IODINATED PHARMACEUTICALS AS PRECURSORS TO TOTAL ORGANIC HALOGEN FORMATION IN THE PRESENCE OF CHLORINATED OXIDANTS AND ABSENCE OF NATURAL ORGANIC MATTER

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IODINATED PHARMACEUTICALS AS PRECURSORS TO TOTAL ORGANIC HALOGEN FORMATION IN THE PRESENCE OF CHLORINATED OXIDANTS AND ABSENCE OF NATURAL ORGANIC MATTER

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ABSTRACT

The aim of this study was to investigate iodinated pharmaceuticals as potential precursors to total organic halogen (TOX) formation in the presence of chlorinated oxidants (i.e., aqueous chlorine and monochloramine) and without NOM present. The reaction mechanism of aqueous chlorine and monochloramine with iopamidol, an iodinated x-ray contrast media (ICM), as a primary contributor of iodide in the formation of total organic iodide (TOI), the precursor to the formation of extremely toxic iodinated-DBPs, was evaluated. Reaction with other ICM with chlorinated oxidants was also investigated. The traditional TOX method was modified to measure total organic chloride (TOCl), total organic bromide (TOBr), as well as TOI.

The aqueous chlorination of iopamidol, iomeprol, iopromide, iohexol and Na-diatrizoate was studied in the pH range 6.5-9 and at 25±1 °C. Under these conditions, iopamidol was transformed releasing iodide into aqueous phase. Once in the aqueous phase, iodide is rapidly transformed to hypoiodous acid (HOI). HOI is a very reactive species with organic material and almost exclusively participates in electrophilic substitution reactions forming iodide containing transformation products. However, HOI can also be oxidized by residual aqueous chlorine to form iodate in absence of natural organic matter (NOM). Transformation of iopamidol was monitored as the loss of total
organic iodide (TOI) and the formation of iodate. The observed loss in TOI concentration appears to be the greatest at pH 7.5, least at pH 6.5, and approximately the same for pH 8.5 and 9. The degradation of TOI can be described by observed first-order kinetics in the presence of excess aqueous chlorine over the pH range of 7.5-9; however, TOI degradation at pH 6.5 appears to be bi-phasic indicating a more complex reaction mechanism is responsible for TOI degradation in the presence of aqueous chlorine.

Iodate formation from the degradation of iopamidol transformation products does not echo iodate formation due to iodide oxidation in the presence of aqueous chlorine, and it does not appear to be described by observed first or second order kinetics. Therefore, it is being proposed that both chlorine species (i.e., HOCl and OCl\(^{-}\)) are responsible for in the degradation of TOI in aqueous systems containing iopamidol and chlorine. The other ICM were also investigated in the presence of aqueous chlorine over the pH range of 6.5-8.5. It was assumed that they were not reactive since the TOI concentration did not change regardless of pH over 72 hours and no other inorganic iodide containing species were identified. Monochloramine experiments with iopamidol result in an insignificant degradation of TOI degradation over the pH range of 6.5-8.5. Similar results were observed in a previous study that in the absence of other reactants, HOI is very stable in the presence of monochloramine and does not result in iodate formation.
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CHAPTER I

INTRODUCTION

1.1 Motivation of the Proposed Research

Iodine containing pharmaceuticals, known as iodinated X-ray contrast media (ICM), have recently been found as source of iodine in the formation of toxic iodinated disinfection by-products (iodo-DBPs) and high molecular weight by-products of unknown toxicity resulting from the transfer of iodide from the ICM into natural organic matter (NOM) during drinking water disinfection with chlorinated oxidants (i.e., chlorine and chloramine) (Duirk et. al., 2011). ICM are pharmaceuticals widely used at medical imaging centers that are either applied orally or intravenously to enable imaging of soft tissues (e.g., organs, veins, blood vessels) (Steger-Hartmann, 1999). These are large molecules (~600-700 Da) with triiodobenzoic acid analogues as their basic structures. ICM are regarded as chemically inert drugs, metabolically stable in the body and are excreted almost completely via urine or feces within one day (Perez et al., 2006). However, due to their incomplete removal during aerobic/anaerobic wastewater treatment and soil aquifer passage and recalcitrant behavior even against activated carbon filtration and ozonation (Sacher et. al. 2001; Putschew et. al. 2000; Ternes et. al., 2003; Ternes et.
al., 2000; Drewes et. al., 2001; Drewes et. al., 2003; Schittko et. al., 2004), ICM are frequently found in wastewater treatment plant effluents and in the receiving surface waters at elevated concentrations (Olesky-Frenzel et. al. 2000, Ternes et. al., 2000, Putschew and Jekel, 2000). So far, native iodide was considered the only known source of toxic iodo-DBPs, but recent studies found that ICM can act as precursors (Duirk et al., 2011). Richardson et. al., (2007) reviewed 30 years of research on the occurrence, genotoxicity, and carcinogenicity of 85 DBPs. Of those DBPs, 11 are regulated by the U.S. Environmental Protection Agency and 74 of are considered emerging DBPs due to their moderate occurrence levels and/or toxicological properties. Although a lot of research has been already conducted, people are still being exposed a mixture of at least 600 identified DBPs (and countless unidentified ones) via dermal, inhalation and ingestion routes (Richardson et. al., 2007). Since, there is still nothing known about the potential toxicity of the many unidentified DBPs, total organic halogen (TOX) can be considered as a surrogate parameter to elucidate the overall DBP formation potential of raw water (Li et. al., 2010). Iodinated X-ray contrast media (ICM) play a very significant role in contributing iodide as the first known organic halogen precursor in the formation of TOX as well as toxic halogenated DBPs (Duirk et. al., 2011).

1.2 Scope of Work

Although ICM are being used widely and found at significant levels in surface waters, few researchers have investigated if ICM are precursors to the formation of iodo-DBPs in drinking water. Duirk et. al. (2011) investigated ICM as a source of iodine in the formation of iodo- trihalomethanes (iodo-THM) and iodo-acid DBPs, both of which are
highly genotoxic and/or cytotoxic in mammalian cells. Since ICM can be precursors in the formation of iodo-DBPs, iodinated pharmaceuticals need to be investigated as potential precursors to TOX formation in the presence of chlorinated oxidants and natural organic matter. The chemistry involved in these ICM reactions appears to be completely different from the known iodide/chlorinated oxidant chemistry. The formation mechanisms of highly toxic iodo-DBPs from the reaction of drinking water disinfectants with ICM needs to be understood in order to mitigate exposure to extremely cytotoxic, genotoxic and carcinogenic iodo-DBPs. Of the ICM investigated, iopamidol appears to be the only ICM that appears to participate in reactions with chlorinated oxidants resulting in iodo-DBP formation (Duirk et. al., 2011). In this study, the transformation of 5 ICM with aqueous chlorine and monochloramine were investigated in the absence of NOM. The transformation of iopamidol will be monitored as the loss of total organic iodide (TOI) over the pH range of 6.5-9. Also, the observed rate of iodide and iodate formation will be monitored as a function of pH. The transformation of other ICM (i.e. iomeprol, iopromide, iohexol, Na-diatrizoate) in the presence of aqueous chlorine will be evaluated over the pH range of 6.5-8.5. Halogen specific TOX (i.e., total organic chloride (TOCl), total organic bromide (TOBr), and total organic iodide (TOI)) will be used to quantify halogen incorporation and identify the role of ICM in the formation of TOX, which leads to the formation of iodo-DBPs.
CHAPTER II

LITERATURE REVIEW

Chemical disinfection is a unit process in water treatment designed to inactivate pathogens. Chlorination, chloramination, ozonation, and chlorine dioxide are common oxidants used for disinfection of potable water and are reactive with natural organic matter (NOM), anthropogenic contaminants, bromide and iodide present resulting and the formation of disinfection by-products (DBPs). Well over 700 DBPs have been identified and some are known carcinogens that can induce cytotoxic effects as well as genomic damage (Richardson et. al., 2007). Total organic halogen (TOX) has gained popularity as a surrogate of the degree of halogen incorporation into organic molecules that are produced as a result of the disinfection process (Stevens et. al., 1985). Around 30% of the TOX has been accounted for (on a median basis) by the sum of the measured halogenated DBPs (Krasner et. al., 2006). Native iodide was previously perceived as the only halogen precursor in the formation of iodinated DBPs; recently, iodinated x-ray contrast media (ICM) are considered to be a potential source of highly toxic iodo-DBPs. However, halogen incorporation pathways and the importance of ICM in the formation of TOX and distribution of iodinated DBPs have yet to be fully compared to inorganic precursors.
This literature review has been presented in three sections. The first section will discuss occurrence of iodinated pharmaceuticals and their toxicity. The second section will briefly describe formation mechanism as well as the incorporation of chloride, bromide and iodide into NOM and the reactions of iodinated pharmaceuticals with chlorinated oxidants resulting in TOX formation. The last section will introduce the health effects and exposure pathways of halogenated DBPs and TOX.

2.1 Iodinated x-ray Contrast Media (ICM) Global Occurrence

ICM are administered either orally or intravenously in order to display soft tissue or vessels and thus providing sufficient contrast in X-ray imaging (Steger-Hartmann et al., 1999). These are administrated in very high doses (up to 200g ICM, corresponding to approximately 100g iodine per application) and worldwide consumption of ICM is approximately 3.5x10^6 kg/year (Perez et al., 2006). ICM are all derivatives of 2, 4, 6-triiodobenzoic acid; therefore, they have a basic structure of three iodine atoms attached to an aromatic ring. The chemical structures for five common ICM iopamidol (IDOL), iomeprol (IMEP), iopromide (IPRO), iohexol (IHEX), diatrizoate (DIAZ) are provided in Figure 2.1.
Oleksy-Frenzel et al. (2000) found concentrations of up to 100 μg I/L in municipal treatment plant effluents in Berlin after specifying adsorbable organo halogens (AOX) into AOCl, AOBr and AOI. Gartiser et. al. (1996) showed that iodinated x-ray contrast media (ICM) are the major source for increased AOX concentrations due to ICM use in medical imaging centers. Before Putschew et. al. (2000), there was no study which proves or disproves that X-ray contrast agents are responsible for high AOX/AOI in environmental samples. They found diatrizoate in all samples- surface water, raw drinking water and surface water with bank filtration in concentration of 1.2-4μg/L, the concentration of iopromide was 1.6μg/L in the surface water and only a trace level was found in the bank filtered water and in the drinking water. They also showed that approximately 25% of the extractable AOI can be identified as specific triiodinated contrast agents. Ternes and Hirsch (2000) investigated the occurrence of ICM in German municipal sewage, sewage treatment plant (STP) effluents, rivers, and groundwater. In
STP effluents, concentrations for iopamidol up to 15 μg/L were measured. Due to the ICM present in STP effluents, the respective receiving rivers and creeks had median ICM concentrations up to 0.49 μg/L for iopamidol and 0.23 μg/L for diatrizoate. In groundwater, they found concentration as high as 2.4 μg/L for iopamidol. Drewes et al. (2001) studied the occurrence of pharmaceuticals basically highlighting triiodinated benzene derivatives used as x-ray contrast media in domestic effluents and their transformation during subsequent groundwater recharge. They used organic iodine measurements as a surrogate for triiodinated benzene derivatives and investigated seven waste water treatment facilities in Texas, Arizona and California where they found organic iodine concentrations (which was taken as a surrogate for triiodinated benzene derivatives) varied between 5 and 40 μg iodine/L. They observed a concentration range of 8-1540 μg iodine/L in groundwater recharge systems after travel times of 8 to 10 years. Schittko et al. (2004) determined average concentration of iopromide as <0.0002 μg/L, diatrizoate 0.166 μg/L, iopamidol 0.166 μg/L and iohexol 0.34 μg/L in the drinking water sources in Germany. Sacher et al. (2005) carried out an extensive monitoring program in Baden-Württemberg, Germany including samples from 105 groundwater wells, which were analyzed for 60 pharmaceuticals compounds. They found diatrizoate (0.13-0.44 μg/L), iohexol (0.03-0.09 μg/L), iomeprol (0.05-0.12 μg/L), iopamidol (0.09-0.22 μg/L) and iopromide (0.09-0.20 μg/L). Seitz et al. (2006) monitored the occurrence of ICM and investigated the impact of the activities of a metropolitan area on the ICM load in the Danube river (Germany) and found the median concentration for diatrizoate, iohexol,
iomeprol, iopamidol and iopromide to be 0.089-0.155 μg/L, 0.04-0.086 μg/L, 0.100-0.160 μg/L, 0.210 μg/L and 0.076-0.100 μg/L respectively.

Using liquid chromatography (LC)/ion trap-mass spectrometry (MS) and H/D exchange, Perez et al. (2006) found three iopromide transformation products (TPs) in a laboratory biodegradation study with conventional activated sludge. Schulz et al. (2008) identified 12 iopromide TPs in soil (under aerobic conditions) and in municipal WWTPs. Similar results were observed for iohexol, iopamidol, and iomeprol (Kormos et. al., 2011). Busetti et. al. (2008) developed a rapid method using direct injection liquid chromatography-tandem mass spectrometry to measure eight ICM. Kormos et. al. (2011) investigated the biotransformation of selected ICM (diatrizoate, iohexol, iomeprol, and iopamidol) in aerobic soil–water and river sediment–water batch systems and proposed microbial transformation pathways for these ICM.

Steger-Hartmann et. al. (1999) investigated iopromide occurrence in STP effluent and surface water and found that it did not elicit any harmful effects in the aquatic environment. Steger-Hartmann (2000) demonstrated different degradable pathways of iopromide and did not find any indication of imposed risk to aquatic life due to the release of iopromide into the aquatic environment. Keith et. al. (2000) conducted experiments investigating the potential risk due to repeated use of ICM at doses up to 5.3g/kg of ICM in rats and dogs. After dosing the animals five times a week over the course of five weeks, ICM did not elicit any morphological or functional changes of toxicological relevance. They examined ICM with even higher doses of 7.7g/kg and no
effect was found. Due to their low toxicity, ICM do not impose any immediate health risk, but the transformation products from ICM could pose a significant health concern.

2.2. Iodide oxidation to iodate

During drinking water treatment, iodide can be oxidized by many disinfectants such as ozone, chlorine dioxide, and chloramines. The primary product of \( \Gamma^- \) oxidation is hypoiiodous acid (HOI), which can undergo several further reactions (only exception is ClO\(_2\)) (Bichsel and Gunten, 1999). The stoichiometry of the reaction of HOCl/OC\(_2\) with \( \Gamma^- \) was investigated at pH 5.3-8.7 and at a molar ratio of \([\text{HOCl}/\text{OCl}^-]:[\Gamma^-]\) of 4:1 by Bichsel and Gunten (1999). The first oxidation step from \( \Gamma^- \) to HOI occurs immediately. For the further reaction, the formation of IO\(_3^-\) was measured together with the sum of \([\text{HOCl}]+[\text{OCl}^-]+[\text{HOI}]\) which was measured as I\(_3^-\) (in excess of \( \Gamma^- \)) by spectrophotometry. The reaction between the HOCl/OC\(_2\) and \( \Gamma^- \) happens as follows:

\[
2\text{HOCl} + \text{HOI} \rightarrow \text{IO}_3^- + 2\text{Cl}^- + 3\text{H}^+
\]

\[
2\text{OCl}^- + \text{HOI} \rightarrow \text{IO}_3^- + 2\text{Cl}^- + \text{H}^+ \quad \text{....} \quad K_{\text{HOCl}+\text{HOI}} = 8.3 \times 10^4 \text{M}^{-2} \text{s}^{-1}
\]

Therefore, it can be assumed that no stable intermediate and no IO\(_4^-\) are formed. IO\(_3^-\) formation was already observed in an earlier investigation (Black et. al., 1965).

When iopamidol comes in contact with chlorine, iodide is released from the aromatic structure. Released iodide gets oxidized to HOI, the rate of which reaction is very rapid and instantaneous in presence of excess HOCl, HOI is then oxidized to iodate. But the rate of this transformation is relatively slow. It takes approximately 3 days to get all the
iodide oxidation into iodate. The study conducted by Bichsel and Gunten (1999) determined the kinetics of several oxidation reactions of HOI. The disproportionation of HOI is a reaction in which HOI (oxidation state +I) reacts with itself leading to a reduced species (I⁻, oxidation state -I) and to an oxidized species (IO₃⁻, oxidation state +V). It can be described by a sequence of the two reactions 1 and 2, whereas reaction 1 is rate determining:

\[ \text{HOI} + \text{HOI} \rightarrow \text{IO}_2^- + \Gamma + 2\text{H}^+ \]  
\[ \text{(1)} \]

\[ \text{HOI} + \text{IO}_2^- \rightarrow \text{IO}_3^- + \Gamma + \text{H}^+ \]  
\[ \text{(2)} \]

The overall reaction can be described by reaction 3:

\[ 3\text{HOI} \rightarrow \text{IO}_3^- + 2\Gamma + 3\text{H}^+ \]  
\[ \text{(3)} \]

In their study, the kinetics of the oxidation of HOI by HOCl/OCl⁻ were investigated under pseudo-first-order conditions ([HOCl/OCl⁻]>>[HOI]). HOI was formed immediately after chlorine addition. They explained the mixed order of the reaction kinetics of the oxidation of HOI by HOCl by two hypothetical pathways. The differences result from an addition of HOI to the O-atom or the Cl-atom of HOCl. The first case results in a new iodine-oxygen bond which leads to iodite (IO₂⁻). IO₂⁻ is quickly further oxidized to IO₃⁻ by HOCl. Such a reaction mechanism would result in a first-order behavior in [HOCl]. Their proposed second pathway leads to the fast formation of an intermediate with an iodine-chlorine bond (e.g., HOI-CIOH). This intermediate can either quickly redissociate to the initial compounds (HOCl, HOI) or alternatively react with a second HOCl. This would lead to a compound such as e.g. HOI-(CIOH)₂ which would
quickly hydrolyze to IO	extsuperscript{3}. If the rate determining step is the reaction of the second HOCl with the inter halogen compound (HOI-CIOH), a second-order kinetic with respect to HOCl will result.

2.3. Total organic halogen (TOX) Formation

Organic halogenated compounds are formed by the reaction of halogenated oxidants with NOM resulting in the formation of DBPs. DBPs are formed upon the reaction of chemical disinfectants with DBP precursors. NOM serves as the organic precursor which is commonly measured by total organic carbon (TOC); bromide and iodide (Br\textsuperscript{-}, I\textsuperscript{-}) serve as the inorganic precursor. THMs (Trihalomethanes), HAAs (Haloacetic acid) as well as other identifiable and non-identifiable organic halogenated compounds are the by-products of the reaction between the chlorinated oxidants and the DBP precursors.

When chlorine is added to water, it hydrolyzes rapidly to produce hypochlorous acid (HOCl):

\[
\text{Cl}_2 + \text{H}_2\text{O} \xrightarrow{K_1} \text{HOCl} + \text{H}^+ + \text{Cl}^- , K_{\text{Cl}_2} = \frac{K_1}{K_1 - 1} \quad \text{..................(2.1)}
\]

For temperatures between 0 and 25°C, \(K_{\text{Cl}_2}\) ranges from 1.3x10\textsuperscript{-4} to 5.1x10\textsuperscript{-4}M\textsuperscript{2} (Wang and Margerum, 1994)

Hypochlorous acid is a weak acid which will dissociate to form the hypochlorite ion (OCl\textsuperscript{-}):

\[
\text{HOCl} \leftrightarrow \text{OCl}^- + \text{H}^+ \quad \text{.................................................................(2.2)}
\]
Total aqueous chlorine concentrations existing as either HOCl or OC1\(^{-}\), referred to as free chlorine, and each species concentration will vary as a function of pH due to pKa = 7.5. Among the different aqueous chlorine species, hypochlorous acid is the reactive form during water treatment (Deborde and Gunten, 2008).

During chlorination, hypochlorous acid can oxidize bromide and iodide. A mechanism via Cl\(^{+}\) transfer from hypochlorous acid to the halide (X\(^{-}\)) has been proposed for these compounds. This mechanism results in an XCl-type intermediate which then mainly leads to OX\(^{-}\) due to hydrolysis (Kumar and Margerum, 1986; Johnson and Margerum, 1991):

\[
\text{HOCl} + \text{Br}^{-} \leftrightarrow \text{HOBr} + \text{Cl}^{-} \tag{2.3}
\]

\[
\text{HOCl} + \text{I}^{-} \leftrightarrow \text{HOI} + \text{Cl}^{-} \tag{2.4}
\]

\[
\text{HOBr} \leftrightarrow \text{OBr}^{-} + \text{H}^{+}; \text{pKa} = 8.7 \tag{2.5}
\]

\[
\text{HOI} \leftrightarrow \text{OI}^{-} + \text{H}^{+}; \text{pKa} = 10.45 \tag{2.6}
\]

At pH range relevant to drinking water treatment, primarily only HOCl will be reactive with the inorganic halogens. While bromide will be oxidized to hypobromous acid (HOBr), iodide can undergo further oxidation beyond HOI/OI\(^{-}\) to form IO\(_3\)^\(-\) in the absence of NOM (Bischel and Gunten, 1999)

\[
\text{HOI} + 2\text{HOCl} \leftrightarrow \text{IO}_3^{-} \tag{2.7}
\]
Chlorine reacts with organic compounds in solution by one or more of three mechanisms (National Research Council, 1980):

1) addition - chlorine atoms are added to a compound;

2) substitution - chlorine atoms are substituted for some other atom that is present in the organic compound; or,

3) oxidation - the organic compound is oxidized and HOCl is reduced to chloride.
In general, oxidation reactions comprise greater than 90% of the chlorine consumed as chlorine demand in natural waters (Jolley and Carpenter, 1983). Addition and substitution reactions account for the remainder of the chlorine-demanding reactions and are responsible for the formation of chlorinated organic compounds. In waters containing bromide (Br\(^-\)), iodide (I\(^-\)) aqueous chlorine will oxidize bromide and iodide to HOBr and HOI which, in turn, will substitute into organic compounds forming brominated and iodinated organic compounds (Kristiana et. al., 2009; Richardson et. al., 2007). This chlorinated, brominated and iodinated organic compounds will comprise the TOX. Hua et. al. (2006) studied the impact of bromide and iodide ions on the formation and speciation of disinfection byproducts. Two natural waters were fortified with various levels of bromide or iodide ions (0-30 μM) and chlorinated in the laboratory. They did not observe any substantial change in TOX concentration for varying bromide concentration but they found significant decrease of TOX concentration with increasing initial iodide concentration, this is because of the lower rate of iodine substitution than that of bromine since substantial amount of iodide was being oxidized to iodate by chlorine. In presence of NOM, the oxidized iodide as well as HOI will produce iodo-THMs and iodo-acids that comprise iodo-DBPs (Richardson et al., 2007).
Recently it has been found that not only the naturally occurring iodide but also the iodine released from the aromatic structure of ICM in the presence of chlorinated oxidants (i.e., chlorine or monochloramine) can act as a precursor to iodo-DBPs. Although the complex detailed formation mechanism is yet to be fully discovered but it is proposed that the released iodide gets incorporated into NOM and results in the formation of toxic iodo-DBPs (Duirk et. al., 2011).

2.4 Halogenated DBP Toxicity

2.4.1. Genotoxicity of Halogenated DBPs

**Genotoxicity of Disinfection By-Products**

Richardson et. al. (2007) found that brominated DBPs are both more genotoxic and carcinogenic than are chlorinated analogues and among all the halogenated DBPs,
iodinated ones are the most genotoxic. The genotoxicity of the four regulated THMs (chloroform, bromodichloromethane, dibromochloromethane, chloroform) has been well studied (Kargalioglu, et al., 2002; Landi et al., 2003; Kogevinas, et al., 2010).

Bromoform, dibromochloromethane, and bromodichloromethane, have not generally induced genotoxic responses except in the presence of glutathione S-transferase theta (GSTT1-1), a common enzyme in mammalian cells (Richardson, et al., 2007). In the presence of GSTT1-1 all three have been observed to induce genotoxic effects in a study of human lung tissue, and in various strains of salmonella (Landi, et al., 2003; Kargalioglu, et al.; 2002). Chloroform, does not generally induce genotoxic effects, with the notable exception that it was weakly correlated to genotoxic effects in human lung tissue (Kargalioglu, 2002; Landi, et al., 2003).

Three of the five regulated HAAs (monobromoacetic acid (MBAA), dibromoacetic acid (DBAA), monochloroacetic acid (MCAA) were mutagenic in bacteria and Chinese hamster ovary cells (Kargalioglu et al., 2002; Plewa, et al., 2002). DCAA has been observed to be only weakly genotoxic, producing effects inconsistently and only at high dosages (<50% effect occurrence rate at dosages ≥0.5 g L⁻¹) (IARC, 2004a). Trichloroacetic acid has not been shown to be genotoxic in peer reviewed studies (IARC, 2004b). Richardson et. al. (2007) revealed that compounds that contain an iodo-group have enhanced mammalian cell cytotoxicity and genotoxicity as compared to their brominated and chlorinated analogues. As a continuation of that work Duirk et. al. (2011) investigated the mammalian cell cytotoxicity and genotoxicity of the reaction mixtures of chlorine or monochloramine with iopamidol and NOM. In these initial
experiments, source water with and without iopamidol was disinfected with chlorine. Results demonstrated that chlorine-disinfected source water that contained iopamidol induced increased genomic DNA damage in mammalian cells. Iopamidol alone was not genotoxic. The chlorinated source water (without iopamidol) was genotoxic, but at levels much lower than with iopamidol. These data indicate that a non-toxic, ubiquitous, pharmaceutical water contaminant can be transformed into highly genotoxic by-products after disinfection.

**Genotoxicity of iodo-THMs**

Based on quantitative structure-activity relationships it has been predicted that Iodo-THMs can cause cancer (Woo et. al., 2002), but until now, there has been no toxicity studies conducted. Current efforts are going on to investigate the mammalian cell genotoxicity and cytotoxicity of the iodo-THMs (Richardson et. al., 2007). Preliminary data indicate that iodoform is highly cytotoxic but not genotoxic to mammalian cells (Plewa et. al., 2007). Iodoform is mutagenic in bacteria (Roldan-Arjona et. al., 1993) but does not induce chromosome aberrations in SHE cells in vitro (Hikiba et. al., 2005).

**Cytotoxicity of iodo-THMs**

Bromoform, chloroform, iodoform, bromochloroiodomethane, bromodichloromethane, dibromochloromethane and dibromoiiodomethane were not genotoxic in CHO cells (Richardson et. al., 2007). However, the iodo-THMs are the most cytotoxic of the group (Richardson et. al., 2007). The rank order of their CHO cell chronic cytotoxicity was
iodoform>dibromoiodomethane>bromochloriodomethane>bromoform>chlorodibromomethane>chloroform>bromodichloromethane (Plewa et. al., 2007).

2.5. TOX Toxicity

Total organic halogen (TOX) is an analytically defined measurement applied to specially drinking waters. In comparison to detection methods for individual DBPs, TOX is an inexpensive measurement to screen a large number of samples for halogenated organic components (Li et. al., 2010). TOX is measured with a view to estimating the total amount of organically bound chlorine, bromine and iodine in water samples. TOX is considered as a collective parameter and a toxicity indicator for all the halogenated organic DBPs present in water sample (Li et. al., 2010). Unknown fraction of TOX can be estimated by comparing the TOX values with the halides attributed to known quantifiable halogenated DBPs (Singer and Chang, 1989; Krasner et. al. 2006; Hua and Rekhow, 2006). Other than the volatile trihalomethanes, haloacetonitriles, haloketones most of the total organic halogen (TOX) are non-volatile that show stronger mutagenic activity than the volatiles (Meire et. al., 1983). Undoubtedly, major health concerns over disinfection by-products are concentrated not only to regulated or unregulated DBPs but should include all non-volatile TOX (Suzuki and Nakanishi, 1987). Johnson and Jensen (1986) studied the TOX produced from the reaction of monochloramine and isolated fulvic acid and found that TOX resulting from chloramination was more hydrophilic and higher in molecular weight than TOX produced by chlorine. Zhang et al. (2000) studied the TOX formation from the reactions of a fulvic acid and different chemical
disinfectants. For the chloramine treated sample, more than 80% of the TOX could not be represented by the commonly known DBPs. A substantial amount of the halogenated DBPs formed by chloramines is unknown. A larger unknown fraction of TOX is produced from chloramination than from chlorination. And thus there remains a major scope of further study to investigate the toxicity associated with the TOX. Savitz et. al. (2006) conducted a study in three US locations of varying DBP levels to evaluate the pregnancy loss due to exposure to drinking water DBPs and found a possible association for TOX, not addressed in any of the previous studies. Given that there are hundreds of chemicals beyond the THMs and HAAs in chlorinated and chloraminated drinking water (Krasner et al., 2006), possibly differing across the study sites, some harmful constituent may be better reflected in the comprehensive measure, TOX, than in any of the other DBP indices examined. Schenck et. al. (2009) evaluated the relationship between mutagenicity and water quality parameters. The study included information on treatment, mutagenicity data, and water quality data for source waters, finished waters, and distribution samples collected from five full-scale drinking water treatment plants, which used chlorine exclusively for disinfection. They found the highest correlation between mutagenicity and the total organic halide concentrations in the treated samples.
CHAPTER III

MATERIALS AND METHODS

This Chapter contains materials, experimental and analytical methods, and apparatus used to conduct the research presented in this thesis. All experiments were conducted at the University of Akron (Akron, OH) in the Auburn Science and Engineering Center Room 411.

3.1 Materials

The organic standards: 2, 4, 6 trichlorophenol (98%) and 4-iodophenol (99%) were purchased from Sigma Aldrich (St. Louis, MO, USA), 2, 4, 6 tribromophenol (98%) was purchased from Acros Organics (NJ, USA). The inorganic standards: NaCl (99%) was purchased from EMD chemicals (Gibbstown, NJ, USA), NaBr (99.5%) and KI (99.5%) were purchased from Fisher Scientific (NJ, USA), and NaI (99%) was purchased from Sigma Aldrich (St. Louis, MO, USA). Aqueous stock solutions and experiments used laboratory prepared deionized water (18 MΩ cm$^{-1}$) (DI water) from a Barnstead NANOpure system (Barnstead-Thermolyne Corporation, Dubuque, IA). The pH for experiments were adjusted using either 1N H$\text{}_2$SO$_4$ or NaOH. All pH measurements were taken with an Orion 5 star pH meter and ROSS ultra combination pH probe (Thermo
All other organic and inorganic chemicals were certified ACS reagent grade and used without further purification. The glassware used in this study was prepared by soaking it concentrated free chlorine solution for 24 hours, rinsed with DI water, and dried prior to use.

3.2 Experimental Methods

Chlorination of ICM experiments were conducted under pseudo first-order conditions with total chlorine, $[\text{Cl}_2]_T$, to iopamidol molar ratios of 20:1. Chlorine was added to solutions (DI water for iodate analysis and Akron, Barberton water for TOX analysis) under rapid-mix conditions using a magnetic stir plate and a PTFE-coated stir bar. Relatively high chlorine dose (100 $\mu$M) was used in this experiment to ensure that the disinfectant was always in excess. Aqueous chlorine stock solutions were diluted to 200 mM and added to the aqueous solution containing iopamidol and buffer in a 500 mL Erlenmeyer flask. Once mixed thoroughly, the solution in the 500 mL Erlenmeyer flask were transferred to individual batch reactors that were sacrificed at discrete sampling intervals.

Monochloramine experiments followed the same experimental protocol, and utilized additions of preformed monochloramine to avoid potential artifacts caused by reactions of excess free chlorine that may briefly exist if monochloramine was formed in situ (Duirk et. al., 2011). Monochloramine solutions were prepared by mixing 5.64 mM ammonium chloride with 3.7 mM hypochlorous acid to achieve the desired 0.7 Cl/N
molar ratio. The solution was allowed to react and equilibrate for 30 min in 10mM bicarbonate buffer, pH 8.5, prior to use.

3.3 Deionized Water ICM Degradation Experiments

Experiments observing TOI degradation and formation of iodate and iodide were carried out at 25°C and sampled at 0h, 6h, 12h, 24h, 48h and 72h. Experiments were conducted in triplicate, unless otherwise specified, at pH 6.5, 7.5, 8.5 and 9 using 1mM of phosphate buffer (pH 6.5 and 7.5), borate buffer (pH 8.5) and carbonate buffer (pH 9). The lower buffer concentration was used to mitigate the interference of excessively large peaks in the ion chromatogram. Four aliquots were then placed into 128mL amber reaction vessels with PTFE septa and stored in dark at 25°C. To examine the formation of IO₃⁻ as a function of pH and time in reaction mixtures containing iopamidol and aqueous chlorine, resorcinol (1,3-dihydroxyphenol) in 20% stoichiometric excess of the initial aqueous chlorine concentration had been used to quench the chlorine residuals since sodium sulfite is potential to reduce IO₃⁻ to I⁻. The direct oxidation of sulfite by iodate occurs when the pH of the solution does not decrease below pH 4 (Rabai and Beck, 1987). To measure TOI, sulfite was used as the quenching agent. For monochloramine experiments, sodium sulfite had been used to quench.

3.4 Analytical methods

3.4.1 TOX Extraction and Analysis

The analysis of halogen-specific TOX was based on the method developed by Hua and Rekhow (2006) with minor modifications. Pre-packed GAC columns (catalog
#MC06454) were obtained from Cosa Instruments (Horsblock Rd, New York, USA). Water samples (30 mL each) were acidified to <pH 2 with 70% ACS grade nitric acid and concentrated via adsorption onto an activated carbon column using a TOX-100 adsorption module (CosaInstruments/Mitsubishi). The extraction flow rate was 3 ml/min. Afterwards, GAC columns were washed with 15 mL KNO₃ solution, 1000mg NO₃⁻/L at pH 2 to remove inorganic halides and other inorganics at 3 ml/min. The activated carbon extraction cartridge was then placed in a quartz sample boat and introduced into the combustion chamber of a TOX-100 analyzer (Cosa Instruments/Mitsubishi). The activated carbon sample was combusted in the presence of oxygen for 15mins at 900°C. The off-gas was collected in a absorption solution of 20mL DI water by way of a custom made absorber (coarse diffuser). The custom diffuser was rinsed with the absorption solution to ensure 100% recovery. The schematic diagram of the gas absorption procedure is presented in figure 3.3.

![Figure 3.1. Schematic of modified TOX gas absorption](image-url)
3.4.2 IC analysis for TOX samples

The DI water was then analyzed for Cl⁻, Br⁻ and I⁻ using a Dionex ICS-3000 ion chromatograph with conductimetric detection and an ASRS®300 4mm anion self-regenerating suppressor. For the analysis of Cl⁻, Br⁻ and I⁻, an AS20 (4x250mm) column (Dionex) with KOH solution as mobile phase having a flow rate of 1ml/min were used. The gradient profile of the method for analysis is presented in figure 3.5.

The sample was delivered by an AS50 autosampler (Dionex) and was injected with a volume of 500μl. PeakNet software (Dionex) was used for automatic control and data processes. Calibration curved used for TOX sample analysis were prepared by running 2, 4, 6-trichlorophenol and 4-iodophenol standards on TOX and analyzed on IC afterwards. Figure 3.6 and 3.7 show the standard curves used for TOX analysis. The concentrations of Cl⁻ and I⁻ (in uM) obtained from the ion chromatographic (IC) analysis

Figure 3.2. Extraction of TOX samples
were used to calculate the sample concentration of TOCl (as uM Cl⁻) and TOI (as uM I⁻) respectively.

3.4.3 Iodate formation analysis on IC

After quenching with resorcinol, the samples were analyzed for IO₃⁻ using a Dionex ICS-3000 ion chromatograph with conductimetric detection and an ASRS®300 4mm anion self-regenerating suppressor. For this analysis an AS20 (4x250mm) column (Dionex) with KOH solution as mobile phase having a flow rate of 1ml/min were used. Calibration curved used for IO₃⁻ analysis were prepared by NaIO₃. In order to measure the TOI for DI water regarding IO₃⁻ analysis Iopamidol standard curve (as Iodide) was used. Figure 3.8 and 3.9 show the standard curve used for the analysis. The gradient profile of the method was the same as for TOX analysis.
Figure 3.3. Gradient profile for TOX analysis
Figure 3.4. Calibration curves for chloride. 

$C_{\text{chloride}} = 0.5$~$250\mu$M

$y = 5.6135x - 5.250$

$R^2 = 0.9964$

Chloride

Figure 3.4. Calibration curves for chloride. $C_{\text{chloride}} = 0.5$~$250\mu$M
Figure 3.5. Calibration curves for iodide. $C_{\text{iodide}} = 0.5–50\mu\text{M}$

The equation for the line is:

$$y = 5.1236x + 1.2031$$

$$R^2 = 0.9988$$

Area ($\mu\text{S} \times \text{min}$) 

Concentration ($\mu\text{M}$)

0 2 4 6 8 10

0 10 20 30 40 50 60
Figure 3.6. Calibration curves for Iodate, $C_{\text{Iodate}} = 0.5\text{~to~}50\mu\text{M}$

The linear equation for the calibration curve is:

$$y = 6.0365x + 2.1461$$

with a coefficient of determination $R^2 = 0.9897$. The data points are plotted on the graph, showing a strong linear relationship between the area ($\square \text{S*min}$) and the concentration ($\mu$M) of Iodate.
Figure 3.7. Calibration curves for Iodide. $C_{\text{iodide}} = 1.5\text{--}150\mu\text{M}$

\[ y = 5.6892x + 0.0574 \]

$R^2 = 0.9992$
CHAPTER IV

RESULTS AND DISCUSSION

This chapter has been divided into three sections detailing the transformation of ICM in the presence of chlorinated oxidants. First, the transformation of iopamidol in the presence of aqueous chlorine, observed rate of TOI degradation and observed rate of iodate formation over the pH range of 6.5-9 was investigated. Second, the transformation of other ICM in the presence of aqueous chlorine was investigated over the pH range of 6.5-9. Finally, the transformation of iopamidol in the presence of monochloramine was investigated over the pH range of 6.5-9.

4.1 Transformation of Iopamidol in the Presence of Aqueous Chlorine

To understand the reaction of iopamidol with aqueous chlorine, iopamidol degradation experiments were conducted in the presence of excess aqueous chlorine over the pH range of 6.5-9 without NOM present. Iopamidol transformation was monitored as the loss of TOI and the formation of iodate. Figure 4.1 shows the trend for iopamidol degradation as a function of pH using TOI concentration as a surrogate for iopamidol. The observed loss in TOI concentration appears to be the greatest at pH 7.5, least at pH 6.5, and approximately the same for pH 8.5 and 9. The observed first-order loss of TOI in
Figure 4.2 confirms that the greatest observed loss of TOI occurs at pH 7.5, and the TOI loss can be assumed to be first order in the presence of excess aqueous chlorine over the pH range of 7.5-9. However, TOI degradation appears to exhibit a bi-phasic observed first-order loss at pH 6.5, which indicates that TOI degradation is a more complex reaction mechanism. Duirk et al., (2011) proposed that hypochlorite ion initiates the transformation of iopamidol; however, the reaction mechanism resulting in the release of iodide from the benzene ring has yet to be fully understood. To gain a more clear understanding of the reaction mechanism, all iodide containing species must be accounted for. This would include iodide and iodate since TOI is a non-specific bulk measurement that does not yield any real significant that will elucidate the formation of active iodide containing oxidants.
Figure 4.1. TOI formation as a function of pH and time in reaction mixtures containing iopamidol and aqueous chlorine. Oxidant residuals were quenched with sulfite. [Cl]_T=100μM, [iopamidol]=5μM, [Buffer]=1mM, and temperature= 25°C. Error bars are represent 95% confidence intervals.
Figure 4.2. First-order observed loss of TOI as a function of pH. [Cl]$_T$=100μM, [iopamidol]=5μM, [Buffer]=1mM, and temperature= 25°C.
Iodate formation was investigated as a function of pH to compliment TOI degradation. Since sulfite reacts with iodate, resorcinol was used as the quenching agent due to its known reaction rates with hypochlorous acid. In our current study, iodate formation appeared to be fastest at pH 7.5, lowest at pH 6.5, and approximately the same at pH 8.5 and 9 (Figure 4.3). At pH 6.5, only 10% of the total chlorine concentrations will be in the OCl\textsuperscript{-}, which is believed to initiate the reaction with iopamidol resulting in the formation of a tri-iodinated transformation product. Therefore, iodate formation was expected to be slower at pH 6.5 than at the higher pHs. This has been confirmed investigating iodate formation by iodide oxidation by aqueous chlorine (Bichsel and von Gunten, 1999). The initial oxidation from iodide to hypoiodous acid is rapid; however, the formation of iodate is primarily due to oxidation by OCl\textsuperscript{-}. Therefore, it was expected the observed rate of iodate formation would increase as pH increases. However, the fastest observed rate of iodate formation occurred at pH 7.5. There are sufficient concentrations of both chlorine species (i.e., HOCl and OCl\textsuperscript{-}) at pH 7.5, since the pKa is 7.5. However, the observed rate of iodate formation decreased at pH 8.5 and 9.

Iopamidol degradation may be faster at higher pH due to the increased concentration of OCl\textsuperscript{-}, but the species responsible for the oxidation/substitution reaction could be HOCl. Bichsel and von Gunten, 1999 found that HOCl rapidly oxidizes iodide to HOI. However, HOI is relatively stable in the presence of excess chlorine with half-lives ranging from 8 min at a concentration of 2 mg/L Cl\textsubscript{2} and a pH of 9 to 10 hours at pH 6 and 0.2 mg/L Cl\textsubscript{2} and a pH of 6. Under our experimental conditions of aqueous chlorine
initial concentration of 100 µM, the half-life of HOI is 2.28min at pH 9 and 9.51min at pH 6.5. This is due to OCl- being more reactive with HOI than HOCl.

Since iodate formation from the degradation of iopamidol does not mimic iodate formation due to iodide oxidation in the presence of aqueous chlorine, the reaction mechanism responsible for the formation of iodide containing oxidants probably will not follow observed first or second order kinetics. It was confirmed that iodate formation does not adhere to either observed first or second order kinetics (Figures 4.4 and 4.5). Therefore, both chlorine species could be responsible for in the degradation of TOI. Hypochlorite ion appears to be responsible for the transformation of iopamidol to an iodide containing transformation product. However, hypochlorous acid maybe responsible for the oxidation/substitution of iodide moieties in that initial transformation product resulting in the formation of HOI. It is not known if the iodide is released from the ring and then oxidized to HOI or there is an active halogen transfer mechanism at the ring. Therefore, an iodide mass balance would be necessary as a function of pH order to determine how HOI occurs.
Figure 4.3. Iodate formation as a function of pH and time in reaction mixtures containing iopamidol and aqueous chlorine ([Cl]_T=100μM, [iopamidol]=5μM, [Buffer]=1mM, and temperature= 25°C)
Figure 4.4 Observed first order iodate formation ([Cl] = 100μM, [iopamidol] = 5μM, [Buffer] = 1mM, and temperature = 25°C)
Figure 4.5 Pseudo second order iodate formation ([Cl]₀=100μM, [iopamidol]=5μM, [Buffer]=1mM, and temperature= 25°C)
Iodide mass balance should reveal the predominant iodide valence as a function of
time. Iodide valence in iopamidol is (I-) and (V) in iodate. In Figures 4.6-4.9, iodate
becomes the dominate iodide containing species after 48 hours regardless of pH.
However, this does not convey any information about intermediate iodide containing
species. Therefore, both quenching methods were used to measure TOI: resorcinol and
sulfite. Since sulfite and ascorbic acid react with iodate (Rabai and Beck, 1987), neither
quenching agent could be used to measure iodate. However if hypoiodous acid
(HOI)forms, neither quench method would allow us to elucidate the formation of this
unstable iodide containing oxidant. Since iodide was not detected using resorcinol as a
quenching agent, it was assumed that if HOI formed that it incorporated into the activated
aromatic ring. Therefore, subtracting the difference between TOI concentrations
quenched with resorcinol, [TOI]_{res}, and the TOI concentrations quenched with sulfite,
[TOI]_{SO3}, would potentially yield the pseudo steady-state formation of HOI (Figures
4.10-4.11). In Figure 4.10, there does not seem to be a significant difference in TOI
concentrations as a function of time or quenching method. This is confirmed in Figure
4.11, which shows the proposed concentration of HOI being the difference between
[TOI]_{res} and [TOI]_{SO3}. Therefore, this could mean that the pseudo steady-state
concentration of HOI is low and constant regardless of pH. Or, it could mean that HOI is
in equilibrium with iopamidol transformation products substituting back into specific
moieties in residual organic material (equation 4.1).

\[
\text{HOI} + \text{IDOL TPs} \xrightarrow{\gamma} \text{IDOLTPs(-I)}
\] \hspace{1cm} 4.1

\[
\text{HOI} + \text{IDOL TPs} \xleftarrow{\gamma} \text{IDOLTPs(-I)}
\]
Figure 4.6 Mass balance between Iodate and Iodide at pH 6.5 ([Cl]₀=100μM, [iopamidol]=5μM, [Buffer]=1mM, and temperature= 25°C)
Figure 4.7 Mass balance between Iodate and Iodide at pH 7.5 ([Cl]₀=100μM, [iopamidol]=5μM, [Buffer]=1mM, and temperature= 25°C)
Figure 4.8 Mass balance between Iodate and Iodide at pH 8.5 ([Cl]$_T=100$μM, [iopamidol]=5μM, [Buffer]=1mM, and temperature= 25°C)
Figure 4.9 Mass balance between Iodate and Iodide at pH 9 ([Cl]_T=100μM, [iopamidol]=5μM, [Buffer]=1mM, and temperature= 25°C)
Figure 4.10 The observed loss of TOI as a function of pH and quenching method ([Cl] = 100μM, [iopamidol] = 5μM, [Buffer] = 1mM, and temperature = 25°C)
Figure 4.11 Proposed pseudo steady-state formation of an iodide containing oxidant (i.e., HOI). ([Cl]_T=100μM, [iopamidol]=5μM, [Buffer]=1mM, and temperature= 25°C)
Proposed iopamidol transformation pathway is presented in Figure 4.12. From preliminary investigations of high molecular weight reaction species, it appears that OCl\(^-\) may be initially attacking one of the amide side chains (Duirk et. al., 2011). This results in the formation of IDOL transformation product TP(I\(_3\)). Then it was proposed that Cl substitutes at one of the iodide positions releasing into the aqueous phase. The released iodide will then oxidized into HOI in the presence of excess aqueous chlorine and further transforms slowly into iodate in the absence of NOM. However, the detailed machanism is not known at this time. OCl\(^-\) is known to act as a nucleophile tetrahedral phosphorous and carbonyl functional groups (England et. al. 1980; Duirk et. al., 2009), which appears to be the case here. However, it is not known how iodide was removed from the ring and oxidized to iodate.

Figure 4.12. Proposed iopamidol transformation pathways.
In order to help elucidate the steps in the proposed pathway, the overstoichiometry for the transformation of TOI into iodate has been proposed below.

1. $\text{OCl}^- + \text{IDOL} (I_3) \rightarrow \text{TP1} (I_3) + \text{Products}$
2. $\text{HOCl} + \text{TP1} (I_3) \rightarrow \text{TP2} (\text{Cl}, I_2) + [\text{I}] + \text{Products}$
3. $\text{HOCl} + \text{TP2} (\text{Cl}, I_2) \rightarrow \text{TP3} (\text{Cl}_2, I) + [\text{I}] + \text{Products}$
4. $\text{HOCl} + \text{TP3} (\text{Cl}_2, I) \rightarrow \text{TP4} (\text{Cl}_3) + [\text{I}] + \text{Products}$

In steps 2-4, an iodide containing intermediate is proposed, $[\text{I}]$. If the overall stoichiometry for the transformation of three moles of TOI to three iodate results in the consumption of 10 moles of chlorine, then iodide would be released from iopamidol ring as HOI. If the overall stoichiometry for the transformation of three moles of TOI to three iodate results in the consumption of 13 moles of chlorine, then iodide would be released from iopamidol ring as $\Gamma$. However, other functional groups in iopamidol also exhibit reactivity with aqueous chlorine and residual chlorine concentrations were almost undetectable. Therefore, the transformation of iopamidol by aqueous chlorine appears to be a more complicated mechanism than the proposed pathway in Figure 4.12.

4.2 Transformation of other ICM in the presence of Aqueous Chlorine

Experiments were conducted to examine the reaction of other ICM (i.e., iomeprol, iopromide, iohexol and Na-diatrizoate) with aqueous chlorine. As with iopamidol, ICM transformation was monitored using TOI and iodate formation as surrogates for discrete analytical methods for the ICM. These ICM do not appear to degrade in presence of aqueous chlorine over the pH range of 6.5-8.5 (Figures 4.13-4.15). TOI concentration did
not change regardless of pH over 72 hours and no inorganic iodide containing species were detected.

Figure 4.13 TOI formation as a function of time at pH 6.5 in reaction mixtures containing iomeprol, iopromide, iohexol, diatrizoate and aqueous chlorine ([Cl$_2$]$_T$=100μM, [ICM]=5μM, [Buffer]=1mM, and temperature= 25°C)
Figure 4.14 TOI formation as a function of time at pH 7.5 in reaction mixtures containing iomeprol, iopromide, iohexol, diatrizoate and aqueous chlorine ([Cl$_2$]$_t$=100μM, [ICM]=5μM, [Buffer]=1mM, and temperature= 25°C)
Figure 4.15 TOI formation as a function of time at pH 8.5 in reaction mixtures containing iomeprol, iopromide, iohexol, diatrizoate and aqueous chlorine ([Cl$_2$]$_T$=100μM, [ICM]=5μM, [Buffer]=1mM, and temperature= 25°C)
4.3 Iopamidol Transformation in the Presence of Monochloramine

The loss of iopamidol was investigated in the presence of monochloramine over the pH range of 6.5-9.0. Reaction conditions were similar to those in for the chlorination ICM experiments; however, TOI was found not to significantly degrade over seven days (Figure 4.16). This does not mean that monochloramine is not reactive with iopamidol. Duirk et al., (2011) has shown that iodo-DBPs do form when monochloramine is added to aqueous solutions containing iopamidol and NOM. Bichsel and von Gunten, (1999) have shown that in the absence of other reactants, HOI is very stable in the presence of monochloramine and does not result in iodate formation. Therefore, quenching this reaction with sulfite should yield iodide (I−) from the oxidation of sulfite to sulfate and the reduction of HOI to I−. Figure 4.17 shows measured iodide concentrations well above the limit of quantification. TOI analysis has a standard error of approximately 1 µM, which would explain the slight variation in TOI concentration. Iodide/HOI appears to be in pseudo steady-state concentration with monochloramine and iopamidol since HOCl/OCl− are only available due to monochloramine hydrolysis/auto decomposition.
Figure 4.16 TOI formation as a function of pH and time in reaction mixtures containing iopamidol and monochloramine ([NH₂Cl]=100μM, [iopamidol]=5μM, [Buffer]=1mM, and temperature= 25°C. SO₃⁻ quench)
Figure 4.17. Iodide formation as a function of pH and time in reaction mixtures containing iopamidol and monochloramine ([NH₂Cl] = 100μM, [iopamidol] = 5μM, [Buffer] = 1mM, and temperature = 25°C. SO₃⁻ quench)
5.1 Summary

The overall objective of this research was to investigate the transformation pathways of ICM with chlorinated oxidants in the absence of NOM. The first objective of this study was to evaluate the reaction mechanism of iopamidol with aqueous chlorine. Therefore, experiments were carried out in reactors containing aqueous chlorine and iopamidol simulating the drinking water treatment conditions in the absence of NOM. The pH was varied over the range of 6.5 to 9 and reaction time was monitored over 0h to 72h. Transformation of iopamidol was monitored as the loss of total organic iodide (TOI) and the formation of iodate. The second objective was to assess the reactivity of other ICM (i.e. iomeprol, iopromide, iohexol, Na-diatrizoate) in presence of aqueous chlorine in the absence of NOM. The final objective was to determine the reactivity of iopamidol with monochloramine in the absence of NOM over the pH range was 6.5-9 and for 7.

The following conclusions can be drawn from overall analysis:

- The observed loss in TOI concentration appears to be the greatest at pH 7.5, least at pH 6.5, and approximately the same for pH 8.5 and 9 for the reaction of iopamidol with aqueous chlorine.
• The observed first-order loss of TOI confirms that the greatest observed loss of TOI occurs at pH 7.5, and the TOI loss can be assumed to be first-order in the presence of excess aqueous chlorine over the pH range of 7.5-9. However, the biphasic observed behavior at pH 6.5 indicates that both chlorine species participate in the degradation of TOI.

• Iodate formation appeared to be fastest at pH 7.5, lowest at pH 6.5, and approximately the same at pH 8.5 and 9.

• As with iopamidol, other ICM transformation in presence of excess chlorine was monitored using TOI and iodate formation as surrogates. These ICM do not appear to degrade in presence of aqueous chlorine over the pH range of 6.5-8.5. TOI concentration did not change regardless of pH over 72 hours and no inorganic iodide containing species were detected.

• Monochloramine experiments with iopamidol were conducted under the same conditions as chlorination and no iodate formation was observed; however, TOI was found not to significantly degrade over seven days. This shows agreement with the previous works which have shown that in the absence of other reactants, HOI is very stable in the presence of monochloramine and does not result in iodate formation.
5.2 Recommendations

In this study, iopamidol reaction mechanisms with chlorinated oxidants over varied pH range were investigated. Since, there has been a little research conducted on this topic, various scope of future work can be recommended. These may include:

- Investigating the ICM as precursors to TOX formation in the presence of chlorinated oxidants and NOM.
- Evaluating transformation pathway of other ICM reacting with aqueous monochloramine.
- Conducting a comparative study between the organic and inorganic iodide containing precursors of TOX formation under the same experimental condition.
- Performing comprehensive kinetic studies with ICM and aqueous chlorine/monochloramine to determine reaction rate coefficients for the degradation of ICM in the presence of chlorinated oxidants.
- Identifying ICM transformation products to elucidate transformation pathways.
- Comparatively study between the difference between ICM and inorganic iodide precursors in the formation and the distribution of iodo-DBPs.
REFERENCES


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