The Chlorination of Triclosan: A Kinetic Study

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Abstract

Triclosan, 5-chloro-2-(2,4 dichlorophenoxy)phenol, is an anti-microbial additive in a plethora of Pharmaceutical and Personal Care Products (PPCPs) including, toothpastes, hand creams and soaps, and acne creams. Because many triclosan containing products are topical solutions that are readily washed down the drain, significant quantities of triclosan can be introduced to wastewater treatment systems and eventually, to surface waters. Consequently, triclosan has become a contaminant of concern. The reactions between triclosan and free chlorine have been examined previously; however, no kinetic data for these reactions have been reported for conditions typical of drinking water treatment. This investigation focused specifically on the kinetics of the triclosan and free available chlorine (FAC) reactions under drinking water treatment conditions. Triclosan readily reacted with free chlorine via a second-order reaction (first order with respect to each species). No significant temperature dependency was observed from 8 to 25 °C. The reaction stoichiometry was determined to be 1:1 (triclosan oxidized per free chlorine reduced and did not vary over the pH range examined (pH 4-12). However, the reaction rate coefficients exhibited a significant pH dependency. A model that incorporates the rate coefficients for the reactions between HOCl and both neutral and anionic forms of triclosan was generated to fit the experimental data. The anionic free chlorine species hypochlorite (OCl^-) was determined to play an insignificant role in the overall rate of reaction, and therefore, only the reactions involving HOCl were incorporated into the model. Additionally, a hypothesized reaction mechanism was tentatively shown to fit the collected data and its strong pH dependency.

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Introduction

Pharmaceutical and personal care products (PPCPs) consist of pharmaceuticals, antibacterial agents, veterinary drugs, illicit drugs, cosmetic ingredients, food supplements, and other personal care products (e.g., soaps, skin creams). Recent studies have shown that PPCPs are ubiquitous environmental contaminants at concentrations ranging from 0.5 to 40,000 ng/L (*1, 2*). The introduction of individual PPCPs into the environment is a function of several parameters, such as the manufactured quantity of material, its method of use and application, and its environmental fate and transport properties (*1*). Wet-weather runoff and wastewater treatment effluents serve as the major pathways for the introduction of many PPCPs into surface water environments (*1*).

Until the mid-1990s, PPCPs were seldom considered to be potential environmental contaminants and little work regarding their environmental fate was conducted. With the advent of improved measurement and separation techniques, however, recent work has illustrated the global spread of contamination by trace levels of PPCPs (*1*). The presence of anthropogenic PPCPs in the environment, even at the ng/L level, has been suggested to have significant implications to natural ecosystems. A recent study intimates a possible link between environmental contamination by PPCPs with hormonal or estrogenic characteristics and increased rates of testicular cancer and female breast cancer (*3*). Over the past decade, the number of antibacterial products marketed domestically has risen to over 700 (*4*). Increased usage of these products, and their subsequent detection in the environment, has raised alarms about the potential development of bacterial resistance to antibiotic compounds and the impacts of these products on non-target species (*5*).

Triclosan (5-chloro-2-(2, 4- dichlorophenoxy)phenol, Figure 1) is the anti-microbial component in a number of PPCPs such as toothpastes, hand creams, soaps, and acne creams. Marketed as Igrasan DP 300™, Irgacare MP™, and most recently as Microban®, triclosan has even been incorporated into plastic products as diverse as kitchen utensils and children's toys (*1*). Because many triclosan containing products are topical solutions that are readily washed down the drain, significant quantities of triclosan can be introduced to wastewater treatment systems. A recent study of triclosan fate in wastewater treatment plants indicates that triclosan removal varies from 0-96% based on the type of secondary treatment processes employed (*6*).

One comprehensive study measured triclosan concentrations of 0.145 – 0.736 nM (42 – 213 ng/L) in biologically treated wastewater effluents (*7*). The resulting triclosan concentrations in the receiving waters ranged from 0.038 – 0.338 nM (11 – 98 ng/L).

As a result of its widespread use and its incomplete removal via wastewater treatment, triclosan was detected in ~58% of the U.S. waterways examined in a recent USGS study (*2*). The presence of triclosan in these waters is problematic for a number of reasons. For instance, recent studies have demonstrated the toxicity of this compound to various fish species (*Rutilus rutilis, Zoarces viviparous, Perca fluviatilis, and Oncorhynchus mykiss*; ref. *8*) as well as other aquatic organisms such as algae (*5*) and water fleas (*Daphnia magna*; ref. *8*). Additionally, because many of these waterways are utilized as source waters for drinking water production, the potential reactivity of triclosan in treated drinking waters is of great interest.

Triclosan, as a chlorinated phenoxy-phenol (pK_a = 7.9, ref. *9*; $K_{ow} = 10^{5.4}$, ref. *7*), has a high affinity to associate with organic material and sediments. The water solubility of the compound is reported to be ~10 mg/L at pH 7.0 (*10*). Triclosan exists in both an uncharged phenolic form and in a negatively charged phenolate form with the relative proportions of these species dependent on the solution pH (Figure 1). Prior work has indicated that the environmental fate of triclosan is strongly affected by its speciation. Photochemical studies suggest that the phenolate form of triclosan is more photoactive than the phenolic form (*9, 11, 12*). However, a study of the oxidation of triclosan by manganese oxides demonstrated the opposite pH effect, with the phenolic form being the more reactive species (*12*). Collectively, these results indicate that the speciation of triclosan must be considered when evaluating its reactivity.

In the United States, most drinking water treatment plants, regardless of system size, use free chlorine (a collective term for the species hypochlorous acid [HOCl] and hypochlorite ion [OCl^-]) as their primary means of disinfection (*13, 14*). However, free chlorine has been shown to react with natural organic matter (NOM) in water, leading to the formation of disinfection by-products (DBPs) such as the trihalomethanes (THMs) and the haloacetic acids (HAAs) (*15-17*). As specified by the US EPA in the DBP State I rule, the maximum contaminant level (MCL) for THMs is 80 μg/L (*18*). Because the EPA has classified several of these DBPs as possible or probable human carcinogens (*19*) and as a result of concerns about their potential causative role in the development of prenatal birth defects (*20-24*), concern is mounting about their presence in drinking water. Some drinking water treatment plants select alternative disinfectants, such as

chloramines and ozone, in order to minimize DBP production (*25*). However, free chlorine remains the disinfectant of choice for most treatment facilities.

Numerous studies indicate that phenolic compounds, such as triclosan, readily react with free chlorine to form chlorinated phenol derivatives that can undergo additional reactions, ultimately resulting in the formation of disinfection by-products such as THMs (*16, 26-31*). Chlorination of phenolic compounds typically commences with the addition of chlorine to the aromatic ring, resulting in the formation of mono-, di-, and tri-chlorophenols (*32*). Resorcinol, a phenolic compound that undergoes these types of reactions, has been extensively studied with regard to its chlorination and its potential role as a reactive constituent in NOM (*16, 26, 27*). Product studies of the chlorination of resorcinol indicate that it initially reacts with free chlorine to form 2-chloro-, 4-chloro-, 2,4-dichloro-, 4,6-dichloro-, and 2,4,6-trichloro-resorcinol intermediates (*33*). These intermediates then undergo additional electrophilic chlorination, ultimately leading to the fissure of the aromatic ring and the formation of a number of smaller chlorinated organic compounds (*34*). Rebenne et al. (*28*) examined the chlorination of resorcinol as a function of pH and determined that the initial rate of reaction is at a minimum between pH 3 and 6 and reaches a maximum between pH 8 and 11. This pH effect was hypothesized to result from differences in the reactivity of the neutral and anionic forms of resorcinol with HOCl. Similar pH dependencies have recently been shown for a wide range of phenolic compounds (*31*).

The interactions between triclosan and free chlorine have been examined previously (*35*, *36*); however, these studies were performed using free chlorine concentrations considerably larger than the levels found under typical drinking water treatment conditions and did not involve any kinetic evaluation. This investigation redresses this issue by quantifying the reaction kinetics and by examining the products of the triclosan-chlorine reactions under conditions more appropriate to drinking water treatment. This study provides insight into the potential problems associated with the presence of triclosan in chlorinated drinking waters.

Materials and Methods

Chemicals of the highest available purity were used as received. Triclosan, 2,3-dichlorophenol, 2,4-dichlorophenol, 3,4-dichlorophenol, and 2,3,4-trichlorophenol were

purchased from Aldrich (>98% purity) and used without further purification. Sodium hypochlorite stock solution (purified grade 4-6% NaOCl) was purchased from Fisher Scientific. All experiments were conducted using distilled, deionized water produced by an Aries 110V water purification system equipped with a dispenser containing a 0.2 μm hollow membrane filter. A Fisher Scientific model 60 pH meter coupled with a Thermo-Orion Ross PerpHect Combination Electrode, was calibrated with standard buffers (pH 4, 7, 10) at ambient temperature and was used for all pH measurements. All glassware was soaked in 10% nitric acid solution for a minimum of 12 hours, was rinsed with distilled water, and was then transferred to a concentrated free chlorine bath where it soaked for a period of 24 hours or more. The glassware was then rinsed with distilled water, followed by deionized water, and then air dried prior to use.

Reaction Kinetics. All experiments were performed in the dark at 8, 17, or 25 °C (± 0.2 °C). Temperature was controlled using a Neslab RTE 100 temperature circulator. Chlorination kinetic experiments were performed with initial free chlorine concentrations that ranged from 2.33 to 3.05 μM (0.165 – 0.217 mg/L) and an excess triclosan concentration of 27.5 μM (7.97 mg/L). The ionic strength was controlled in all experiments at a level of 0.1 M; a 2 mM sodium bicarbonate pH buffer was also utilized. pH was adjusted to the desired value using varied volumes of HCl and NaOH solutions accordingly. Using a Chaney Adaptor equipped syringe, reactions were initiated by injecting a 49.9 ± 0.147 μL aliquot of 13.8 mM (4000 mg/L) triclosan stock (in 100% methanol) into a capped 40 mL amber vial containing 25 mL of free chlorine solution of known composition. The final methanol concentration in the reaction vials was 0.199%; this level is considerably below the level where co-solvent effects reportedly occur (*37*). After an allotted period of time, the free chlorine concentration in each vial was quantified using a modified DPD photometric method (*38*). In this protocol, 1.25 mL aliquots of N,N-Dimethyl-*p*-phenylenediamine (DPD) indicator (4.19 mM) and 1.25 mL of phosphate buffer (0.507 M PO_4^{3-}) were directly added to the reaction vessel. The contents of the vial were then mixed for ten seconds prior to analysis. The resulting absorbance readings at 515 nm were compared to a standard curve obtained that day, and the residual free chlorine level was determined. As the rate coefficient for the DPD-chlorine reaction (1.4 - 1.7 s^{-1} at pH 6.2; ref. *39*) is considerably larger than those for the chlorination of triclosan (see discussion that follows), the addition of a

significant excess of DPD, relative to triclosan, effectively quenches the triclosan-free chlorine reactions.

The overall progress of the free chlorine-triclosan reactions was determined by measuring the free chlorine concentration as a function of time. As a result of the rapidity of the reaction kinetics, however, each time point in a kinetic experiment corresponds to an average concentration determined for a set of at least three individual reactors, each of which had been spiked with the same amount of triclosan and sampled at the same point in time. Accordingly, the error associated with each time point reflects the error of replicate reactors.

Reaction Stoichiometry. Experiments to determine the stoichiometry of the triclosan-free chlorine reactions were conducted using an excess triclosan concentration (27.5 μM). Free chlorine solutions were prepared at pH 4, 7, and 9 with 0.1 M ionic strength and 2 mM $NaHCO_3$ pH buffer. Free chlorine concentration was measured initially using the DPD titration method (*40*). Several initial concentrations of free chlorine were employed (1.56 – 19.7 μM). These studies were initiated by spiking a reactor with triclosan stock and the solutions were then allowed to react until no free chlorine residual could be detected (~1 day).

Triclosan and Chlorophenol Extraction. Triclosan and its daughter products were concentrated using solid phase extraction (SPE) with 3M Empore™ High Performance SDBS Extraction Cartridges. Each cartridge was conditioned by sequential rinsing with 0.5 mL aliquots of acetone and methanol, followed by the elution of 1 mL of distilled, deionized water through the cartridge; extreme care was taken to avoid drying out the solid phase. Prior to extraction, the reacted solutions were adjusted to pH 2 and a predetermined aliquot of each sample was drawn through the cartridge at a rate of 5 mL/min. The amount extracted varied based upon the compound being quantified. For triclosan, a 5 mL aliquot was used, resulting in a 10× concentration, whereas for daughter-product quantification, a 25 mL aliquot was employed, concentrating the sample 25×. Once the reaction solutions were loaded onto the cartridges, they were dried using vacuum suction. The extracted analytes were eluted using acetone (GC Resolve grade) and collected in 2 mL amber-crimp-top autosampler vials.

Triclosan and Chlorophenol Quantification and Analysis. Triclosan and its degradation products were quantified using pentafluorobenzyl bromide (PFBBr) derivatization and gas chromatography-mass spectrometry (GC-MS) detection (*41*). The acetone extracts obtained from SPE were derivatized by adding 100 μL 0.5% PFBBr (2,3,4,5,6-Pentafluorobenzyl bromide 99+%; Aldrich) and 100 μL aqueous 10% KCO_3. The sample vials were then crimp sealed and heated in a water bath at 80 °C for 45 minutes. In control experiments, this period of time was found to be adequate for the complete derivatization of triclosan (Figure 2). Upon removing the samples from the water bath, they were cooled to room temperature and then concentrated using a gentle nitrogen gas stream until ~100 μL remained. Methylene chloride (500 μL for triclosan analysis and 1000 μL for product analysis) was then injected into each sample, and the vials were sealed.

GC-MS analyses were performed using 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. The temperature of the GC oven varied with time; for the first 1.5 minutes, the temperature was 70 ºC, after which it was ramped to 160 ºC at 20 ºC/min, followed by further ramping at 8 ºC/min to 280 ºC. The temperature was held at 280 ºC for 1 minute before the oven was cooled 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. Derivatized triclosan samples were run in SIM acquisition mode with a solvent delay of 5 minutes, and $[M\text{-}PFB]^-$ ions (m/z 468) were monitored. Derivatized daughter-product samples were analyzed in SCAN mode with a solvent delay of 5 minutes. The chlorophenol products were quantified based on their retention times and mass spectra.

THM Quantification. Experiments to quantify THM production were performed under headspace-free conditions in 42.3 ± 0.27 mL amber vials. The vials were filled with pH adjusted disinfectant solutions having an ionic strength of 0.1 M (NaCl) and a 2 mM $NaHCO_3$ pH buffer. To initiate the reaction, a 49.9 ± 0.147 μL aliquot of 13.8 mM (4000 mg/L) triclosan stock solution was injected into the reaction vessel. The samples were then allowed to react for an allotted period of time. The THM concentrations in the experimental solutions were then quantified using a liquid-liquid extraction procedure that is a slight modification of EPA method

551 (*42*, and EPA method 551.1). At specified intervals, 100 µL of 40 g/L sodium sulfite (Na_2SO_3) was injected into the reaction vial to halt the triclosan – disinfectant reactions. After discarding 5 mL of reaction solution, 8 g of NaCl was added and dissolved by shaking the capped vial. Using a gas tight syringe, 2 mL of pentane were added to the reaction solution and the vial was then shaken vigorously for at least one minute. The organic and aqueous phases were allowed to separate; the organic phase was removed using a Pasteur pipette and then placed into an autosampler vial that was immediately sealed. The auto-sampler vial was then put into a -20 °C freezer until it could be analyzed on the GC.

THM analyses were performed on a Hewlett Packard 5890 GC system equipped with an electron capture detector (ECD). A DB-1 column with a length of 30 m, a width of 0.25 mm, and a film thickness of 1 µm was employed (J&W Scientific). The make-up flow was set at ~30 mL/min while the column flow was set at ~1.5 mL/min. 1 µL of sample was injected. The injector temperature was 200 ºC, the ECD temperature was 290 ºC, and the GC temperature varied with time. From t=0 minutes to t=5 minutes the oven temperature was 50 ºC; the temperature was then increased at 20 ºC/min until it was held at 170 ºC for one minute.

Results and Discussion

Kinetics of the Triclosan-Free Chlorine Reactions. The kinetics of the reactions between free chlorine and triclosan were determined by observing the loss of free chlorine in the presence of a ten-fold molar excess of triclosan. With triclosan present, free chlorine loss occurs readily (Figure 3). When triclosan was absent, however, the free chlorine residual was stable for extended periods of time (> 8 hrs; data not shown). The observed loss of free chlorine in the presence of triclosan indicates that free chlorine and triclosan readily react. However, even in the presence of a 10× excess of triclosan, free chlorine loss exhibited bi-phasic kinetics. At pH 7, these kinetics are characterized by a fast initial process that is responsible for ~65% of the free chlorine loss and a much slower process that is responsible for the remaining 35%. A similar trend was noticed by Norwood et al. in the chlorination of the phenolic compounds orcinol and 3,5-dimethoxy-4-hydroxycinnamic acid; for both of these compounds, the initial chlorine consumption was rapid but leveled out after approximately 10 minutes (*29*). Gallard and von

Gunten also observed bi-phasic kinetics in their study of chloroform production resulting from the chlorination of various phenols (phenol, 3-chlorophenol, 2,4,6- trichlorophenol, 2,3,4,6-tetrachlorophenol, and 4-methylphenol) (*31*). Because the kinetic data is bi-phasic, it is necessary to employ the method of initial rates to isolate the reaction of interest from potential reactions occurring between reaction products and free chlorine (*43*).

Under conditions where triclosan is present in sufficient excess, a pseudo-first-order approximation for free chlorine loss is appropriate and pseudo-first-order rate coefficients (k_{init}; s^{-1}) were determined using the method of initial rates (*43*). These k_{init} values are related to the overall apparent second-order rate coefficient (k_{app}; $M^{-1}s^{-1}$)

$$\frac{d[\text{FAC}]}{dt} = -k_{app}[\text{triclosan}]_T[\text{FAC}]_T \quad (1)$$

by the following expression:

$$k_{init} = k_{app}\,[\text{triclosan}]_0 \quad (2)$$

where $[\text{triclosan}]_T$ represents the total concentration of triclosan and phenolate-triclosan, $[\text{FAC}]_T$ is the total concentration of free available chlorine (i.e., $[\text{HOCl}] + [\text{OCl}^-]$), and $[\text{triclosan}]_0$ is the initial excess triclosan concentration. Experiments were conducted to verify that first order dependencies for both free chlorine and triclosan are appropriate.

Order with Respect to Free Chlorine. Initially, it was assumed that free chlorine decay in the presence of excess triclosan could be characterized as a first-order process, and accordingly, the initial rate data were linearized by utilizing the pseudo-first-order expression:

$$\ln [\text{FAC}] = - k_{init}\, t + \ln [\text{FAC}]_0 \quad (3)$$

where [FAC] is the measured free chlorine concentration at time t, $[\text{FAC}]_0$ is the initial free chlorine concentration, and k_{init} is the pseudo-first-order rate coefficient obtained from the slope of a first-order plot. At the 95% confidence level, the slopes (k_{init} values) for a range of initial free chlorine concentrations (2.63 - 11.3 μM) were approximately equal, thus supporting the assumed first-order dependency on the free chlorine concentration. This first-order reaction dependency for free chlorine was independently determined at pH 4, 7, and 10 (Figures 4, 5, and 6) thereby suggesting that it applies over this entire range and that differences in the speciation of either triclosan or free chlorine do not affect the reaction order.

Order with Respect to Triclosan. To determine the order with respect to triclosan, the expression for k_{init} was linearized:

$$\ln k_{init} = \beta \ln [\text{triclosan}] + \ln k_{app} \quad (4)$$

A plot of ln k_{init} versus ln [triclosan] for fixed pH values yielded slopes of approximately 1, thus indicating that β, the aqueous phase reaction order with respect to triclosan, was one (Figure 7). The lack of a pH effect indicates, as was the case with the free chlorine reaction order, that the reaction order with respect to triclosan was also not a function of either free chlorine or triclosan speciation.

pH dependence and Mechanism. Apparent reaction rate coefficients (k_{app}) were determined using experimental k_{init} values and Eq. 2 (Table 1). As shown in Figure 8, these k_{app} values are a function of the solution pH. For pH values less than 9, k_{app} is approximately constant (= 952 ± 99.9 $M^{-1}s^{-1}$), however, for more alkaline pH values k_{app} decreases rapidly. This pH dependency is likely the result of differences in the reactivity of the different forms of free chlorine (i.e., HOCl vs. OCl^-) as well as the speciation of triclosan; previous studies suggest that the OCl^- species is the less reactive of the two (*28, 31, 44*). The expression given by equation 1 is the net result of a series of parallel reactions involving the various species of triclosan and free chlorine:

$$HOCl \xleftrightarrow{K_{Cl}} OCl^- + H^+ \quad (5)$$

$$\text{triclosan} \xleftrightarrow{K_{a,\text{triclosan}}} \text{phenolate-triclosan} + H^+ \quad (6)$$

$$\text{triclosan} + HOCl \xrightarrow{k_7} \text{products} \quad (7)$$

$$\text{phenolate-triclosan} + HOCl \xrightarrow{k_8} \text{products} \quad (8)$$

On the basis of this reaction mechanism, k_{app} has the following general form:

$$k_{app} = \{k_7\alpha_0 + k_8\alpha_1\}\alpha_{Cl} \quad (9)$$

where α_{Cl} is the ionization fraction for hypochlorous acid, and α_0 and α_1 are the ionization fractions for the phenol and phenolate forms of triclosan, respectively. A similar reaction mechanism has been previously employed to describe the kinetics of the reactions between substituted phenolic compounds and free chlorine (*28, 31*).

Calculated k_{app} values are plotted in Figure 8 as a function of the solution pH. The collected k_{app} data was further evaluated by fitting Eq. 9 to the data using a non-linear equation

solver (SigmaPlot, SPSS Software). Additional reactions between OCl^- and each triclosan species were considered; however, the inclusion of these parameters did not improve the model fit. Calculated values for the rate coefficients for reactions 7 - 8 are tabulated in Table 2 along with literature values for the chlorination of other phenols. In all cases, the rate coefficients for the chlorination of the neutral form of each compound are less than the rate coefficients for the chlorination of the phenolate, indicating that deprotonated phenolic compounds react more quickly with free chlorine than the protonated forms. With the notable exception of orcinol, the reaction between the neutral form of triclosan and free chlorine was more rapid than that for any other phenolic (i.e. protonated) compound tested (i.e., $k_{7\ triclosan} > k_{7\ compound\ x}$). However, the reaction between phenolate-triclosan (i.e. deprotonated triclosan) and free chlorine was slower than that measured for six of the compounds, but it was faster than the rates measured for 4-chlorophenol and 2,4-dichlorophenol. These differences can be attributed to the presence of the various substituents on the compounds' ring structures and their respective electron withdrawing and electron donating capabilities (*37*). For example, substituents such as $–CH_3$ release electrons whereas –Cl and –OH attract electrons. The site of substitution on the aromatic ring also acts to partially determine the reaction rate (*45*).

As evident upon examining the rate coefficients in Table 2, the presence of $–CH_3$ in the meta position increases the rate coefficient, while adding –Cl in the ortho or para positions decreases the rate coefficient. As it relates to triclosan, the dichlorophenoxy group has an overall activating effect comprised of strong resonance effects countered by weak electron withdrawing effects. The meta position chlorine also contributes to the electron withdrawing abilities of triclosan. However, the large ortho substituent contributes greatly to the steric hindrance of triclosan (*12*). Thus, trends within a given phenolic compound class were observed, and steric factors reflect differences between phenolic compounds classes. As a result of the large differences in the structures and substituents of the compounds in Table 2, a simple trend between the rate coefficients for the chlorination of triclosan and the other phenolic compounds cannot be established, thus suggesting that these rate coefficients are influenced by a combination of electronic and steric factors.

Table 1 – k_{init} and k_{app} values for the chlorination of triclosan as a function of pH. $[FAC]_0$ = 2.33- 3.13 µM; $[Triclosan]_0$ = 27.5 µM; $[NaHCO_3]$ = 2 mM; T = 25 ºC; µ = 0.1 M

pH	k_{init} (s^{-1})			k_{app} ($M^{-1}s^{-1}$)
4.07	2.63×10^{-2}	±	7.18×10^{-3}	953
4.51	2.67×10^{-2}	±	3.79×10^{-3}	968
5.50	2.27×10^{-2}	±	6.60×10^{-3}	821
6.00	3.08×10^{-2}	±	7.10×10^{-3}	1120
6.50	2.11×10^{-2}	±	3.03×10^{-3}	763
7.01	2.80×10^{-2}	±	5.02×10^{-3}	1013
7.51	2.74×10^{-2}	±	2.09×10^{-3}	894
8.00	3.17×10^{-2}	±	5.61×10^{-3}	1150
8.50	2.38×10^{-2}	±	3.32×10^{-3}	862
9.00	1.76×10^{-2}	±	2.24×10^{-3}	638
10.01	3.21×10^{-3}	±	2.24×10^{-4}	116
11.06	3.66×10^{-4}	±	8.10×10^{-5}	13.2
11.98	1.04×10^{-4}	±	2.01×10^{-6}	3.76

Table 2 – Rate coefficients for the chlorination of several phenols.

Compound	Rate Coefficients		Reference
	k_7 ($M^{-1}s^{-1}$)	k_8 ($M^{-1}s^{-1}$)	
triclosan	7.9×10^2	7.8×10^3	This work
4-chloro-phenol	2×10^{-2}	2.2×10^3	(*31*)
2,4-dichlorophenol	not determined	3.0×10^2	(*30*)
resorcinol (3-hydroxy-phenol)	$<3.3 \times 10^2$	1.4×10^6	(*28*)
phenol	3.6×10^{-1}	2.2×10^4	(*31*)
4-methylphenol	9×10^{-2}	2.7×10^4	(*31*)
4-chlororesorcinol	$<6.5 \times 10^1$	1.4×10^5	(*28*)
4,6- dichlororesorcinol	4.7×10^1	3.2×10^4	(*28*)
orcinol (3-hydroxy-5-methyl-phenol)	1.3×10^3	5.2×10^6	(*28*)

Reaction Stoichiometry. Experiments were conducted to evaluate the stoichiometry of the triclosan-free chlorine reactions. These experiments utilized a fixed triclosan concentration of 27.5 µM and a range of initial free chlorine concentrations (2.82 – 22.7 µM). After allowing the free chlorine to completely decay, the final triclosan concentration was determined. In these

experiments, the solution pH was varied (pH = 4, 6.5, 9) in an attempt to determine if the reaction stoichiometry was pH dependent. The collected stoichiometry data from experiments at each of these initial pH values falls on the same regression line, thereby suggesting that the reaction stoichiometry was not significantly affected by solution pH (Figure 9). A plot of Δ[triclosan] versus Δ[FAC] yields a slope of 1.20 ± 0.36, indicating a stoichiometric relationship of approximately 1:1. This 1:1 relationship indicates that for each molecule of free chlorine reduced that one triclosan molecule is oxidized.

Dependency of the Triclosan-Free Chlorine Reactions on Temperature. Chlorination reactions were performed at 25 °C, 17 °C, and a limited number at 8 °C (± 0.2 °C) to examine the possibility that changes in temperature could significantly affect the triclosan-free chlorine reaction kinetics. However, over the temperature range examined, no significant temperature effects were apparent at any tested pH (Figures 10 and 11). Rebenne et al. observed similar trends when examining the chlorination of resorcinol from 4 to 25 ºC (*28*). A temperature dependency could be apparent at temperatures > 25 ºC. However, measuring k_{init} at higher temperatures would be extremely difficult using the current experimental method due to the speed of the reactions; additionally, temperatures above 25 ºC are not typically relevant to drinking water conditions.

Products of the Triclosan-Free Chlorine Reactions. Prior studies by Onodera and co-workers (*35*) suggest that the reaction scheme for the chlorination of triclosan shown in Figure 12 is plausible at high reactant concentrations. However, no previous work has verified that this reaction mechanism is applicable under conditions similar to those observed in water treatment. Using conditions employing an excess triclosan concentration (27.5 μM), 2,4-dichlorophenol was formed after reacting for ten minutes in free chlorine solutions (2.33 - 3.05 μM) at pH 4, 6, 7, and 8 (Figure 13). No chlorophenol products were formed at pH 10 after thirty-five minutes; however, two GC peaks with mass fragments that correspond to the PFBBr derivatives of products B and C in Figure 12 were observed for the pH 10 reaction after ten minutes. These peaks were not observed for the other pH conditions, presumably as a result of the speed of the triclosan-free chlorine reactions at lower pH values. The formation of these two compounds occurs when a chlorine atom is added to triclosan at either the ortho- or para- position (relative to

the hydroxyl group). Chlorine substituted in the ortho or para positions reportedly decreases reaction rates (*45*). Thus, since products B and C have either ortho or para substituted chlorines, the observed formation of either of these compounds at high pH values is consistent with an overall decrease in the rate of chlorine decay under these conditions. As these intermediates break down, -chlorophenol products are formed via halo-de-alkoxylation (ether cleavage), as indicated in the 10 minute samples at lower pH values. Thus, the amount of chlorophenol formed was pH dependent (Figure 13).

Preliminary investigations into the production of trihalomethanes (THMs) during the chlorination of triclosan were conducted. Under conditions employing an excess chlorine concentration, trace levels of chloroform were produced after five minutes. When triclosan was in excess, however, no chloroform was detected after one hour.

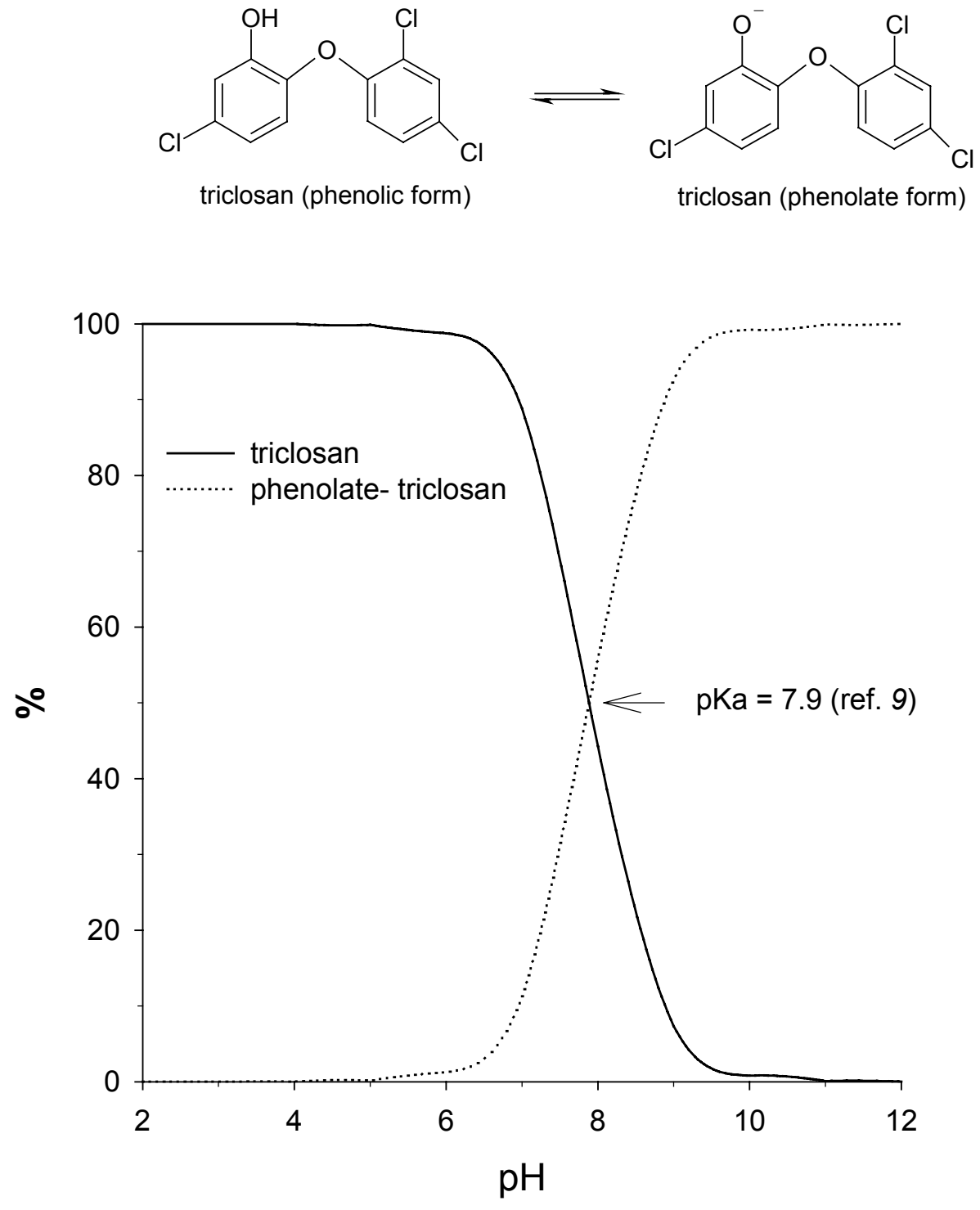

Figure 1: Triclosan structure and speciation as a function of solution pH.

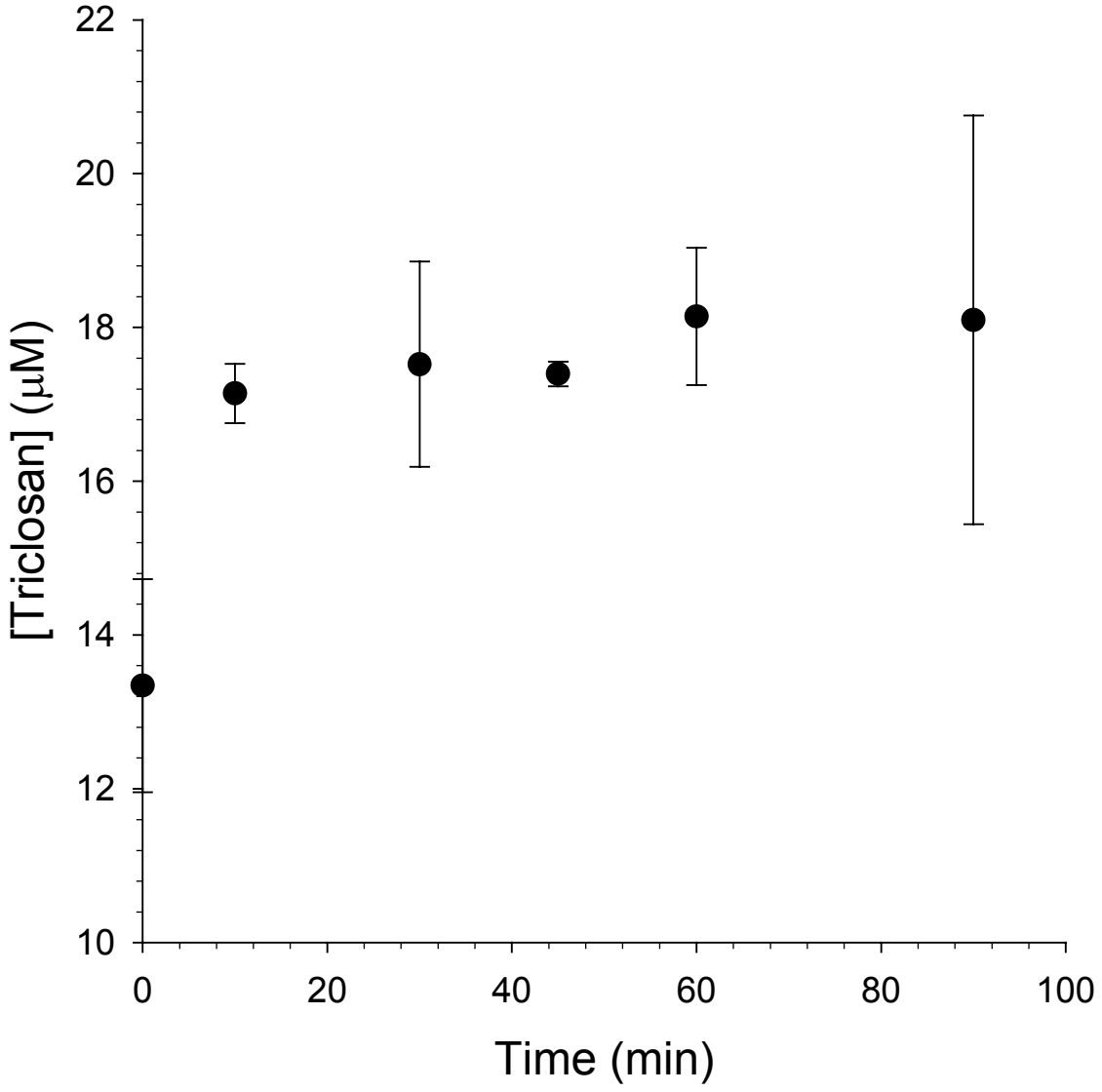

Figure 2: Optimization of the PFBBr – triclosan derivatization reaction. $[Triclosan]_0$ = 17.3 μM; T = 22 ºC.

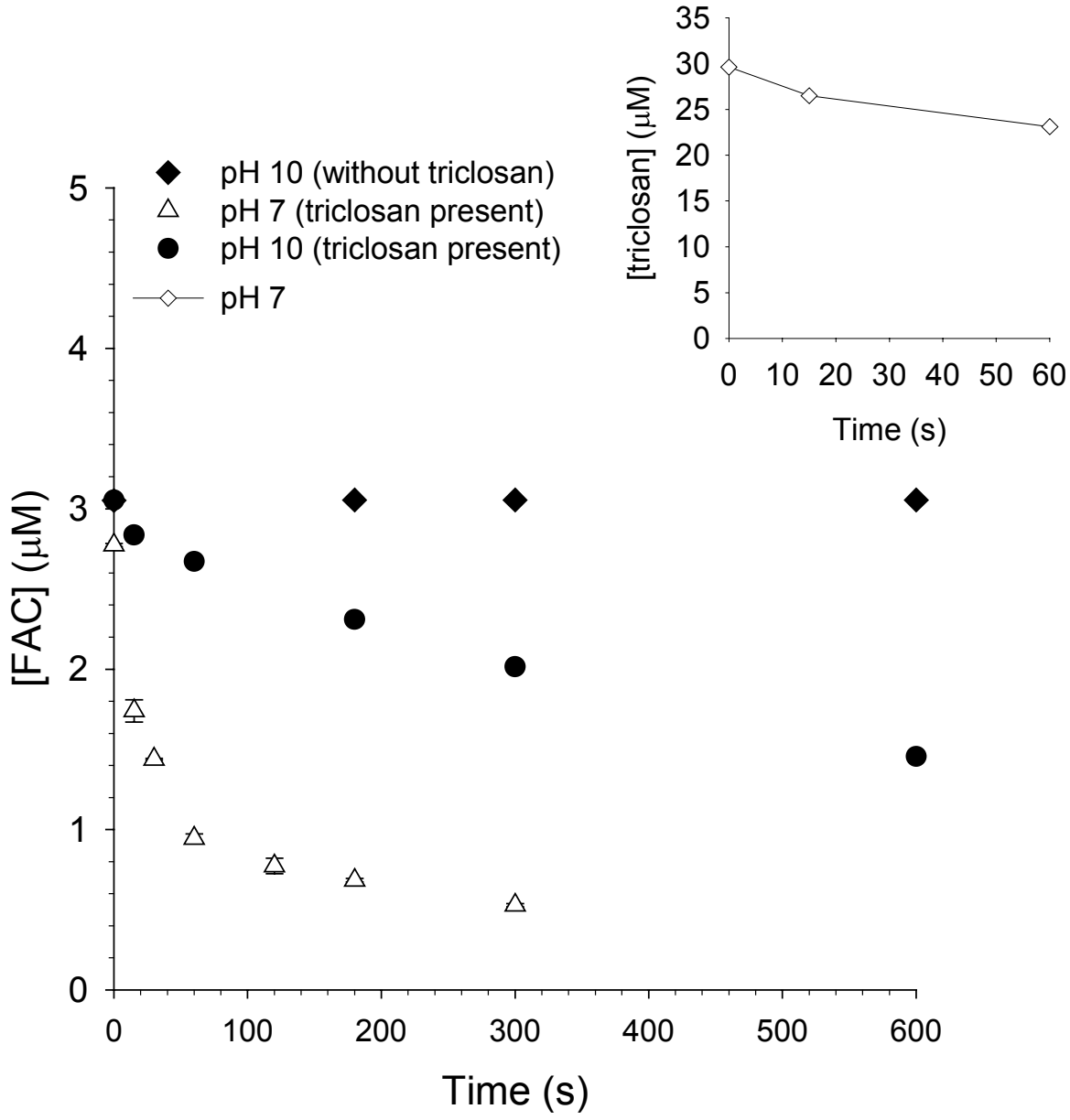

Figure 3: Free chlorine decay versus time at pH 7 and 10 with and without the addition of triclosan; $[FAC]_0$ = 2.90 - 3.04 μM; $[Triclosan]_0$ = 27.5 μM (when present); $[NaHCO_3]$ = 2 mM; T = 25 ºC; μ = 0.1 M; Inset: triclosan decay at pH 7 under the same reaction conditions.

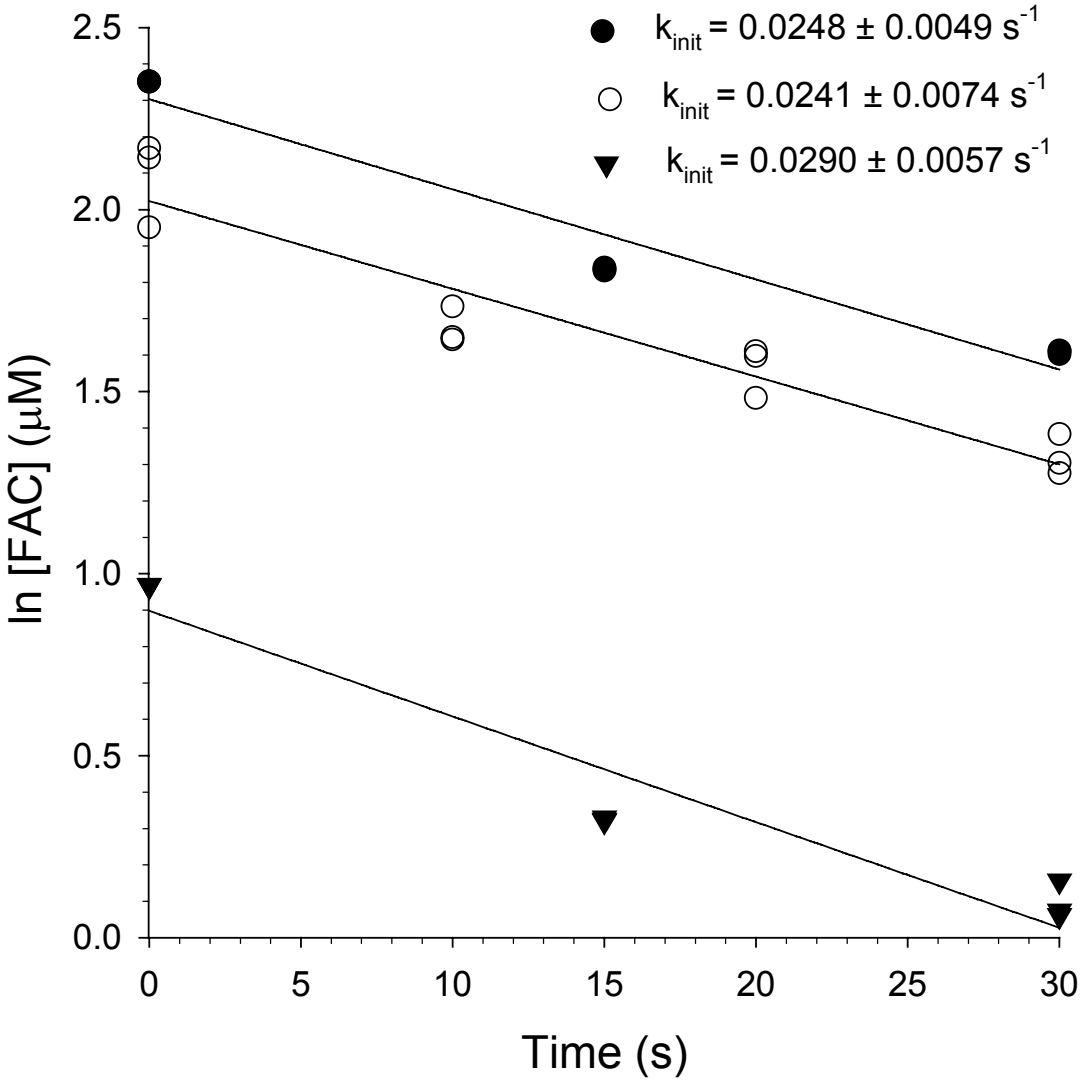

Figure 4: Order with respect to FAC at pH 4; $[FAC]_0$ = 2.63 - 10.5 µM; $[Triclosan]_0$ = 27.5 µM; $[NaHCO_3]$ = 2 mM; T = 25 ºC; µ = 0.1 M. Error in k_{init} corresponds to 95% confidence intervals.

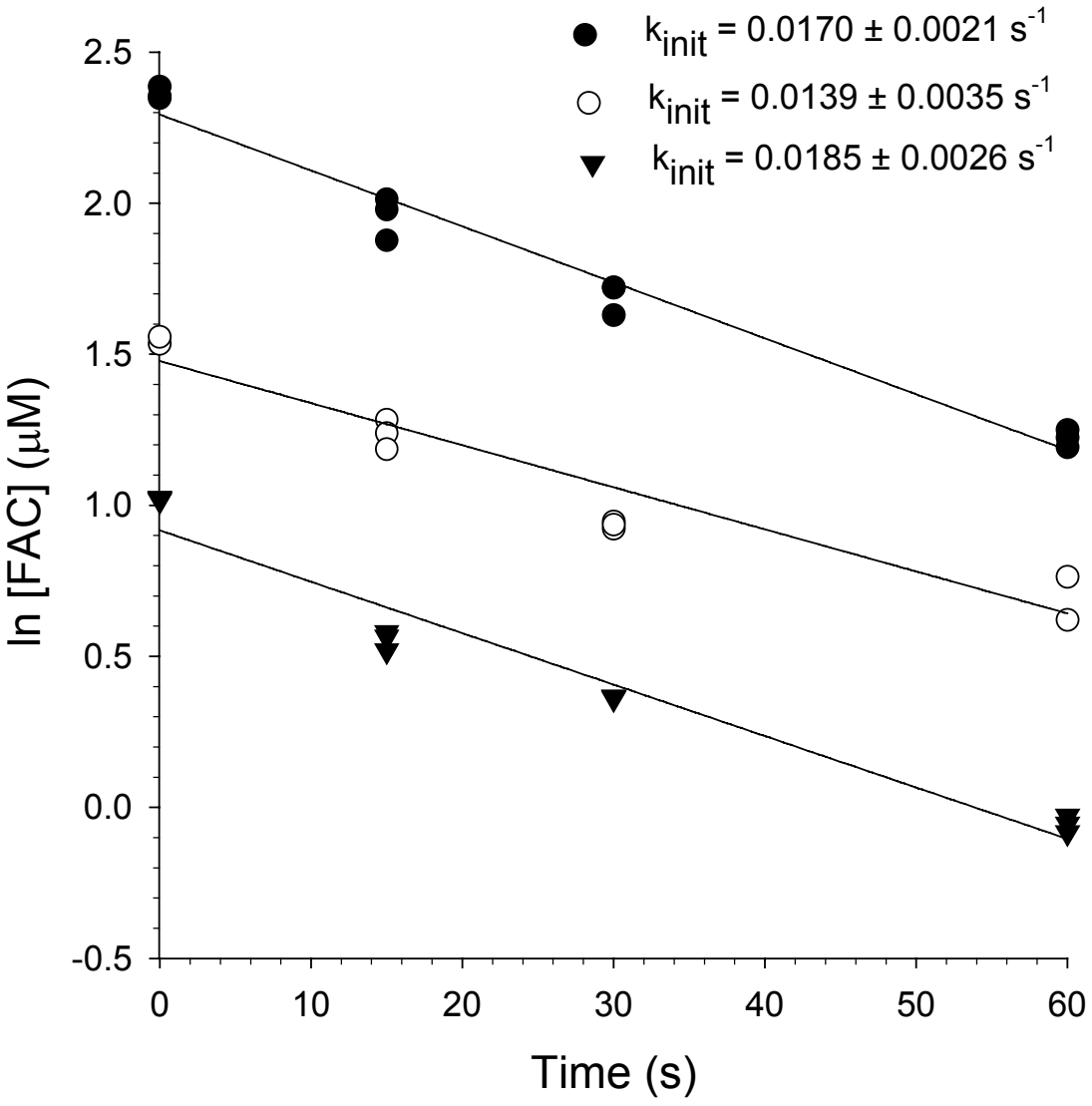

Figure 5: Order with respect to FAC at pH 7; $[FAC]_0$ = 2.77 - 10.6 µM; $[Triclosan]_0$ = 27.5 µM; $[NaHCO_3]$ = 2 mM; T = 25 ºC; µ = 0.1 M. Error in k_{init} corresponds to 95% confidence intervals.

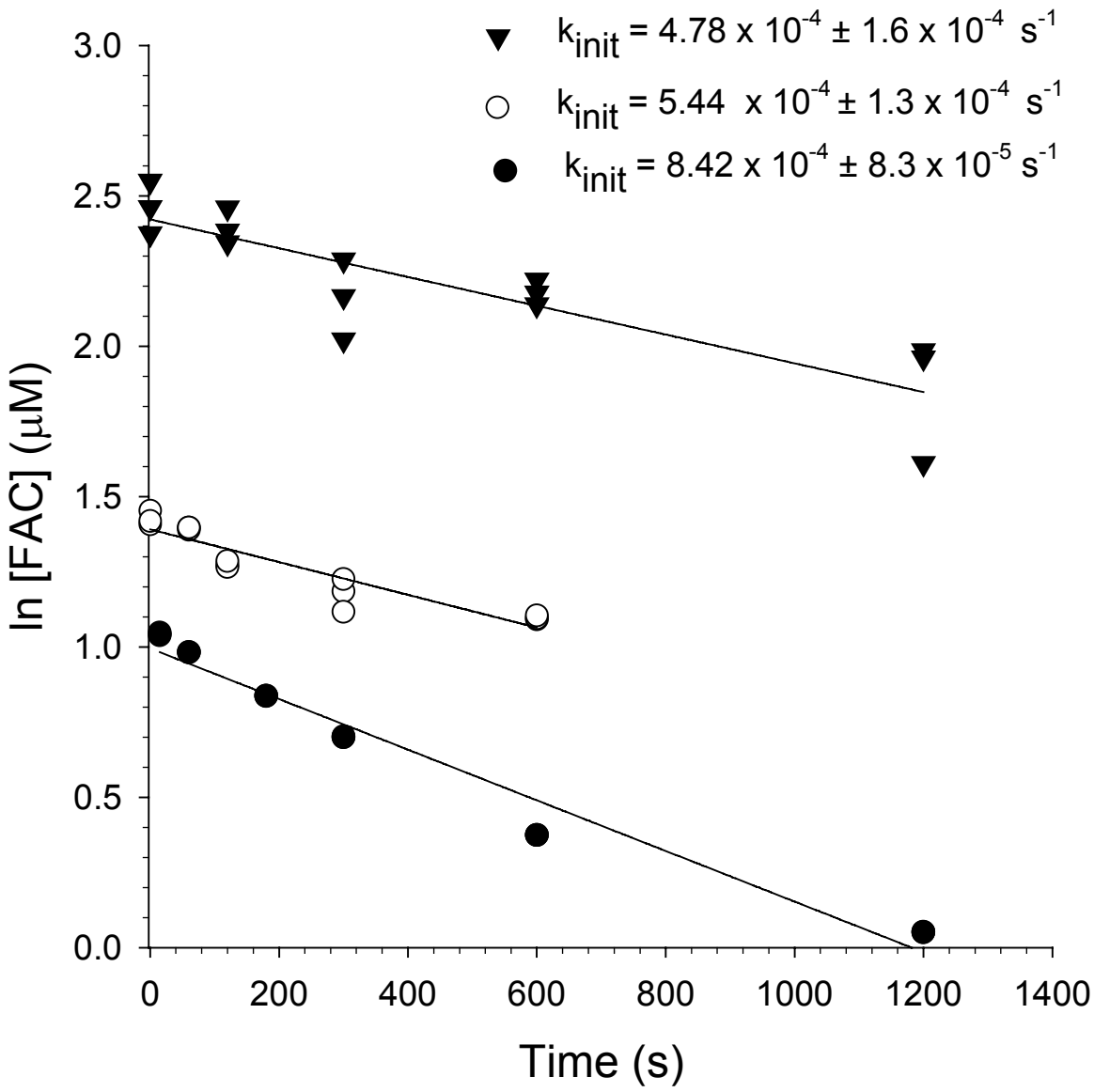

Figure 6: Order with respect to FAC at pH 10; $[FAC]_0$ = 3.05 - 11.3 µM; $[Triclosan]_0$ = 27.5 µM; $[NaHCO_3]$ = 2 mM; T = 25 ºC; µ = 0.1 M. Error in k_{init} corresponds to 95% confidence intervals.

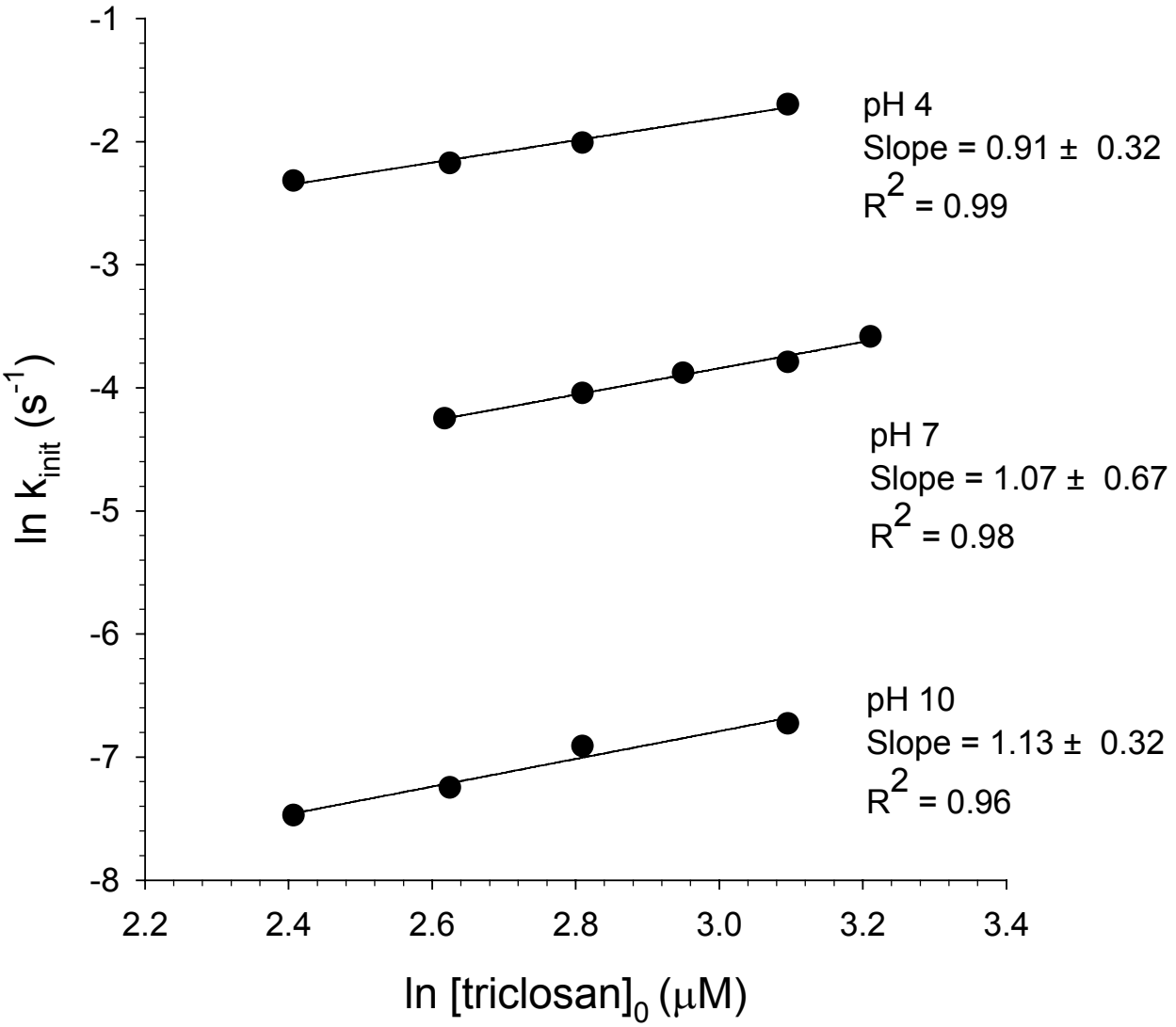

Figure 7: Order with respect to triclosan; $[FAC]_0$ = 10.5 - 11.0 μM for pH 4; $[FAC]_0$ = 1.24 - 1.89 μM for pH 7; $[FAC]_0$ = 2.07 - 2.34 μM for pH 10; $[Triclosan]_0$ = 11.1 - 24.8 μM; $[NaHCO_3]$ = 2 mM; T = 22 ºC; μ = 0.1 M. Error in slopes corresponds to 95% confidence intervals.

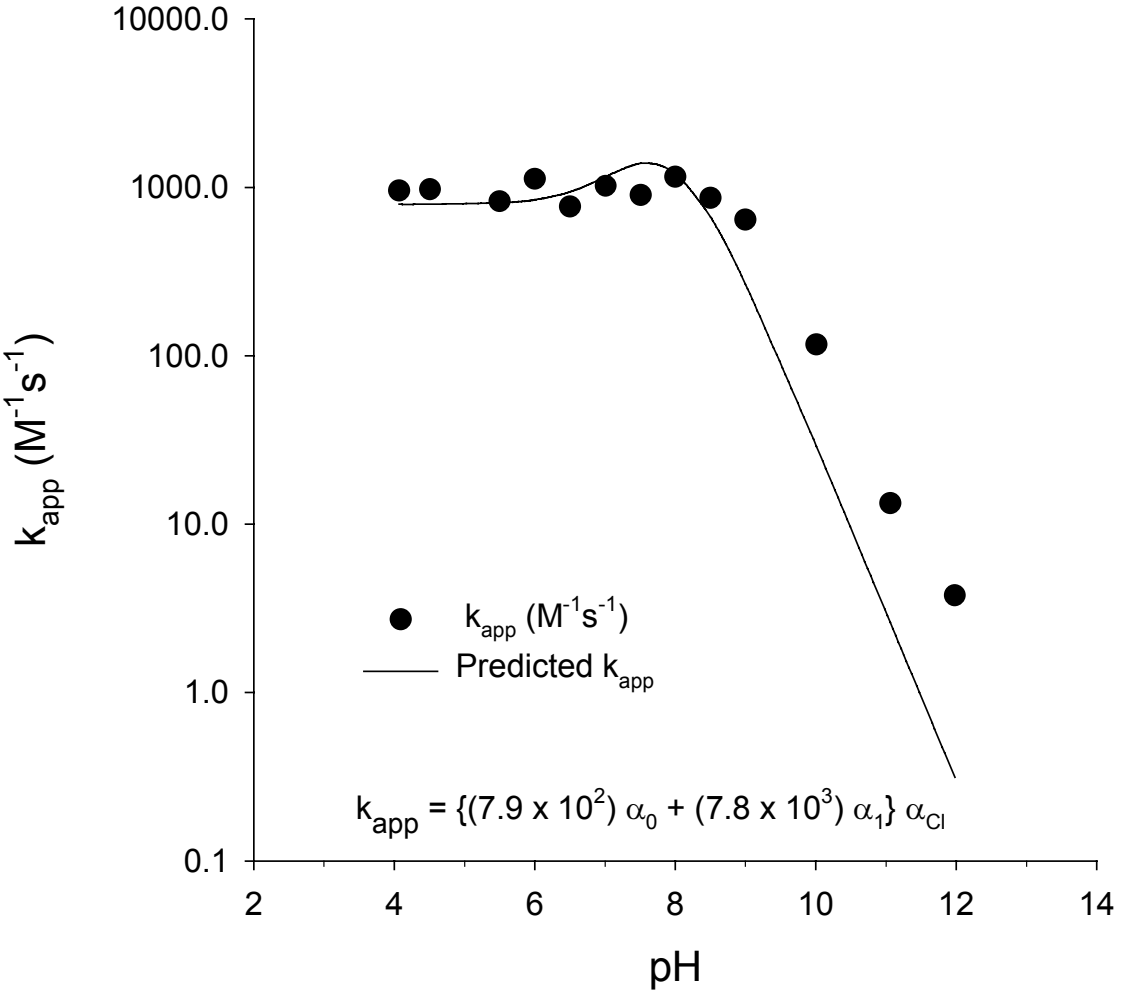

Figure 8: Apparent second-order rate coefficient (k_{app}) as a function of pH; $[FAC]_0$ = 2.33 - 3.13 µM; $[Triclosan]_0$ = 27.5 µM; $[NaHCO_3]$ = 2 mM; T = 25 ºC; µ = 0.1 M

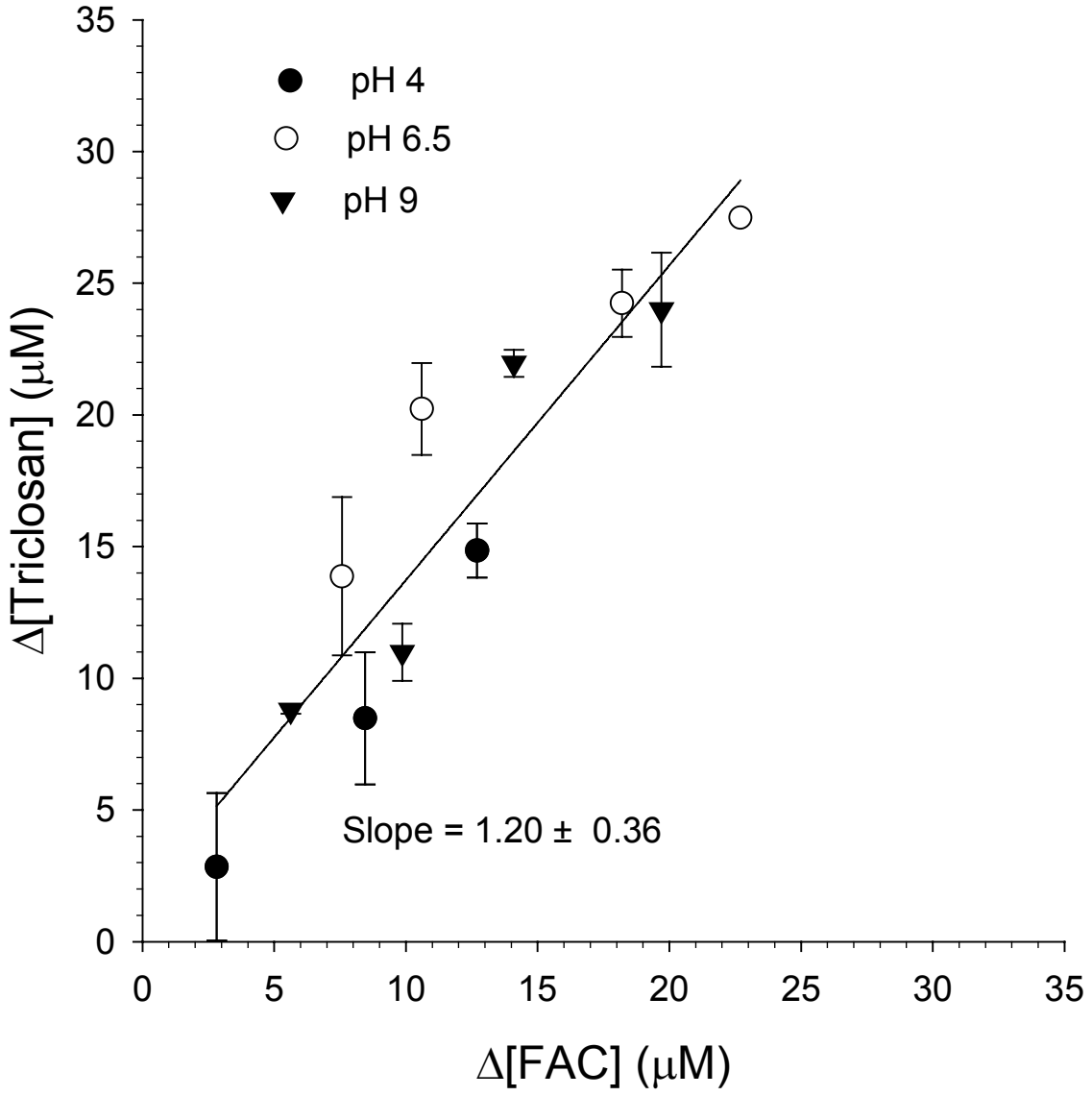

Figure 9: Triclosan-free chlorine stoichiometry; $[FAC]_0$ = 2.82 - 22.7 μM; $[Triclosan]_0$ = 27.5 μM; $[NaHCO_3]$ = 2 mM; T = 25 ºC; μ = 0.1 M. Error in slope corresponds to 95% confidence interval.

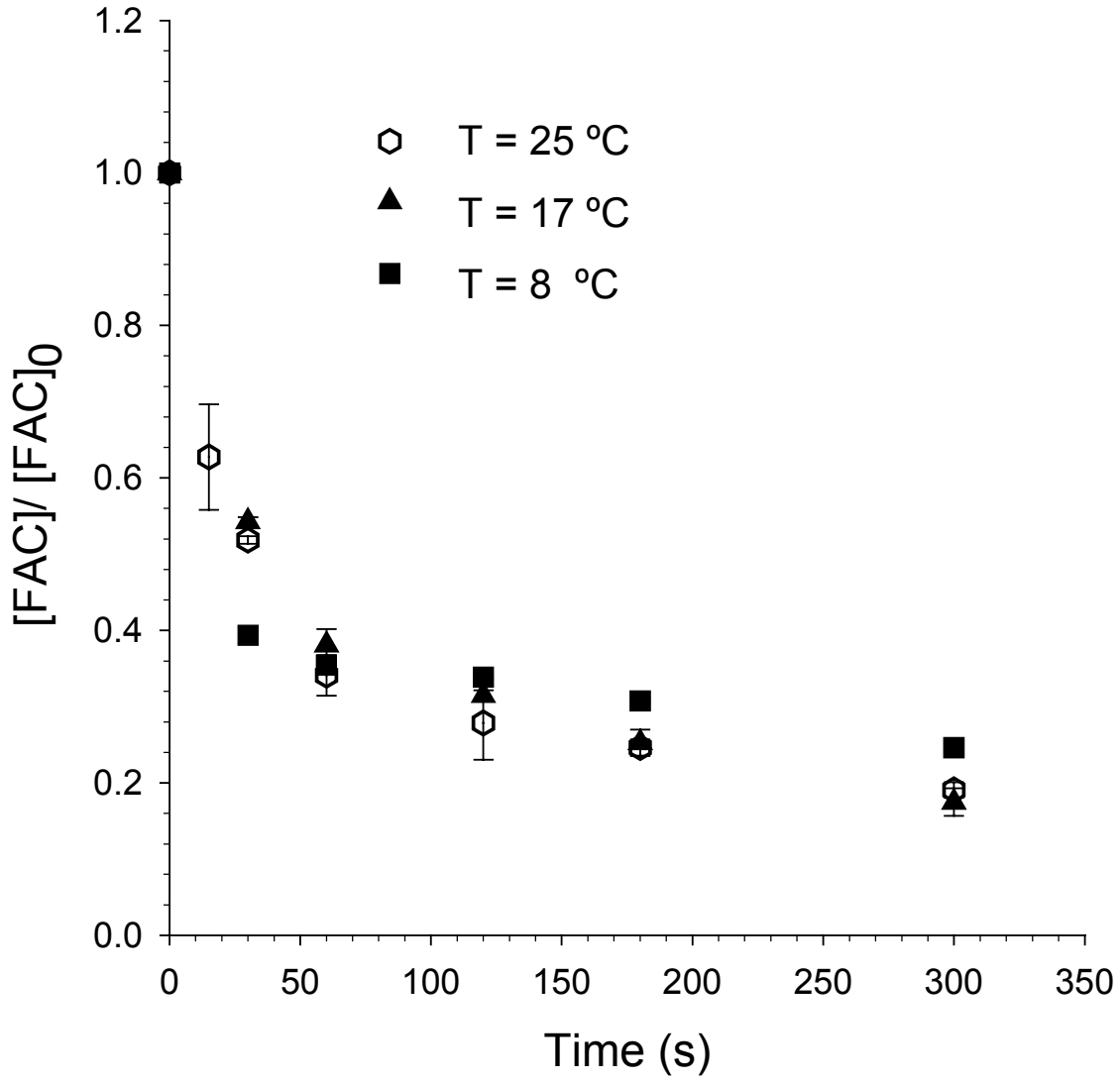

Figure 10: Examination of the temperature dependency of triclosan- free chlorine reaction kinetics at pH 7; $[FAC]_0$ = 2.41 - 2.77 µM; $[Triclosan]_0$ = 27.5 µM; $[NaHCO_3]$ = 2 mM; T =8, 17, and 25 ºC; pH = 7; µ = 0.1 M

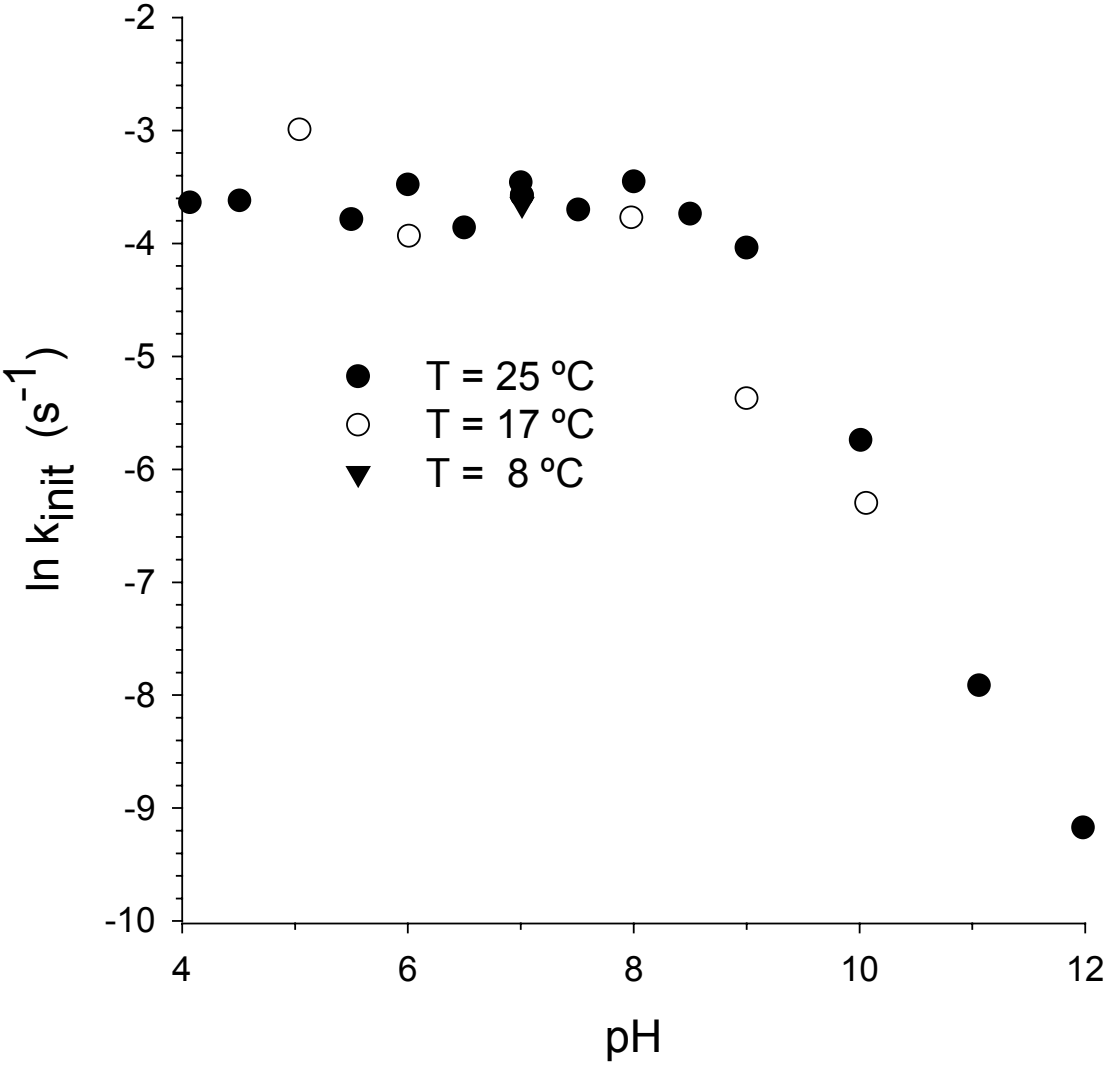

Figure 11: Examination of the temperature dependency of k_{init} as a function of pH; $[FAC]_0$ = 2.33- 3.23 µM; $[Triclosan]_0$ = 27.5 µM; $[NaHCO_3]$ = 2 mM; T = 8, 17, and 25 ºC; µ = 0.1 M

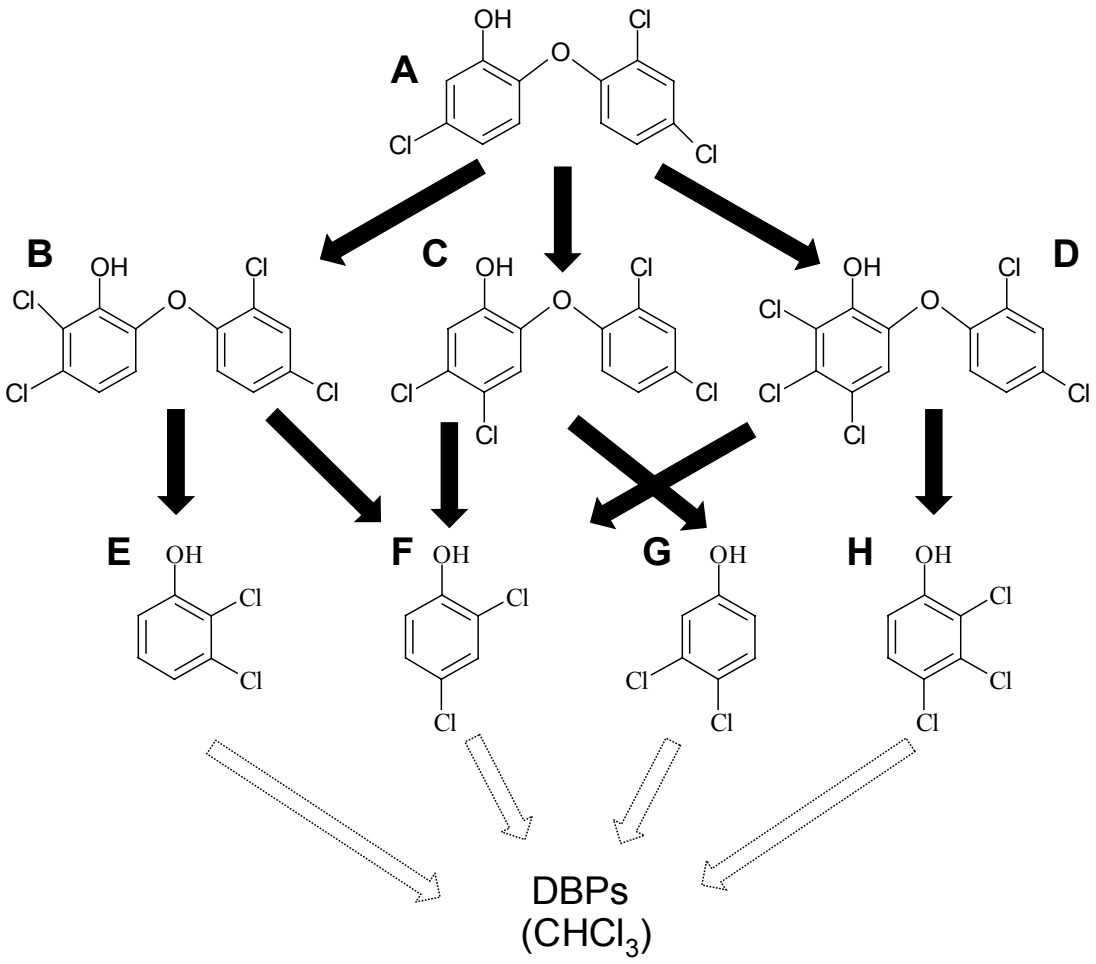

Figure 12. Proposed triclosan degradation pathway. In the presence of free chlorine, triclosan (A**) undergoes electrophilic aromatic substitution, leading to the formation of two chlorinated ether isomers (**B**: 5,6-dichloro-2-(2,4-dichlorophenoxy)phenol;** C**: 4,5-dichloro-2-(2,4-dichlorophenoxy)phenol) and one pentachlorinated ether (**D**: 4,5,6-Trichloro-2-(2,4-dichlorophenoxy)phenol). Halo-de-alkoxylation (ether cleavage) results in the formation of four chlorophenols: (**E**: 2,3-dichlorophenol;** F**: 2,4-dichlorophenol;** G**: 3,4-dichlorophenol;** H**: 2,3,4-trichlorophenol). In the presence of excess free chlorine, additional reactions potentially lead to the formation of a number of DBPs, of which $CHCl_3$ is expected to be the major species in the absence of bromide.**

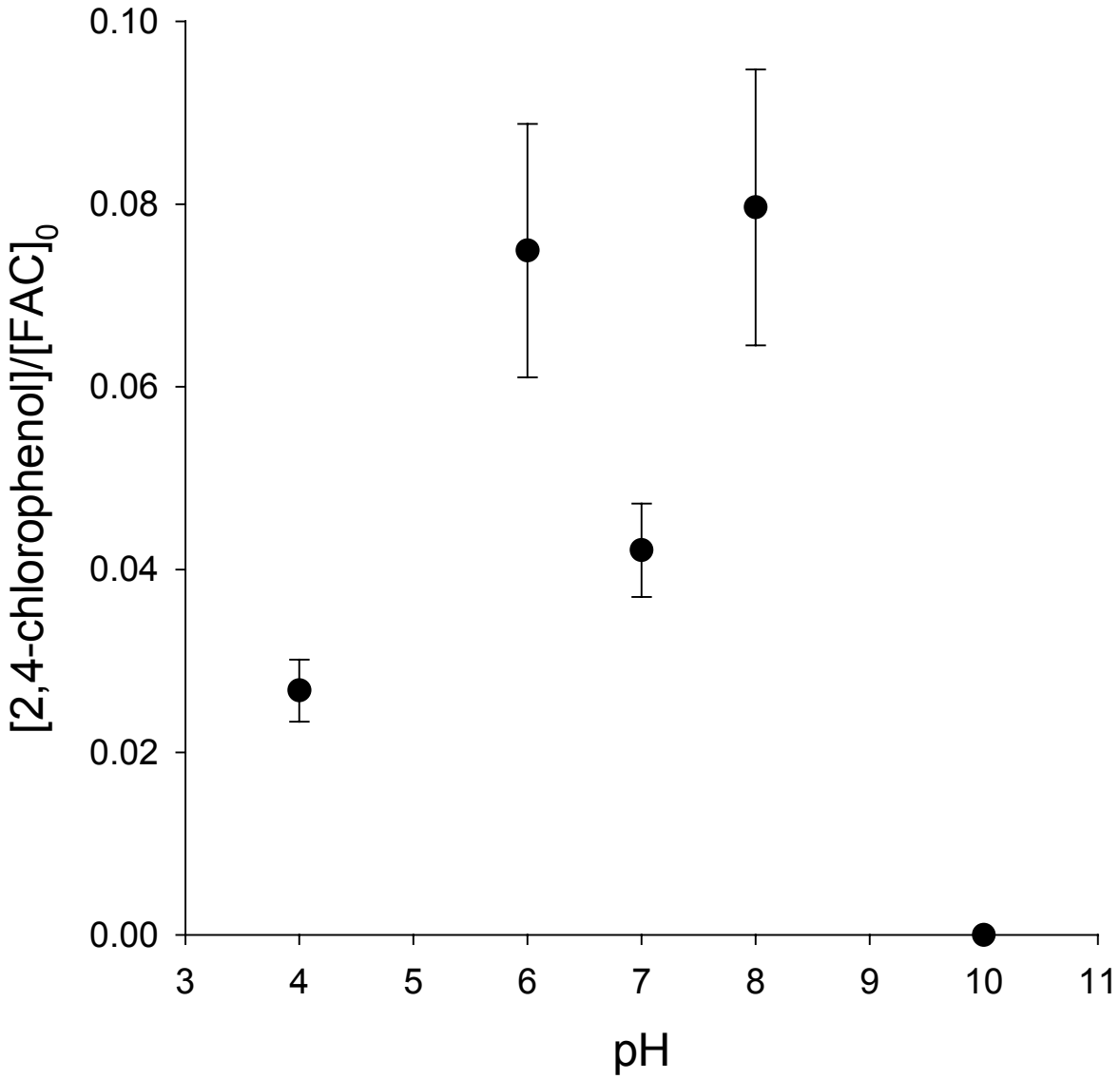

Figure 13: 2,4-dichlorophenol formation as a function of pH; $[FAC]_0$ = 2.41 - 2.89 µM; $[Triclosan]_0$ = 27.5 µM; $[NaHCO_3]$ = 2 mM; T = 25 ºC; µ = 0.1 M

Environmental Significance

When investigating the reaction between triclosan and free chlorine under conditions of excess triclosan, minute quantities of 2,4- dichlorophenol and chlorinated triclosan intermediates were formed (Products B,C,D, and F in Figure 12). Product formation was restricted by the amount of free chlorine (i.e. the reaction was free chlorine limited). Yet, the circumstances are reversed under typical drinking water conditions, with free chlorine in excess. Thus, under drinking water conditions, triclosan is the limiting factor. Because reported concentrations of the initial parent compound (triclosan) in the source waters used for drinking water treatment are extremely low, on the order of μg/L, maximum product yields are expected to be small and similar to those of this study. Additionally, this study suggests that reaction kinetics and therefore product formation do not vary significantly between pH 6 and 9; consequently, pH fluctuation would not produce varying effects. Thus, the triclosan – free chlorine reaction under drinking water conditions is not expected to produce large quantities of chlorophenol.

The intermediate products indicated in Figure 12 and tentatively identified by GC-MS may be of some concern. It is expected that higher concentrations of these intermediate products will be produced under conditions of excess free chlorine than excess free triclosan. Because the toxicity of these compounds has not been examined, the health effects of these species are unknown. Consequently, this examination suggests that in drinking water facilities where the triclosan – free chlorine reaction occurs, chlorophenol production will not be a significant issue, but the formation of chlorinated triclosan intermediates may be of concern. More research must be performed to address this potential problem. Measurement of the production of chloroform and other THMs from the reaction of triclosan and free chlorine is currently on-going.

Conclusions

This study specifically investigated the kinetics of the chlorination of triclosan. Under drinking water treatment conditions, triclosan readily reacts with free chlorine via a second-order reaction (first order with respect to each species). While the reaction orders were not pH dependent, a significant pH dependency was observed for the reaction kinetics. No significant

temperature dependency was observed from 8 to 25 °C. Over the pH range examined (pH 4 - 12), the reaction stoichiometry was determined to be one.

As shown in Figure 8, k_{app} is relatively pH independent for pH values < 9 but decreases appreciably at more alkaline pH values. One potential reason for this pH effect was theorized. It was hypothesized that if hypochlorous acid were the major contributor to the reaction, then at alkaline pH the reaction would be retarded due to the minute percentage of free chlorine in the form of HOCl at these higher pH values. A similar hypothesis was reported by Rebenne et al (*28*). This concept is partially supported through the model which incorporates only the protonated chlorine species. However, more research must be done to substantiate this assertion.

Theoretically, k_{app} is not a function of reactant concentration, and accordingly, this reaction rate coefficient could be applied to systems regardless of reactant concentrations. However, reactions under conditions of excess free chlorine must be performed and evaluated in order to validate this model.

The calculated rate coefficients for the reaction of HOCl with triclosan and phenolate-triclosan were 7.9×10^2 and 7.8×10^3 $M^{-1}s^{-1}$, respectively. When compared with the literature values for the chlorination of eight phenolic compounds, the rate coefficients for the chlorination of the neutral form of each compound are less than the rate coefficients for the phenolate, indicating that the deprotonated phenols react more quickly with free chlorine than the protonated forms. The reaction of triclosan with free chlorine was more rapid than those values for all of the other compounds with the exception of orcinol. The reaction of phenolate-triclosan and free chlorine was slower than six of the compounds but faster than 4-chlorophenol and 2,4-dichlorophenol. These differences can be attributed to the varied substituents on the compounds' ring structures and their respective electron withdrawing and electron donating capabilities (*37*). Accordingly, a simple trend between the rate coefficients from the chlorination of triclosan and the other phenolic compounds cannot be drawn which suggests that these reaction coefficients are the culmination of a variety of factors.

Preliminary product analyses support the mechanism proposed in Figure 12, which details the potential degradation pathway for triclosan. Initially, triclosan is chlorinated in the ortho and/or para positions, relative to the hydroxyl group. Then, these intermediate compounds undergo halo-dealkoxylation (ether cleavage), resulting in the potential formation of four individual chlorophenols. The chlorophenols continue to react under conditions of excess

chlorine to produce disinfection by-products, including THMs. Different research endeavors support various aspects of this mechanism (*31, 35, 36, 46*); yet, this mechanism needs to be clarified more fully. Consequently, product quantification and mechanism validation are currently on-going.

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Vita

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