Aqueous oxidation of acetaminophen with monochloramine

O. Abou Mehrez, F. Masri, M. Baroudi and F. Dossier-Berne

ABSTRACT

The reactivity of the common pain reliever acetaminophen (paracetamol or 4-acetamidophenol) with monochloramine in aqueous solution was investigated in this study. Initially, monochloramine demands of acetaminophen (AAP) and its chlorination byproduct, 1,4-benzoquinone, were determined in excess of oxidant at pH 8.5 and 25 °C. Monochloramine demands of AAP and 1,4-benzoquinone were respectively 1.2 ($\pm$0.2) and 4.4 ($\pm$0.3) mol/mol after 72 h of reaction. Chlorination reactions were also conducted under the same experimental conditions in order to compare the oxidant demands and the reactivity of free chlorine and monochloramine toward AAP and 1,4-benzoquinone. Chlorine demands of AAP and 1,4-benzoquinone were much more important than monochloramine demands and respectively accounted for 13.4 ($\pm$0.2) and 6.8 ($\pm$0.5) mol/mol. The reaction of AAP with monochloramine was monitored using reversed-phase high performance liquid chromatography with ultraviolet absorbance (HPLC-UV). AAP reacted with monochloramine to form simultaneously two first byproducts. The half-life of reaction was estimated to be 90 min. The apparent second-order rate constant (k_{app2}) for the reaction of AAP with monochloramine at pH 8.5 was 231 $M^{-1} \cdot h^{-1}$.

Key words | 1,4-benzoquinone, acetaminophen, chlorine, monochloramine, oxidant demands, second-order rate

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INTRODUCTION

In recent years, the occurrence and fate of emerging pollutants in aquatic environments and their detection in drinking water sources has become a worldwide concern (Caracciolo *et al.* 2015). Among the major categories of emerging pollutants are pharmaceuticals and illicit drugs (Fram & Belitz 2011). Research on these compounds has revealed their increasing occurrence in environmental samples as well as their adverse effects on organisms. Unfortunately, pharmaceutical active compounds cannot be entirely removed during conventional wastewater treatment processes. Therefore, they have been detected with their transformation products in natural waters (Acero *et al.* 2015).

Acetaminophen (AAP), also known as paracetamol or 4-acetamidophenol, is a common analgesic pharmaceutical used for fever, headaches and other minor pain. As a high-consumption drug in the world, AAP has been widely detected in natural waters and wastewaters. It has been reported that the concentration levels of AAP in the aquatic environment and drinking water are typically in the nanogram to microgram per litre range (Petrie *et al.* 2016). Even when its concentrations are low in water, AAP may react during water disinfection processes (Xagoraraki *et al.* 2008; Postigo & Richardson 2014).

It is well known that disinfection by chlorination is an essential step for disinfecting wastewater and drinking water (Ma *et al.* 2015). However, in the presence of natural organic matter, chlorine forms undesirable disinfection byproducts (DBPs). Kosaka *et al.* (2017) have found that

halobenzoquinones are DBPs formed after water chlorination containing *para*-substituted phenolic compounds. In previous studies, it was shown that compounds with significantly high toxicity and mutagenicity were generated from chlorination of emerging pollutants (El Najjar *et al.* 2013). Particularly, the reactivity of AAP with chlorine leads to the formation of DBPs and may greatly threaten the safety of drinking water (Cao *et al.* 2016). Bedner & MacCrehan (2006) reported that during chlorination of AAP, 11 different chlorination products were observed, including the toxic quinoidal oxidation products N-acetyl-p-benzoquinone imine (NAPQI) and 1,4-benzoquinone; 1,4-benzoquinone has accounted for 25% of initial AAP at 1 h chlorination time. Chlorinated products were also formed such as chloro-4-acetamidophenol and dichloro-4-acetamidophenol.

As a secondary drinking water disinfectant, monochloramine has been used to maintain a residual of biocide in water distribution systems. It is produced by the reaction of hypochlorous acid with ammonia and is quantitatively formed at ammonia-to-chlorine ratio (N/Cl) higher than 1 mol/mol at pH $\approx$ 8. While monochloramine is less reactive with organic matter than free chlorine, it is inherently unstable at neutral pH even in the absence of reactive substances. These reactions are often referred to as 'autodecomposition' of monochloramine in water (Vikesland *et al.* 2001).

Disinfection with monochloramine is often used to reduce the production of DBPs such as trihalomethanes and haloacetic acids as compared with chlorination. Although monochloramination significantly reduces these DBP levels, the formation of other byproducts such as haloacetonitriles, haloacetamides and N-nitrosamines in the presence of nitrogenous contaminants have been reported (Ge *et al.* 2014; Nihemaiti *et al.* 2017). Recently, Yan *et al.* (2018) have shown that there is the same strong correlation between decreased aromaticity of dissolved organic matter and oxidant consumption during chlorination and monochloramination of water. A unique correlation between decreased aromaticity of dissolved organic matter and dihaloacetic acid formation was also demonstrated with both disinfectants. These authors nevertheless observed a lower oxidant demand and a lower formation of dihaloacetic acids by monochloramination than by chlorination. Wan *et al.* (2013) reported that chloramination of tetracycline

antibiotics generated at least 13 discernible products. Several studies have investigated monochloramine reactivity on hydroxybenzenes such as phenol, resorcinol and aminophenol and the formation of transformation byproducts (Heasley *et al.* 2004; Cimetière *et al.* 2009; Abou Mehrez *et al.* 2016).

In this paper, the reaction of AAP with monochloramine in aqueous solution is studied. Experiments were conducted in excess of oxidant, at pH 8.5 and 25 °C. Monochloramine and chlorine demands of AAP and its chlorination byproduct 1,4-benzoquinone were determined after 72 h of reaction time under similar experimental conditions. Reactivity of AAP and 1,4-benzoquinone toward monochloramine and free chlorine was examined. The monochloramination reaction of AAP was monitored using reversed-phase high performance liquid chromatography with ultraviolet absorbance (HPLC-UV). HPLC analysis allowed the quantification of residual AAP and the detection of first byproducts formed over the reaction time. The chlorination kinetic of AAP in water has been investigated by Soufan (2011) and Pinkston & Sedlak (2004). However, the kinetic reaction of AAP with monochloramine has not been studied before. Therefore, this work presents a study for the monochloramination kinetic of AAP in aqueous solution and the apparent second-order rate constant was determined at pH 8.5.

EXPERIMENTAL SECTION

Preparation of solutions

AAP and 1,4-benzoquinone were purchased from Sigma-Aldrich, with a purity $\geq$98%. Solutions of these compounds were prepared daily in pure water and traces of methanol (<2% volume fraction) at 100 mM. Chlorine solution was prepared by diluting a commercial solution of sodium hypochlorite (NaOCl, 0.1 N, BDH) stored in the dark at 4 °C.

Monochloramine solutions were prepared at different concentration levels by slowly adding free chlorine into an ammonium chloride water solution in a well-stirred reactor. A molar ammonia-to-chlorine ratio (N/Cl) of 2:1 was used. The pH of the monochloramine solution was adjusted to 8.5 ($\pm$0.1) with 20 mM of carbonate buffer. At these conditions, the stability of the monochloramine solution was enhanced.

## Experimental procedures and analysis

For the chlorination and monochloramination experiments, the temperature was kept constant at 25 °C in all cases, and the pH was 8.5 ($\pm$0.1). In order to determine the oxidant demands, each experiment was realized in triplicates and conducted in a batch reactor, in excess of oxidant with respect to AAP and 1,4-benzoquinone. The molar ratio of oxidant to organic compound was 20:1. Blank solutions of oxidant were realized to evaluate oxidant auto-decomposition over the reaction time. Solutions were kept for 72 h to determine the oxidant demands. Initial and total residual chlorine and monochloramine concentrations were determined by iodometric titration with aqueous sodium thiosulphate (0.01 N).

Regarding the monochloramination kinetics, samples were taken at various reaction times for the analysis of monochloramine residual. Then, the excess oxidant was reduced by adding a microvolume of sodium thiosulphate solution (0.1 N), and 2 mL of the sample were transferred to chromatographic vials respectively for HPLC-UV analysis. HPLC analysis for AAP and its oxidation products was carried out on an Agilent Technologies 1200 series coupled to a variable wavelength detector G1314D using a Discovery column HS C18 (25 cm × 4.6 mm, 5 μm diameter particles). The injected volume was 50 μL. The mobile phase (flow rate 0.3 mL·min^{-1}) was composed of two eluents in a gradient mode: pure water acidified with 0.1% of formic acid and pure methanol (HPLC grade, purity $\geq$99.9%).

RESULTS AND DISCUSSION

Oxidant demand

Figure 1 shows the oxidant demands of AAP and 1,4-benzoquinone calculated by deducting the oxidant consumption in blank solution from the oxidant consumption in sample solutions after 72 h. The oxidant consumption in blank solution after 72 h was negligible for chlorine and 0.06 mM (3% of the initial concentration) for monochloramine. These demands are expressed in units of moles of oxidant per moles of initial organic compound. Consumption of
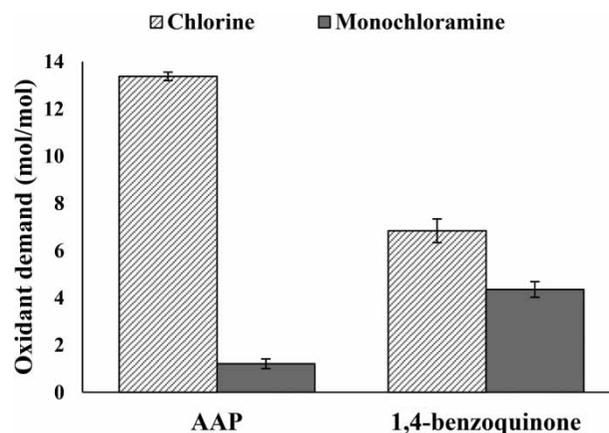
Figure 1 | Chlorine and monochloramine demands of AAP and 1,4-benzoquinone. [Oxidant]$_0$ = 2 mM; [AAP]$_0$ = 100 μM; [1,4-benzoquinone]$_0$ = 100 μM; pH 8.5 $\pm$ 0.1; reaction time = 72 h; 25 °C.

oxidants was due to the initial attack of oxidant on AAP and 1,4-benzoquinone as well as on their oxidation byproducts.

AAP chlorine consumption was nearly 11-fold higher than its monochloramine consumption. Chlorine and monochloramine demands of AAP were respectively 13.4 ($\pm$0.2) and 1.2 ($\pm$0.2) mol/mol. The significant lowest monochloramine demand of AAP confirms that monochloramine is a weaker oxidant than free chlorine. Results also allow suggesting the formation of less reactive byproducts during monochloramination than chlorination in aqueous solution. Bedner & MacCrehan (2006) and Cao *et al.* (2016) found that AAP exhibited significant reactivity with chlorine and its oxidation produced quinoidal products, such as NAPQI and 1,4-benzoquinone. Another chlorination pathway led to the formation of chlorinated 4-acetamidophenol products. Therefore, the formation of reactive chlorine-transformation byproducts explained the high chlorination demand of AAP observed in this study.

Regarding the chlorine consumption of 1,4-benzoquinone, chlorine demand was less important than AAP and reached 6.8 ($\pm$0.5) mol/mol. However, the monochloramine demand of 1,4-benzoquinone, 4.4 ($\pm$0.3) mol/mol, was observed to be higher than AAP. Different reaction pathways between the chlorination and monochloramination of AAP could explain the low monochloramine demand of AAP compared with 1,4-benzoquinone. The monochloramination of AAP was supposed not to produce 1,4-benzoquinone under these experimental conditions.
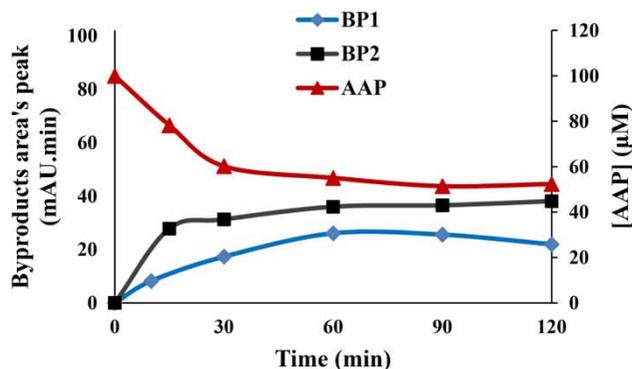
Compared with 4-aminophenol obtained by the amide hydrolysis of AAP, AAP consumed less chlorine and monochloramine after 72 h at pH 8.5. Chlorine and monochloramine demands of 4-aminophenol were respectively found to be 14.9 ($\pm$0.9) and 7 ($\pm$0.2) mol/mol (Abou Mehrez *et al.* 2015a). Monochloramine demands were found in several studies to be more important with substituted phenols (resorcinol, aminophenols) than unsubstituted phenol (Cimetière 2009; Abou Mehrez *et al.* 2015a). In contrast to that, AAP has a lower monochloramine demand than unsubstituted phenol (3.3 mol/mol). Indeed, the amide and hydroxyl groups of the AAP aromatic ring at the *para* position give it a low reactivity with monochloramine.

Monochloramination of AAP

Under the experimental conditions used, the degradation of AAP during monochloramination occurred simultaneously with the formation of two first byproducts BP1 and BP2 (Figure 2). Quantification of residual AAP was performed on HPLC-UV. The absence of 1,4-benzoquinone formation during the monochloramination of AAP was confirmed due to a commercial standard.

The half-life of the reaction was graphically estimated to be 90 min under these conditions. Further study for the identification of BP1 and BP2 will be investigated. In this paper, the kinetic of monochloramine with AAP was studied.

A pseudo-first-order kinetic approach was used to describe the degradation kinetics of different organic compounds with monochloramine (Cimetière *et al.* 2009; Abou Mehrez *et al.* 2015b; Lane *et al.* 2015). Therefore, the apparent second-order rate constant (k_{app2}) for the monochloramination of AAP at pH 8.5 has been determined under pseudo-first-order conditions. In this approach, the oxidant was at least present in ten-fold excess with respect to AAP, such that its concentration was nearly constant. Particularly, the monochloramination rate of AAP can be expressed as

$$-\frac{d[AAP]_t}{dt} = k_{app2} [NH_2Cl] \cdot [AAP]_t \qquad (1)$$

where $[AAP]_t$ is the total concentration of AAP.

As monochloramine concentration was considered constant throughout the experiments, Equation (1) can be simplified to

$$-\frac{d[AAP]_t}{dt} = k_{app1} [AAP]_t \qquad (2)$$

where k_{app1} is the pseudo-first-order rate constant, $k_{app1} = k_{app2} [NH_2Cl]_0$ and $[NH_2Cl]_0$ is the initial concentration of monochloramine.

It is possible to determine k_{aap1} experimentally by acquiring concentrations of AAP versus time, and regressing the data as:
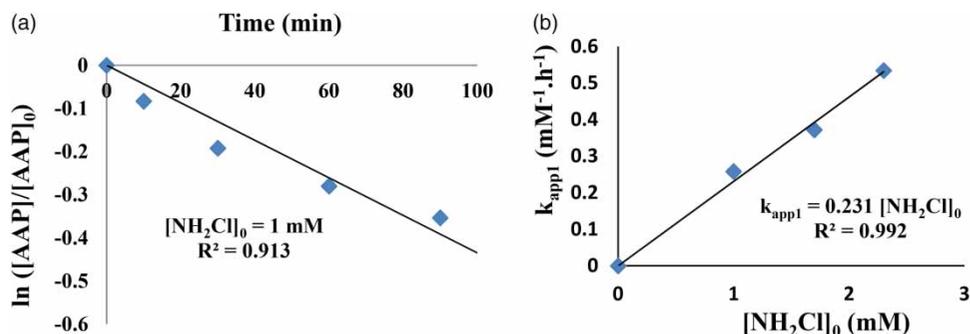
$$\frac{\ln[AAP]_t}{\ln[AAP]_0} = -k_{app1} \cdot dt \qquad (3)$$

where $[AAP]_0$ is the initial concentration of AAP.

For each experiment, k_{app1} was determined from the slope of the linear time-course plot of $\ln([AAP]_t/[AAP]_0)$.

The pseudo-first-order kinetic constant was found to be directly proportional to the monochloramine concentration. The apparent second-order rate constant for the monochloramination of AAP at pH 8.5 was 231 $M^{-1} \cdot h^{-1}$ (Figure 3(b)). This rate constant was much lower than the chlorination apparent second-order rate of AAP (4.8×10^4 $M^{-1} \cdot h^{-1}$) reported by Soufan (2011) at pH 7.

In comparison with other phenolic compounds, monochloramination k_{app2} of AAP was lower than that observed with resorcinol (320 $M^{-1} \cdot h^{-1}$) and 3-aminophenol (715 $M^{-1} \cdot h^{-1}$) at pH 8.6 (Cimetière 2009; Abou Mehrez *et al.* 2015b).

Figure 2 | Degradation of AAP during monochloramination and the area's peak evolution of first byproducts BP1 and BP2. $[NH_2Cl]_0 = 2.3$ mM; $[AAP]_0 = 100$ μM; pH 8.5 $\pm$ 0.1; 25 °C.

Figure 3 | Monochloramination of AAP: (a) determination of the pseudo-first-order rate constant for $[NH_2Cl]_0 = 1$ mM; (b) determination of the apparent second-order rate constant at pH 8.5.

CONCLUSIONS

The aqueous monochloramination of AAP was studied in a batch reactor where oxidant was in excess. Monochloramine solutions were prepared under conditions that minimize free chlorine reactions (molar N/Cl of 2:1 and pH 8.5). The results showed that monochloramine demands of AAP and its chlorination byproduct, 1,4-benzoquinone, were respectively 1.2 ($\pm$0.2) and 4.4 ($\pm$0.3) mol/mol after 72 h of reaction at 25 °C. Under the same experimental conditions, chlorine demands of AAP and 1,4-benzoquinone were determined in order to compare the reactivity of chlorine and monochloramine toward these compounds. The chlorine demands of AAP and 1,4-benzoquinone were respectively 13.4 ($\pm$0.2) and 6.8 ($\pm$0.5) mol/mol after 72 h of reaction. Results obtained have shown less reactivity of AAP and 1,4-benzoquinone with monochloramine than chlorine. In particular, AAP exhibited 91% more chlorine consumption than monochloramine. HPLC analysis was performed to follow the degradation of AAP throughout the monochloramination experiment. The half-life of reaction was estimated to be 90 min and two unknown first monochloramination byproducts were observed. No formation of 1,4-benzoquinone was observed during the monochloramination of AAP under the experimental conditions used. The kinetic study has shown that the reaction of AAP with monochloramine had a second-order rate, first order with respect to monochloramine and AAP. The apparent second-order rate constant (k_{app2}) for the monochloramination of AAP at pH 8.5 was 231 $M^{-1}\cdot h^{-1}$. This rate constant is very much lower than that observed during AAP chlorination at pH 7.

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