including viscosity, miscibility, melting point, conductivity, and intermolecular interactions.[97,109,110] An example of this is apparent in the comparison of 1-ethyl-3-methylimidazolium and 1-octyl-3-methylimidazolium cation moieties, where the latter is capable of much greater non-polar interactions than the former. It has been estimated that there are up to 10^{14} possible combinations of cation and anion,[97] providing ample possibilities for solvent system customization. These advantages have encouraged the development of uses for ionic liquids in a variety of applications and processes.

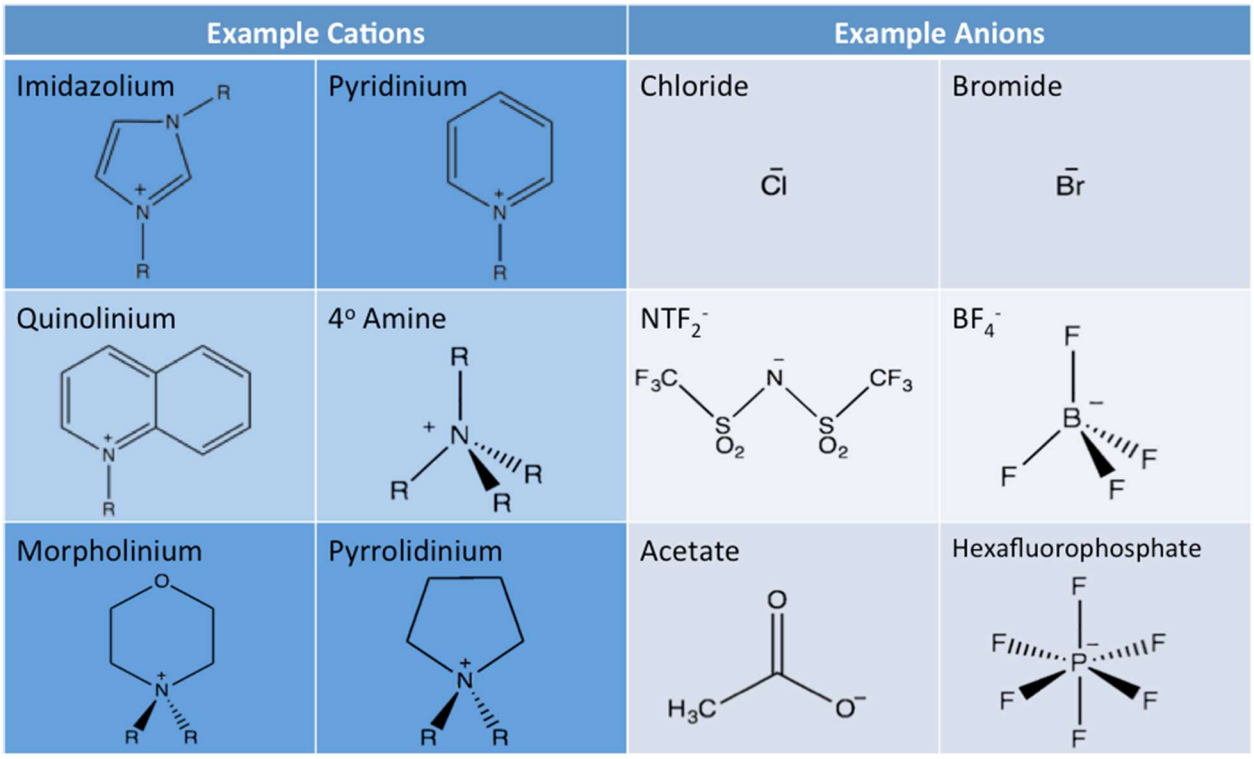

Figure 1.2 – Example ionic liquid constituent cations (left) and anions (right). All "R" groups denote specific points available for functionalization for process optimization.

1.3.1 Uses of Ionic Liquids

Research into uses for ILs has expanded dramatically over the last two decades. In the year 2000, a few hundred publications on uses of ILs were published, whereas in 2015 over 5000 papers on uses of ILs were published.[111] Comprehensive summaries of uses for ILs have been explored elsewhere,[94,106] so this section serves only to highlight a few major categories of potential and current uses of ILs.

The largest-scale current application of ionic liquids is a technique referred to as biphasic acid scavenging utilising ionic liquids (BASIL), which was developed by BASF.[117] During synthesis processes, it is common for acids to be precipitated as by-products of reactions. This can be an obstacle for ensuring product stability and purity, as acids (such as HCl) can react further generating unwanted by-products, or act as impurities in the final sample; therefore, it is imperative to remove the acid by-products[117,118]. In the BASIL process, this is done by the addition of N-methylimidazole to the reaction mixture, which protonates to N-methylimidazolium and can coordinate with the conjugate base of the acid[117,118]. IL phases formed after acid-scavenging are then separated by mechanical methods, such as decanting or draining[117,118]. Once separated, the methylimidazole can be regenerated by the addition of a strong base, such as sodium hydroxide, allowing for the recycling of imidazole.

Some applications where ILs have shown promise or have been established for use include the use of ILs as process solvents,[99,113,118-122] as tools for analytical techniques,[114-116,123-127] as solvents for biopolymer dissolution,[94,128-135] as carbon capture solvents,[136-139] for desalination,[140-144] waste water treatment,[145] for removal of heavy metal ions from water,[146-148] and as injection solvents in drilling and pumping for hydrocarbon

extraction.[149,150] Research is also ongoing to investigate the use of IL-water mixtures for analytical separations, as mixing an IL with water greatly modifies the system's properties.[113] This may lead to water content as another important parameter for tuning an IL phase.[113]

Current small-scale uses of ILs include analytical applications, such as novel separation and sample extraction techniques.[112-116] One such example makes use of ILs as separation agents in a biphasic extraction system.[112] By adding strongly ionic salts to aqueous systems, ILs can be forcibly separated out of solution as a separated liquid phase, allowing for unique polar-ionic liquid-liquid extraction techniques.[112] 1-butyl-3-methylimidazolium chloride (BMImCl) has been demonstrated as an effective extraction solvent, but ILs with longer alkyl chain functionalization are more capable of forming aqueous biphasic systems.[112]

Another technique under development is to add ILs to aqueous mobile phases during liquid chromatography. Adding ILs to aqueous phases can modify the separation process, as it allows the user to add intermolecular interactions in a unique mode of solvent gradient elution, depending on the IL selected.[114] By doing so, it is possible to induce the formation of a secondary ionic layer adsorbed to a non-polar stationary phase, changing elution conditions.[114] In addition, one may make use of aqueous ILs for enhanced separation by spiking ILs to a critical micelle concentration, enhancing liquid chromatographic separations by encasing analytes within IL micelles.[115]

ILs are anticipated to be used on a large scale for biopolymer dissolution. As economic and social pressures build to move away from petroleum products to satisfy consumer needs, demand for some alternately sourced polymer products could be fulfilled

by the use of abundant biopolymers such as chitin or cellulose. The ability of ILs to act as solvents for stable polymers is thought to be due to their ability to interfere with some intermolecular interactions such as hydrogen bonding and dipole forces.[98,128,151] There has been abundant research detailing how ILs can be and have been applied to the dissolution of chitin, [98,129,130,135] keratin, [98] and cellulose.[98,128,131,132,152]

The economics of chitin extraction and reconstitution by ILs is currently being tested; a large-scale chitin extraction plant is currently running in the United States.[153] Chitin is an abundant biopolymer that can be sourced from shellfish, insects, and fungi,[98] As a long-chain polymer of N-acetylglucosamine, chitin is soluble in 1-butyl-3-methylimidazolium acetate, which has significant advantages over previous dilute-acid based chitin solvation systems.[134,154] Typically, mixtures capable of dissolving chitin also require complex organic and/or strongly acidic compounds, leading to concerns over worker safety and product purity, as harsh reactants can affect the integrity of the final products. [154] Chitin dissolved in this process could be reclaimed from the IL-chitin mixture by rinsing formed gel intermediates in water or methanol.[154] Chitin biopolymers are anticipated to be useful as textiles to be subsequently used to weave garments,[133] used in wound care dressings,[154] or used to synthesize biodegradable micro-beads for cosmetics and personal care products.[155] One limitation is that chitin regenerated from dissolution by ILs may in some cases have unpredictable properties, though work is ongoing to address this challenge.[135]

ILs are also being developed for use in water treatment processes including desalination,[140-144] wastewater treatment,[145] and removal of heavy metal content.[146-148] The need for fresh drinking water continues to grow, and desalination may help to supply for this need.[7] Forward-osmosis (FO) techniques are being developed as novel approaches to

desalination[156,157] and water treatment,[145-148,156,157] because distillation and reverse-osmosis (RO) based desalination techniques require large amounts of energy.[7] FO operates on principles of forward osmotic pressure; rather than pumping to overcome a high osmotic pressure differential (as is done in RO), FO works by circulating contaminated water on one side of a membrane and circulating a concentrated draw solution along the other side, generating an osmotic pressure gradient from the dilute solution of water to the draw solvent. [156,157] It is necessary to subsequently separate fresh water from the dilute drawing agent, which may be achieved by techniques such as reverse osmosis, membrane distillation, or nanofiltration. [156,157]

Some FO schemes make use of ILs as draw solvents.[140,141,158] In IL-based upper critical solution temperature (UCST) FO systems, ILs may allow for separation based on melting point.[140] In a UCST FO system, draw solvent is heated to 60-70°C, then collected and allowed to return to ambient temperature, precipitating the ILs as the solution chills. However, in IL-based forward osmosis draw solvent desalination techniques, ILs can be detected in the finished freshwater product.[140,143] Therefore IL-based FO water treatments may need to be paired with techniques such as RO, nanofiltration, or membrane distillation.[156,157] However, these techniques may only partially remove ILs from water.[159-162] If desalination systems built on an IL-based forward-osmosis draw-forward technique are implemented, they may unintentionally add ILs directly to the dissolved organic content of a drinking water supply immediately prior to disinfection. This would be a distinctly negative outcome.

Given the breadth of the current and/or potential applications of ILs, there is potential for ILs to be released to the environment and/or to impact drinking water. Given

that potential there is a need to investigate the impacts of ILs may have should they be discharged to the environment and detected in sources of drinking water.

1.3.2 Environmental impacts of ionic liquids

It remains unclear whether ionic liquids are as environmentally benign as their "green" reputation implies. There are compelling reasons to avoid calling ILs completely "green chemicals" despite some clear advantages over conventional organic solvents.[163-165] One reason that ILs may not be entirely "green" is that IL manufacturing is not environmentally benign. IL synthesis pathways may require numerous reactions,[166] and a need for harsh reagents at various stages of synthesis.[105] Some of these impactful reagents include hazardous materials such as bromoalkanes and toluene, which have been previously established as hazardous materials.[105,166] Procedures to synthesize ILs also have relatively low yields, further preventing efficient synthesis.[105]

ILs are distinctly advantageous over conventional solvents because they are non-volatile,[102] but ILs are also considerably water-soluble. There is some concern that that ILs may have environmental impacts when released through aqueous waste streams. [98,167-169] It is also difficult to remove ILs from water. Classic approaches to water treatment such as reverse osmosis,[159] nanofiltration,[160,162] membrane distillation[161] biological breakdown,[170-172] cannot completely remove ILs from water. Complete removal of ILs from water requires energy-intensive, impractical processes such as vacuum distillation and electrolysis.[173-175] As a consequence, no efficient system has yet been proposed to completely recover ILs from aqueous waste streams.[176] This combination of expectations has prompted toxicity evaluations in aquatic species,[110,167,168] evaluations of environmental fate and

behaviour,[126,177-183] as well as reviews summarizing the potential ecological impacts of ILs.[98,105,110,168,184,185]

There are concerns about the toxicity of ILs released to the environment. Toxic effects from IL exposure have been observed in a wide variety of organisms, including *in vitro* evaluations of bacteria,[186] and *in vivo* evaluations wheat and cress,[187] duckweed,[188] algae,[189,190] mussels, fairy shrimp, brine shrimp, rotifers,[190] zebrafish,[191] and frogs.[192] For example, *in vivo* studies of *Rana nigromaculata* (Dark spotted frog) have been conducted to evaluate 1-octyl-3-methylimidazolium bromide toxicity.[192] In early tadpole development, the acute median mortality concentration (LC_{50}) of 1-octyl-3-methylimidazolium bromide was 85.1 mg/L (79.9 – 90.6).[192] Noted exposure effects included developmental issues such as edema, and lack of spinal strength.[192]

In an *in vivo* evaluation of *Daphnia magnia* (Zebrafish), the LC_{50} of 1-butyl-3-methylimidazolium (BMIm), paired with either bromide, chloride, hexafluorophosophate, or tetrafluoroborate ranged from 8 – 19 mg/L.[191] In comparison to sodium salts paired with the same anions, the LC_{50} of BMIm salts were at least 2 orders of magnitude more toxic, suggesting that toxic effects were more strongly influenced by the IL cation than the anion.[191] In all chronic exposure scenarios (ranging from 0 – 3.2 mg L^{-1}), exposure of *D. magnia* to BMIm salts moderately decreased brood size.[191]

There are some observed structural determinants of IL toxicity. Long alkyl chain,[107] and aromatically functionalized[107,186] ILs tend to be more toxic, suggesting a relationship between greater hydrophobicity of side-chain functionalization and higher acute IL toxicity. For example, in *Scenedesmus quadricauda*, a freshwater algae species, median effective concentration (EC_{50}) values (using growth inhibition as a toxic endpoint) assessed

for 1-butyl-3-methylimidazolium, hexyl-3-methylimidazolium, and octyl-3-methylimidazolium exposures corresponded to the length of side-chains, with respective EC_{50} values of 4.76, 0.078, and 0.005 mg/L, respectively, in fresh water.[189]

Although ILs are toxic to freshwater algae, they are much less toxic to oceanic algae, as high salinity effectively lessens IL toxicity.[193] This suggests that primary impacts of ILs released to the environment will happen to freshwater ecosystems rather than oceanic aquatic ecosystems.

ILs are relatively non-toxic in terrestrial animal models. Lethal endpoints in mice models have been assessed for 3-hexyloxymethyl-1-methylimidazolium tetrafluoroborate.[167] The median lethal dose (LD_{50}), of 3-hexyloxymethyl-1-methylimidazolium tetrafluoroborate in mice was near ~1000 mg/kg oral doses,[167] For reference, this dose is a similar order of magnitude to the oral LD_{50} of sodium chloride in mice, which is ~4000 mg/kg.[194] However, teratogenic effects have also been observed in mice dosed with BMImCl. At doses of 169-225mg/kg/day in mice, litters had significantly lower birth weights. These teratogenic effects had an associated no-observed-adverse-effect-level of 113mg/kg/d.[195] The acute oral median lethal dose (LD_{50}) in rats dosed with BMImCl was ~1400 mg/kg,[167] as compared to mice at ~1000 mg/kg. The relative safety of ILs was further demonstrated by finding dermal exposure causes few effects, even at high concentrations, even when dissolved in water.[167]

One of the concerns about potential environmental impacts ILs may have is that they may increase DOM in source water.[177] Because ILs exploit both ionic and non-polar interactions in order to be advantageous over other solvent types, they may act as

surfactants in the environment.[177] ILs in surface water can re-dissolve previously soil-bound humic content, increasing DOM.[179]

Imidazolium-based ILs are estimated to have aqueous environmental half-lives anywhere from several days to a month[175], to 107±45 days[196] dependent on sunlight and water depth.[175] Aliphatic cations such as pyrrolidinium may be even more persistent, with an estimated environmental half-life of 135 ± 25 days.[196] Therefore, these compounds may be sufficiently persistent to cause downstream impacts.

Despite the amount of work done to evaluate the potential environmental impacts of ILs, a gap remains between the volume of work that exists characterizing the utility of ILs, and work characterizing potential risks of IL release. [111] Significant work remains to be done to characterize the potential environmental impacts of ILs may have as environmental water contaminants.

1.4 Synthesis, hypothesis, and scope of thesis

ILs have been predicted as environmental contaminants in water. [109,167-169] However, little has been done to assess the impacts of ILs as contaminants in water used as sources for disinfected drinking water. My research therefore aims to address a small part of this gap based on two premises:

a) Some IL cation moieties also share structural similarities to previously confirmed NA precursors; this similarity apparent between a cation moiety such as pyrrolidinium, and the previously confirmed NDMA precursor polyDADMAC.[85]

b) ILs are anticipated to be persistent environmental water contaminants, if they are released to a fresh water sources.

Therefore

c) It is conceivable that ILs may act as precursors to generate *N*-nitrosamines under disinfection conditions, particularly if chloramine is used for disinfection.

To test this hypothesis, I proposed my thesis research focusing on two objectives:

a) Examine nitrosamine formation potential when representative ILs react with chloramine under varying conditions. I will use an established liquid chromatography-tandem mass spectrometry (LC-MS/MS) method capable of simultaneously detecting 14 NAs[55] to survey, detect, identify, and quantify nitrosamines generated from ILs.
b) To explore the NA formation mechanisms during chloramination of the selected ILs

Finally, I will evaluate the results and present the conclusions of this research, as well as suggest directions for future research examining the impacts ionic liquids may have on drinking water.

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2 *N*-nitrosamine formation from chloramination of two common ionic liquids

2.1 Introduction

Ionic liquids (ILs) are a broad category of polyatomic organic salts composed of bulky unsymmetrical cation-anion pairs. The steric bulk of IL anion-cation pairs contributes to melting temperatures below 100 °C.[1,2] ILs are considered "green" alternatives to conventional solvents.[1,3] Because of their negligible vapour pressure (minimal occupational hazards) [1,4] and minimal flammability (minimal explosive risk),[2] various ILs have been studied for use in a variety of applications.[5-9] Although ILs are minimally released to the atmosphere because of their low volatility, they may contaminate the aqueous environment because they are considerably water-soluble. As the ILs are increasingly adopted, accidental releases or discharge of ILs to the aqueous environment through wastewater is anticipated.[2,10-12]

There are a few reasons that the release of ILs to the environment is a concern. ILs exhibit toxicity comparable to that of conventional organic solvents, as has been demonstrated in various toxicity evaluations of cell cultures, bacteria,[13] algae,[14,15] invertebrates, [15] and other aquatic freshwater organisms.[10,15-18] Common IL cation moieties (e.g., imidazolium and pyridinium) are also relatively resistant to biodegradation[19,20] and photodegradation.[21-23] This makes ILs somewhat persistent in surface water, with estimated half-lives of several days to several months.[21,25] Such long half-lives may result in downstream impacts from ILs, including impacts they may have on drinking water quality. ILs may also plausibly leach to drinking water if they are used in drinking water treatment processes, such as desalination,[8,24-27] wastewater treatment,[28] and to remove heavy

metals.[29-31] If IL-contaminated water is used as a source for drinking water, ILs may act as precursors to disinfection by-products (DBPs).

Disinfection of drinking water is essential for deactivating pathogens to ensure safe drinking water. However, DBPs unintentionally form from reactions between natural organic matter and disinfectants like chlorine and/or chloramine. The final concentrations and proportions of DBPs in drinking water are strongly influenced by amounts of precursor contaminants in source water.

N-nitrosamines (NAs) are a group of DBPs that have been classified as probable human carcinogens.[32-34] Major classes of NA precursors are amines, including secondary,[35-37] tertiary,[38-42] and quaternary amines.[42-44] These amine-containing compounds are often anthropogenic in origin.[39,41,45]

One example of a previously identified anthropogenic NA precursor is polydiallyldimethylammonium chloride (polyDADMAC), a quaternary amine polymer commonly used in water treatment as a coagulant. PolyDADMAC contains a quaternary amine core structure, and has been shown to transfer the amine group to *N*-nitroso-dimethylamine (NDMA) during chloramination of drinking water.[42,44,46] Common IL cation species contain quaternary amines centres bonded in configurations similar to those of polyDADMAC. Therefore these IL cations may be capable of acting as precursors to NAs.

There is concern that ILs may contaminate environmental waters;[2,10-12,47] however, little has been done to assess the potential downstream effects of ILs on drinking water. Therefore, we have examined ILs as potential nitrosamine precursors using a previously established liquid chromatography tandem mass spectrometry (LC-MS/MS) method.[48] Two commonly used ILs 1-ethyl-1-methylpyrrolidinium bromide (EMPyrBr) with a saturated

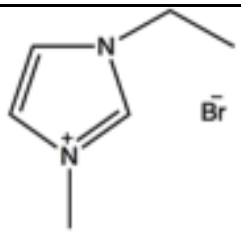
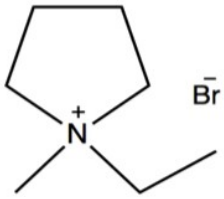
ring structure and 1-ethyl-3-methylimidazolium bromide (EMImBr) with an unsaturated ring structure were chosen for this study. The objective of this study was to evaluate these two ILs for their ability to generate detectable NAs under bench-scale chloramination with varying reaction conditions.

2.2 Materials and Methods

2.2.1 Materials

1-ethyl-1-methylpyrrolidinium bromide (EMPyrBr) (≤98.5%), 1-ethyl-3-methylimidazolium bromide (EMImBr) (≤99%), and a standard mix containing nine NAs (EPA 8270 Appendix IX mix) were obtained from Sigma Aldrich (St. Louis, MO). Some properties of the selected ionic liquids are summarized in **Table 2.1**. NAs contained in the EPA 8270 Appendix IX NA mix are summarized in **Table 2.2**. Two deuterated standards, *N*-nitrosodimethylamine-d_6 (NDMA-d_6) and *N*-nitrosomethylethylamine-d_3 (NMEA-d_3), were obtained from Toronto Research Chemicals (Toronto, ON). Optima LC-MS grade water, methanol, and dichloromethane used were obtained from Fisher Scientific (Fairlawn, NJ, USA). Sodium hypochlorite (NaOCl) solution (reagent grade, 10-15% available chlorine) was obtained from Acros Organics (Fair Lawn, NJ, USA). The concentration of free chlorine in the NaOCl solution was measured to be 100 ± 3 g/L (1.34 ± 0.05 mol/L) by a chlorine amperometric titrator (Autocat 9000, HACH). All glassware was cleaned, rinsed with LC-MS grade solvents, and baked for a minimum of 24 hours at 180°C.

Table 2.1 Selected chemical properties of the two studied ionic liquids

Ionic liquid	Structure	Molecular formula	Molecular weight
1-ethyl-3-methylimidazolium bromide (EMImBr)		$[C_6H_{11}N_2]^+ [Br]^-$	191.07 g/mol
1-ethyl-1-methyl pyrrolidinium bromide (EMPyrBr)		$[C_7H_{16}N]^+ [Br]^-$	194.11 g/mol

2.2.2 Preparation of monochloramine

A 100 mM borate buffer was prepared by dissolving 2.47g of boric acid in 300 mL of water, adjusting pH to 8.4 by the addition of 1.00 M NaOH, followed by dilution to 400 mL. 100 mM of monochloramine (NH_2Cl) was freshly generated by mixing free-chlorine containing and ammonia-containing components. The molar ratio of Cl_2 to N was maintained at 0.7:1 to prevent formation of dichloroamine ($NHCl_2$).[36] First, 2.84 mL NaOCl solution (1.34 M as specified in **section 2.2.1**) was diluted in 20 mL of water to 200 mmol/L. 0.3054 g of NH_4Cl were dissolved in 4 mL of water and 16 mL of pH 8.4 100 mM borate buffer to concentration of 240 mM NH_4Cl. The NH_4Cl and NaOCl components were gradually combined by adding small aliquots (5-6 mL) of the NaOCl component to the NH_4Cl solution with vigorous stirring and intermittent cooling to maintain solution temperature < 5°C. Prepared NH_2Cl was left for 1 hour prior to use.

2.2.3 Formation of NAs from the reactions of ionic liquids with monochloramine

Chloramination of ILs was performed by mixing 1 mL of 100 mM borate buffer (pH = 8.4), 500 µL of 50 mM ionic liquid stock solution, and 250 µL of 100 mM NH_2Cl (freshly prepared as described in **Section 2.2.2**), and diluting to 5 mL in LC-MS grade water. Millimolar concentrations used for these treatment of these ILs are similar to previous studies examining proof-of-concept evaluations of NA precursors. [49,50] After 24 h, reactions were quenched by the addition of an excess of ascorbic acid (20 mg), and without sample preparation and/or extraction, these samples were directly analyzed by an established LC-MS/MS method to detect known NA species.[48]

2.2.4 Effect of IL and NH_2Cl concentrations on formation of NAs

To identify a molar ratio for optimized yield of NAs at high concentration of ILs (5 mM), reaction mixtures containing various concentrations of NH_2Cl (0.5 mM-20 mM) were prepared as described in **Appendix A**, then extracted and analyzed as described in **section 2.2.5** .

To explore the lower limit of the concentrations of ILs capable of producing detectable NAs, various concentrations of ILs were treated with chloramine using a 2:1 molar ratio of IL:NH_2Cl. Specifically, reaction mixtures were prepared with 1 mL of 100 mM borate buffer (pH = 8.4), varied volumes of 50 mM IL stock solutions (25, 50, 100, 150, 250, and 1000 µL respectively), and corresponding additions of 12.5, 25, 50, 75, 125, 250, and 500 µL of 100 mM NH2Cl solution. Then the solutions were diluted to 5.0 mL using LC-MS grade water. After 24 h, an excess of ascorbic acid (20 mg) was added to quench remaining NH2Cl.

To better evaluate NA formation nearer realistic chloramination conditions, low concentrations (250 μM) of either IL were chloraminated with different concentrations of NH2Cl. Each reaction solutions contain 1 mL of 100 mM borate buffer (pH = 8.4), 250 μL of 5 mM IL stock and the corresponding doses of 50 μL, 100 μL, 250 μL, 500 μL, and 750 μL of 5 mM solution of NH2Cl. Then the solutions were diluted to a final volume of 5.0 mL. These final concentrations of reaction samples were 250 μM of either IL, with varied doses of 50, 100, 250, 500, and 750 μM of NH2Cl. After 24 h, ascorbic acid (10 mg) was added to quench remaining NH2Cl.

After chloramination and quenching, all IL solutions were extracted by liquid-liquid extraction (LLE) as described in **section 2.2.5** and quantified by a previously established liquid chromatography-tandem mass spectrometry (LC-MS/MS) method.[48]

2.2.5 Liquid-liquid extraction and LC-MS/MS quantification of NAs

N-nitrosomethylethylamine-D_3 (NMEA-D3) was added to samples prior to extraction as a surrogate standard. The recovery of the surrogate standard was found to be representative of the recovery of NAs detected, as is shown in **Appendix B**. Each aqueous reaction mixture was extracted three times each by 4.5 mL of dichloromethane to samples in clean 15 mL vials with PTFE-lined lids, which were agitated vigorously to interface, and vented intermittently. A total of 12-13 mL of dichloromethane was collected from each reaction mixture and evaporated down to <0.05 mL by incubation at 35°C under gentle nitrogen flow. After evaporation, NDMA-d6 was added as an internal standard, and samples were reconstituted to 200 μL with water. Samples were stored at 4°C and analyzed within 24 hours by liquid chromatography-tandem mass spectrometry as previously reported.[48]

Chromatographic separation of analytes was performed using an Agilent 1100 high performance liquid chromatograph (Agilent, Waldbronn, Germany) coupled to a Kinetex C_8 column (100 x 3mm ID, 2.6 µm particle size, Phenomenex, Torrance, California). Mobile phase A was 10 mM ammonium acetate with 0.01% acetic acid, and mobile phase B was 100% methanol. Analyte separation was achieved using a gradient elution as follows: linearly increase B from 35% to 90% from 0 to 5 minutes, hold 90% B from 5 to 8 minutes, then return the column to initial conditions of 35% B from 8.1 to 17 minutes to re-equilibrate the column. Mass spectrometer analysis conditions were as follows: collision gas, 6 psi; curtain gas, 30 psi; gas 1, 60 psi; gas 2, 20 psi; ionspray voltage, 5500 V; temperature, 200 °C. This method is capable of detecting *N*-nitrosodimethylamine (NDMA), *N*-nitrosomethylethylamine (NMEA), *N*-nitrosodiethylamine (NDEA), *N*-nitrosopyrrolidine (NPyr), *N*-nitrosomorpholine (NMor), *N*-nitrosodipropylamine (NDPA), *N*-nitrosodibutylamine (NDBA), *N*-nitrosopiperidine (NPip), and *N*-nitrosodiphenylamine (NDPhA). MRM-specific detection parameters are listed below in **Table 2.3**.

Table 2.2 – Optimized MRM parameters for the detection of *N*-nitrosamines

Nitrosamine	Parent ion	Product ion(s)	Declustering potential	Entrance potential	Collision energy	Cell exit potential
NDMA	75	43	30	5	18	18
NMEA	89	61	23	6	15	28
NDEA	103	75	52	5	18	30
NPyr	101	55	30	7	21	21
NMor	117	87	48	6	17	36
	117	57	25	6	22	25
NDPA	131	89	37	6	17	36
	131	43	20	6	29	17
NDBA	159	103	50	5	17	23
	159	57	50	5	23	23
NPip	115	69	51	6	23	26
	115	41	46	6	23	26
NDPhA	199	169	50	6	19	23
	199	66	50	5	43	28
NMEA-d_3	92	64	38	10	26	26
NDMA-d_6	81	46	35	5	25	19

2.3 Results and Discussion

2.3.1 HPLC-MS/MS analysis for formation of NAs from ionic liquids

The initial reaction solutions of NH_2Cl with EMImBr, NH_2Cl with EMPyrBr, and IL control samples were analyzed for the nine known NAs (as in EPA appendix IX NAs/8270 mix) to examine whether ILs could act as precursors to common NAs. The LC-MS/MS analysis shows the formation of new peaks in the reaction mixtures but not in the controls (i.e. EMImBr or EMPyrBr solution without chloramination). Extracted ion chromatograms (XICs) of NMEA are shown in **Figure 2.1(a).** NMEA was detected in chloraminated

solutions of EMImBr and EMPyrBr solution (5 mM), but not in the controls. The peak at 2.22 min detected in the reaction solutions matched with that of the NMEA standard, supporting the identification of NMEA formation from chloramination of EMImBr and EMPyrBr. In **Figure 2.1(b)**, NPyr was also detected in the chloraminated EMPyrBr reaction mixture according to the same rationale. This supports that NPyr is also produced during chloramination of EMPyrBr. EMImBr can generate NMEA, and EMPyrBr can generate both NMEA and NPyr in chloramination reactions.

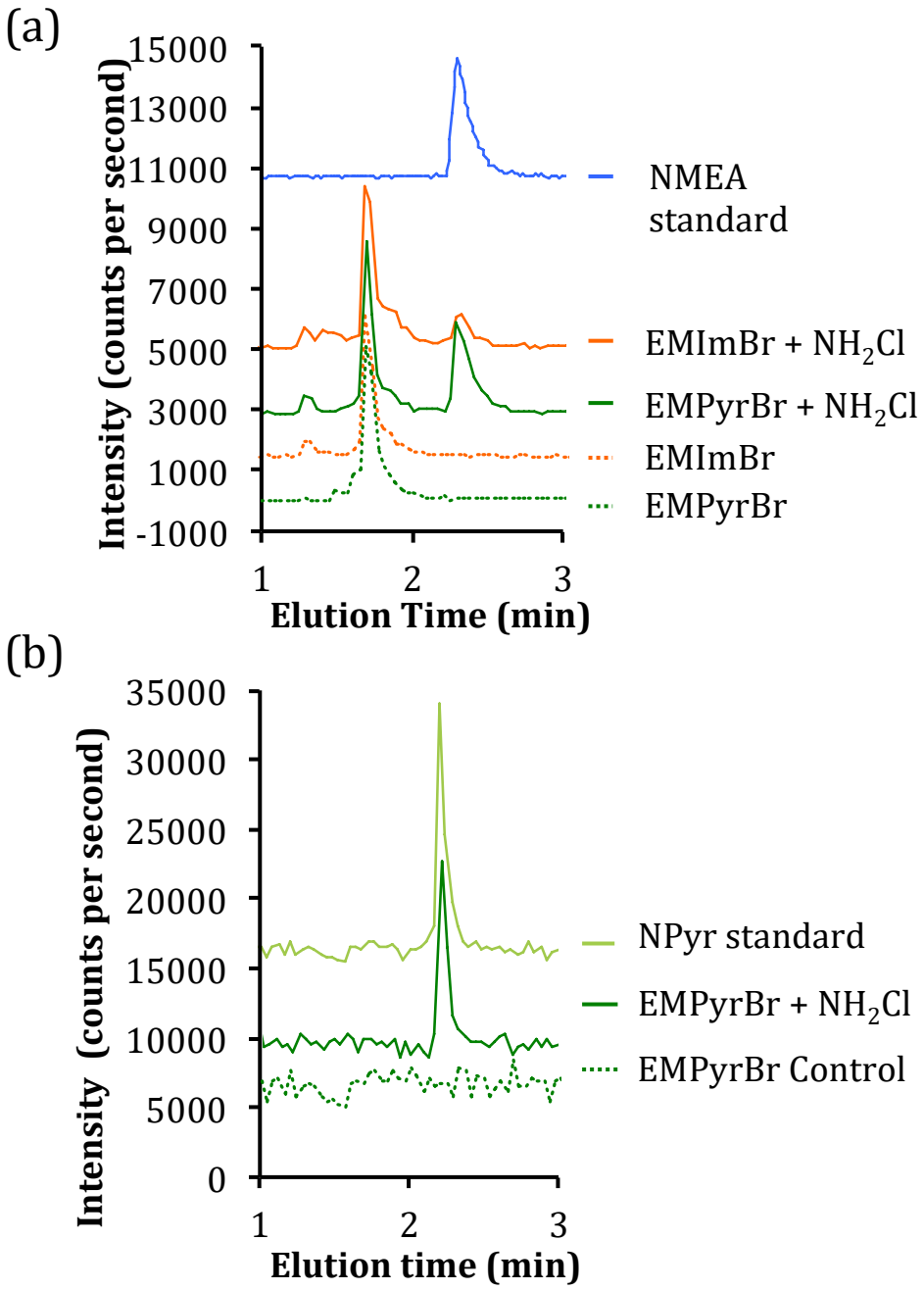


Figure 2.1 – Extracted multiple-reaction monitoring (MRM) ion chromatograms of (a) both IL species with and without NH_2Cl treatment compared to an NMEA standard, and (b) EMPyr with and without NH_2Cl treatment compared to an NPyr standard

2.3.2 NA yield across varied ILs concentration at constant molar ratio of ILs to NH_2Cl

After positively identifying NAs in the chloramination of both selected ILs, we evaluated the yield of NMEA and NPyr when EMImBr and EMPyrBr concentrations ranging from 100 μM to 20 mM reacted with a range of NH_2Cl doses (0.05 to 10 mM) at a constant molar ratio. In each sample, the molar ratio between ILs and NH_2Cl was kept at 2:1, which was chosen based on initial reactions described in the **Section 2.2.4** and **Appendix B.** **Figure 2.2** presents reaction yields in terms of (each NA)/(each IL) in (ng/mg) to facilitate the comparison to NA yields from polyDADMAC.[42] The yield of NMEA from the reaction between EMImBr and NH_2Cl was up to 3.1 ± 0.3 ng/mg, while the reaction between EMPyrBr and NH_2Cl produced both NMEA and NPyr with yields up to 8.0 ± 0.1 ng/mg and 2.3 ± 0.1 ng/mg, respectively. NAs were still detectable when the concentrations of ILs (either EMImBr or EMPyrBr) were as low as 500 μM**.**

Figure 2.2(a) also shows that the NMEA yield from EMImBr reaches the maximum at [2 mM EMImBR]:[1 mM NH_2Cl], and decreased with subsequent increases in the reactant concentrations. Similarly for the yields of NMEA and NPyr from the reaction of EMPyr reached a maximum at [3 mM EMPyr]:[1.5 mM NH_2Cl], and decreased with subsequent increases in the reactant concentrations (**Figure 2.2(b)**). This counterintuitive observation implies that reaction conditions may no longer favour the formation of NAs at higher reactant concentrations.

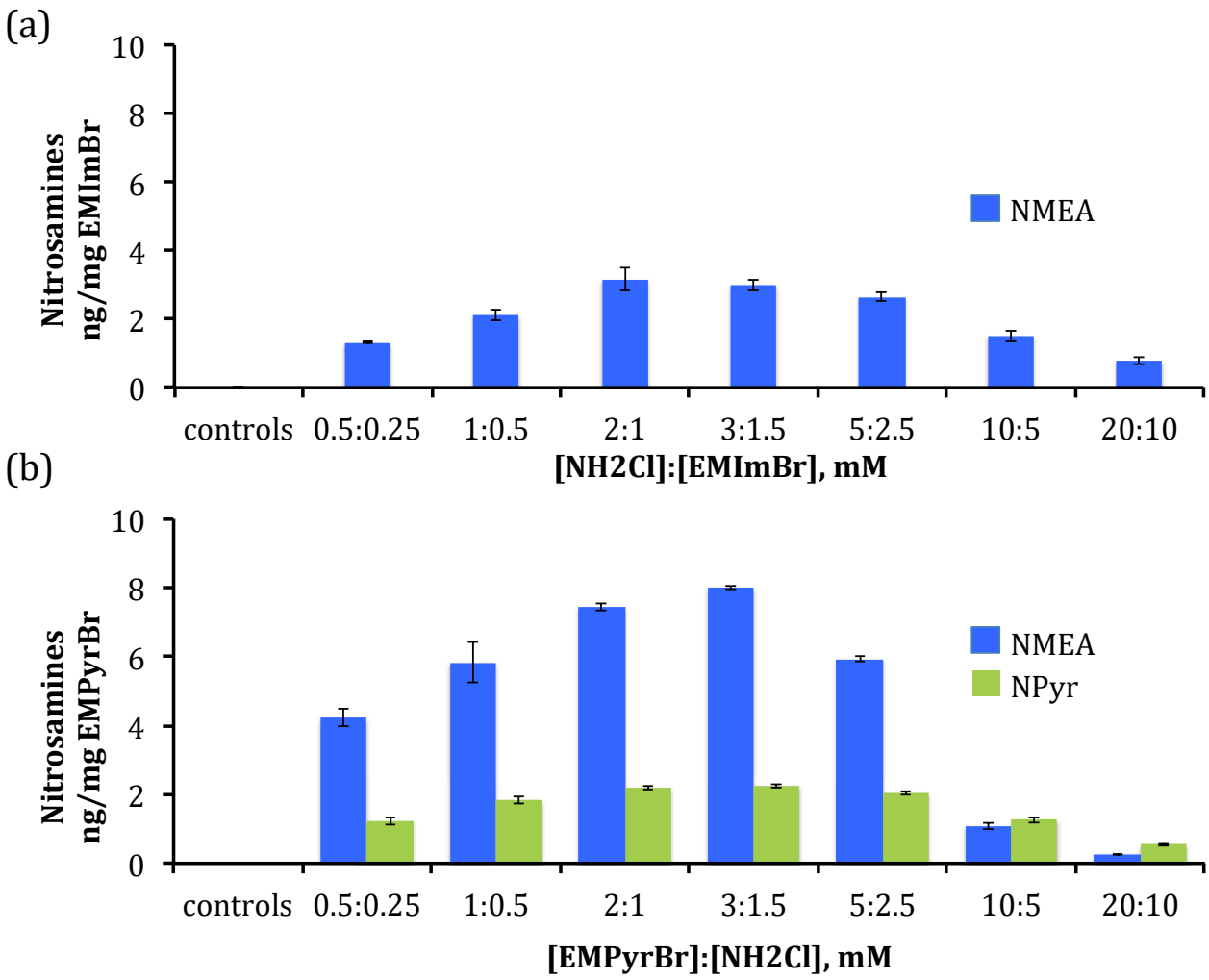


Figure 2.2 – NMEA and NPyr yields from the reaction of NH_2Cl with (a) EMImBr and (b) EMPyrBr at a constant 2:1 ratio of [IL]:[NH_2Cl]. Results are reported with standard deviation from n = 3 samples in each case.

2.3.3 Formation of NAs as a function of the molar ratio of ILs:NH_2Cl

We also evaluated NA formation when IL concentrations were kept at 250 µM, with varying molar ratios (5:1, 5:2, 1:1, 1:2, and 1:3) of IL/NH_2Cl (doses at 50, 100, 250, 500, and 750 µM NH_2Cl). The lowest concentration of NH_2Cl used (50 µM) is close to the typical NH_2Cl dose range of 1.5-2.5 mg/L (~22.5 - 37.5 µM/L NH_2Cl) employed during real water

treatment.[51] Yields of NMEA and NPyr from these reactions are summarized in **Figure 2.3**. The yields of NAs (NMEA or NPyr) increased with increasing doses of NH_2Cl (from 50 μM to 750 μM) from both IL species. The NMEA yield was as high as 1.7 ± 0.2 ng/mg of EMImBr, and as high as 5.0 ± 0.6 ng/mg from EMPyrBr This can be compared to the results presented in **Figure 2.2**, as at higher concentrations, the total NA yields of EMImBr and EMPyrBr were as high as 3.1 ± 0.3 ng/mg, and 10.2 ± 0.2 ng/mg, respectively. These yields are on the same order of magnitude as those of purified polyDADMAC (i.e., 8-10 ng/mg), an accepted precursor for *N*-nitrosamines as DBPs in drinking water.[42]

Under all reaction conditions studied, EMPyrBr produces a higher amount of NMEA than EMImBr. Mechanisms for NA generation from compounds structurally similar to EMPyrBr (i.e. PolyDADMAC) have been previously reported.[46,52] The pyrrolidinium cation moiety has a very similar structure to polyDADMAC, so EMPyrBr likely generates NAs following analogous reaction pathways. A proposed pathway for the generation of NMEA from the chloramination of EMPyrBr is proposed in **Figure 2.3.**

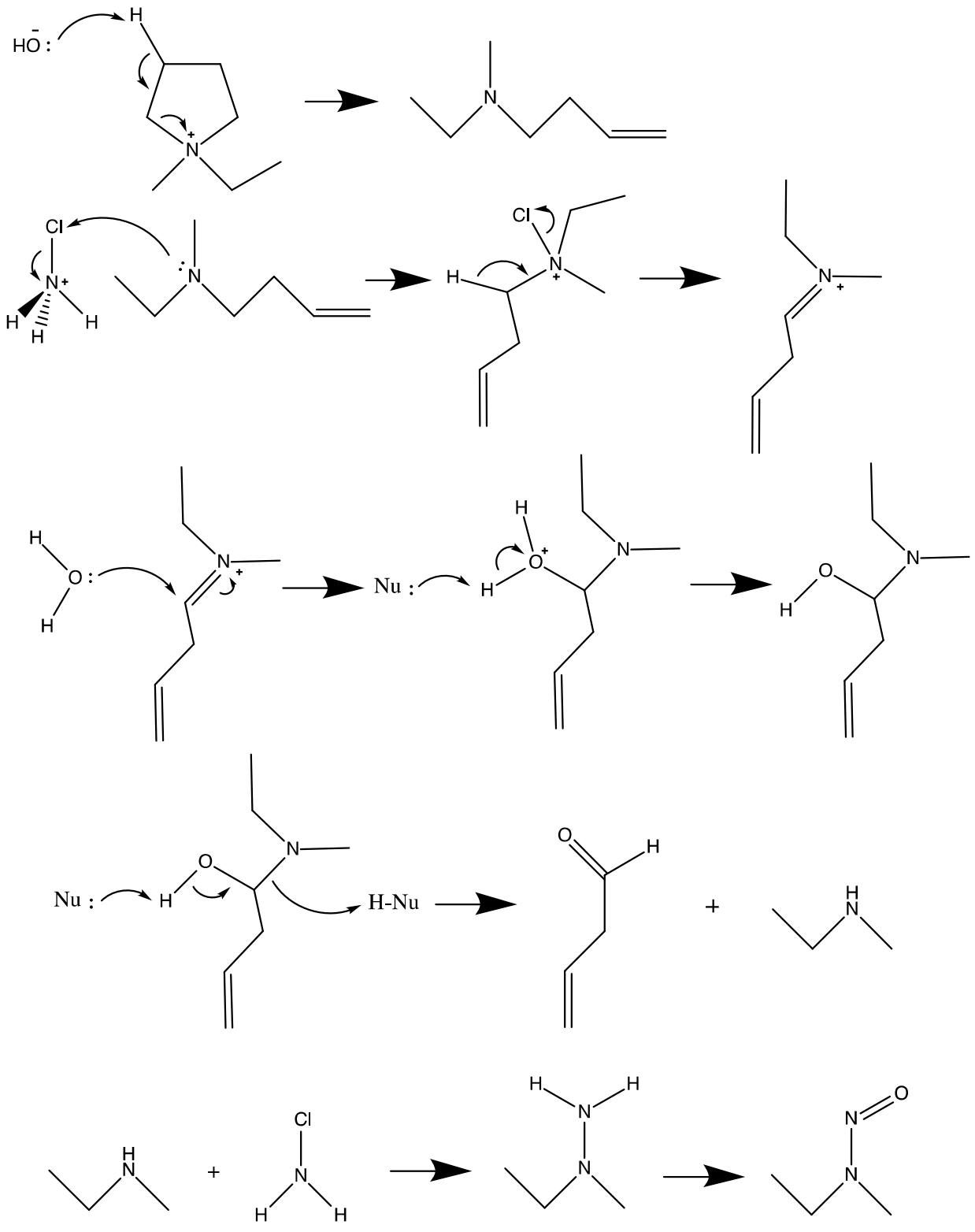


Figure 2.3 – A proposed mechanism for the generation of NMEA from the chloramination of an EMPyr cation

Imidazolium ring structures may undergo hydrolysis to open ring structures under oxidative conditions,[21,23,53,54] and ring opening may similarly be achieved by hydrolysis under alkaline conditions.[55] However, there is a substantial energy barrier to ring opening of imidazolium moieties by hydrolysis,[53] which may cause lower overall NA yield of EMImBr of NAs than from EMPyrBr.

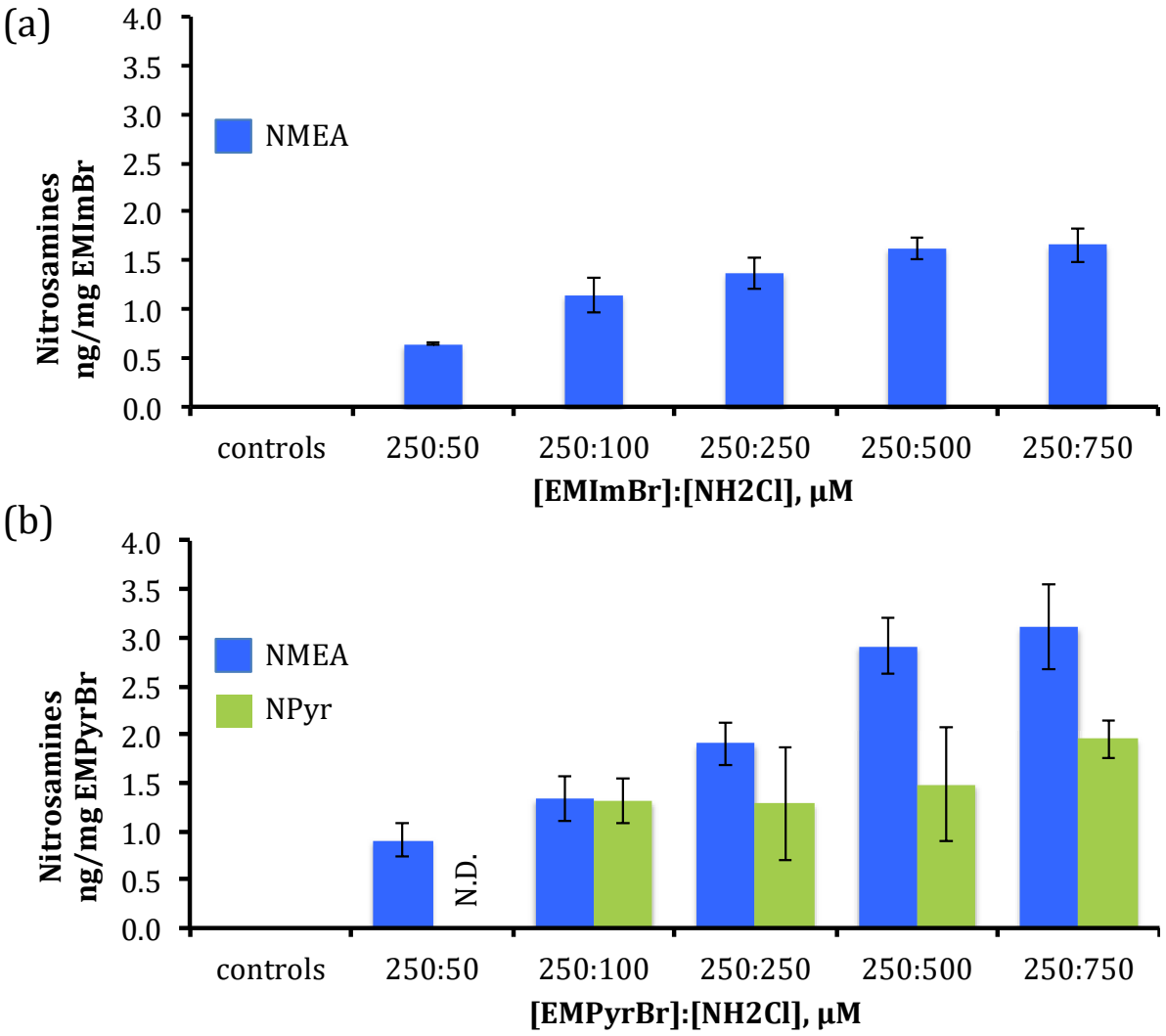


Figure 2.4 - NMEA and NPyr yields from 250 µM of (a) EMImBr and (b) EMPyrBr with increasing dose of chloramine at µM concentrations. Results are reported with standard deviation from n = 3 samples in each case.

2.4 Conclusions

This study confirms that the selected ionic liquids are capable of acting as precursors to NAs under laboratory conditions. Yields of NAs from ILs were similar to yields of NDMA from purified polyDADMAC. [42] Yields of NAs from EMImBr were consistently lower than those from EMPyrBr. This difference in NA yields may be due to the difference in relative structural stabilities of ring structures, as there is a significant energy barrier to ring opening of imidazolium cation moieties by hydrolysis.[53]

Precursors concentrations used in these experiments were high, but guidelines for NA concentrations in drinking water range from 10-100 ng/L.[56-60] The results suggest that disposal of wastes containing high concentrations of ILs should be properly managed to avoid release to water sources to help prevent increases of NAs in drinking water.

Although some IL cations share structural similarity with polyDADMAC, it is important to highlight the differences between the how ILs and polyDADMAC can contribute to increases in NA concentrations in drinking water. PolyDADMAC is deliberately added at 0.1 – 0.2 mg/L concentrations during flocculation.[61] This is a consistent concentration that can increase NDMA concentrations detectable amounts during water treatment. On the other hand, ILs are anticipated as environmental contaminants, and could be released by either accidental release(s) or continuous low-level release through aqueous waste streams.[12] In either case, it is reasonable to expect that ILs released to environmental source water would become extremely dilute in the environment. Furthermore, ILs are expensive, and so in cases where ILs are continuously released through waste streams, there are substantial economic incentives to minimize loss of ILs.[12] If ILs are released to environmental fresh water sourced for drinking water, they

should be expected to exist at low concentrations, contributing minimally to final concentrations of NAs. Therefore ILs cannot possibly act as NA precursors at nearly the same scale as polyDADMAC except in special circumstances, such as through accidental releases of large volumes of ILs, or in cases where ILs might be used to desalinate or otherwise treat water.[8,24,25,28] Therefore ILs should be expected to have minimal impact on drinking water quality in most cases.

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3 Evaluating the persistence of 1-ethyl-3-methlyimidazolum bromide during chloramination

3.1 Introduction

In chapter two, it was observed that both of the selected ionic liquids (ILs), 1-ethyl-3-methylimidazolium bromide (EMImBr) and 1-ethyl-1-methylpyrrolidinium bromide (EMPyrBr), could act as precursors to previously identified *N*-nitrosamine (NA) disinfection byproducts (DBPs) when treated with monochloramine (NH_2Cl). During NH_2Cl treatment, other NA precursors such as ranitidine, can reach molar yields of *N*-nitrosodimethylamine molar yields up to 60%.[1] The maximum observed molar yield of NMEA from EMPyrBr was 8.0 ± 0.1 ng NMEA/mg EMPyr, or a 0.0013% molar yield. The maximum observed molar yield of NPyr from EMPyrBr was 2.3 ± 0.1 ng NPyr/mg EMPyr, or a 0.00049% molar yield. Yields of *N*-nitrosomethylethylamine (NMEA) from the chloramination of EMImBr were especially low, with the maximum observed molar yield of NMEA from EMImBr at 3.1 ± 0.3 (ng NMEA)/(mg EMImBr), or 0.00055%. The NA yields from either IL were therefore quite low.

Productive NA precursors like ranitidine contain 3° amines, which are generally more productive NA precursors than 4° amines, as are found in ILs. In the proposed reaction mechanism by which polydiallyldimethylammonium chloride (polyDADMAC), an NA precursor that contains a 4° amine in a heterocyclic ring structure, the heterocyclic ring structure must be broken, generating 3° amine intermediates.[2] If ring breakdown does not take place, the formation of NAs during NH_2Cl treatment would also therefore be effectively prevented. If the selected cation species are resistant to oxidation by NH_2Cl, keeping the

ring structures intact, it could help explain the relatively low yields of NAs cationic heterocycles like EMPyr, EMIm, and polyDADMAC.

It was unclear how resistant EMImBr might be to oxidation by NH_2Cl. Since the NA yield from the reaction of EMImBr and NH_2Cl, it was possible that a substantial amount of EMImBr remained after 24 h of chloramination. On the other hand, imidazolium cation moieties have been previously observed to degrade under oxidative reaction conditions.[3-6] Therefore it was unclear whether the EMIm cation should be expected to breakdown during NH_2Cl treatment.

One of the premises on which original hypothesis of this thesis was justified is that ILs may contaminate drinking water sources. Although ILs may act as NA precursors, it would also be relevant to understand whether or not ILs would resist breakdown during disinfection, as then consumers would directly consume ILs through contaminated drinking water. Therefore a liquid chromatography system with UV detector (LC-UV) was used to quantify EMImBr after treatment with NH_2Cl. EMImBr is amenable to detection by LC-UV, which allows for rapid quantification of the analyte.[6] Quantifying EMImBr after NH_2Cl treatment would provide perspective on both (a) yields of *N*-nitrosamines re-framed as a percentage of degraded precursor, and (b) the stability of EMImBr in reaction with NH_2Cl, which would be indicative of whether or not ILs in contaminated source water would also be found in finished drinking water. No attempt was made to quantify EMPyrBr post-reaction, however, because it is not amenable to detection by LC-UV.

3.2 Methods and Materials

LC-MS grade acetonitrile and water were obtained from Fisher Scientific (Fairlawn, NJ, USA). HPLC grade ammonium acetate, glacial acetic acid, and 1-ethyl-3-

methylimidazolium bromide (EMImBr) (≤99%) were obtained from Sigma Aldrich (St. Louis, MO, USA). Sodium hypochlorite (NaOCl) solution (reagent grade, 10-15% available chlorine) was obtained from Acros Organics (Fair Lawn, NJ, USA). All glassware used was either new and clean from the manufacturer, or washed as described in **section 2.2.1**.

3.2.1 Detection and quantification of 1-ethyl-3-methlyimidazolium bromide by LC-UV

Liquid chromatography with a UV detector (LC-UV) was used for detection, and quantification of EMImBr was adapted from the previously established method by Pati et al.[6] Dr. Ping Jiang replicated and optimized this method using an Agilent 1100 series LC system with a variable wavelength UV detector (Agilent Technologies, Santa Clara, CA, USA).

LC-UV quantification was conducted by injecting 20 µL of sample, followed by separation using an isocratic elution of 10% mobile phase A (acetonitrile) with 90% mobile phase B (10 mM ammonium acetate with 0.1% v/v acetic acid) at a flow rate of 1 mL min^{-1} on a 100 mm x 3 mm ID mm C_8 column with 2.6 µm particle size. Detection and quantification of EMImBr was achieved by measuring absorbance at 210 nm, as per the procedure by Pati et al.[6]

Quantification of EMImBr was achieved by use of external calibration curves. A 50.0 mM standard of EMImBr was prepared by diluting 389 mg in 40.0 mL of Optima LC-MS grade water. A 1.00 mM standard of EMImBr was prepared by diluting 200 µL of 50.0 mM EMImBr to 10.0 mL in water. From this 1.00 mM EMImBr standard, samples were prepared to 20, 50, 80, 100, and 200 µM EMImBr in triplicate, and results were collected to build a

calibration curve. Calibration samples were prepared and analyzed in duplicate. Calibration curve samples were prepared and analyzed within the 24 h prior to sample analysis.

3.2.2 NH_2Cl – ionic liquid reaction sample preparation

NH_2Cl and pH 8.4 $B(OH)_3$ buffer was prepared freshly as described in **section 2.2.3**. Samples of EMImBr were treated with NH_2Cl in two separate procedures. In the first sample set, EMImBr formation potential samples were prepared to a constant 2:1 molar ratio of [EMImBr]:[NH_2Cl]. Sample component volumes and final concentrations are summarized in **Table 3.1**. Samples were allowed to react for 24 h. Sample aliquots of 1.00 mL were taken from these reactions, diluted to a 100 μM target concentration of EMImBr (assuming 100% recovery of EMImBr), and analyzed by LC-UV. The dilution factor varied sample-to-sample (i.e. 0.50 mM EMImBr samples required a 5x dilution, 1.00 mM EMImBr samples required 10x dilution, etc.). These samples were prepared and analyzed in triplicate for each concentration. The remaining 5.00 mL of sample was quenched by the addition of ascorbic acid, extracted as described in **section 2.2.2**, and analyzed for NMEA content. NMEA detected from these samples was reported in the previous chapter in **Figure 2.4**.

Table 3.1 - Reaction components, respective volumes, and final reactant concentrations used in the first set of reactions prepared for quantification of EMImBr after NH_2Cl treatment. All samples were prepared in triplicate.

		[EMImBr] : [NH_2Cl], mM				
		[0.50] : [0.25]	[1.00] : [0.50]	[2.00] : [1.00]	[3.00] : [1.50]	[5.00] : [2.50]
Reaction components	100 mM NH_2Cl	15 µL	30 µL	60 µL	90 µL	150 µL
	100 mM $B(OH)_3$ buffer, pH 8.4	1200 µL	1200 µL	1200 µL	1200 µL	1200 µL
	50.0 mM [EMImBr]	60 µL	120 µL	240 µL	360 µL	600 µL
	Water (Optima)	4725 µL	4650 µL	4500 µL	4350 µL	4050 µL

A second set of EMImBr-NH_2Cl treatment samples was prepared to assess degradation of EMImBr during NH_2Cl treatment at concentrations close to those used during disinfection at water treatment plants (~1.5-3 mg/L NH_2Cl).[7] NH_2Cl was freshly prepared as described in **section 2.2.3**. Sample component volumes and final concentrations are summarized in **Table 3.2**. To more accurately prepare samples to low concentrations of disinfectant, 100 µL of 100 mM prepared NH_2Cl stock was diluted to 1.00 mM in LC-MS grade water to a final volume of 10.0 mL. NH_2Cl doses were varied while the concentration of EMImBr was held constant. Samples were prepared to 6.00 mL total volume. After 24 h, 1 mL aliquots were removed from each of the 6.00 mL reactions. The remaining 5.00 mL from each sample was quenched by the addition of ascorbic acid, extracted as described in **section 2.2.2**, and analyzed for NMEA content.

Table 3.2 - Reaction components, respective volumes, and final reactant concentrations used in the second set of reactions prepared for quantification of EMImBr after NH_2Cl treatment. All samples were prepared in triplicate.

		[EMImBr] : [NH_2Cl], mM			
		[10 µM] : [100 mM]	[50 mM] : [100 mM]	[100 mM] : [100 mM]	[150 mM] : [100 mM]
Reaction components	1.00 mM NH_2Cl	60 µL	300 µL	600 µL	900 µL
	100 mM $B(OH)_3$ buffer, pH 8.4	600 µL	600 µL	600 µL	600 µL
	1 mM EMImBr	600 µL	600 µL	600 µL	600 µL
	Water (Optima)	4740 µL	4500 µL	4200 µL	3900 µL

3.3 Results and Discussion

3.3.1 Initial assessment of EMImBr degradation under chloramine reaction conditions

Calibration samples were prepared to a concentration range of 20 – 200 µM EMImBr. The first calibration curve was prepared and analyzed immediately prior to quantification of EMImBr in the first sample set and is plotted below in **Figure 3.1**. Linearity was acceptable, with an R^2 of 0.989. Calibration samples were only prepared in duplicate, and samples were to be prepared to concentrations in the middle of the calibration range, so limits of detection and quantification were not calculated.

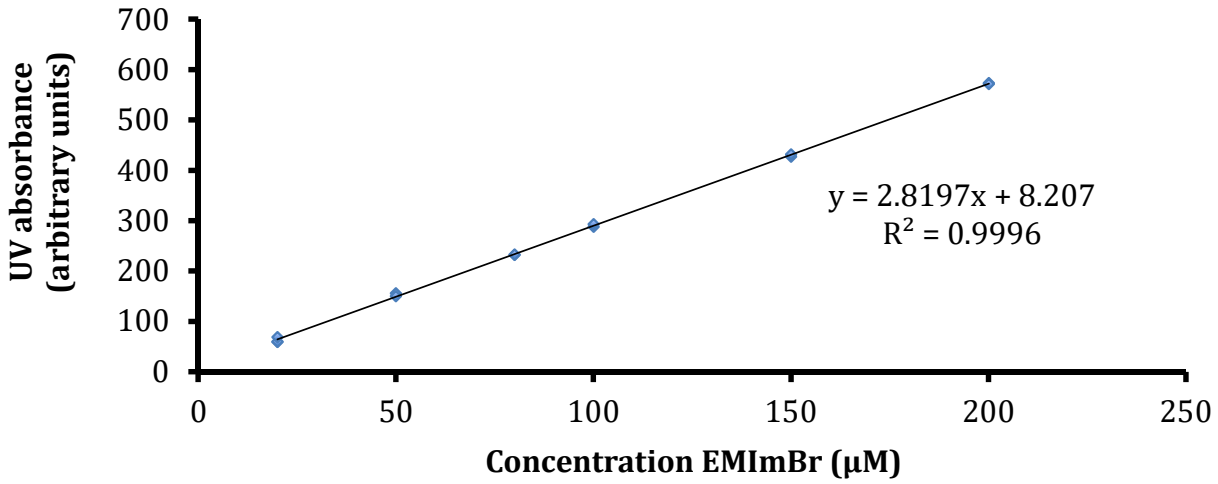

Figure 3.1 – The calibration curve samples collected immediately prior to the assessment of the first EMImBr–monochloramine reaction sample set. Samples were prepared in duplicate at each concentration.

Each sample was diluted from mM concentration levels to a target concentration of 100 µM EMImBr (assuming EMImBr was 100% resistant to breakdown during NH_2Cl treatment). In **Figure 3.2**, these diluted samples are compared to the 100 µM standard prepared for use in the external calibration curve. In **Figure 3.2,** it appears that the concentration of EMImBr increased in each sample that had been treated with NH_2Cl. However, these apparent increases are questionable. From **Figure 3.2**, it was back-calculated that 100 µM standards were determined to have an EMImBr concentration of 90 µM, and so samples may have been either improperly prepared or quantified. There was also a possibility of sample dilution error, as each of these samples had been individually diluted from millimolar concentrations to a target concentration of 100 µM. In addition, because sample analyses had only been conducted after 24 h, there was no way to attribute an increase in UV absorbance to the influence of the reaction, as this apparent difference in absorption at 210 nm may have been due to other sample components. It was unclear

whether other reaction components, including the buffer and/or NH_2Cl, may have been directly responsible for the relatively higher sample signal when compared to the 100 mM EMImBr standard.

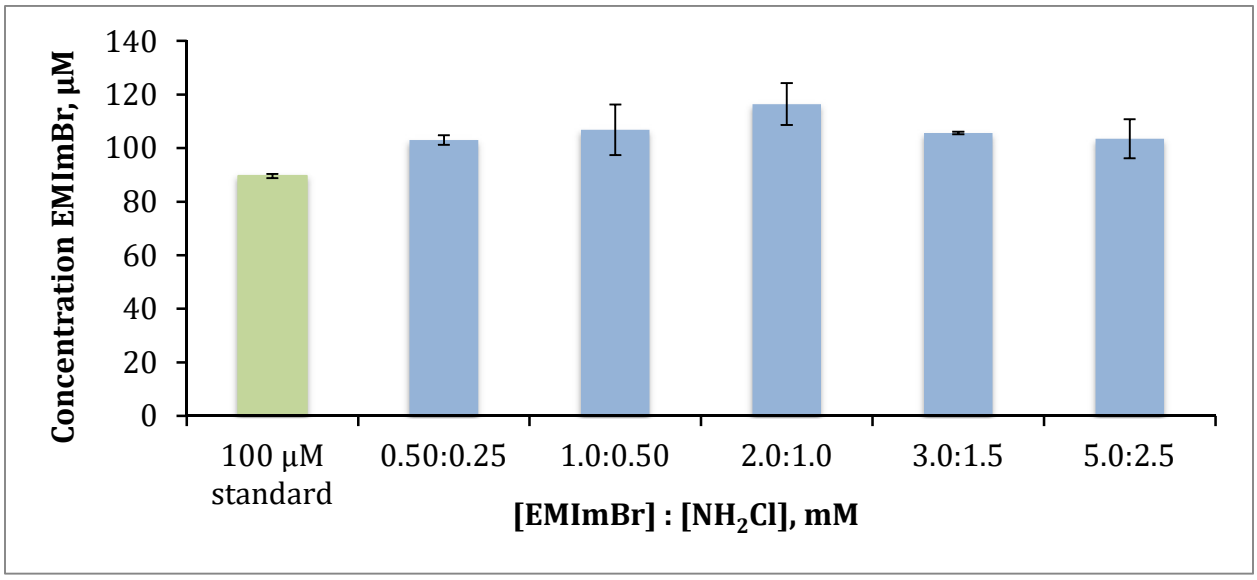

Figure 3.2 - Results of the quantification of EMImBr by LC-UV after initial treatments with NH_2Cl. Samples are plotted with standard deviation from triplicate samples.

3.3.2 Second assessment of EMImBr breakdown under chloramine reaction conditions

The first reason this sample set was prepared was to assess EMImBr as a precursor of NMEA at NH_2Cl concentrations near practical doses used by municipal drinking water providers (i.e. 1.5 – 3 mg/L). When this set of samples was extracted by liquid-liquid extraction and analyzed by LC-MS/MS as described in **section 2.2.5**, NMEA concentrations were all below the method limit of detection (≤0.021 µg/L). Thus, no NMEA was detected from the extraction of any of the samples in this sample set.

The second reason this second sample set was prepared was to assess whether or not EMImBr would similarly undergo an apparent increase when treated with NH_2Cl, as

was observed in **Figure 3.2**. By more carefully designing this experiment, it was possible to test whether the apparent difference in EMImBr concentrations observed in **Figure 3.2** was due to increased UV absorbance, or attributable to reaction conditions or due to the addition of other sample components. Samples were prepared to 100 µM concentrations of EMImBr to minimize the possibility of introducing sample variability by dilution error of reaction solutions. The calibration curve used to quantify samples from this set is plotted in **Figure 3.3**. The linearity was improved from the previous calibration, with an R^2 value of 0.9996.

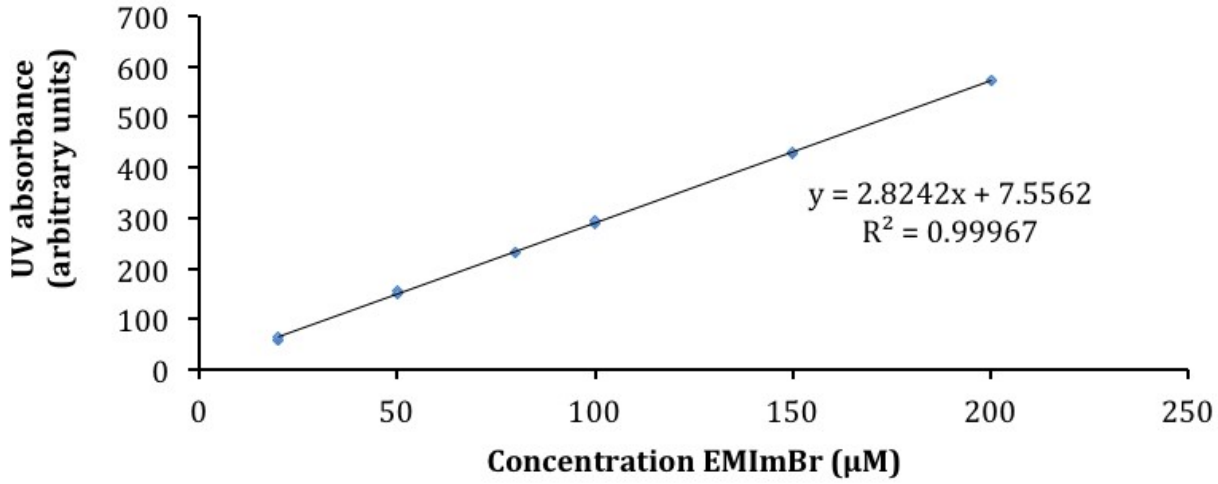

Figure 3.3 – The calibration curve collected immediately prior to quantification of the second EMImBr–monochloramine reaction sample set. Standards were prepared in duplicate at each concentration.

The results from the quantification of EMImBr in the second sample set are plotted in **Figure 3.4**. From this figure, it appears that there were significant increases in the apparent concentration of EMImBr after 24 h in most samples. Although NH_2Cl absorbs slightly at 210 nm, this t = 0 h to t = 24 h comparison allows for the exclusion of NH_2Cl as a direct influence on the UV absorbance of samples since t = 0 h samples did not differ

significantly from the 100 µM standard. Dilution errors could also be excluded as a source of difference between t = 0 h and t = 24 h, as in this case samples were not diluted prior to quantification.

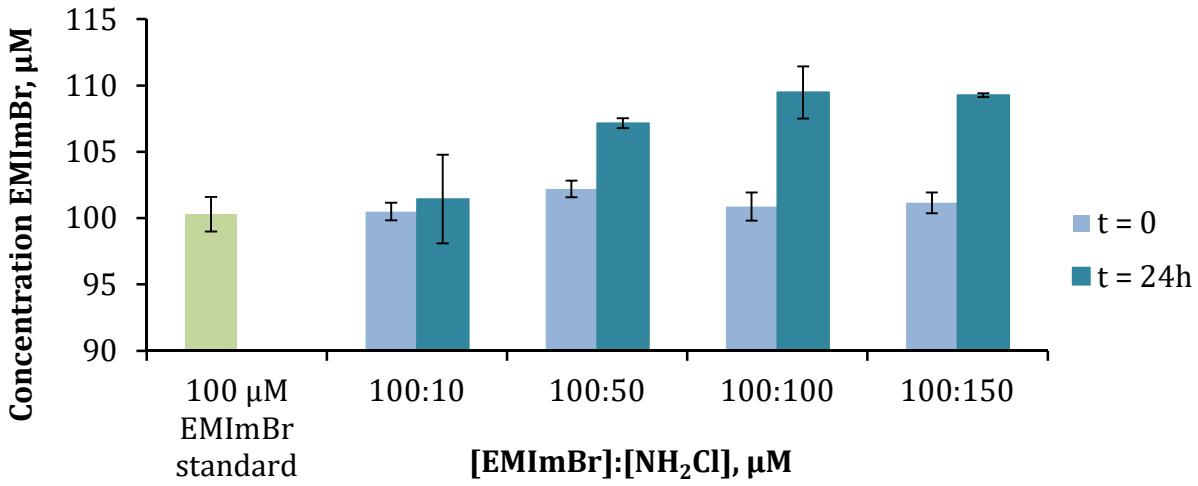

Figure 3.4 – Concentrations of EMImBr observed in the reaction between NH_2Cl and EMImBr at low concentrations from t = 0 h to t = 24 h. The 100 µM standard was not re-evaluated after 24 h. All points are plotted with standard deviation from n = 3 replicates.

Figure 3.4 shows that the UV signal detected increased after 24 h across most samples. This suggests that reactants are generating a product or products with higher UV absorbance than EMImBr.

There seems to be some relationship between increasing dose of NH_2Cl, and a somewhat proportional increase in apparent concentration of EMImBr in **Figure 3.4**. This is likely not attributable to the slightly alkaline conditions from the $B(OH)_3$ buffer. All samples were mixed with mM concentrations of $B(OH)_3$ buffer, whereas NH_2Cl concentrations in samples were prepared to only µM levels. Thus, if increased pH influenced the UV signal of the samples, such as by induction of alkaline hydrolysis of EMImBr, as has been observed in imidazolium cations,[8] one would expect a consistent

increase in signal across all samples after 24 h, regardless of NH_2Cl dose. However, the results in **Figure 3.4** are somewhat proportional to the concentrations of NH_2Cl. This suggests that the observed increases are more likely due to a product or products of the reaction between NH_2Cl and EMImBr, rather than a product of the hydrolysis of EMImBr.

The product(s) increasing the UV absorbance must elute at nearly the same time as EMImBr. EMImBr eluted from the column near the dead volume, and so resolution of EMImBr from the co-eluting product or products was not feasible using the same C_8 column used in the quantification procedure.

3.4 Conclusions

In this work, I made use of a simple, rapid LC-UV detection method for the quantification of EMImBr. Samples treated with NH_2Cl resulted in increases in sample signal that could not be attributed to an increase in the concentration of EMImBr. These observed changes are attributable to reaction conditions rather than dilution errors. Results suggest that a product is generated from the reaction of EMImBr and NH_2Cl that has a higher molar absorptivity at 210 nm than EMImBr. These results are inconclusive, but suggest that in future research it may be worthwhile to attempt to identify other major reaction products.

3.5 References

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4 Conclusions and Future directions

4.1 Introduction

Disinfection is necessary to prevent the spread of waterborne pathogens through drinking water.[1,2] However, drinking water disinfection inevitably generates disinfection by-products (DBPs). Some classes of DBPs, including *N*-nitrosamines (NAs), have demonstrated significant carcinogenicity,[3] and so legislation and guidelines are in place in some jurisdictions to minimize public exposure to NAs through drinking water. [4-8] To avoid the formation of NAs in finished drinking water, it is important to reduce the occurrence of NA precursors in source water. This includes a variety of compounds containing 2° amines, [9-11] 3° amines,[12-15] and 4° amines.[15-17]. Examples include many anthropogenic compounds, with over-the-counter medications like ranitidine,[13] prescription drugs like carbamezapine,[18] opiates like methadone,[19] and water treatment polymers like polydiallyldimethylammonium chloride (polyDADMAC).[17,20] An emerging class of water contaminants that have the potential to be potent NA precursors are ionic liquids (ILs).

Research into uses for ILs is prolific, and a variety of uses for ILs had been identified.[21] There are clear advantages to using ILs, in comparison to traditional organic solvents, because of their minimal vapour pressure.[22,23] Widespread use of ILs is anticipated, and as ILs are used on an increasing scale, the chance that ILs will be released to the environment should also be expected to increase. Therefore ILs are anticipated as environmental contaminants,[24-27] but they may also cause secondary impacts if drinking water sources are affected. Furthermore, ILs may also be introduced to drinking water intentionally if they are used in drinking water treatment strategies.[28,29] Because some cations used in ILs contain 4° amines, a structural similarity to other previously identified NA precursors, we

hypothesized that ILs may act as NA precursors during monochloramine (NH_2Cl) treatment.

My work aimed to assess whether or not selected ILs could act as NA precursors under disinfection conditions. This chapter presents the conclusions from this work and suggests directions for future research.

4.2 Advancements in knowledge

4.2.1 Selected ionic liquids can generate *N*-nitrosamines in reaction with monochloramine

Both 1-ethyl-3-methylimidazolium bromide (EMImBr) and 1-ethyl-1-methylpyrrolidinium bromide (EMPyrBr) were evaluated for their ability to act as precursors to NAs under disinfection conditions. I prepared and analyzed formation potential (FP) samples, in which the selected ILs were treated with NH_2Cl. Both ILs selected were observed to act as NA precursors during NH_2Cl treatments. EMImBr was found act as a precursor to *N*-nitrosomethylethylamine (NMEA), and EMPyrBr was found to act as a precursor to both NMEA and *N*-nitrosopyrrolidine (NPyr). Therefore, further assessments of EMImBr and EMPyrBr were prepared, where reactant concentrations were varied in order to compare the relative productivity of the two selected ILs during variable reaction conditions. Under all conditions, EMPyrBr was a more productive NA precursor than was EMImBr. The maximum observed yield of NMEA from the reaction of NH_2Cl and EMImBr was 3.15 ± 0.33 (ng NMEA/mg EMImBr). The maximum observed yields of NMEA and NPyr from the reaction of NH_2Cl and EMPyrBr were 8.0 ± 0.1 (ng NMEA/mg EMPyrBr) and 2.3 ± 0.1 (ng NPyr/mg EMPyrBr), respectively. These yields are of similar magnitude to that of

polyDADMAC, which has been previously observed to act as a precursor to *N*-nitrosodimethylamine (NDMA) during chloramination.[15] At micromolar concentrations, both ILs could act as NA precursors with near-realistic DWTP doses of NH_2Cl.

These results suggest that the release of ILs into drinking water and/or source water should be prevented, emphasizing the need for responsible management and disposal of ILs after use. This may also discourage the use of ILs in water treatment technologies, as this could increase final NA concentrations in drinking water.

To evaluate the NA FP of the selected ILs under alternate conditions, reactions were also prepared to evaluate the effects of pre-oxidation by free chlorine (Cl_2) on the yields of NAs from EMImBr and EMPyrBr. A detailed account of this experiment and the results can be found in Appendix C. Experimental conditions were prepared to model another disinfection strategy wherein water is pre-treated with Cl_2, and subsequently treated with NH_2Cl for residual disinfection. NAs were not detected in any IL-NH_2Cl reaction mixtures if ILs were pre-oxidized by Cl_2. This disagrees with previous evaluations of NA FP from polyDADMAC, which is structurally similar to EMPyrBr. When polyDADMAC is pre-treated with Cl_2, and afterwards treated with NH_2Cl, polyDADMAC can still act as a precursor to NDMA.[17] These apparently conflicting results cannot be explained by the data reported here, and so this require further experiments and characterization to explain how pre-oxidation of ILs by Cl_2 might prevent subsequent generation of NAs during NH_2Cl treatment.

4.2.2 Data suggestive of alternate product formation from reactions of imidazolium and NH_2Cl

It was important to assess the extent to which EMImBr and/or EMPyrBr were/were not degraded during chloramination; both cation moieties necessarily must degrade to act as NA precursors, and so proportions of cation degradation may be related to final yields of NAs. In order to quantify ILs in solution, Dr. Ping Jiang replicated an LC-UV detection method for the quantification of EMImBr. I applied the same LC-UV method to quantify EMPyrBr in water; however, EMPyrBr was not amenable to UV detection.

While quantifying EMImBr after 24 h NH_2Cl treatment, EMImBr concentrations appeared to increase. However, these results were replicated in a second, more carefully designed experiment, which demonstrated that this apparent increase was attributable to reaction conditions that generated a product with absorbance greater than that of EMIm at the same wavelength (210 nm). No attempt was made to identify this product(s). Further work will be required to characterize this unidentified product(s) that exhibited similar UV absorbance and chromatographic retention.

4.3 Conclusions

I successfully demonstrated that IL species can act as precursors to NAs under laboratory conditions. My findings imply that the release of ILs to the environment through aqueous waste streams should be avoided. Water treatment technologies that employ the use of ILs should also prevent the leaching of ILs into finished drinking water to prevent potential formation of NAs.

ILs have clear advantages over conventional solvents, but they must be prudently managed to ensure that they cause lesser impacts than their organic counterparts. This study emphasizes the importance of having a waste management strategy in place that does not include discharge of ILs to sources of fresh water.

These results also provide reason to be cautious about water treatment technologies using ILs. The benefits of using water treatment technology reliant on ILs (i.e. forward-osmosis desalination,[30-34] and/or removal of heavy metals from water[145-147]) must be weighed against the potential ILs may have to increase final concentrations of NAs.

4.4 Future directions

4.4.1 Evaluation of varied reaction conditions on yields of NMEA in NH_2Cl FP reactions from both ILs

Mechanisms by which either of the selected ILs could act as NMEA precursors would require that the ring structures be opened. Ring opening of imidazolium cations by alkaline hydrolysis has been observed under alkaline conditions.[35-38] Therefore, future studies should assess the influence of pH on NA yields from ILs under disinfection conditions, as it is likely that NA yields at high concentrations were limited by insufficient OH^- at high concentrations of reactants.

In this study, both IL cations were paired with bromide anions, so reaction yields may also have been influenced by the formation of bromamines during chloramine treatment.[39] Future studies may seek to assess the influence of cation pairing on the NA yields of ILs during reactions with NH_2Cl.

It may also be informative to conduct non-targeted quantification of total NAs generated during disinfection of ILs. Detection and quantification of NAs by use of liquid chromatography tandem mass spectrometry allows for sensitive and specific detection of previously identified NA species,[40] but excludes as-of-yet unidentified NA species. Techniques have since been developed to use either iodic acid[41] or UV radiation[42] to indiscriminately liberate NO radicals from NAs, regardless of functional groups (i.e. dimethyl vs diphenylamine).[41,42] Liberated NO then reacts with generated ozone to produce NO_2; by generating NO_2, some excited-state NO_2* is generated, which facilitates indirect quantitation of initial NAs by detection of proportional emission from NO_2* → NO_2 de-excitation.[41,42] These techniques allow for non-targeted quantification of total NAs.

If either technique mentioned above were applied to IL NA FP reactions, it may provide perspective on the productivity of ILs as NA precursors. In results reported herein, yields of NAs detected from NH_2Cl treatment of either IL were low. The low yields of the specific NAs detected in my work may be re-framed in context of total NA yields.

4.4.2 Non-targeted analysis of disinfection by-products from imidazolium moieties

In the reaction of EMImBr and NH_2Cl, NMEA was formed with a 0.0005 % molar yield at the highest observed yield. Therefore, it is probable that the remaining 99.9995 % of EMImBr may follow other reaction pathways to form other DBPs. No attempt was made during my research to characterize alternate products from the disinfection of imidazolium. Non-target analysis of products generated by the disinfection of imidazolium may also help to illustrate the reaction pathway by which imidazolium degradation products act as NA precursors, as this remains unclear.

These experiments could also be an opportunity to examine the extent to which imidazolium cations break down, or resist breakdown, during treatment with NH_2Cl. It is unclear whether EMIm degraded during NH_2Cl treatment. If EMIm does not degrade during NH_2Cl treatment, NA formation potential could be attributable to impurities.

It may also be helpful to separately analyze products from NH_2Cl treatment of ethyl-deuterated imidazolium and methyl-deuterated imidazolium analogues. By identifying deuterated products (i.e. NMEA-D_3 or NMEA-D_5), it may be feasible to identify which parts of the imidazolium moiety are finally incorporated into NA products.

Non-targeted analysis of alternate products from the disinfection of EMImBr may also be indicative of degradation pathways of other imidazolium-containing heterocycles from natural waters. Such natural compounds include histidine and guanine, which have not been characterized for their ability and/or tendency to form DBPs.

4.4.3 Non-targeted analysis of disinfection by-products of pyrrolidinium moieties

Pyrrolidinium cations are similar in structure to polyDADMAC, as they share five-membered heterocyclic ring structures that have positive charges centered on aliphatic 4° amines. Non-targeted analysis of pyrrolidinium under varied disinfection conditions could be helpful because DBPs generated by the reaction of pyrrolidinium could allow for the characterization of aliphatic 4° amine breakdown products. This would provide insight into the breakdown mechanisms of pyrrolidinium, as well as providing an opportunity to survey for alternate DBPs that may be formed from similar molecules like polyDADMAC.

Non-targeted analysis of products from the disinfection of pyrrolidinium may also indicate the reaction pathways by which EMPyrBr may act as a precursor to NPyr. The mechanism by which EMPyrBr may act as a precursor to NPyr has not been evaluated.

These experiments could also be an opportunity to evaluate the extent to which pyrrolidinium cations break down, or resist breakdown, during treatment with NH_2Cl. If EMPyr does not degrade during NH_2Cl treatment, NA formation potential could be attributable to impurities.

4.4.4 Non-targeted analysis of products from the chlorination of EMPyr

When either EMImBr or EMPyrBr were pre-oxidized by Cl_2, subsequent treatment with NH_2Cl did not yield detectable concentrations of NAs. This is unexpected, as previous evaluations of Cl_2 pre-oxidation on final yields of NDMA from polyDADMAC have generated detectable amounts of NDMA.[17] Therefore, it may be worthwhile to evaluate how chlorination may structurally modify EMIm and/or EMPyr to prevent the subsequent generation of NAs in reactions with NH_2Cl.

4.4.5 Evaluation of *N*-nitrosamine formation potential of ionic liquids after UV pre-oxidation

An important premise for my research was that ILs are anticipated as environmental water contaminants. Therefore, ILs may also be expected to contaminate water sources used to supply drinking water. However, because ILs may also be transformed or degraded by the chemistry of their aquatic environment prior to uptake by drinking water treatment plants (DWTPs), this premise may be limited in scope.

The environmental half-lives of some ILs have been shown to persist for a few days or up to a month, and are dependent on weather, sunlight, and dissolved organic carbon concentrations.[43,44] This indicates that ILs readily degrade in water, which could result in products that are NA precursors after uptake into a DWTP. Among the products that have been characterized after UV degradation of imidazolium, products with opened ring structures have been characterized, including products with 3° amines.[44] This is significant because tertiary amines could plausibly be more productive NA precursors than 4° aromatic amines.[15]

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Appendix

Appendix A: Optimizing reaction conditions to detect *N*-nitrosamines generated by the chloramination of selected ionic liquids

A.1 Experimental

Reaction mixtures were prepared to explore a molar ratio of ILs and NH2Cl for the maximum formation of *N*-nitrosamines. Each mixture contained 1 mL of 50.0 mM IL stock solution and 1 mL of 100 mM borate buffer (pH = 8.4). To each reaction mixture, various amounts (25, 75, 125, 250, 500,750, and 1000 μL) of 100 mM NH2Cl were added. Each solution was then diluted to 5.00 mL with Optima water. The final reaction conditions were 20 mM buffer with 5 mM of IL and 0.50 – 20 mM NH2Cl. After 24 h, remaining monochloramine was quenched by the addition of an excess (20 mg) of ascorbic acid. Samples were extracted by the liquid-liquid extraction method reported in the materials and methods, and quantified by a previously established LC-MS/MS detection method.[36]

A.2 Results and Discussion

The concentrations of NAs generated in these reactions are reported in **Figure A1**. For both ILs, a 2.5 mM treatment of NH_2Cl generated acceptably high concentrations of NMEA. Although this ratio was less than ideal for the combined yield of NMEA and NPyr from the chloramination of EMPyrBr, it was optimum ratio to maximize the yield of NMEA from EMImBr. Therefore this reactant ratio (i.e., [ILs]:[NH_2Cl] = 2:1) was chosen for subsequent sample preparation.

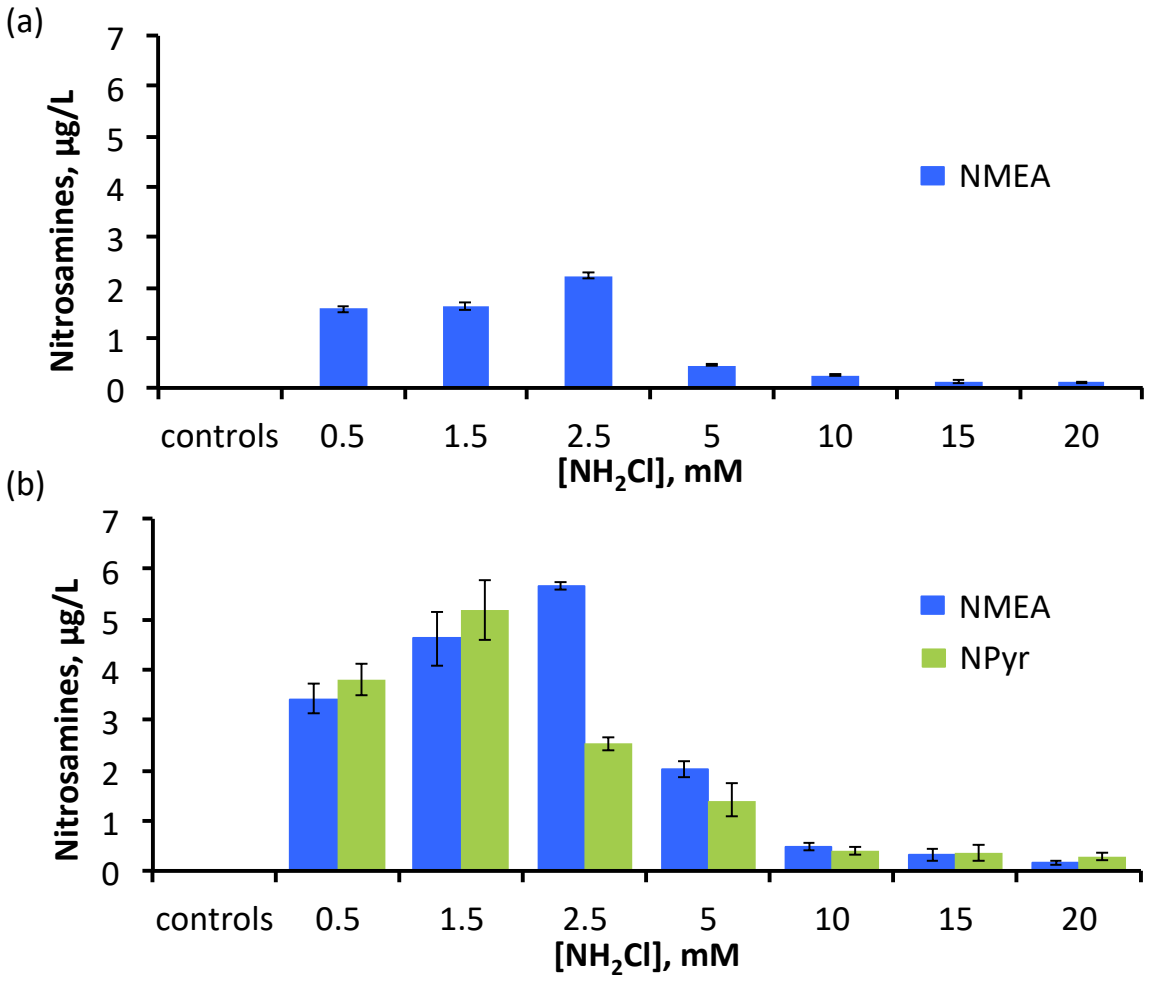

Figure A1 – Concentrations of NMEA and NPyr from the reaction of varied doses of NH_2Cl with 5 mM of both (a) EMImBr and (b) EMPyrBr. Results are reported with standard deviation from n = 3 samples.

Appendix B: Liquid-liquid extraction and LC-MS/MS quantification of NAs

B.1 Experimental

An LLE method was developed for the extraction and pre-concentration of NAs. 500 µL of prepared 8.00 µg/L *N*-nitrosomethylethylamine-D_3 (NMEA-D_3) was added to samples prior to extraction as a surrogate standard for the recovery of *N*-nitrosomethylethylamine (NMEA) and *N*-nitrosopyrrolidine (NPyr). Aqueous samples were extracted three times each by the addition of 4.5 mL of dichloromethane (DCM) to samples in 15 mL vials, which were agitated vigorously, and vented intermittently. A total of 12-13 mL of dichloromethane was collected from each sample and evaporated down to <0.05 mL by incubation at 36°C under gentle nitrogen flow. After evaporation, NDMA-d_6 was added as an internal standard, and samples were reconstituted to 200 µL with water. Samples were stored at 4°C and analyzed within 24 hours by liquid chromatography-tandem mass spectrometry as previously reported. [1]

Analyte recovery from LLE was assessed to evaluate whether NMEA-D_3 would be an appropriate surrogate standard to calculate corrected concentrations of NMEA and NPyr. Samples were prepared in triplicate to 0.200, 0.600, and 1.00 µg/L of EPA 8270 IX NA mix, with 0.80 µg/L of NMEA-D_3 in 5.00 mL of LC-MS grade water. Samples were extracted according to the procedure above, and quantified by LC-MS/MS.

B.2 Results and Discussion

It was necessary to isolate NAs from reaction mixtures in order to avoid/minimize the potential ion suppression effects, and contamination, of high concentrations of ionic

liquids. In order to isolate and pre-concentrate NAs generated by the reaction of the selected ILs, a LLE technique was developed.

LLE cannot achieve the very low limits of detection possible with SPE, as SPE concentrates analytes from larger initial sample volumes. However, the FP samples generated in this work were consistently prepared to only 5 mL, so it would be impossible to achieve the enrichment factors achieved by use of SPE by Qian et al. [1] SPE would not necessarily offer superior limits of detection for small sample volumes. LLE could be favourable when compared to SPE in this case. LLE requires less labour and has lower procedural complexity as compared to SPE. Therefore, LLE was evaluated for analyte recovery and limits of detection when paired with the MS/MS MRM mode NA quantification technique reported by Qian et al.[1]

The relative recoveries of NMEA and NPyr were compared to the recovery of NMEA-D_3, and are reported in **Figure B1**. As is apparent in **Figure B1(a)** percent recovery of NMEA as compared to recovery of NMEA-D_3 was relatively proportional. This recovery was not perfectly proportional, as R_2 = 0.971, but this was still acceptable. In **Figure B1(b)**, percent recovery of NPyr as compared to NMEA-D_3 could be considered proportional, as the R^2 was 0.995. NPyr had consistently higher percent recovery than did NMEA-D_3; this is reflected in both the slope and Y-intercept of **Figure B1(b)** as compared to **Figure B1(a)**. The slopes from **Figure B1** were used to correct apparent NMEA and NPyr analyte recoveries in all samples that followed.

This data was also used to calculate method limits of detection (LOD) and limit of quantification (LOQ). The instrument LOD and LOQ for NMEA were 0.11 and 0.38 µg/L

respectively, while the instrument LOD and LOQ for NPyr were 0.39 and 1.2 µg/L respectively, both based on n = 9 calibration samples prepared to 0.50 µg/L.

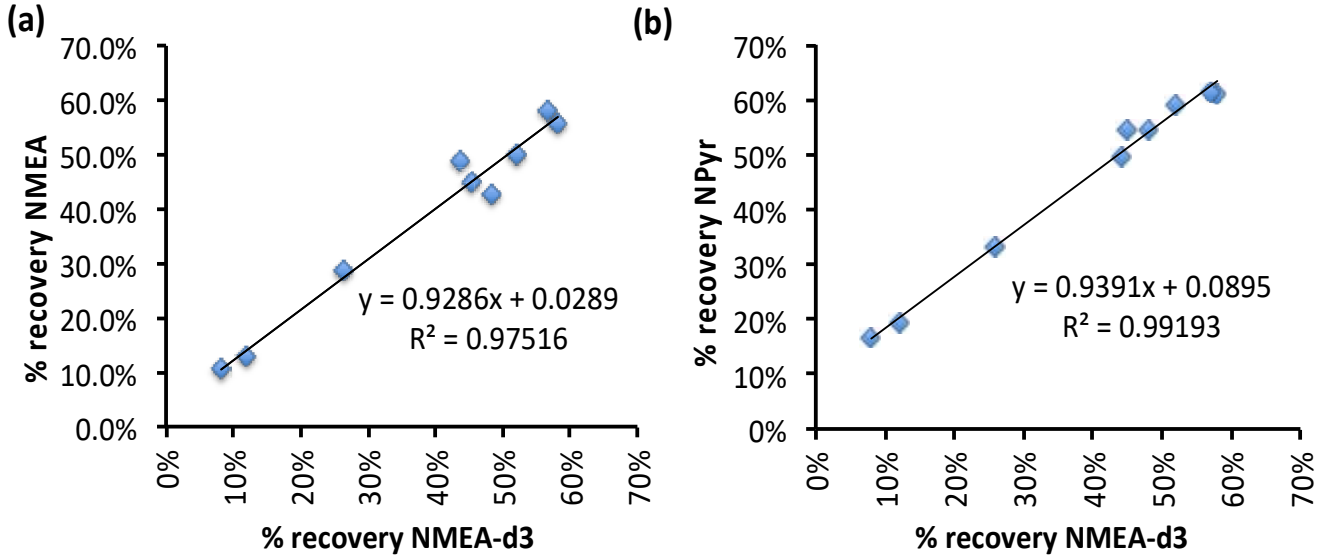

Figure B1 – Relative rates of recovery from liquid-liquid extraction (a) comparing the percent recovery of NMEA to the percent recovery of NMEA-D_3, and (b) comparing the percent recovery of NPyr to the percent recovery of NMEA-D_3.

The method LOD (MLOD) and method LOQ (MLOQ) improved after I gained experience performing my procedures. When relative recovery of analytes and surrogate standards were assessed (as in **Figure B1**), average recovery of NMEA-D_3 was 39.1 ± 19.0 %. In the most recent extracted samples, average recovery of NMEA-D_3 was 70 ± 19 %. This improvement in analyte recovery led to an improvement in theoretical MLOD and MLOQ of NMEA from 80 and 260 ng/L respectively, to 21 and 79 ng/L respectively. A similar improvement was made for NPyr, as MLOD and MLOQ were improved from 60 and 192 ng/L respectively to 20 and 70 ng/L respectively.

The following stands as advice for future individuals attempting similar methods. When evaporating DCM, it is easy to proceed to dryness by accident, especially if it is necessary to evaporate down to small volumes to < 50 µL. If samples were allowed to evaporate to/near total dryness, analyte recovery was typically ~ 5-15%. Although the 12-13 mL volume of DCM collected during this LLE procedure usually evaporated in ~30-35 minutes, samples did not finish evaporating down to < 0.05 mL simultaneously. As some samples finish evaporation, they may be placed to the side until other samples finish evaporating down to the necessary volume. This is a critical point where analyte loss can occur. Because DCM is volatile, aliquots of < 0.05 mL will evaporate in a short time, even when removed from N_2 flow, leading to poor analyte recovery. Therefore, I recommend preventing analytes from evaporating by adding a small volume of water (50 – 85 µL, depending on the volume of DCM condensate remaining) to remaining DCM to effectively "cap" these samples, and prevent analyte loss. Once water has been added, danger of condensate proceeding to dryness is reduced.

Appendix C: Pre-oxidation of ILs by free chlorine and subsequent reaction with NH_2Cl

C.1 Experimental

Chloramine can be used either as a primary or secondary disinfectant.[2] Therefore both EMImBr and EMPyrBr were disinfected by free chlorine with subsequent chloramination in order to discern the influence of free Cl_2 on NA yields. Free Cl_2 demand was evaluated for both ILs at varied time points to allow for the evaluation of the effect of pre-oxidation using free chlorine, as has been done previous similar primary + secondary FP experiments.[3] Buffer was prepared by dissolving 17.75 g of Na_2HPO4 in 700 mL of LC-MS grade water, and adjusting pH down to 7.5 by the addition of 1 M HCl, and diluting the final volume to 1.00 L. A 150 mM stock solution of free Cl_2 was prepared by diluting 2.14 mL of 10% w/v free Cl_2 solution. Fresh stock solutions of EMImBr and EMPyrBr were prepared to 50.0 mM by dissolving 285.0 mg of EMImBr and 289.5 mg of EMPyrBr into 30.0 and 29.8 mL of LC-MS grade water respectively. Reaction mixtures were prepared by adding 1 mL of 125 mM Na_2HPO_4 pH 7.5 buffer, 500 µL of either 50.0 mM EMImBr or EMPyrBr, 500 µL of 150 mM free Cl_2, and 3.00 mL of LC-MS grade water. The final reaction conditions were 25 mM Na_2HPO_4 buffer, 5.0 mM of either EMImBr or EMPyrBr, and 15 mM free Cl_2. Samples were allowed to react until time points of 5, 15, 30, 45, 60, and 120 minutes, at which points 470 µL aliquots were removed, and diluted in 199.5 mL of LC-MS grade water for the measurement of free Cl_2 by automated amperometric forward titration of free Cl_2 (Autocat 9000, HACH). Samples were prepared and measured in triplicate to determine the exact amounts of formic acid necessary to quench residual free Cl_2 at the designated time points.

Subsequent samples were prepared to 15.0 mL with identical IL and Cl_2

concentrations as in prior samples. After designated time points (10 min, 30 min, 60 min, and 120 min), 2.50 mL aliquots from these 15.0 mL samples were transferred into vials containing exact amounts of formic acid necessary to quench remaining free Cl_2 (calculated using measurements made from the prior samples). Aliquots were agitated to ensure thorough mixing of the formic acid with the chlorinated aliquot. After agitating, 1 mL of 100 mM $B(OH)_3$ pH 8.4 buffer, 750 µL of 5.0 mM NH_2Cl, and water were added to a final volume of 5.00 mL. Sample conditions were either 2.5 mM EMImBr or EMPyrBr, and 7.5 mM NH_2Cl, 20 mM $B(OH)_3$, and 12.5 mM Na_2PO_4 buffers. Samples were allowed to react in the dark at room temperature for 24 hours before being quenched by the addition of excess ascorbic acid (20 mg). Samples were then extracted by liquid-liquid extraction as described in **Appendix B** and quantified by LC-MS/MS.[1]

C.2 Results and Discussion

Both EMImBr and EMPyrBr were evaluated for their respective free chlorine demand across a 2-hour period. The free chlorine demands of both EMImBr and EMPyrBr are plotted in **Figure C1**. This figure shows that both Cl_2 was consumed in both reactions with a very small difference in overall Cl_2 demand. This figure also shows that initial Cl_2 doses were not precisely 15.0 mM, as initial dose varied by up to ± 3.5% from the extrapolated slope intercepts.

Pre-oxidation effectively prevented the generation of NAs from both IL species. No NAs were detected in samples treated with Cl_2, nor samples treated with Cl_2 and subsequent chloramination. Chlorination therefore decreased the tendency of either IL species to act as NA precursors during chloramination. It is unclear how chlorination

prevents the generation of NAs, as no attempt was made to characterize alternate reaction products.

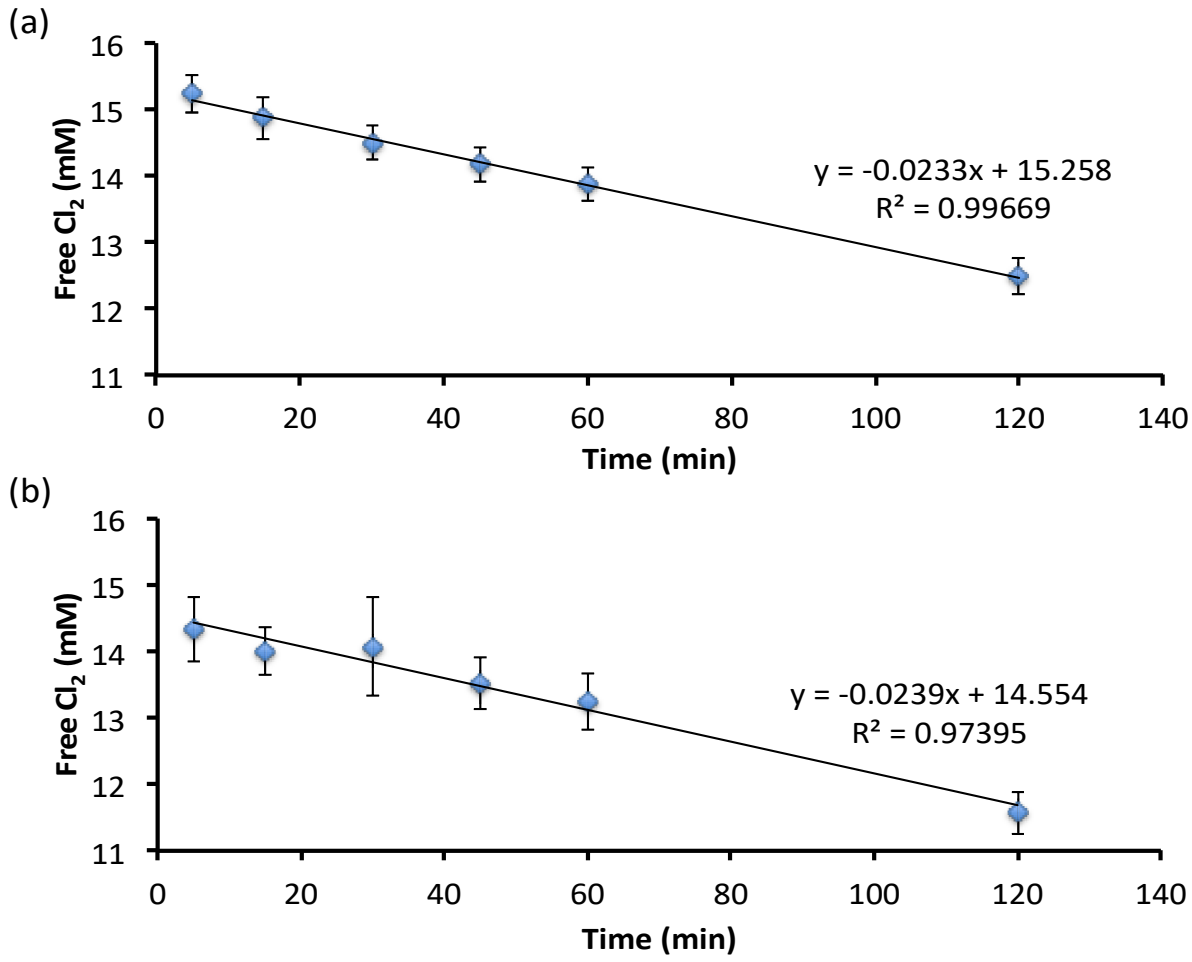

Figure C1 – Free chlorine demand of both (a) EMImBr and (b) EMPyrBr under consistent reaction conditions. For all time points measured, results are reported with standard deviation from n=3 samples in each case.

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