The Mechanisms, Products, and Kinetics of Triclosan-Free Chlorine Reactions

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(ABSTRACT)

The kinetics, products, and reaction pathways of triclosan/free chlorine reactions were investigated for the pH range 3.5-11. Although pH dependent speciation occurs in both triclosan and free chlorine, only the reaction between HOCl and the phenolate-triclosan was found to play a significant role in the kinetics. The second order rate constant for the reaction between phenolate-triclosan and HOCl was found to be 5.40 ($\pm$1.82) $\times$ 10^3 $M^{-1}s^{-1}$. Three chlorinated triclosan intermediates were tentatively identified based on mass spectral analysis. Additionally, 2,4-dichlorophenol, 2,4,6-trichlorophenol, and chloroform formed under excess free chlorine conditions. The majority of the chloroform formed during the reactions does not form via 2,4-dichlorophenol and 2,4,6-trichlorophenol oxidation. Therefore, the majority of chloroform is likely formed via the oxidation of triclosan's phenolic ring. Based on the identified products, a reaction pathway was proposed for the oxidation of triclosan in the presence of free chlorine.

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Introduction

Triclosan, (5-chloro-2-(2,4 dichlorophenoxy)phenol; Figure 1) is the most commonly used antimicrobial agent today. Antimicrobial products such as toothpastes, acne creams, deodorants, and hand soaps often contain between 0.3% and 3% triclosan. Although introduced over thirty years ago, the application of triclosan has increased dramatically over the last ten years. Currently, it is incorporated into kitchen tiles, children's toys, cutting boards, toothbrush handles, bowling ball finger inserts, and athletic clothing, among other things. Nearly 700 triclosan-containing products entered the American market between 1992 and 1999 [1].
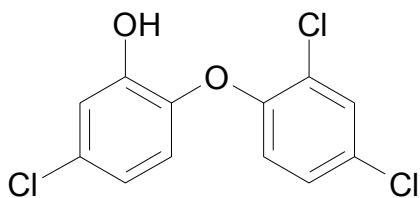
Figure 1: Triclosan

Triclosan is used in many products because it exhibits antibacterial as well as antifungal and antiviral properties [2]. Until recently, the compound was solely believed to act as a non-specific biocide that disrupts bacterial membrane functionality; with its effectiveness dependent on the lipid content of the cell membrane [3]. Since 1998, however, several studies have indicated that triclosan can act as a site-specific biocide. These studies, which examined the effects of triclosan on *e. coli* [4, 5], *mycobacterium smegmatic* [6], and *m. tuberculosis* [7] concluded that triclosan preferentially reacts with enoyl reductase, an enzyme essential to fatty acid synthesis. The site-specific activity of triclosan suggests that organisms may develop resistance, which would render the compound ineffective as a biocide. Advocates of triclosan argue that the high doses typically employed in antibacterial goods result in cell lysis from a number of effects [8]. Recent studies identify mechanisms of triclosan resistance [4, 5, 9]. In one study, mutant *e. coli* strains were able to survive in a 25% antibacterial-soap solution [10]. Some of the identified mechanisms are similar to those associated with antibiotic resistance [11], and consequentially there is concern that microbial exposure to triclosan could promote microbial resistance to antibiotics.

As a result of the widespread application of triclosan, large quantities of the compound are washed down household drains and enter sewage systems. Surveys have measured triclosan in the influent of wastewater treatment plants at concentrations ranging from 0.062 to 21.9 µg/L

[12-16]. Using measured wastewater treatment plant influent concentrations, Lindstrom estimated a gross average of triclosan usage in Switzerland of ~200 mg per persons per year [12].

Triclosan removal at wastewater treatment plants (WWTPs) varies with the type of secondary and tertiary treatment employed, with reported removal percentages between 0 and 100% [13-15, 17, 18]. Continuous activated sludge processes generally have consistently high, triclosan removal percentages of >90% [13, 15, 18], while attached growth processes have lower removal percentages and are less consistent [13]. A relatively high octanol-water coefficient (K_{ow}) of 4.8 [19] indicates the compound has a tendency to sorb to organic material and thus wasted sludge (biosolids) can contain up to 30% of the incoming triclosan [15, 17, 18]. Federle and co-workers [18] elucidated the fate of triclosan in an activated sludge process by monitoring the biodegradation of ^{14}C radiolabeled triclosan. They determined that triclosan degradation was much faster and more extensive in acclimated activated sludge reactors than in unacclimated reactors. Shock studies showed that sludge acclimated to 35 µg/L triclosan was not adversely affected by two, four-hour shock loads of 750 µg/L triclosan [18]. Consequently, relatively high levels of triclosan in wastewater should not adversely affect activated sludge treatment processes. Reported WWTP effluent triclosan concentrations range from 0.042 – 22.1 µg/L [16, 17, 20]. The incomplete removal of triclosan via wastewater treatment and the land-application of triclosan laden biosolids results in the continued release of triclosan into the aquatic environment.

In addition to residual concentrations of triclosan in wastewater treatment effluent and land-applied biosolids, triclosan can be introduced into the environment via stormwater drainage. Due to aging sewage infrastructures in some U.S. cities, raw sewage can contaminate stormwater canals [21]. Consequently, untreated sewage is released to surface waters. Boyd measured triclosan in 12 of 14 samples taken from New Orleans stormwater canals that drain into the Mississippi River and Lake Pontchartrain at a median concentration of ~15 ng/L.

Several recent studies have detected triclosan in natural waters and sediments. A study by the USGS surveyed 139 U.S. streams considered highly susceptible to contamination by numerous pharmaceuticals, hormones, and other organic contaminants [22], and in this study triclosan was detected in 57.6% of the streams at a median concentration of 0.14 µg/L and a maximum concentration of 2.3 µg/L. Recent reports suggest that triclosan is readily removed

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from natural waters via biodegradation, photolysis, and association with solid surfaces, and reported in-stream removal rates have been in the range of 0.21-0.33 h^{-1} for Mag Brook in England [16] and 0.06 h^{-1} in Cibolo Creek in Texas [23]. These rates, however, only account for the removal of triclosan from the aqueous phase and do not account for its association with sediments and suspended particles.

The fate of triclosan in the environment is highly dependent on its pH dependent speciation. The pK_a of triclosan is 7.9 [24] and thus when natural waters are alkaline, the anionic phenolate form predominates and when waters are acidic, the neutral phenolic form predominates. In surface waters, photodecomposition plays a major role in triclosan decay [12, 17, 25]. Because the phenolate form is more photodegradable ($t_{1/2}$ = 6 minutes) than the phenolic form ($t_{1/2}$ = 2.5 hrs), slightly alkaline waters favor photodecomposition of triclosan.

Because of its high octanol-water partition coefficient (K_{OW} = 4.8), triclosan has a tendency to adsorb to particulates and therefore readily settles in sediments. A depth profile of the triclosan concentration in Lake Griefensee sediment reflects 1) The increased usage of triclosan over the past forty years and 2) The upgrade of WWTPs in the catchment area with biological treatment around thirty years ago [17]. Triclosan was measured in the sediment of the Pawtuxet River in Rhode Island at several locations downstream of the discharge of a chemical plant [19]. Concentrations in the river sediment cores were as high as 100 ppm. The study found that the concentrations in the water and sediment decreased with increasing distance from the plant [19]. Triclosan has been measured in marine sediments near a wastewater treatment effluent at levels between 0.27 and 130.7 µg/kg where the effluent concentrations ranged from 0.4 to 22.1 µg/L [20].

Triclosan is ubiquitous in surface waters, especially those in which wastewater effluent is a constituent, and thus some source waters used for drinking water supply contain triclosan [26, 27]. Currently there are no federal regulations that necessitate periodic monitoring for the presence of PPCPs in drinking water and the FDA only requires testing for a particular PPCP if the concentration in surface waters and soils is expected to exceed 1 µg/L and 100 µg/kg, respectively [28]. However, some recent cases have reported the presence of small amounts of PPCPs, in general [26, 29, 30], and triclosan, in particular [31], in drinking water.

Water reuse, both planned and unplanned, is becoming an increasing part of the hydrologic cycle in both arid and temperate climates Under these circumstances, wastewater

effluent discharge often constitutes a substantial portion of a municipal drinking water treatment plant's influent supply. As water reuse becomes increasingly important, the potential to measure significant levels of PPCPs in source waters will increase. California, a state that is typically at the forefront of environmental regulations, is currently establishing monitoring programs for endocrine disrupting chemicals and pharmaceuticals in their indirect potable reuse program [28]. Although no adverse affects of drinking small amounts of PPCPs have been reported, the presence of anthropogenic chemicals in drinking water is undesirable. Collectively, concentrations of PPCPs could be much greater than 1 μg/L in source waters [32], and little research has been done on the combined toxicological and endocrine disrupting effects of these compounds on humans.

In general, there is less known about the fate of PPCPs in drinking water treatment than during wastewater treatment. Drinking water treatment plants rarely analyze for PPCPs and when they do, concentrations of the individual compounds are often lower than easily achieved analytical detection limits [28]. Water utilities do not generally focus on the removal of PPCPs. Few papers have examined how PPCPs react during drinking water treatment [28, 33, 34]. A complete understanding of the kinetics, mechanisms, and byproducts is necessary to address the impacts of these micropollutants on drinking water treatment.

Because there are thousands of PPCPs and few reports on their fate during drinking water treatment, predicting the behavior of a PPCP is often done by examining the behavior of similar compounds that have been reported in the literature. In general, antimicrobials are not effectively removed during coagulation/flocculation and thus for many treatment plants the removal of PPCPs occurs via interactions with the oxidants employed to disinfect the water.

The use of oxidizing chemicals (e.g., free chlorine, ozone, chlorine dioxide) to remove pesticides and other anthropogenic compounds is well established. Ozone, in particular, is especially effective at oxidizing organic compounds [28, 33, 34]. Although there is little research available on the reactions between chlorine dioxide and PPCPs, its high reactivity with pesticides and PAHs suggest that it would efficiently remove PPCPs [28]. Free chlorine is commonly used as a disinfectant and as an oxidant for reduced inorganic species during drinking water treatment. In general, however, free chlorine is not as strong of an oxidant as either ozone or chlorine dioxide [28] and thus chlorine may not oxidize micropollutants such as PPCPs to the same extent. Because triclosan is a phenol and an ether, reactions between compounds

containing these functional groups and free chlorine may offer some insight into the reactions of chlorine and triclosan.

There have been several studies examining the kinetics and products involved with the chlorination of phenols [35-44]. When phenolic compounds are halogenated, the -O$^-$/ -OH group activates substitution at the ortho and para positions. When it reacts with free chlorine, phenol is first chlorinated to form either 2-chlorophenol and 4-chlorophenol, these species are then further chlorinated to form 2,6-dichlorophenol or 2,4-dichlorophenol, which can then be further chlorinated to 2,4,6-trichlorophenol [42, 44]. Onodera has proposed that the para position of 2,4,6-trichlorophenol is first hydrolyzed and then oxidized with HOCl resulting in the intermediate 2,6-dichloro-p-BQ [40]. Further oxidation leads to chlorinated carboxylic acids [35, 37, 39] and trihalomethanes [41, 45].

Reaction rates between substituted phenols and free chlorine are accelerated by electron donating substituents like –CH$_3$, and the rates decrease with addition of electron withdrawing substituents like -Cl and -NO$_2$ [43]. Additionally, with electron withdrawing substituents, reactions rates are greater when the substituents are in the meta positions than when they are in the ortho or para positions. [42, 46]. The relative reactivity of ortho and para chlorinated phenols follow the general trend: phenol > 4-chlorophenol, 2-chlorophenol > 2,4-dichlorophenol, 2,6-dichlorophenol > 2,4,6-trichlorophenol [42].

At least two prior studies have examined the chlorination of triclosan [47, 48]. In both of these studies, the reactions between triclosan and free chlorine resulted in production of two monochlorinated triclosan intermediates and a dichlorinated triclosan intermediate. Onodera and co-workers also detected 2,4-dichlorophenol and 2,3,4-trichlorophenol. Unfortunately, the applicability of these studies to drinking water treatment conditions is unknown. Kanetoshi's study was performed in non-aqueous solvent at concentrations greatly exceeding those that would be encountered during drinking water treatment. Neither study examined the kinetics of the reactions and the prospect that triclosan could act as a precursor for trihalomethanes was not addressed. At this time there have been no comprehensive studies examining the reactions between free chlorine and triclosan.

The objective of this study is to explore the kinetics and products of triclosan-free chlorine reactions under conditions typical during drinking water treatment.

Materials and Methods

Reagent grade water was purified by deionization and distillation. Glassware was prepared by sequentially soaking it in a 10% nitric acid water bath and then in a concentrated chlorine bath. Triclosan was purchased from Aldrich (>98% purity) and was used without further purification. Stock triclosan solutions were prepared by dissolving 100 mg triclosan in 50 mL of reagent grade methanol. Stocks of free chlorine were prepared with a commercial solution of sodium hypochlorite (purified grade 4-6% NaOCl; Fisher Scientific). Chlorophenol standards, trihalomethane standards, and 1,2-dibromopropane were purchased from Chem Service (West Chester, PA). The pH measurements were obtained with a Fisher Scientific model 60 meter coupled with a Thermo-Orion Ross PerpHect Combination Electrode.

Preparation of Experimental Solutions

All reactions were performed using reagent grade water containing 2 mM sodium bicarbonate pH buffer (Na_2HCO_3). Kinetic experiments were conducted in 40 mL screw top amber vials containing 25 mL of free chlorine solution of known concentration. Initial free chlorine concentrations ranged from 2.72 to 25.0 µM (0.192 - 1.77 mg/L as Cl_2). Initial triclosan concentrations ranged from 2.5 to 27.6 µM. Chlorine concentrations were determined using a modified DPD photometric method [49].

Reactions were initiated by spiking an aliquot of 4000 mg/L triclosan stock into the reaction vial using a syringe equipped with a Cheney Adaptor. The vials were then shaken for several seconds. The final methanol concentration in the reaction vials never exceeded 0.2%. Control experiments indicate that this concentration of methanol does not exert a quantifiable free chlorine demand (Appendix Figure S1). After an allotted period of time, the free chlorine in the reaction vessel was quenched with 1.5 mL aliquots of N,N-dimethyl-p-phenylenediamine (DPD) indicator (4.19 mM) and 1.5 mL of phosphate buffer (0.507 M PO_4^{3-}). The vessel contents were well mixed and the indicator color was allowed to develop for one minute. Absorbance readings at 515 nm were then compared to a standard curve to determine the free chlorine concentrations. The rate coefficient for the DPD-free chlorine reaction (1.4 - 1.7 s^{-1} at pH 6.2; [50]) is considerably larger than those that determined for the chlorination of triclosan. Therefore, the addition of a significant excess of DPD relative to triclosan should effectively quench the triclosan-free chlorine reactions. The overall progress of the free chlorine-triclosan

reactions was determined by measuring both the free chlorine and/or the triclosan concentration as a function of time. Each measurement was obtained in triplicate.

Triclosan and Daughter-Product Analysis

Samples for the quantification of triclosan and its non-volatile daughter products were quenched with a 3× molar excess of sodium sulfite. This quenching agent was found to be unreactive towards the triclosan daughter products and was determined to have the same activity as ascorbic acid (Appendix Figure S2). The quenched samples were adjusted to pH 2 with 0.1 M HCl and solid phase extracted (SPE) with 3M Emport™ High Performance SDBS Extraction Cartridges. Prior to use, each cartridge was rinsed with 1 mL acetone and allowed to dry under vacuum. Pretreatment of the cartridges was carried out with sequential addition of 0.5 mL methanol and 1.0 mL reagent grade water; care was taken to avoid drying out the solid phase during pretreatment. A 20 mL aliquot was then drawn through the cartridge at a rate of 5 mL/min and samples were extracted with 1 mL acetone. Following solid phase extraction, the triclosan and daughter phenolic compounds were derivatized with pentafluorobenzyl bromide [51, 52]. 100 µL of 5% PFBBr in acetone and 100 µL 10% aqueous potassium carbonate (KCO_3) were spiked into the acetone eluates. The sample vials were crimp-sealed and set in a water bath at 80 ºC for 45 minutes. This reaction period was determined to be sufficient for the complete derivatization of triclosan and its daughter-products (Appendix Figure S3). After cooling, the samples were dried under nitrogen until ~ 0.1 mL remained, at that time 1.0 mL methylene chloride and 5 µL internal standard (~ 1040 mg/L 1,3,5-tribromobenzene) were injected into the sample vials which were then sealed.

GC-MS analysis of derivatized and underivatized triclosan and its daughter products was performed on an Agilent 6890/5973 system that contained a DB-5ms GC-column (Agilent Technologies, 30 m × 0.25 mm, film thickness = 0.25 µm). Helium served as the carrier gas with a column flow rate of 1.3 mL/min. After holding at an initial temperature of 70 ºC for 1.5 minutes, the temperature was ramped to 160 ºC at 20 ºC/min, followed by a second ramp at 8 ºC/min to 280 ºC. The temperature was held at 280 ºC for 1 minute prior to oven cool down. Pulsed splitless injection was employed with a pulse pressure of 206.8 kPa (1.1 min) and a 1.0-minute purge time delay. 1 µL of sample was injected. Samples were run in full scan mode (range *m/z* = 80 – 550). Derivatized triclosan was identified based on its elution time of 23.9 minutes and monitored with a molecular ion at *m/z* 468 and a fragment ion at *m/z* 252 (M^+ - Cl –

PFB). Derivatized chlorophenols were identified based on their elution times and major ions which were determined with purchased standards.

Trihalomethane Formation and Quantification

Experiments were performed to monitor the formation of trihalomethanes under headspace free conditions in 40 mL amber screw-top vials. Samples were analyzed for trihalomethanes after the chlorine was quenched with sodium sulfite. Trihalomethane analysis was performed according to USEPA Method 502.2 (USEPA 1995). Samples were purged in a Tekmar 2016 Purge and Trap Autosampler. The autosampler was attached to a Tekmar (Cincinnati, OH) 3000 Purge and Trap Concentrator equipped with a Supelco (Bellefonte, PA) VOCARB 300 Purge Trap K. A Tremetrics (Austin, TX) 9001 gas chromatograph with a Tracer (Austin, TX) 1000 Hall detector was employed. The GC was equipped with a J&W Scientific DB-624 column (30 m × 0.53 mm, film thickness = 3 µm). The carrier gas was nitrogen.

Prior to injection into the autosampler port, 5 mL trihalomethane samples were spiked with 10 µL of 10 mg/L 1,2-dibromopropane (internal standard) resulting in 20 µg/L 1,2-dibromopropane. Samples were purged for 7 minutes and then baked from the trap at 250º C for 10 minutes. The GC temperature program involved an initial temperature of 45º C held for three minutes. The temperature was then ramped to 200 ºC at 11ºC/min. Sample results were integrated by a Hewlett Packard Series II Integrator.

Results and Discussion

Experiments have demonstrated that triclosan and free chlorine readily react (Figure 2). When triclosan was absent, the loss of free chlorine was negligible, and when free chlorine was absent, triclosan was stable. To determine the rate coefficients for the reactions between triclosan and free chlorine, experiments were conducted in the presence of 10× excess triclosan. Under these conditions, a pseudo-first order approximation for the loss of free chlorine is appropriate. Pseudo-first-order rate coefficients (k_{obs}; s^{-1}) were determined at several pH values using the method of initial rates (Figure 3). These k_{obs} values are related to the overall apparent second-order rate coefficient (k_{app}; $M^{-1}s^{-1}$)

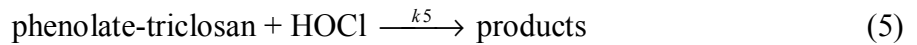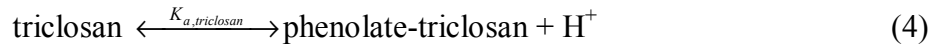$$\frac{d[\text{FC}]}{dt} = -k_{app}[\text{triclosan}]_{\text{T}}[\text{FC}]_{\text{T}} \tag{1}$$

by the following expression:

$$k_{obs} = k_{app} [\text{triclosan}]_{T, t=0} \tag{2}$$

where $[\text{triclosan}]_T$ represents the total concentration of triclosan and phenolate-triclosan, $[FC]_T$ is the total concentration of free chlorine (i.e., $[HOCl] + [OCl^-]$), and $[\text{triclosan}]_{T, t=0}$ is the initial excess triclosan concentration. Control experiments verified that first order dependencies for both free chlorine and triclosan are appropriate (data not shown).

Kinetic Model Development

Apparent second-order rate coefficients, k_{app} for several pH values were determined using Equation 2. These k_{app} values were then plotted versus the solution pH (Figure 4). As Figure 4 illustrates, the reactions between triclosan and free chlorine are pH dependent. Reaction rates increase with pH to pH 6.5 and then decrease as pH increases above pH 8. This pH dependence can be rationalized based on the acid-base speciation of both free chlorine and triclosan:

$$HOCl \xleftrightarrow{K_{Cl}} OCl^- + H^+ \tag{3}$$

$$\text{triclosan} \xleftrightarrow{K_{a,triclosan}} \text{phenolate-triclosan} + H^+ \tag{4}$$

$$\text{phenolate-triclosan} + HOCl \xrightarrow{k5} \text{products} \tag{5}$$

Based on this reaction mechanism, k_{app} has the following form:

$$k_{app} = \{k_5 \alpha_1\} \alpha_{Cl} \tag{6}$$

where α_1 is the ionization fraction of phenolate-triclosan and α_{Cl} is the ionization fraction for hypochlorous acid.

The collected k_{app} data was evaluated by fitting Eq. 6 to the experimental data using the curve-fitting function of SigmaPlot (SPSS Software; Figure 4). In addition to reactions 3-5 listed above, other potential pH dependent reactions were considered. Typically, the reactivity of OCl^- is negligible in comparison to HOCl, and based on alternate model fits, the reactions between OCl^- and triclosan and OCl^- and phenolate-triclosan were insignificant. Phenolic compounds, such as triclosan, are generally more reactive upon deprotonation. This effect occurs because O^- is better at activating the benzene ring toward substitution reactions than OH [53]. Gallard and von Gunten [41] included the reaction between HOCl and the neutral form of monosubstituted phenols in their kinetic models. Rebenne [53] determined that inclusion of this term was necessary for 4,6-dichlororesorcinol and orcinol, but not for resorcinol or 4-chlororesorcinol. Under our conditions, inclusion of a term involving HOCl and triclosan was unnecessary. Studies on the chlorination of phenols have also noted the presence of an acid catalyzed effect at low pH values and have included such terms in their reaction models [41, 42]. Although there

could be a slight catalytic effect of H^+ below pH 6, the potential formation of Cl_2 (as discussed below) at these low pH values causes the kinetic characterization to become difficult.

In the present study, the reaction between phenolate triclosan and HOCl was the only reaction found to significantly contribute to the observed reaction kinetics. The rate coefficient for this reaction is given in Table 1 along with parallel values for the chlorination of substituted phenols that have been presented in the literature.

Table 1: k_5 values of several substituted phenols

Phenolic Compound	pKa [ref.]	k_5 ($M^{-1}s^{-1}$)	Reference
Triclosan	7.9 [19]	5.40 ($\pm$1.82) $\times 10^3$	this study
Phenol	9.99 [54]	2.19 ($\pm$0.08) $\times 10^4$	[41]
4-chlorophenol	9.43 [54]	2.17 ($\pm$ 0.33) $\times 10^3$	[41]
2,4-dichlorophenol	7.85 [54]	3.03 ($\pm$ 0.09) $\times 10^2$	[42]
2,4,6-trichlorophenol	6.15 [54]	12.84 ($\pm$ 0.69)	[42]
resorcinol	9.43 [54]	1.36 ($\pm$ 0.26) $\times 10^6$	[53]
4,6-dichlororesorcinol	7.53 [53]	3.21 ($\pm$ 0.76) $\times 10^4$	[53]

As shown in Table 1, the k_5 rate coefficient for the reaction between HOCl and phenolate-triclosan is within the range of values obtained for other substituted phenols.

It has been previously suggested that the presence of Cl^- in solutions containing free chlorine and phenolic compounds may result in an increase in the apparent reaction rate at pH values below 6 [41, 42, 53]. When chloride is present, the equilibrium of the reaction between elemental chlorine and free chlorine shifts towards elemental chlorine:

$$H^+ + Cl^- + HOCl \leftrightarrow Cl_2 + H_2O \tag{7}$$
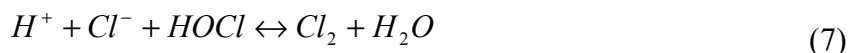
Elemental chlorine is generally considered a stronger oxidant than free chlorine, and its presence could result in faster reaction rates. To determine if the reaction rates at low pH were affected by the addition of HCl for pH adjustment, an additional set of experiments were conducted at pH 5 and pH 6 where the pH was adjusted with H_2SO_4 (Figure 4). Examination of Figure 4 shows that there is a significant difference in the measured rate coefficients when H_2SO_4 is used to lower the pH. This effect clearly indicates the rate enhancing effects of chloride addition.

Because the kinetics are complicated at low pH values by the presence of Cl$^-$ and the formation of Cl$_2$, only reaction rates above pH 6 were employed in the development of the model (equation 6; Table 1). When H$_2$SO$_4$ was used to adjust the pH (Figure 4) the experimental k_{app} values at pH 4 and pH 5 are closer to those predicted by the model than those from the HCl adjusted samples. The discrepancy at low pH between the k_{app} values measured with H$_2$SO$_4$ for pH adjustment and the model is a result of the ~4.5 μM chloride present in the solutions due to the chloride content of the stock sodium hypochlorite. Accordingly, it is believed that if there were no chloride present in the experiments conducted below pH 6, the reaction rate coefficients would more closely align with the model prediction.

Kinetic Model Verification

To evaluate the performance of the model given by equations 3-6, experiments were performed under excess free chlorine conditions at pH values of 4, 7, and 10. Figures 2, 5, and 6 illustrate the free chlorine and triclosan reaction kinetics for pH values of 7, 4, and 10, respectively. Model predictions, based on the previously determined rate coefficient (Table 1), of free chlorine and triclosan decay for these conditions are plotted for comparison. As shown in these figures, the model predictions for both triclosan and free chlorine at pH 4 (Figure 5) and pH 10 (Figure 6) correlate reasonably well with the experimental data. At pH 7 (Figure 2), however, the observed free chlorine demand greatly exceeds the predicted decay. Underprediction of free chlorine demand by the model at this pH is a result of the chlorine demand exerted by the rapidly forming intermediates

Product Identification

A GC chromatogram illustrating the peaks of intermediates and products detected in a chlorine excess experiment is shown in Figures 7a and 7b. Two mono-chlorinated triclosan intermediates have been identified based on mass spectral analysis (Figure 7a). Intermediates A and B had identical mass spectrums with the molecular ions at *m/z* 504 and fragment ions at *m/z* 288 (M$^+$ - PFB - Cl) and 181 (M$^+$ - C$_{12}$H$_5$Cl$_4$O$_2$) (Figure 7c). Based on results described in the literature [47], it is believed that the isomers are 5,6-dichloro-2-(2,4-dichlorophenoxy)phenol and 4,5-dichloro-2-(2,4-dichlorophenoxy)phenol) (Figure 7a). Additionally, a di-chlorinated intermediate, presumably 4,5,6-Trichloro-2-(2,4-dichlorophenoxy)phenol (Figure 7a), was identified based on its molecular ion at *m/z* 539 and a fragment ion at *m/z* 181 (M$^+$ - C$_{12}$H$_4$Cl$_5$O$_2$; Figure 7d). Analytical standards are unavailable for these compounds. The formation and decay

of these intermediates appears to be a strong function of pH (Figure 8, 9, 10). All three species form to the greatest extent at pH 7, with intermediates A and B forming and then decaying. This behavior suggests that these species are acting as true intermediates at pH 7. Conversely, within the timescale of the measurements, the concentration of intermediate C continues to rise (Figure 10). This behavior indicates that this compound is relatively stable and does not appear to act as a precursor to the chlorophenol products (discussed below).

2,4-dichlorophenol (Figure 7b) was detected in the free chlorine excess experiments. It was identified based on its elution time and its molecular ion at m/z 343 and fragment ion at m/z 181 (M^+ - $C_6H_3Cl_3O$; Figure 7e). Unlike the kinetics of triclosan decay and the formation of the chlorophenoxyphenol intermediates, wherein activity was greatest at circumneutral pH, 2,4-dichlorophenol accumulated fastest at pH 4 (Figure 11). The formation of 2,4-dichlorophenol is believed to occur via cleavage of the carbon-oxygen bond in triclosan.

2,4,6-trichlorophenol (Figure 7b) was detected based on its elution time as well as the molecular ion at m/z 376 and fragment ions (Figure 7f) at m/z 181 (M^+ - $C_6H_3Cl_3O$) and 252 (M^+ - PFB - Cl). The formation of 2,4,6-trichlorophenol appears to be pH dependent (Figure 12) and its formation is delayed relative to 2,4-dichlorophenol. To address if 2,4,6-trichlorophenol was forming via chlorination of 2,4-dichlorophenol, an experiment was performed where 2,4-dichlorophenol was reacted with an excess of free chlorine. Figure 13 illustrates the decay of 2,4-dichlorophenol and the formation of 2,4,6-trichlorophenol at pH 7. Based on these results and the fact that ethers react very slowly with free chlorine [42], it can be assumed that 2,4,6-trichlorophenol forms via chlorination of 2,4-dichlorophenol.

Reactions with a ten-fold excess of free chlorine were performed in order to test for the formation of chloroform. Figure 14 shows the formation of chloroform for reactions with pH values of 5, 6, 8, and 9. Chloroform formed fastest at neutral pH and formed slower under acidic or basic conditions. After reacting for 49 hours, 1.53 μM of chloroform had formed in the pH 8 reaction while the initial triclosan concentration was 2.5 μM. To determine if the chloroform was being produced from the 2,4-dichlorophenol intermediate, a reaction between 2,4-dichlorophenol and free chlorine was performed (Figure 15) with the same initial concentrations. The concentrations of chloroform formed during the 2,4-dichlorophenol/free chlorine reactions are an order of magnitude lower than the concentrations of chloroform formed during the triclosan/free chlorine reactions. Therefore, the majority of chloroform formed during the

triclosan/free chlorine reactions is not produced via oxidative breakdown of the 2,4-dichlorophenol intermediate.

Extension of Kinetic Model

To develop a more rigorous kinetic model for free chlorine loss, the inclusion of reactions between the intermediates and free chlorine should be considered. With this goal in mind, experiments were conducted to assess the effect that reactions between 2,4-dichlorophenol, produced as a reaction intermediate, and free chlorine have on the free chlorine loss kinetics. k_{obs} values were determined by monitoring the decay of free chlorine in the presence of 10× excess 2,4-dichlorophenol. The k_{app} values were then calculated from the relationship:

$$k_{app} = k_{obs}[2,4-dichlorophenol]_0$$

(8)

Figure 16 illustrates the experimental k_{app} values as a function of reaction pH. The k_{app} values measured in these experiments agree with previously reported k_{app} values for free chlorine reactions with 2,4-dichlorophenol (Figure 16;[41]). These reaction rates are an order of magnitude lower than those measured for the triclosan-free chlorine reactions. Therefore, the reaction of 2,4-dichlorophenol with free chlorine probably does not contribute greatly to the chlorine decay measured during the triclosan-free chlorine reactions.

Hypothesized Reaction Mechanism

Other than 2,4-dichlorophenol and 2,4,6-trichlorophenol, no additional dichlorophenols or trichlorophenols were detected in the reaction solutions. Based on the structures of the intermediates that have been tentatively identified and the observed formation of 2,4-dichlorophenol, it is plausible that 2,3-dichlorophenol, 3,4-dichlorophenol, and 2,3,4-trichlorophenol could form from triclosan's phenol ring (Figure 7). However, since none of these chlorophenols were detected it appears likely that 1) triclosan's phenol ring is cleaved either immediately before or after cleavage of the ether bond or 2) these chlorophenols react too quickly to be detected.

At the current time, little research has been done to examine the reaction rates of 2,3-dichlorophenol, 3,4-dichlorophenol, and 2,3,4-dichlorophenol with free chlorine. However, based on k_{obs} rates presented by Mary [46] it is possible to develop some insight into the potential reactivity of these compounds with free chlorine. From Mary's data it is apparent that 3,4-dichlorophenol reacts ~ 10× faster than 2,4-dichlorophenol under alkaline conditions (pH > 12). One would anticipate that similar reactivity trends would exist for 2,3-dichlorophenol since

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3,4-dichlorophenol has a meta and an ortho chlorine substituent and 3,4-dichlorophenol has a meta and a para chlorine substituent. It is difficult to assess what the relative reaction rate of 2,3,4-trichlorophenol would be. The addition of chlorine in the meta position slightly decreases the reaction rate from 4-chlorophenol to 3,4-dichlorophenol [46]. Based on this trend, a significant increase in the reaction rate from 2,4-dichlorophenol to 2,3,4-trichlorophenol would not be expected. If these assumptions are correct, 2,3,4-trichlorophenol should be detected if the ether cleavage of the dichlorinated triclosan intermediate results in 2,3,4-trichlorophenol (Figure 7).

A reaction pathway is proposed based on the intermediates and products that have been detected and monitored under excess free chlorine conditions (Figure 17). Triclosan is first chlorinated to form one of two chlorophenoxy-phenol intermediates (A and B). The two intermediates are further chlorinated to form a dichlorinated triclosan compound (C). Ether cleavage of the chlorophenoxyphenol results in 2,4-dichlorophenol from the 2,4-phenoxy ring. The 2,4-dichlorophenol is chlorinated to form 2,4,6-trichlorophenol which after ring cleavage results in endproducts including chloroform. The 2,3,4-trichlorophenol ring of triclosan probably cleaves immediately after ether cleavage. Otherwise, 2,3,4-trichlorophenol would be detected. Oxidation of the cleaved 2,3,4-trichlorophenol ring eventually leads to endproducts including chloroform. It is believed that the majority of the chloroform formed during the free chlorine-triclosan reactions results from the 2,3,4-trichlorophenol.

Engineering Significance of Results

The results presented above are relevant to the scientific community for the following reasons:

1. Reactions between triclosan and free chlorine are rapid at pH values typically encountered in drinking waters. Figure 14 demonstrates that chloroform can form when only 0.75 mg/L triclosan reacts with an excess of free chlorine. If 1 mL of a soap that was 2% triclosan was diluted to 5 L in a kitchen sink, the resulting triclosan concentration would be about 4 mg/L. Therefore, the potential exists for substantial amounts of chloroform to form during household use of triclosan.

2. The reactions between triclosan and free chlorine result in the production of 2,4-dichlorophenol. 2,4-dichlorophenol is a known source of taste and odor problems. In the

reactions where 2,4-dichlorophenol was monitored, concentrations were much higher than the average threshold odor concentration of 2 µg/L (~12 nM). Therefore, even if triclosan is mostly degraded at drinking water treatment plants, there still exists the possibility of taste and odor problems resulting from the reaction by-products.

3. Understanding the reaction between triclosan and chlorine is a small step to understanding how micropollutants react during drinking water treatment. Not only do we need to be assured that these compounds are adequately removed from source waters, but we also need to determine what is formed during the oxidation processes as there exists the possibility of forming other hazardous compounds.
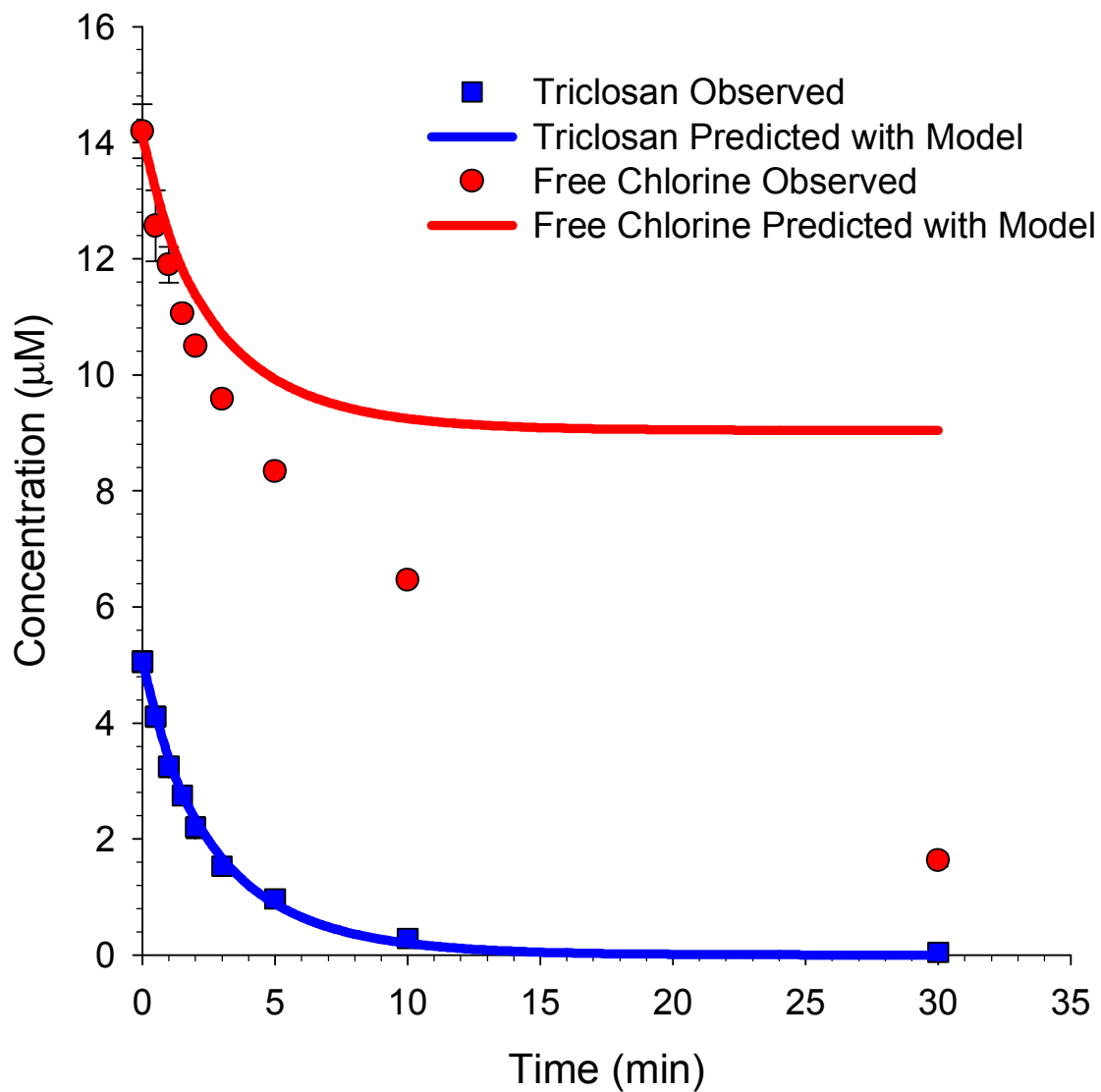
Figure 2: Triclosan and free chlorine decay. Reaction conditions: pH 7, [Triclosan]$_0$ = 5.05 μM; [Free Chlorine]$_0$ = 14.2 μM; [NaHCO$_3$] = 2 mM.

Figure 3: Free chlorine decay in the presence of 10 × excess triclosan. Reaction conditions: pH 5.5; [Triclosan]$_0$ = 27.5 μM; [Free Chlorine]$_0$ = 2.8 μM; [NaHCO$_3$] = 2 mM.
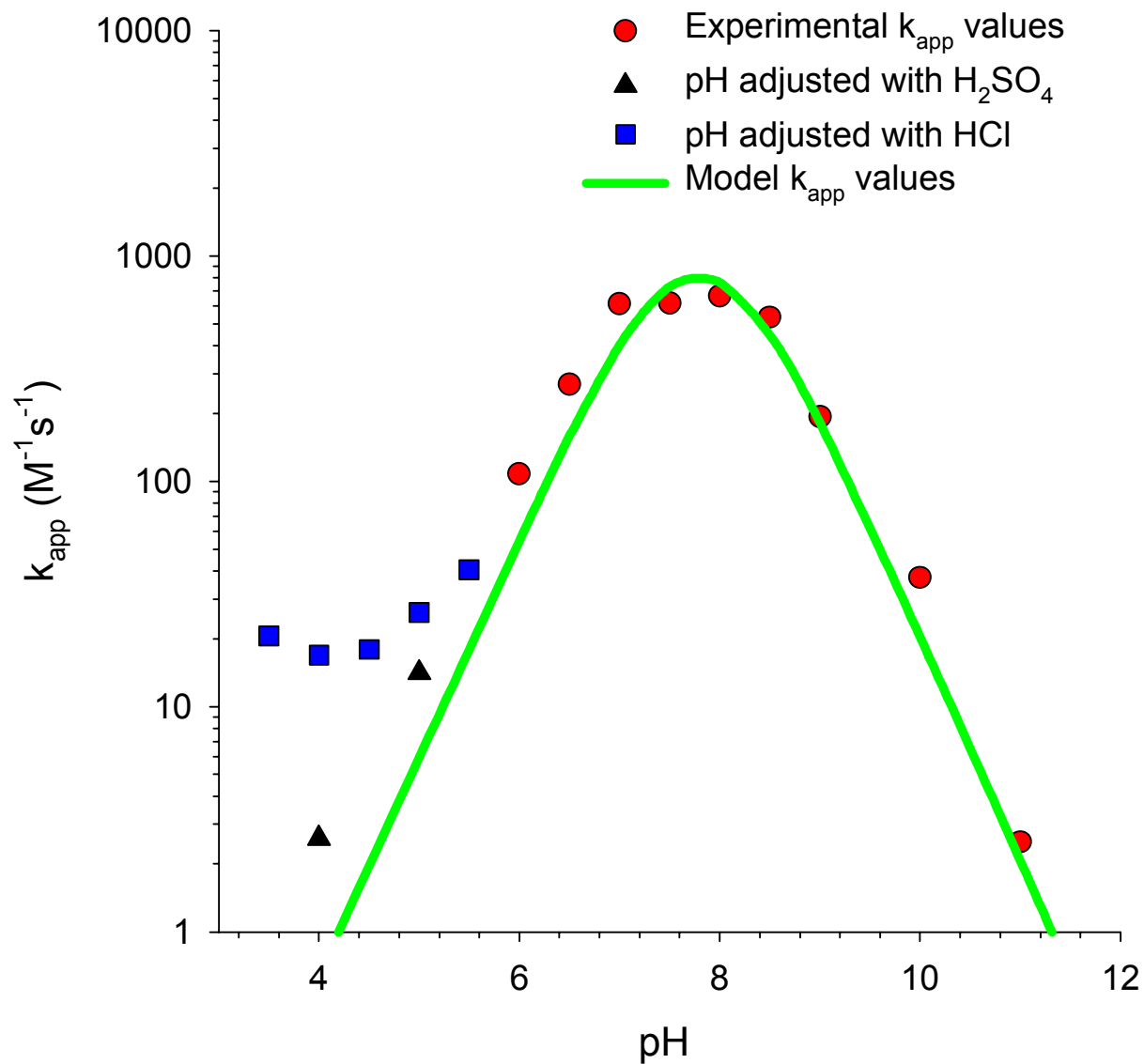
Figure 4: k_{app} **vs. pH. Reaction conditions: [Free Chlorine]$_0$ = 2.33 - 3.23 μM; [Triclosan]$_0$ = 27.5 μM; [NaHCO$_3$] = 2 mM.**
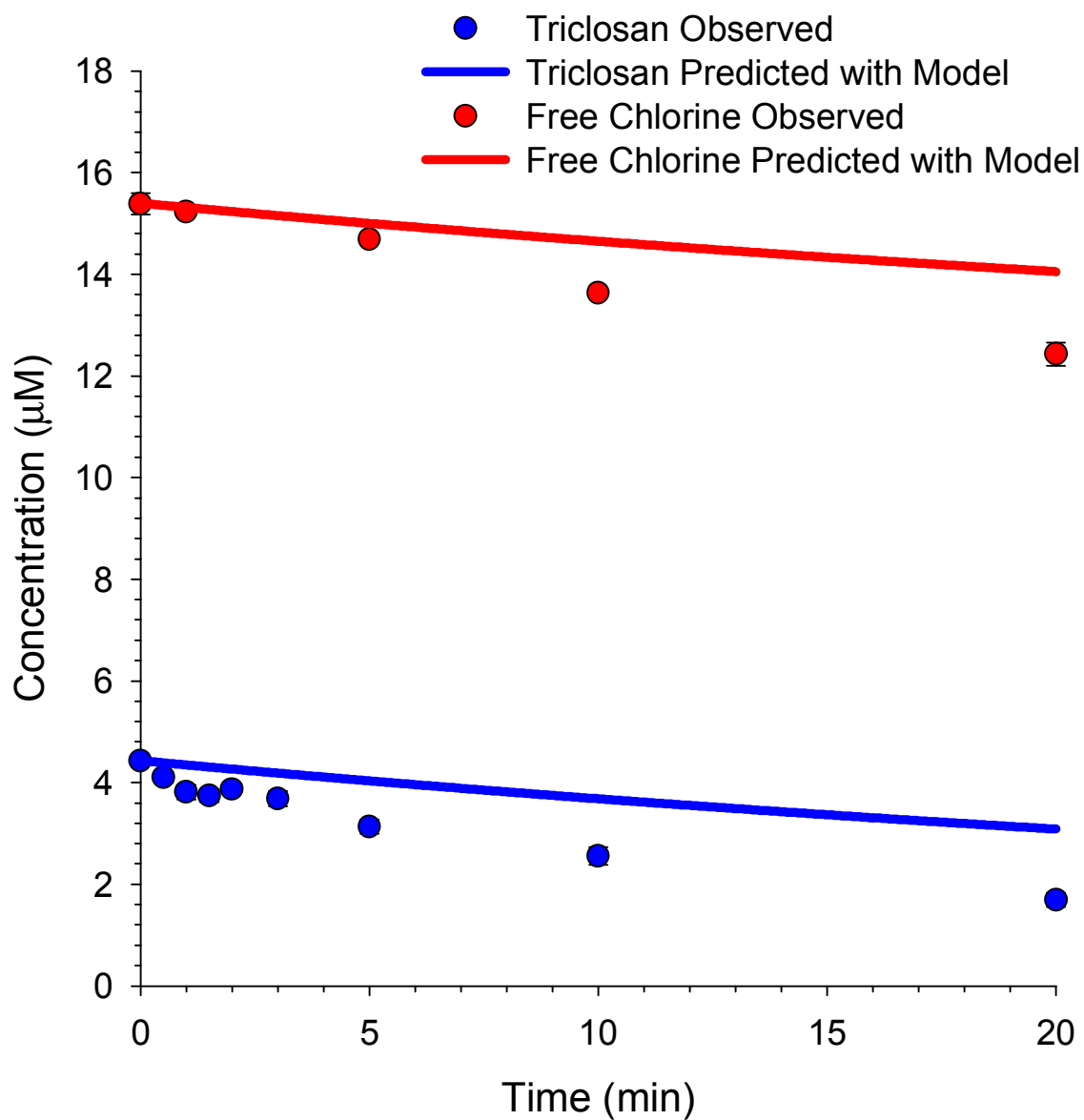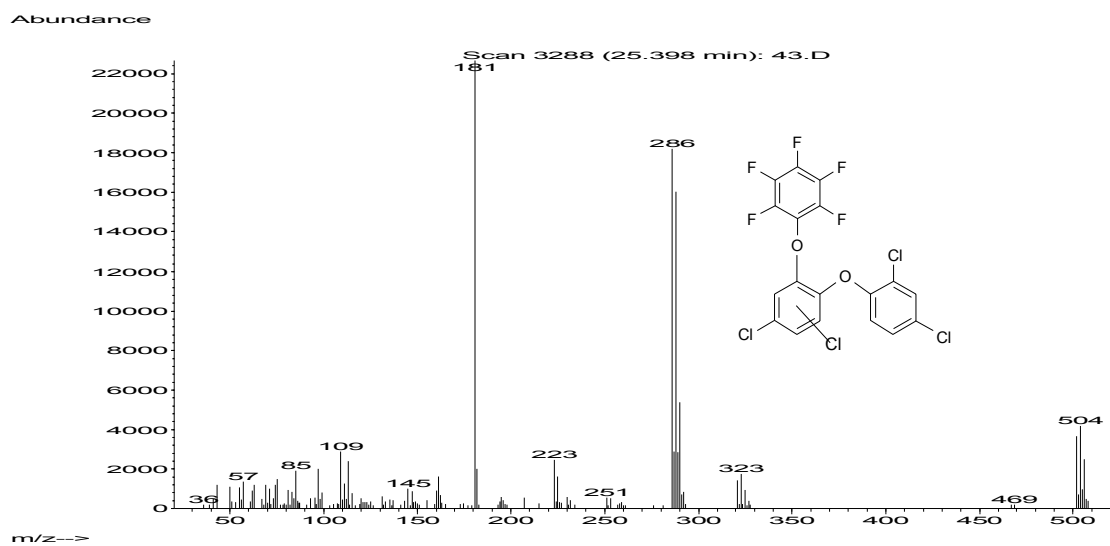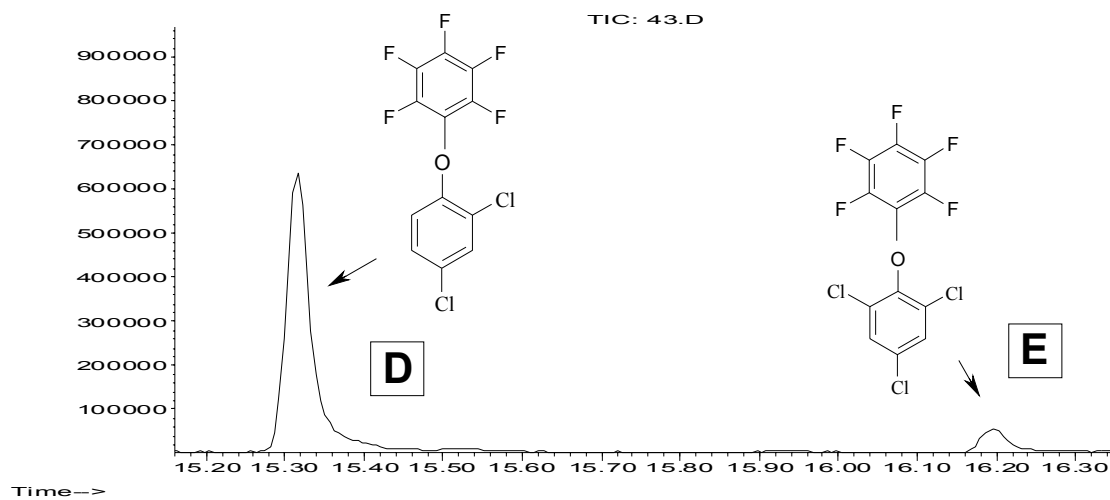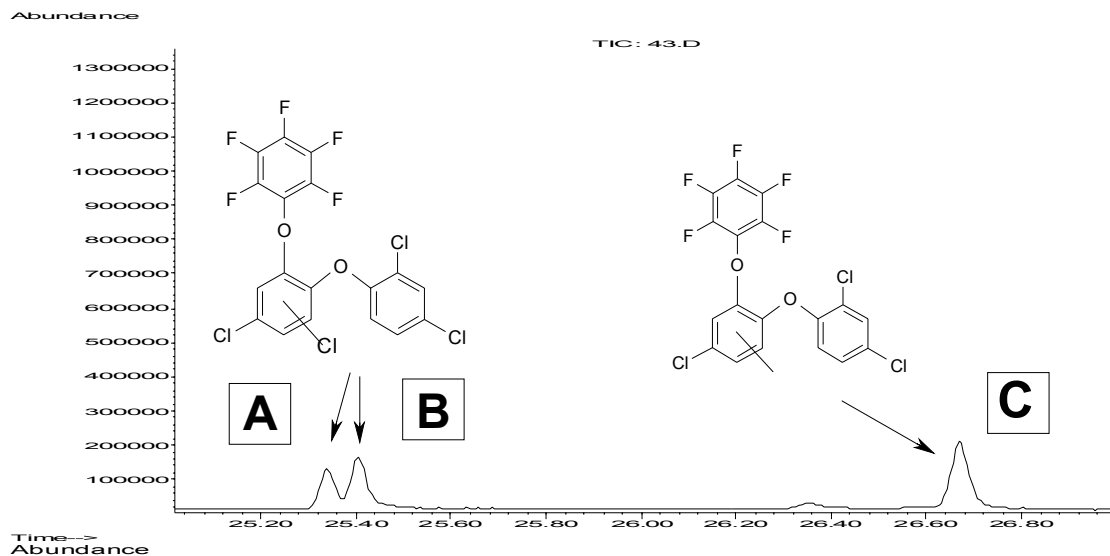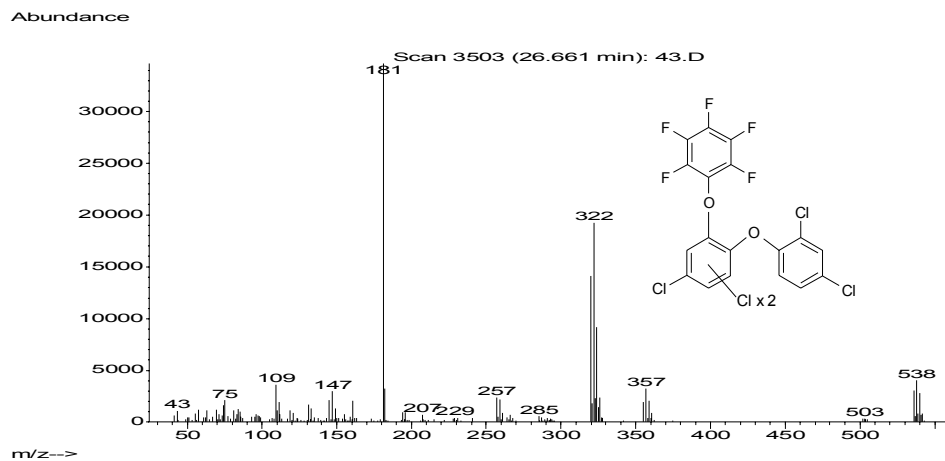
**Figure 5: pH 4 predicted decay vs. experimental decay. Reaction conditions: [Triclosan]$_0$ = 5.05 µM; [Free Chlorine]$_0$ = 14.2 µM; [NaHCO$_3$] = 2 mM.**

Figure 6: pH 10 predicted decay vs. experimental decay. Reaction conditions: [Triclosan]$_0$ = 5.05 mM; [Free Chlorine]$_0$ = 14.2 mM; [NaHCO$_3$] = 2 mM.
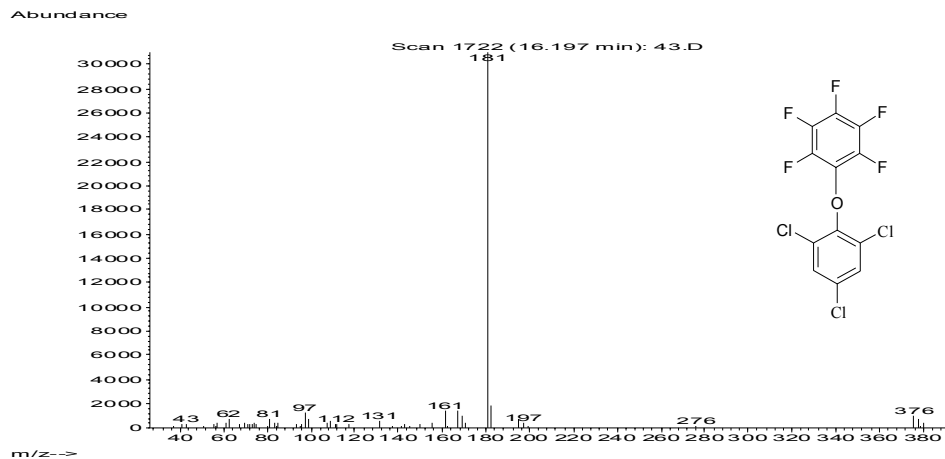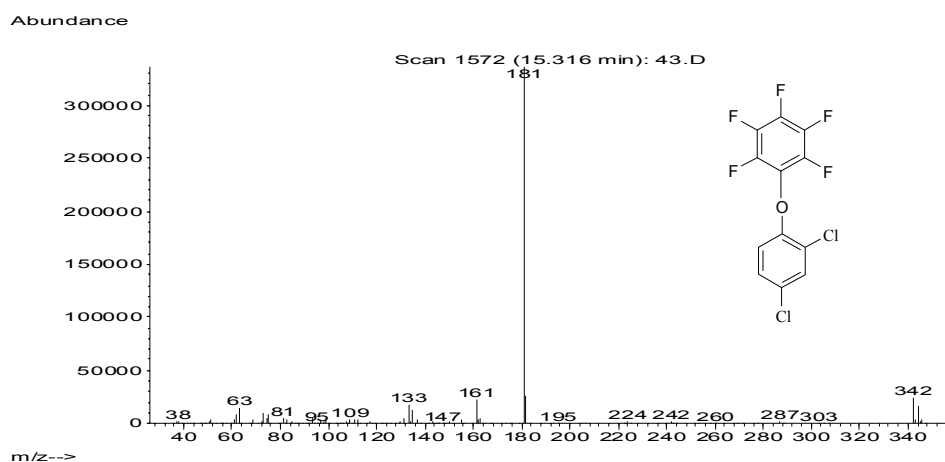
Figure 7: a) GC chromatogram of PFB-derivatized chlorophenoxy phenol intermediates A, B, and C; b) GC chromatogram of PFB-derivatized chlorophenol intermediates D and E; c) Mass spectrum of PFB-derivatized monochlorinated triclosan intermediate (intermediate A or B); d) Mass spectrum of PFB-derivatized dichlorinated triclosan intermediate (intermediate C); e) Mass spectrum of PFB-derivatized 2,4-dichlorophenol; f) Mass spectrum of PFB-derivatized 2,4,6-trichlorophenol.
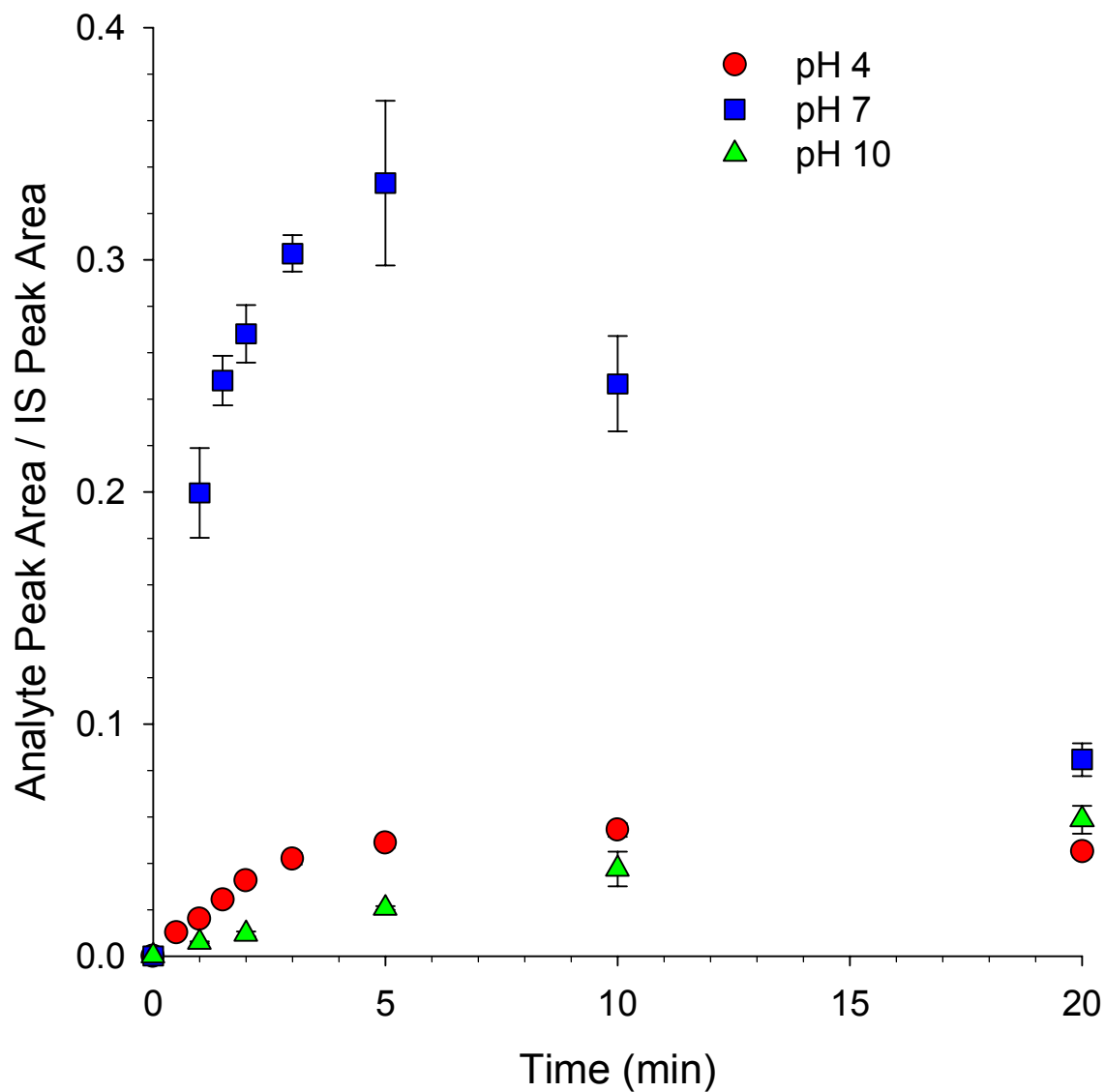
Figure 8: **Formation and decay of monochlorinated triclosan (Figure 6 intermediate A or B) for pH 4, 7, and 10. Reaction conditions: $[\text{Triclosan}]_0 = 5.05 \ \mu M$; $[\text{Free Chlorine}]_0 = 14.2 \ \mu M$; $[\text{NaHCO}_3] = 2 \ mM$.**
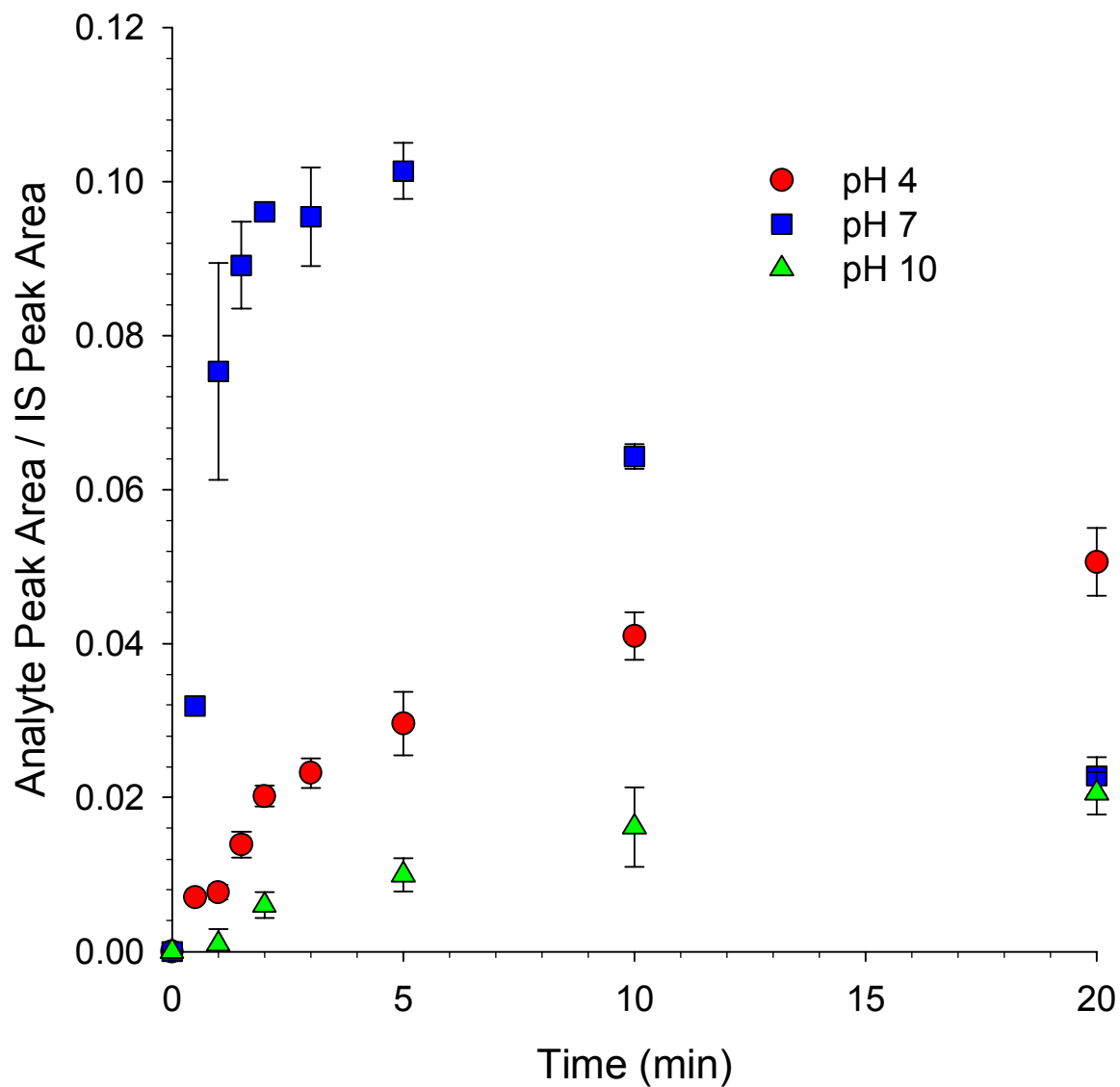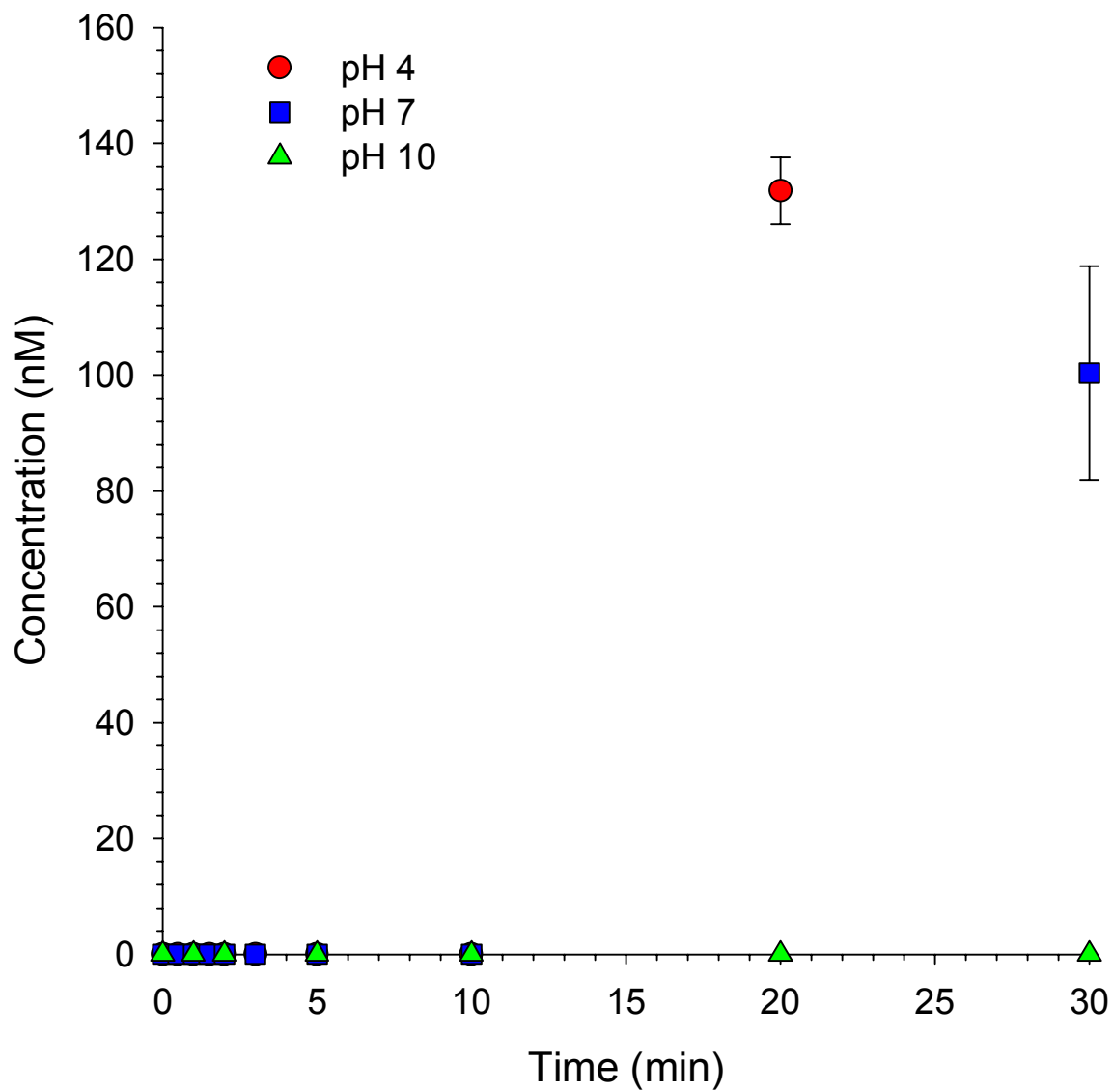
Figure 9: Formation and decay of a monochlorinated triclosan (Figure 6 intermediate A or B) for pH 4, 7, and 10. Reaction conditions: [Triclosan]$_0$ = 5.05 μM; [Free Chlorine]$_0$ = 14.2 μM; [NaHCO$_3$] = 2 mM
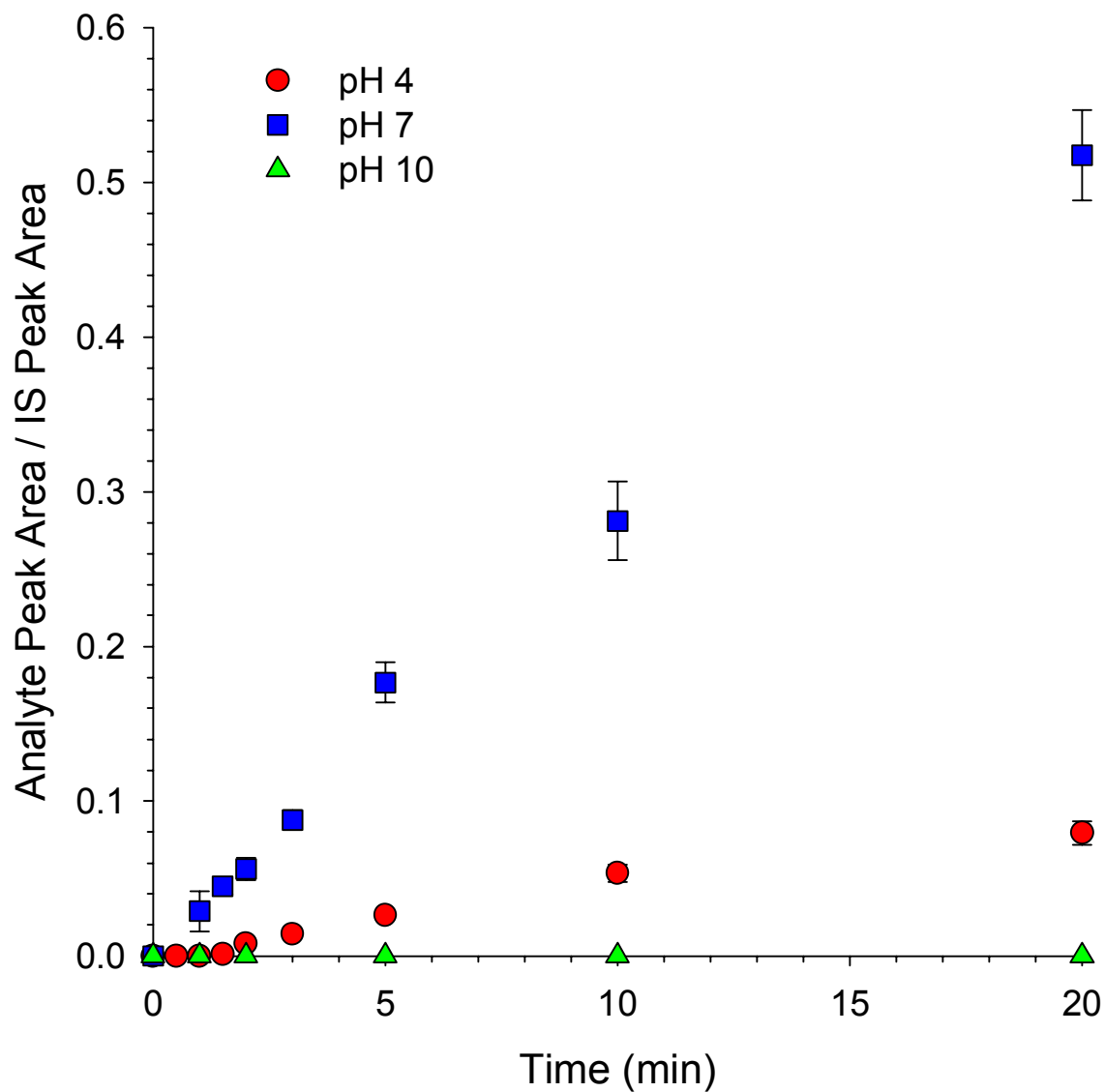
Figure 10: Formation of a di-chlorinated triclosan (Figure 6 intermediate C) for pH 4, 7, and 10. Reaction conditions: [Triclosan]$_0$ = 5.05 μM; [Free Chlorine]$_0$ = 14.2 μM; [NaHCO$_3$] = 2 mM.
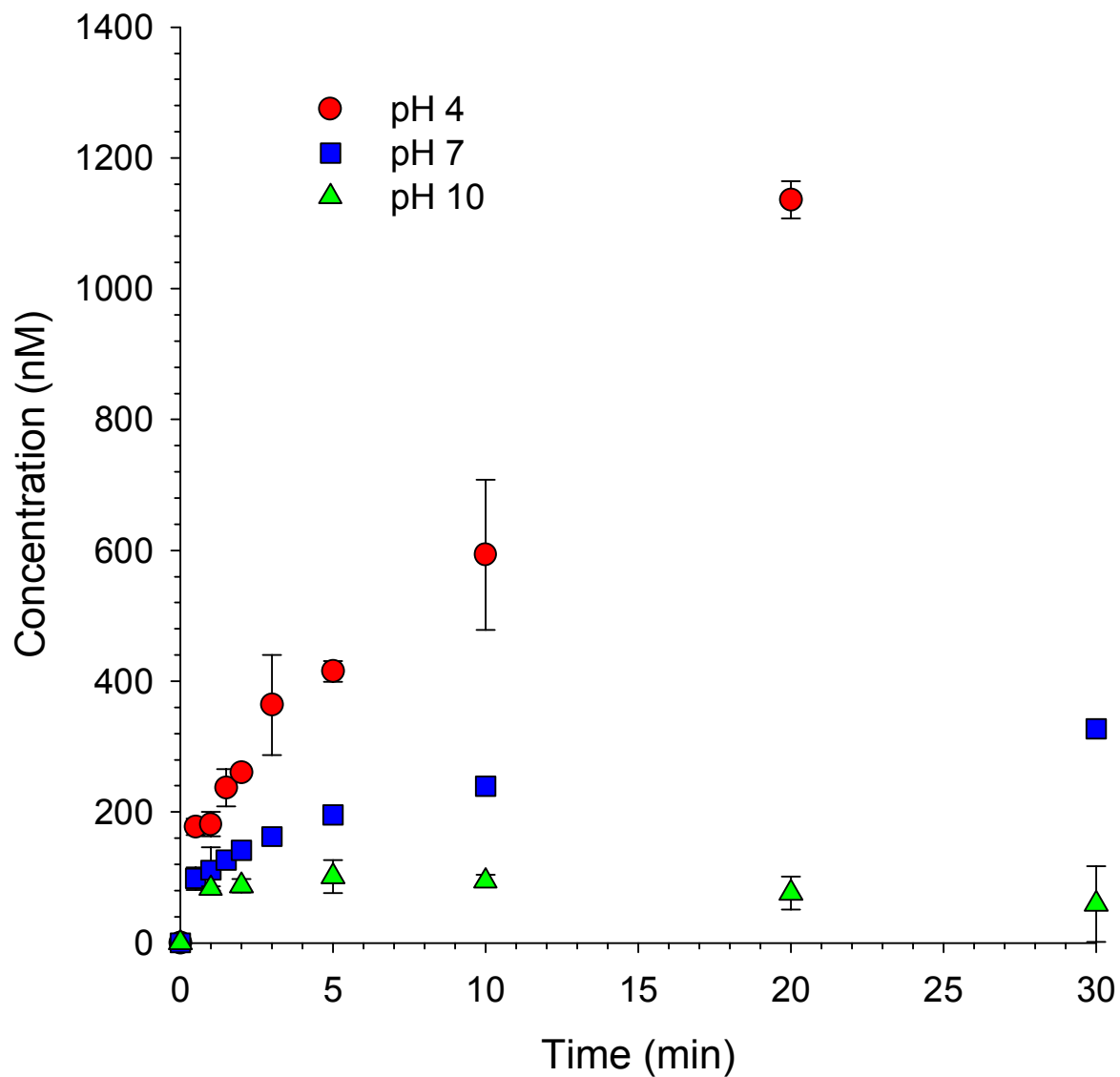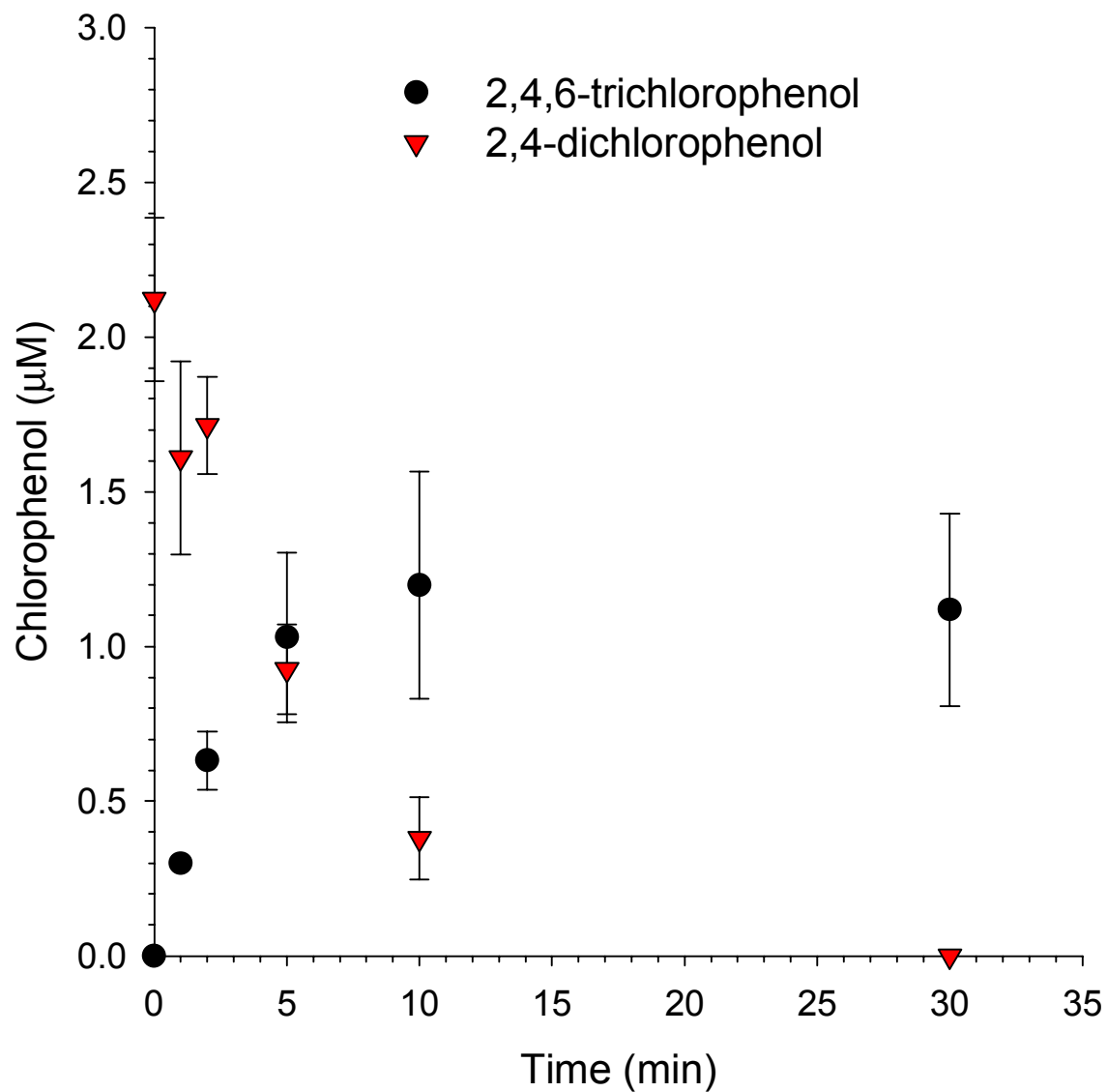
Figure 11: Formation of 2,4-dichlorophenol as a function of solution pH. Reaction conditions: [Triclosan]$_0$ = 5.05 µM; [Free Chlorine]$_0$ = 14.2 µM; [NaHCO$_3$] = 2 mM.

Figure 12: Formation of 2,4,6-trichlorophenol as a function of solution pH. Reaction conditions: [Triclosan]$_0$ = 5.05 µM; [Free Chlorine]$_0$ = 14.2 µM; [NaHCO$_3$] = 2 mM.

Figure 13: Reaction of 2,4-dichlorophenol with free chlorine. Reaction conditions: pH 7; [2,4-dichlorophenol]$_0$ = 25 μM; [Free Chlorine]$_0$ = 2.5 μM; [NaHCO$_3$] = 2 mM.
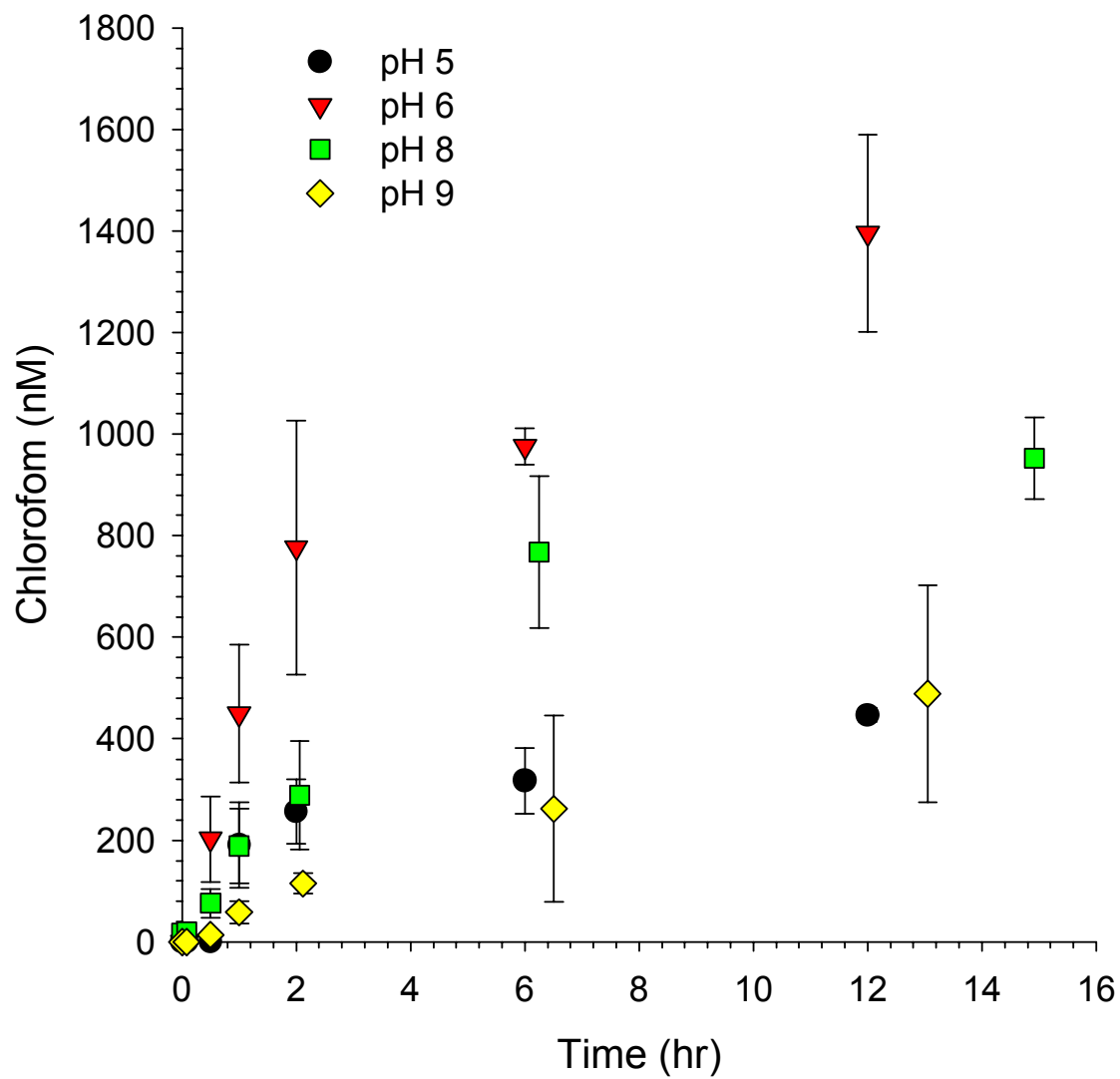
Figure 14: Chloroform formation as a function of solution pH. Reaction conditions: [Triclosan]$_0$ = 2.5 µM; [Free Chlorine]$_0$ = 25 µM; [NaHCO$_3$] = 2 mM.
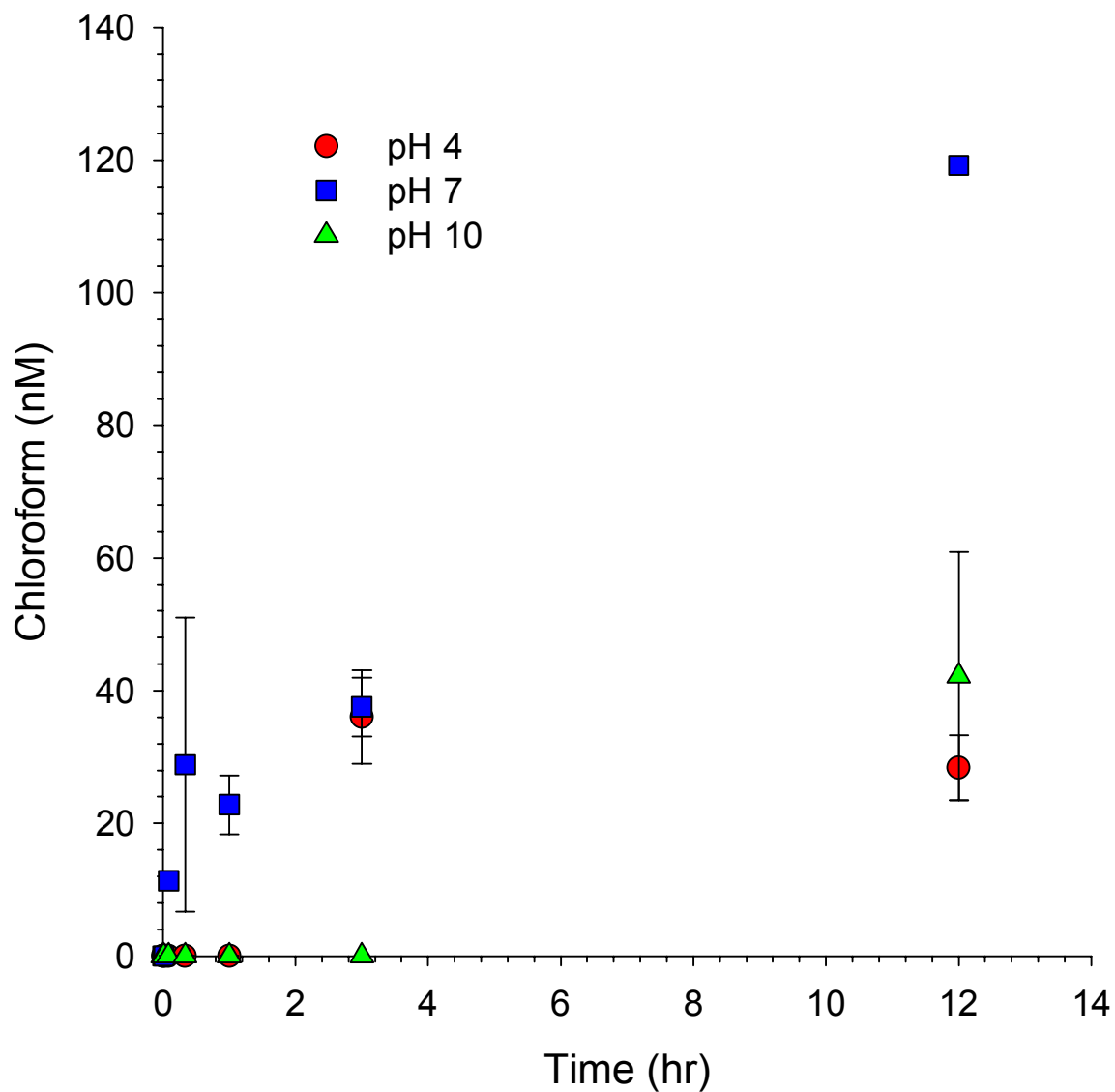
Figure 15: Formation of chloroform during 2,4-dichlorophenol/free chlorine reactions as a function of pH. Reaction conditions: [2,4-dichlorophenol]$_0$ = 2.5 μM; [Free Chlorine]$_0$ = 25 μM; [NaHCO$_3$] = 2 mM.
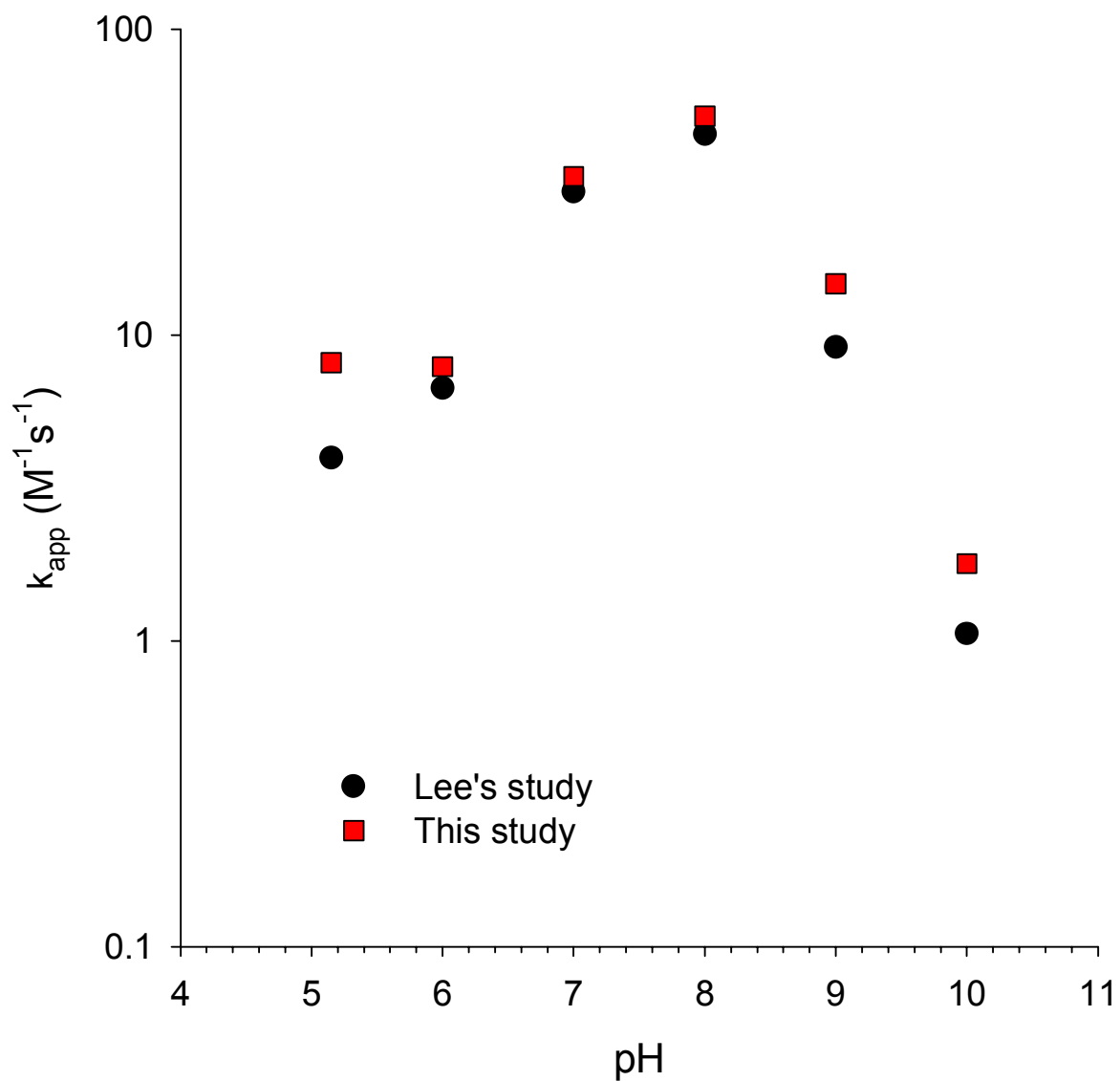
Figure 16: k_{app} verses pH for 2,4-dichlorophenol/free chlorine reactions. Reaction conditions: [2,4-dichlorophenol]$_0$ = 25 μM; [Free Chlorine]$_0$ = 2.89 - 3.15 μM; [NaHCO$_3$] = 2 mM.
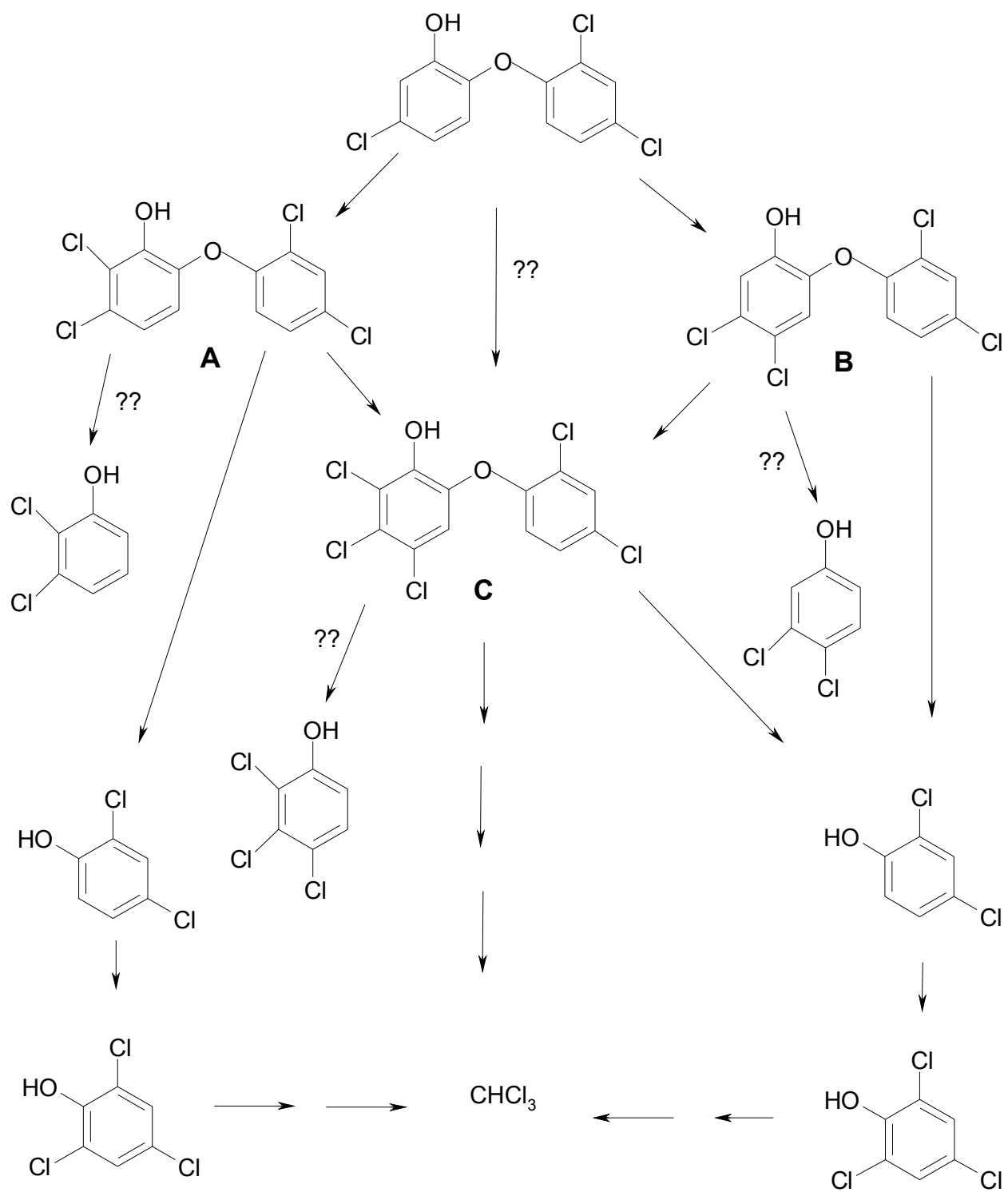
Figure 17: Proposed reaction pathway of triclosan in the presence of excess free chlorine.

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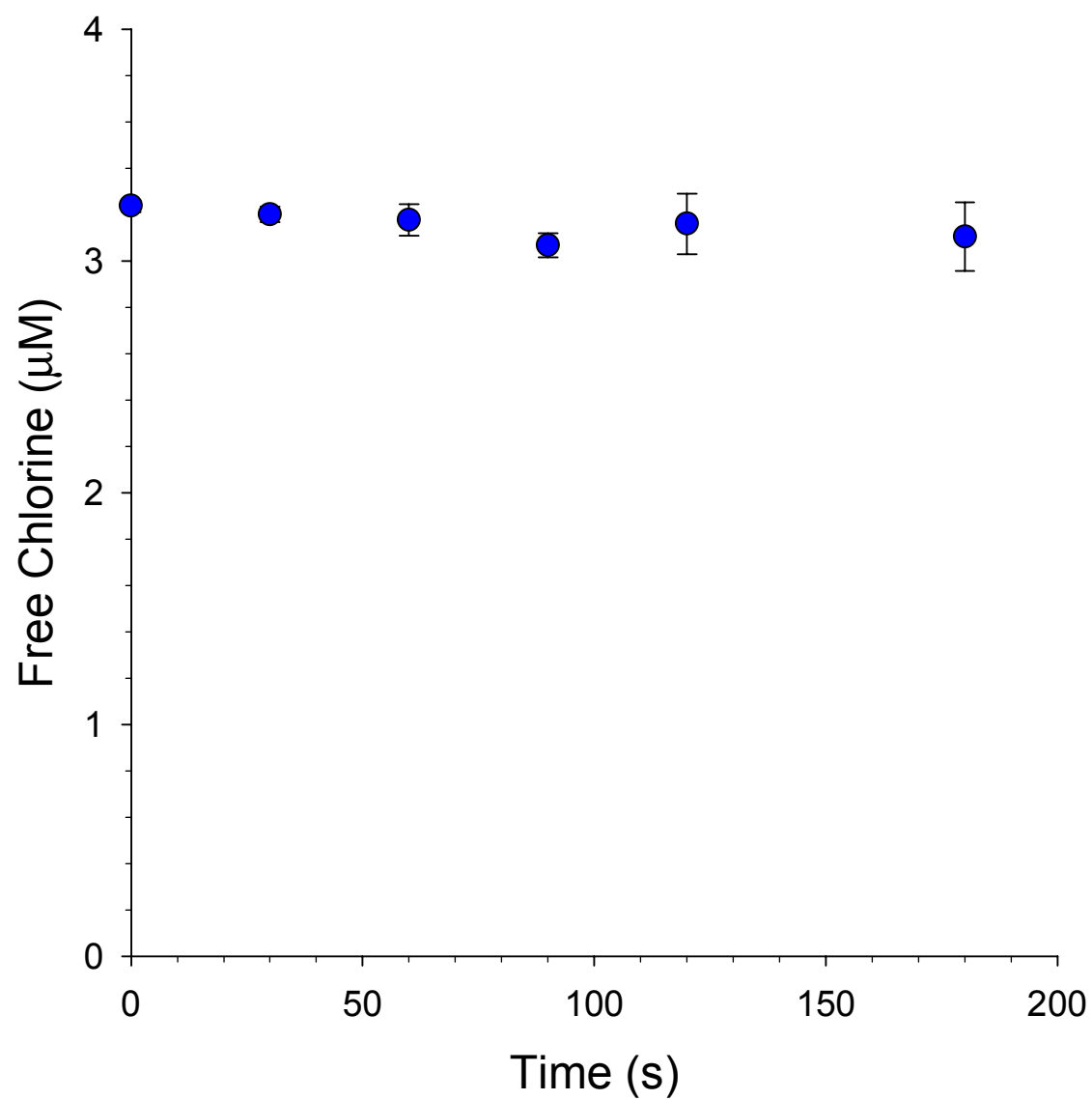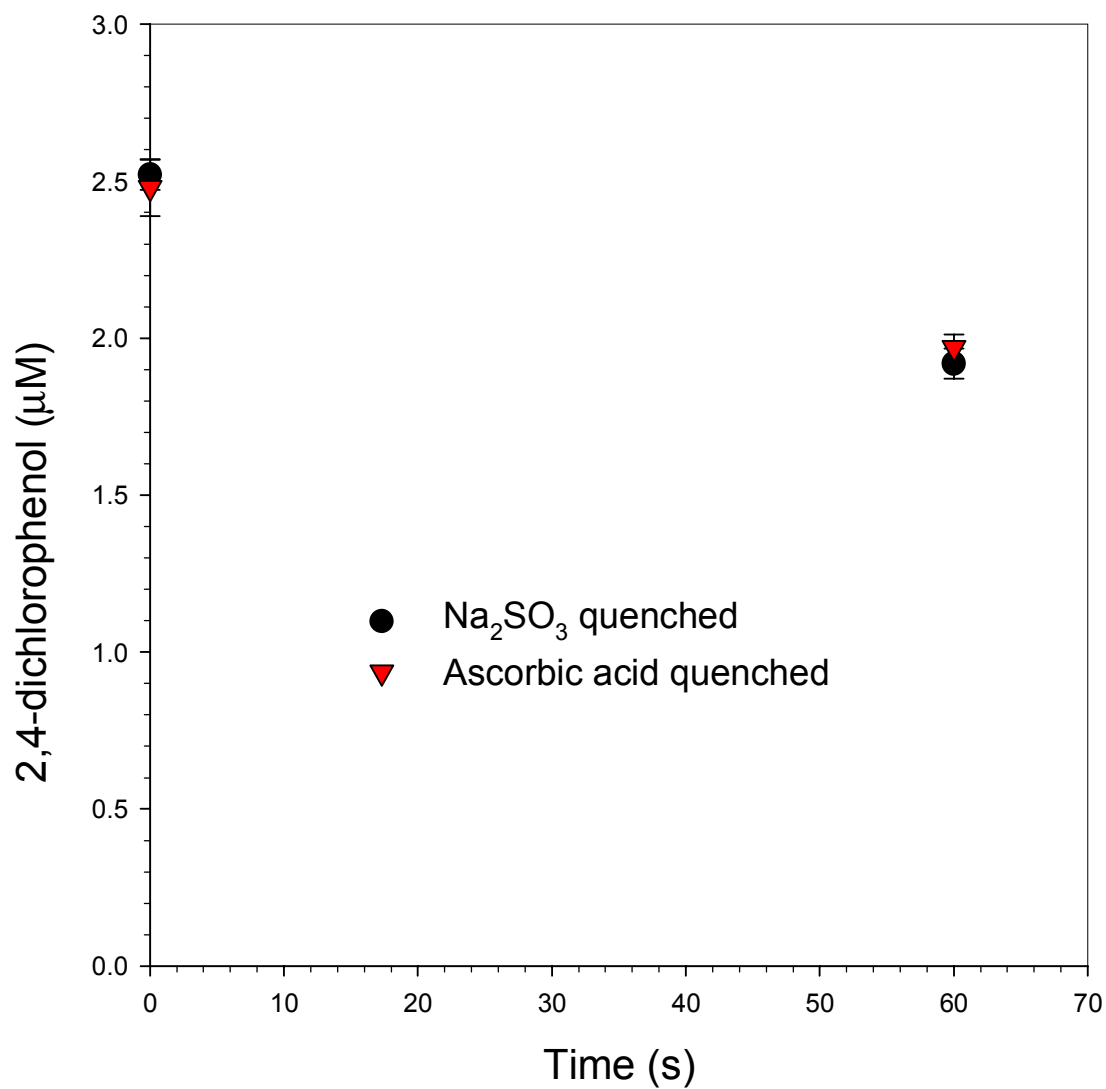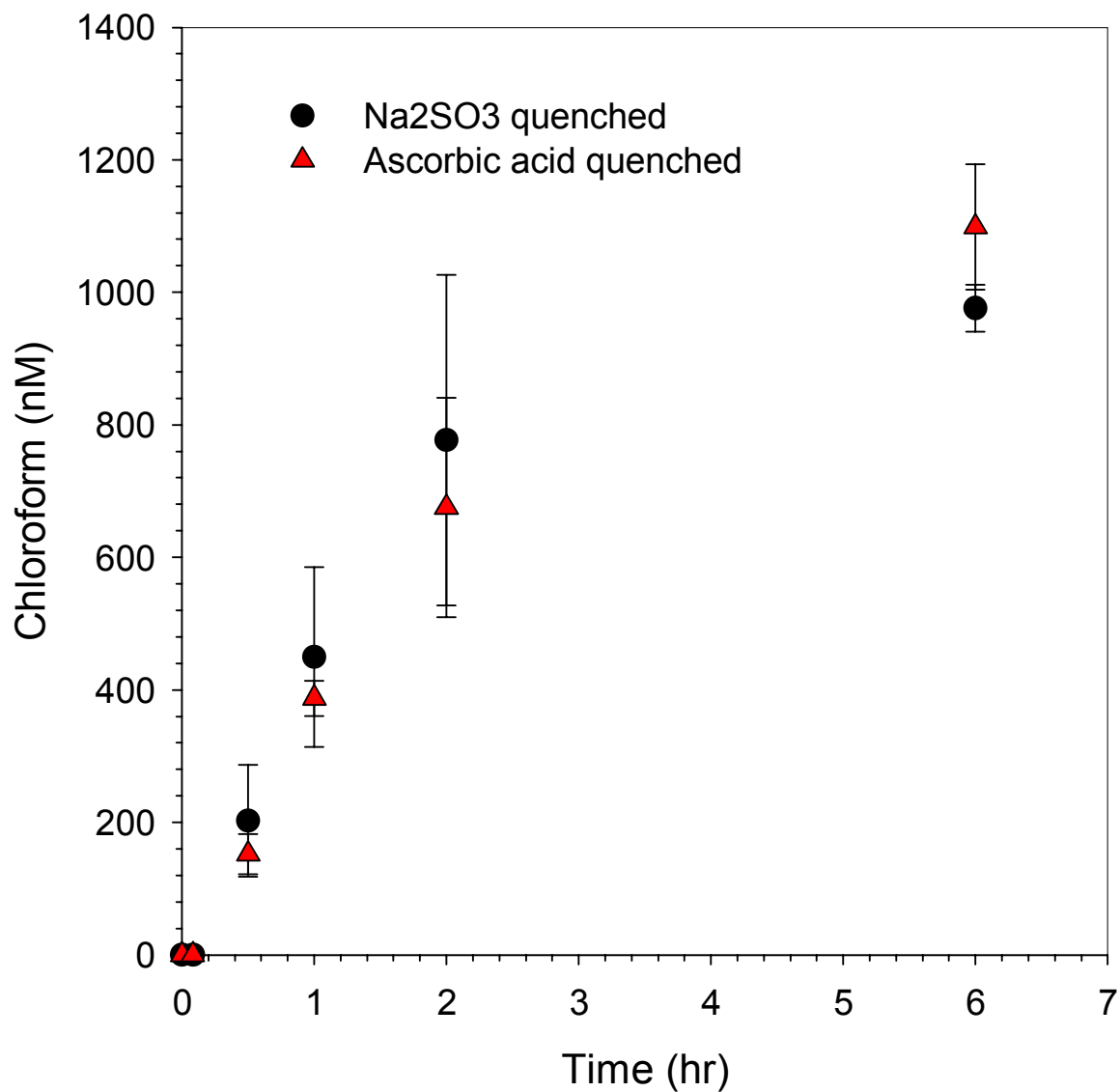
**Figure S1a: Examination of free chlorine reactivity towards methanol at pH 5; $[FC]_0 = 3.24$ µM; $[CH_3OH] = 49.3$ mM; $[NaHCO_3] = 2$ mM; $\mu = 0.1$ M (NaCl).**
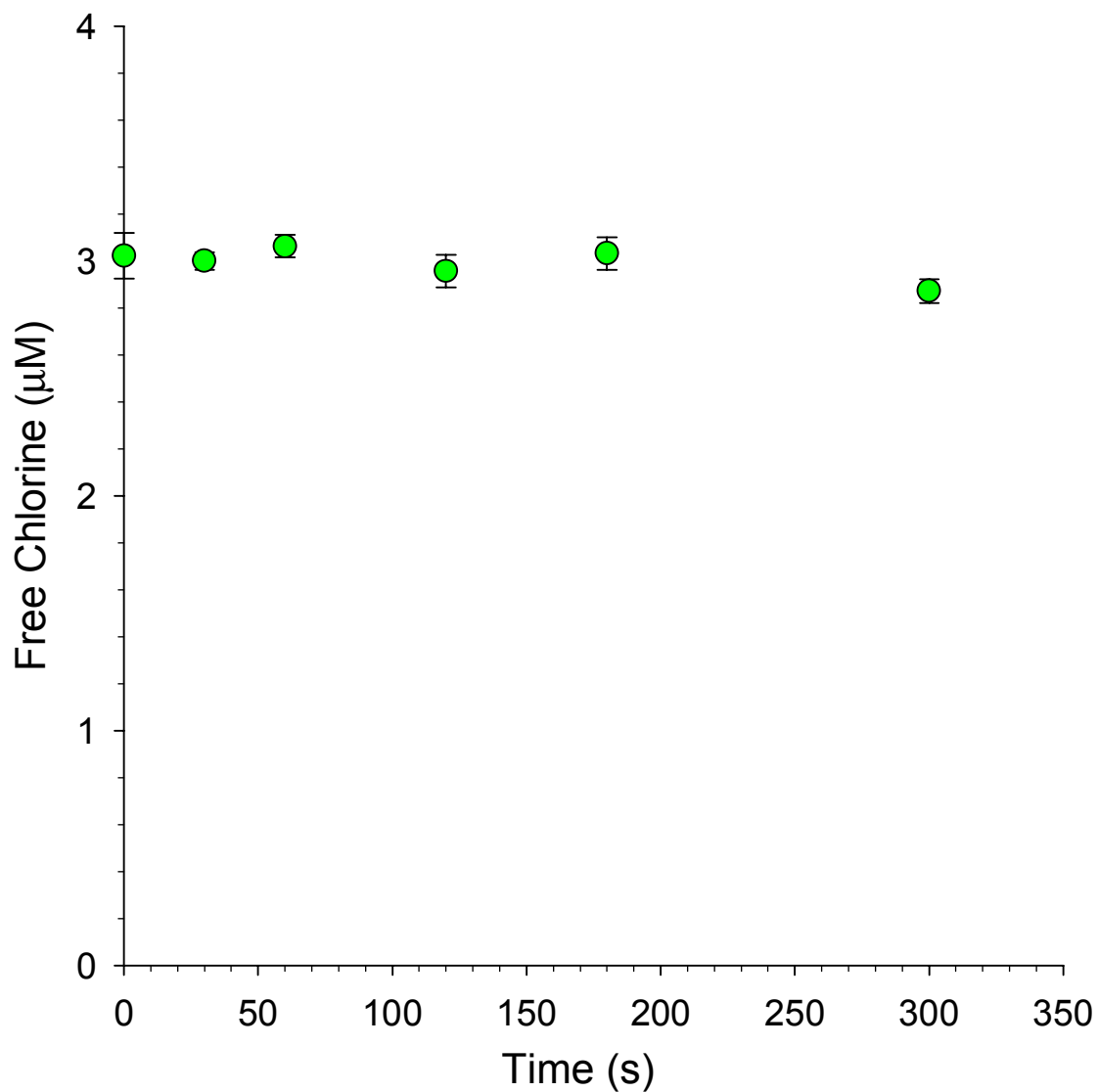
Figure S1b: Examination of free chlorine reactivity towards methanol at pH 10; [FC]$_0$ = 3.24 μM; [CH$_3$OH] = 49.3 mM; [NaHCO$_3$] = 2 mM; μ = 0.1 M (NaCl).

Figure S2a: Effect of quenching agent on 2,4-dichlorophenol/free chlorine reactions. Reaction Conditions: pH 7; [2,4-dichlorophenol]$_0$ = 2.5 µM; [Free Chlorine]$_0$ = 25 µM [NaHCO$_3$] = 2 mM.

Figure S2b: Effect of quenching agent on chloroform formation during triclosan-free chlorine reactions. Reaction Conditions: pH 6; [Triclosan]$_0$ = 2.5 µM; [Free Chlorine]$_0$ = 25 µM; [NaHCO$_3$] = 2 mM.
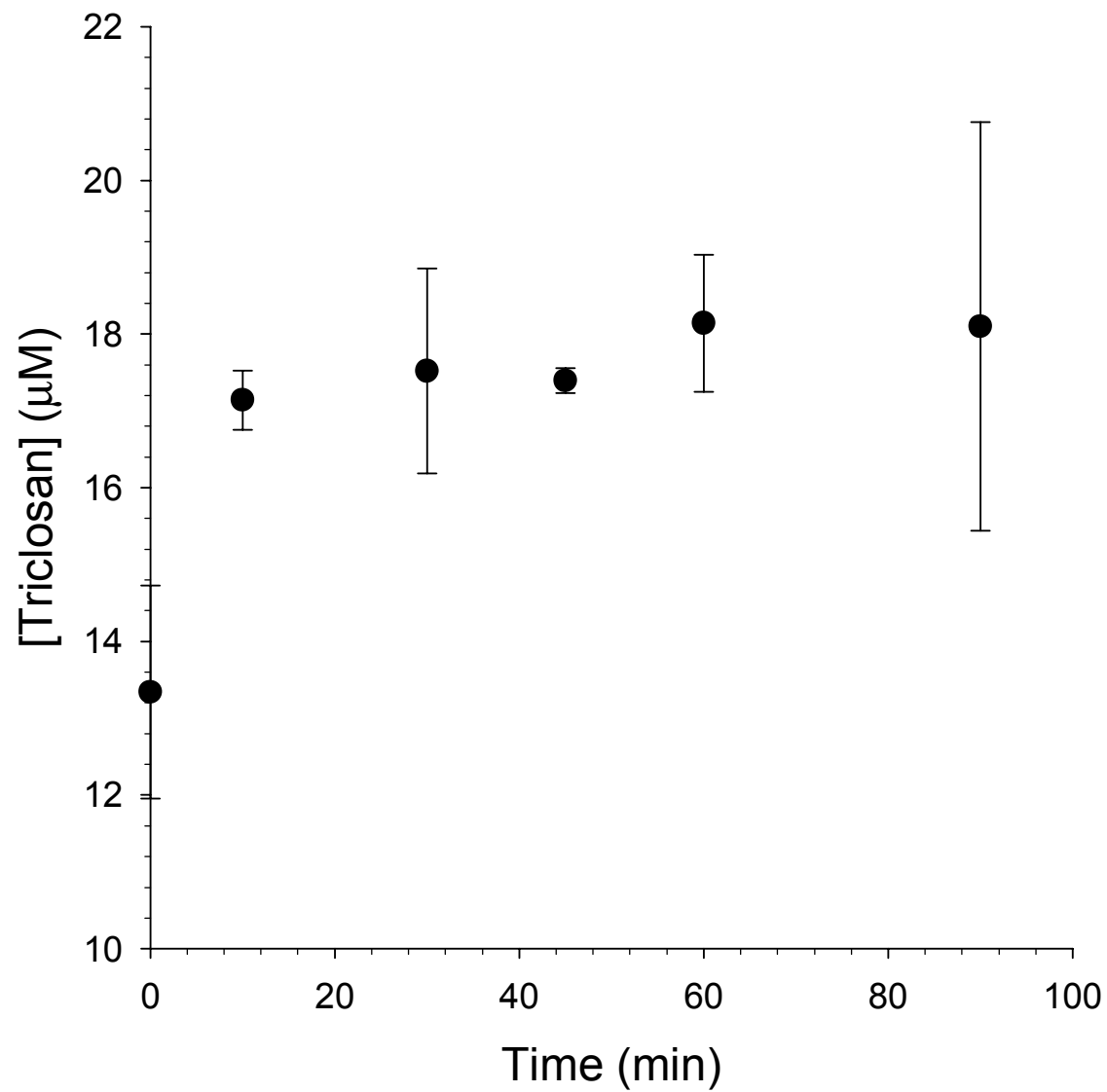
Figure S3: Optimization of the PFBBr – triclosan derivatization reaction. [Triclosan]$_0$ = 17.3 μM.

Vita

Krista Rule was born in Pasco, Washington, on March 15, 1979 to John and Maggie Rule. She attended the University of Idaho starting in the fall of 1997 and earned a B.S. in Professional Chemistry in May of 2001. After graduation she worked for a year as an analytical chemist at Anatek Labs Inc. in Moscow, Idaho. In August of 2002 she began her graduate studies in Environmental Engineering at Virginia Polytechnic Institute and State University in Blacksburg, Virginia. Her M.S. ENE degree was completed in May of 2004. She is presently working towards a Ph.D. in Environmental Engineering at Virginia Polytechnic Institute and State University.