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Formation of Chloroform and Chlorinated Organics by Free-Chlorine-Mediated Oxidation of Triclosan

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The widely used antimicrobial agent triclosan (5-chloro-2-(2,4-dichlorophenoxy)phenol) readily reacts with free chlorine under drinking water treatment conditions. Overall second-order kinetics were observed, first-order in free chlorine and first-order in triclosan. Over the pH range of 4−11.5, the kinetics were pH sensitive as a result of the pH dependent speciation of both triclosan and free chlorine. Using a Marquardt−Levenberg routine, it was determined that this pH effect indicates that the dominant reaction in this system is between the ionized phenolate form of triclosan and hypochlorous acid (HOCl). The overall second-order rate coefficient was determined to be $k_{ArO^-} = 5.40\ (\pm 1.82) \times 10^3\ M^{-1}\ s^{-1}$. Three chlorophenoxyphenols and two chlorophenols were identified by gas chromatographic−mass spectroscopic analysis. The chlorophenoxyphenol compounds include two monochlorinated triclosan derivatives (5,6-dichloro-2-(2,4-dichlorophenoy)phenol and 4,5-dichloro-2-(2,4-dichlorophenoxy)-phenol) and one dichlorinated derivative (4,5,6-trichloro-(2,4-dichlorophenoxy)phenol); these species form via bimolecular electrophilic substitution of triclosan. 2,4-Dichlorophenol was detected under all reaction conditions and forms via ether cleavage of triclosan. In experiments with excess free chlorine, 2,4,6-trichlorophenol was formed via electrophilic substitution of 2,4-dichlorophenol. Chloroform formation was observed when an excess of free chlorine was present. A Hammett-type linear free-energy relationship (LFER) using Brown−Okamoto parameters (σ^+) was established to correlate the reactivity of HOCl and the phenolate forms of triclosan and other chlorophenols ($\log k_{ArO^-} = -(10.7 \pm 2.2)\Sigma\sigma^+_{o,m,p} + 4.43$). This LFER was used to obtain estimates of rate coefficients describing the reactivity of the intermediates 5,6-dichloro-2-(2,4-dichlorophenoy)phenol ($k_{ArO^-} \approx 6 \times 10^2$), 4,5-dichloro-2-(2,4-dichlorophenoxy)phenol ($k_{ArO^-} \approx 3 \times 10^2$), and 4,5,6-trichloro-(2,4-dichlorophenoxy)phenol ($k_{ArO^-} \approx 4 \times 10^1$).

Introduction

Triclosan (5-chloro-2-(2,4 dichlorophenoxy)phenol) is a commonly used antimicrobial agent found in products such as toothpastes, acne creams, deodorants, and hand soaps at concentrations that range from 0.1 to 1%. Although introduced over 30 years ago, the application of triclosan has increased dramatically over the last 10 years. Currently, it is incorporated into kitchen tiles, children's toys, cutting boards, toothbrush handles, and athletic clothing, among other things.

Triclosan is used in many products because it exhibits antibacterial as well as antifungal and antiviral properties (*1*). Until recently, the compound was believed to solely act as a nonspecific biocide that disrupts bacterial membrane functionality (*2*). 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* (*3*), *Mycobacterium smegmatic* (*4*), and *M. tuberculosis* (*5*), 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, however, that the high doses employed in antibacterial goods result in cell lysis from several simultaneous effects (*6*). Nevertheless, studies identify mechanisms of triclosan resistance that are similar to those associated with antibiotic resistance (*7*), and consequentially there is concern that triclosan exposure could promote microbial immunity.

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 wastewater treatment plant (WWTP) influents at levels ranging from 0.062 to 21.9 μg/L (*8*−*12*). Triclosan removal within WWTPs varies with the type of secondary and tertiary treatment employed, with reported removal percentages between 0 and 100% (*9*−*11*, *13*, *14*). Activated sludge processes generally have high triclosan removal percentages of >90% (*9*, *11*, *14*), while attached growth processes have lower removal percentages and are less consistent (*12*). A relatively high octanol−water partition coefficient ($\log K_{ow}$) of 4.8 (*15*) indicates the tendency of the compound to sorb to organic material, and thus wasted sludge (biosolids) can contain up to 30% of influent triclosan (*11*, *13*, *14*). Reported WWTP effluent concentrations range from 0.042 to 22.1 μg/L (*12*, *13*, *16*).

The incomplete removal of triclosan via wastewater treatment, the land-application of triclosan laden biosolids (*11*, *13*, *14*), and leaking sewer pipes (*17*) result in the continued release of the compound into the aquatic environment. Recent studies have detected triclosan in natural waters and sediments. A comprehensive study by the United States Geological Survey surveyed 139 U.S. streams considered highly susceptible to contamination by numerous pharmaceuticals, hormones, and other organic contaminants (*18*). 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. Reports suggest that triclosan is readily removed from natural waters via biodegradation (*8*, *19*, *20*), photolysis (*8*, *21*, *22*), and association with solid surfaces (*13*, *15*). Reported in-stream removal rates are in the range of 0.21−0.33 h^{-1} for Mag Brook in England (*12*) and 0.06 h^{-1} in Cibolo Creek in Texas (*23*). These rates, however, only account for triclosan removal from the aqueous phase and do not account for its potential accumulation in sediments. In fact, triclosan has been measured in marine sediments near a WWTP effluent pipe at levels between 0.27 and 130.7 μg/kg (*16*).

The fate of triclosan in the environment is significantly influenced by its pH dependent speciation. The pK_a of

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triclosan is 7.9 (*8*), and thus the anionic phenolate form (described hereafter as phenolate-triclosan) predominates when natural waters are above pH 7.9; when waters are below pH 7.9, the neutral phenolic form is the primary species. Both the photodecomposition (*8*, *13*, *22*) and the MnO_2 surface-catalyzed oxidation (*24*) of triclosan are extremely sensitive to triclosan speciation.

Some source waters used for drinking water supply have been found to contain triclosan (*25*, *26*). In general, considerably less is known about the fate of pharmaceutical and personal care products (PPCPs), such as triclosan, in drinking water treatment than in wastewater treatment. Drinking water plants rarely analyze for PPCPs and when they do, concentrations of individual compounds are often lower than easily achieved analytical detection limits (*27*). Currently, there are no U.S. 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 (*27*). Recent cases have, however, reported the presence of PPCPs, in general (*25*, *28*, *29*), and triclosan, in particular (*30*), in treated drinking water. A complete understanding of the fate of PPCPs within water treatment plants and in treated drinking waters is therefore necessary to address the impacts of these micropollutants on the safety of drinking water.

In general, PPCPs are not effectively removed by coagulation−flocculation and thus for many treatment plants the elimination of these compounds occurs via interactions with the oxidants employed to disinfect the water (*27*, *31*, *32*). The effectiveness of oxidizing chemicals (e.g., ozone, free chlorine) in removing pesticides and other anthropogenic compounds is well established. Ozone, in particular, is effective at oxidizing many PPCPs, although the toxicological effects of the products formed from these reactions are not well understood (*27*, *31*, *32*). Free chlorine is not as strong of an oxidant as ozone (*27*), and thus it does not readily mineralize PPCPs. A recent study has shown that highly chlorinated analogues are produced when free chlorine interacts with PPCPs such as bisphenol A (*33*). The unknown health effects and ecological ramifications of these chlorinated analogues is a subject of concern.

Triclosan is a phenolic-ether, and thus studies examining the reactions between free chlorine and compounds containing these functional groups offer insight into the potential reactions of chlorine and triclosan. Numerous studies have examined the kinetics and products of the reactions that occur between free chlorine and phenolic compounds (*34*−*40*). When phenols undergo bimolecular electrophilic substitution (S_E2), the $-OH/-O^-$ substituent of the phenol ring activates its ortho- and para- positions toward electrophilic attack by oxidants such as chlorine (*40*, *41*). Thus, when free chlorine reacts with phenol, 2-chlorophenol and 4-chlorophenol are the initial products. These species are further chlorinated to form 2,6-dichlorophenol or 2,4-dichlorophenol, both of which are further chlorinated to produce 2,4,6-trichlorophenol (*38*, *40*). In the presence of excess free chlorine, Onodera et al. (*36*) proposed that the para position of 2,4,6-trichlorophenol is hydrolyzed and oxidized by HOCl to produce the intermediate 2,6-dichloro-*p*-benzoquinone. Further oxidation of this intermediate leads to the production of chlorinated carboxylic acids (*34*, *35*) and trihalomethanes (*37*, *41*).

Although two prior studies (*42*, *43*) examined the chlorination of triclosan, the applicability of these studies to drinking water treatment conditions is unknown. In these previous studies, the reactions between triclosan and free chlorine resulted in production of two monochlorinated triclosan intermediates, a dichlorinated intermediate, 2,4-dichlorophenol, and 2,3,4-trichlorophenol. Unfortunately, one of these studies did not provide quantitative product measurements (*42*) and the other was performed using triclosan impregnated fabric as the source material (*43*). Furthermore, neither study examined the kinetics of the reactions and the prospect that triclosan could act as a precursor to chloroform. At this time, there have been no comprehensive investigations examining the reactions between free chlorine and triclosan. The objective of this study was to characterize the kinetics and products of triclosan-free chlorine reactions under conditions typical of 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. The pH measurements were obtained with a Fisher Scientific model 60 pH 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. Sodium hydroxide, hydrochloric acid, and sulfuric acid were used to adjust the solution pH. 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 (0.72−8.0 mg/L). Chlorine concentrations were determined using the DPD photometric method (*44*).

Reactions were initiated by spiking an aliquot of triclosan stock into a reaction vial using a Cheney Adaptor equipped syringe. The final methanol concentration in the reaction vials never exceeded 0.2% and was therefore below the level where cosolvent effects occur (*45*). Control experiments indicate that this concentration of methanol does not exert a quantifiable free-chlorine demand. For the experiments in which free-chlorine decay was monitored, the free chlorine in the well-mixed 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 mixed and the indicator color was allowed to develop for 1 minute. Absorbance readings at 515 nm were then compared to a standard curve to determine the free-chlorine concentration. The rate constant for the DPD−free-chlorine reaction (1.4−1.7 s^{-1} at the phosphate buffer pH of 6.2; ref *46*) is considerably larger than those determined for the chlorination of triclosan. Therefore, the addition of a significant excess of DPD relative to triclosan effectively quenches reactions between triclosan and free chlorine. Overall reaction progress was determined by measuring the free-chlorine concentration as a function of time. Each measurement was obtained in triplicate.

Triclosan and Daughter-Product Analysis. Samples for quantification of triclosan and its nonvolatile daughter products were quenched with a 3× molar excess of sodium sulfite. This quenching agent was unreactive toward both triclosan and its daughter products. The quenched samples were adjusted to pH 2 with 0.1 M HCl and solid phase extracted with 3M Empore High Performance SDBS Extraction Cartridges. Prior to use, each cartridge was rinsed with 1 mL acetone and dried under vacuum. Conditioning 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. An aliquot of 20 mL was drawn through the cartridge at a rate of 5 mL/min and samples were eluted with 1 mL acetone. Following solid-phase extraction, triclosan and daughter phenolic compounds were derivatized with pentafluorobenzyl bromide (PFBBr; ref *47*). Aliquots of 100 μL of 5% PFBBr in acetone and 100 μL 10% aqueous potassium carbonate were spiked into the acetone eluates. The sample vials were crimp-sealed and set in a water bath at 80 °C for 45 min. This reaction period was determined to be sufficient for the complete derivatization of triclosan. 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.

GC-MS analysis of PFB-derivatized triclosan and the PFB-derivatized phenolic daughter products was performed on an Agilent 6890/5973 system containing 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 being held at 70 °C for 1.5 min, the temperature was ramped to 160 °C at 20 °C/min, followed by a second ramp at 8 °C/min to 280 °C. The temperature was held at 280 °C for 1 min 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-min purge time delay. An aliquot of 1 μL was injected, and the samples were run in full scan mode (range m/z = 80−550). Derivatized triclosan was identified on the basis of its elution time of 23.9 min 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 on the basis of their elution times and major ions were determined using purchased standards.

Chloroform Formation and Quantification. Experiments were performed to monitor chloroform formation under headspace-free conditions in 40-mL amber screw-top vials. Samples were analyzed for chloroform after the chlorine was quenched with sodium sulfite. Chloroform and bromodichloromethane were quantified using either a liquid−liquid extraction (LLE) procedure according to U.S. EPA Method 551 or by purge and trap (P&T) capillary gas chromatography according to U.S. EPA Method 502.2.

Liquid−liquid pentane extraction was used for THM quantification in chlorinated soap samples. Because addition of 2 mL of pentane to surfactant-containing soap samples often resulted in formation of an emulsion of pentane and water, these samples were centrifuged at 2700 rpm and 2 °C for 30 min to separate this emulsion. This step made it possible to isolate 1 mL of the organic pentane layer. Following this step, the chloroform and bromodichloromethane concentrations in the pentane extracts were quantified using an Agilent 5890 gas chromatograph. The chromatograph contained an Agilent DB-1 column (0.25 mm ID × 30 m) and an electron capture detector (ECD). The instrument was set according to the following parameters: The initial oven temperature was 30 °C and was held for 9 min. The temperature was then increased to 40 °C at a rate of 1 °C/min and was held for 5 min. The injector temperature was set at 200 °C and the detector temperature at 290 °C. The response of the ECD detector to chloroform and bromodichloromethane was calibrated using serial dilutions of analytical standards.

The purge and trap method (U.S. EPA Method 502.2) was employed for all samples that did not contain soap. Samples were purged in a Tekmar 2016 Purge and Trap Autosampler attached to a Tekmar 3000 Purge and Trap Concentrator equipped with a Supelco VOCARB 300 Purge Trap K. A Tremetrics 9001 gas chromatograph with a Tracer 1000 Hall detector was employed. The GC was equipped with an Agilent DB-624 column (30 m × 0.53 mm, film thickness = 3 μm) and the carrier gas was nitrogen. Prior to analysis, 5-mL samples were spiked with 10 μL of 10 mg/L 1,2-dibromopropane internal standard. Samples were purged for 7 min and then were baked from the trap at 250 °C for 10 min. The GC temperature program involved an initial temperature of 45 °C held for 3 min, followed by a temperature ramp to 200 °C at 11 °C/min. Sample results were integrated using a Hewlett-Packard Series II Integrator.

Results and Discussion

Experiments show that triclosan and free chlorine readily react and that the kinetics are a function of the solution pH (Figure 1). When triclosan was absent, the loss of free chlorine was negligible, and when free chlorine was absent, triclosan was stable (data not shown). To determine rate constants 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 free chlorine loss is appropriate. Pseudo-first-order rate constants (k_{obs}; s^{-1}) were determined at several pH values using the method of initial rates. The linear portion of the free-chlorine decay curves (<73% loss) was used to calculate k_{obs} (percent decays for each experiment are tabulated in Supporting Information Table S1 along with the corresponding regression coefficients). The k_{obs} values were then plotted versus the solution pH (Figure 2). As shown, reaction rates increase as pH changes from pH 3.5 to pH 6.5 and then decrease as pH increases above pH 8. This pH effect can be rationalized on the basis of the pH dependent speciation of both free chlorine and triclosan:

$$HOCl \xleftrightarrow{K_{Cl}} OCl^- + H^+ \quad (1)$$

$$\text{triclosan} \xleftrightarrow{K_{a,triclosan}} \text{phenolate-triclosan} + H^+ \quad (2)$$

$$\text{phenolate-triclosan} + HOCl \xrightarrow{k_{ArO^-}} \text{products} \quad (3)$$

On the basis of this reaction mechanism, the loss of triclosan and free chlorine can be described as follows:

$$\frac{d[FC]_T}{dt} = \frac{d[\text{triclosan}]_T}{dt} = -k_{ArO^-}[\text{phenolate-triclosan}][HOCl] \quad (4)$$

where $[FC]_T$ and $[\text{triclosan}]_T$ represent the total concentrations of free chlorine (i.e., $[HOCl] + [OCl^-]$) and triclosan ($[\text{triclosan}]_T = [\text{triclosan}] + [\text{phenolate-triclosan}]$), respectively. Experiments verified that the first-order dependencies shown in eq 4 for both free chlorine and triclosan are appropriate (Supporting Information Figures S1−S4). For an excess triclosan concentration, eq 4 can be simplified:

$$\frac{d[FC]_T}{dt} = -k_{obs}[HOCl] \quad (5)$$

where $k_{obs} = k_{ArO^-}[\text{phenolate-triclosan}]$.

Collected k_{obs} data for pH values between 6 and 11 was evaluated using a Marquardt−Levenberg least-squares minimization algorithm (SigmaPlot, SPSS Software) to obtain the pH independent parameter k_{ArO^-}. Using this approach, a value of 5.40 (±1.82) × 10^3 $M^{-1}s^{-1}$ for k_{ArO^-} was determined. As shown in Figure 2, this single parameter provides a good fit to the collected data. The rate constant (k_{ArO^-}) for triclosan is given in Table 1 along with literature values for the electrophilic substitution of other chlorophenols. As shown,

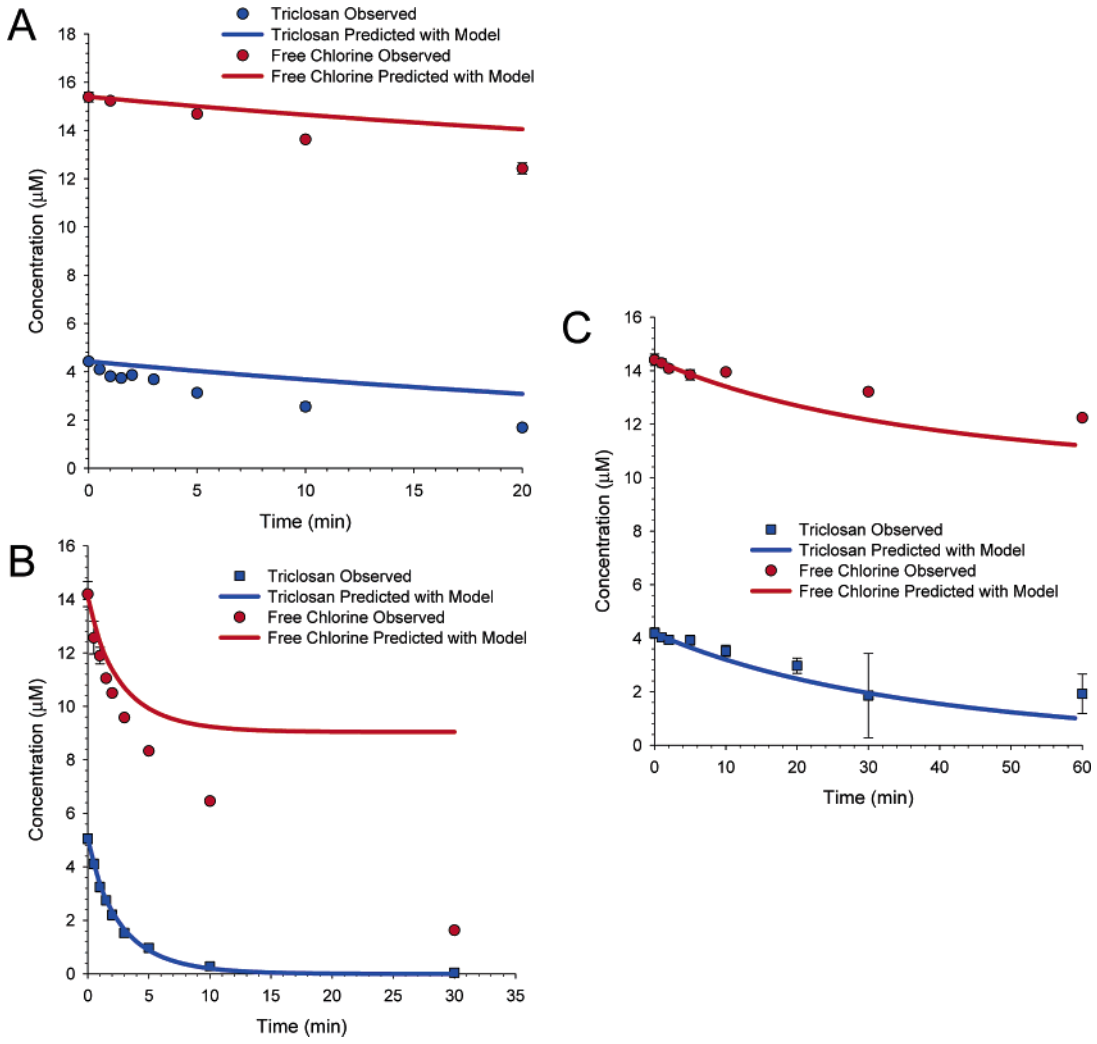

FIGURE 1. Experimental results and model predictions for triclosan and free-chlorine loss as a function of pH. (A) pH 4, (B) pH 7, (C) pH 10. Reaction conditions: $[\text{triclosan}]_0 = 5.05\ \mu M$; $[\text{free chlorine}]_0 = 14.2\ \mu M$; $[NaHCO_3] = 2$ mM.

the k_{ArO^-} rate constant for HOCl and phenolate-triclosan is within the range of values obtained for other substituted phenols.

When developing the model for this system, other potential pH dependent reactions were considered in addition to reactions 1−4; on the basis of alternate model fits, however, the reactions of OCl^- with triclosan, OCl^- with phenolate-triclosan, and HOCl with triclosan were deemed insignificant. For phenols, the reactivity of OCl^- is typically negligible in comparison to HOCl (*37*−*39*). Furthermore, phenolic compounds, such as triclosan, are generally more reactive upon deprotonation. This effect occurs because O^- is better at activating the aromatic ring toward substitution reactions than OH (*48*). A reaction between HOCl and the neutral form of substituted phenols has been included in many kinetic models of substituted phenol reactivity (*37*, *48*) yet excluded in others (*48*). Under our conditions, inclusion of such a term was unnecessary. Some studies on the chlorination of phenols have noted the presence of an acid-catalyzed reaction, possibly involving the species H_2OCl^+, at low pH values, and these studies have included such terms in their reaction models (*37*, *38*). Although our data suggest that there could be a slight catalytic effect of H^+ below pH 6, the potential formation of Cl_2 at these low pH values causes the kinetic characterization to become difficult and we thus refrain from including such a reaction in the model.

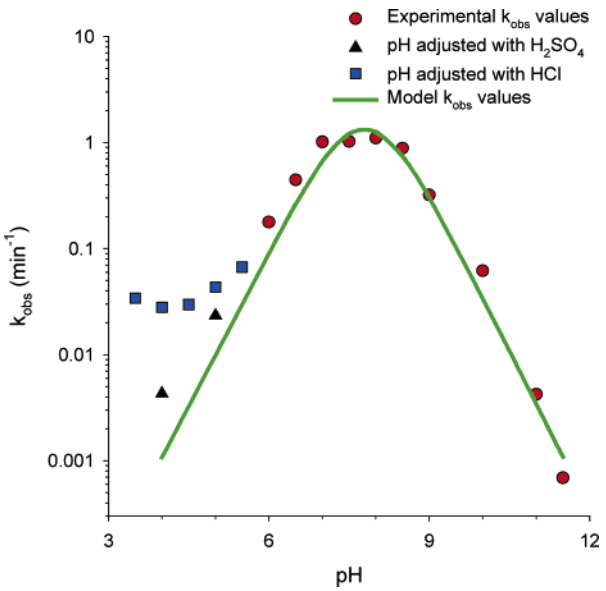

FIGURE 2. Observed pseudo-first-order rate constants (k_{obs}) vs pH for the electrophilic substation of triclosan by free chlorine. Reaction conditions: $[\text{free chlorine}]_0 = 2.33-3.23\ \mu M$; $[\text{triclosan}]_0 = 27.5\ \mu M$; $[NaHCO_3] = 2$ mM.

TABLE 1. Rate Constants for the Electrophilic Substitution of Triclosan and a Series of Chlorinated Phenols

	compound	pK_a [ref]	$\Sigma\sigma^+_{o,m,p}$[a]	k_{ArO^-} ($M^{-1}s^{-1}$)	half-life ($t_{1/2}$)[b]	source
1	phenol	9.95 [*45*]	0	2.19 (±0.08) × 10^4	0.05 min	*c*
2	4-chlorophenol	9.29 [*45*]	0.11	2.17 (±0.33) × 10^3	0.48 min	*d*
3	4-chlorophenol	9.29 [*45*]	0.11	3.16 (±0.22) × 10^3	0.33 min	*e*
4	2-chlorophenol	8.44 [*45*]	0.086	2.42 (±0.08) × 10^3	0.43 min	*e*
5	2,4-dichlorophenol	7.85 [*45*]	0.21	3.03 (±0.09) × 10^2	3.41 min	*e*
6	2,6-dichlorophenol	6.97 [*37*]	0.17	1.94 (±0.08) × 10^2	5.32 min	*e*
7	2,4,6-trichlorophenol	6.19 [*45*]	0.3	1.28 (±0.07) × 10^1	80.7 min	*e*
8	triclosan	7.9 [*15*]	0.07[c]	5.40 (±1.82) × 10^3	0.19 min	this study
A	5,6-dichloro-2-(2,4-dichlorophenoxy)phenol	???	0.16[c]	6 × 10^2	1.72 min	estimated using LFER
B	4,5-dichloro-2-(2,4-dichlorophenoxy)phenol	???	0.18[c]	3 × 10^2	3.44 min	estimated using LFER
C	4,5,6-trichloro-2-(2,4-dichlorophenoxy)phenol	???	0.27[c]	4 × 10^1	25.8 min	estimated using LFER

[a] $\Sigma\sigma^+_{o,m,p}$ values calculated using literature values (*52*) for σ^+_m and σ^+_p. σ^+_o was estimated using (*53*): $\sigma^+_o = 0.66\ \sigma^+_p$. [b] Estimated by assuming pseudo-first-order conditions with a free-chlorine excess. pH 7; [free chlorine]$_0$ = 14.1 μM. [c] Estimated by assuming that the σ^+_p value for $-OC_6H_5$ (= −0.5; ref *54*) is the same as that for $-OC_6H_3Cl_2$. [d] Reference *37*. [e] Reference *38* as cited by ref *37*.

It has been suggested that the presence of Cl^- in solutions containing both free chlorine and phenolic compounds may cause an increase in the apparent reaction rate at pH values below 6 (*37*, *38*, *48*). When chloride is present, the equilibrium of the reaction between elemental chlorine and free chlorine shifts toward elemental chlorine ($K_{hydrolysis} = 4.0 \times 10^{-4}$; ref *37*):

$$H^+ + Cl^- + HOCl \leftrightarrow Cl_2 + H_2O \qquad (6)$$

Elemental chlorine is generally considered a stronger oxidant than HOCl, and its presence could result in faster reaction rates. At the outset of these experiments, HCl was used for pH adjustment below pH 7. To determine if reaction rates at low pH were affected by the use of HCl, a set of experiments was conducted at pH 4 and pH 5 where the pH was adjusted with H_2SO_4. As shown in Figure 2, the measured k_{obs} values are considerably lower when H_2SO_4 is used to lower the pH instead of HCl. This result clearly indicates the rate-enhancing effects of chloride addition.

Because the reaction kinetics are complicated at low pH values by the presence of Cl^- and the formation of Cl_2, only k_{obs} values obtained above pH 6 were employed in the development of the model. When H_2SO_4 was used to adjust the solution pH, the experimental k_{obs} values at pH 4 and pH 5 are close to those predicted by the model. The continued discrepancy at low pH between the k_{obs} values obtained using H_2SO_4 for pH adjustment and the model is presumed to be a result of the ∼4.5 μM chloride present in the solutions because of the chloride content of the stock sodium hypochlorite. Were no chloride present in these experiments, the reaction rate constants would more closely align with the model prediction.

Kinetic Model Validation. To validate the performance of the model given by eqs 1−5, experiments were performed under excess free-chlorine conditions at pH values of 4, 7, and 10. Figure 1A−C compares the reaction kinetics for both free chlorine and triclosan with model predictions for both species. As shown, the model predictions for both triclosan and free chlorine at pH 4 and pH 10 correlate reasonably well with the experimental data. At pH 7, however, the observed free-chlorine demand greatly exceeds the predicted decay even though triclosan removal is well predicted. Underprediction of free-chlorine loss by the model at this pH value is a result of the chlorine demand exerted by the reaction intermediates.

Product Identification and Kinetic Evaluation. A GC chromatogram illustrating the intermediates and products detected when triclosan is oxidized in the presence of excess free chlorine is shown in Figure 3. Two monochlorinated triclosan intermediates (denoted A and B) and a dichlorinated triclosan intermediate (denoted C) were identified on the basis of mass spectral analysis. Intermediates A and B had identical mass spectra with a molecular ion at m/z 504 and fragment ions at m/z 323 (M^+−PFB) and 286 (M^+−PFB−Cl). Intermediate C had a molecular ion at m/z 538 and fragment ions at m/z 357 (M^+−PFB) and m/z 322 (M^+−PFB−Cl). Chlorine isotope analysis of the mass spectra for the molecular ion regions of each of these compounds confirmed that intermediates A and B were triclosan plus one chlorine and that intermediate C was triclosan plus two chlorines (Supporting Information Figure S5 and Table S2). On the basis of the mass spectrum and a review of the literature (*42*), we identify products A and B to be the isomers 5,6-dichloro-2-(2,4-dichlorophenoxy)phenol and 4,5-dichloro-2-(2,4-dichlorophenoxy)phenol and the dichlorinated intermediate (product C) is identified as 4,5,6-trichloro-2-(2,4-dichlorophenoxy)phenol (Supporting Information Table S3). The reaction solutions were monitored for several di- and trichlorophenol daughter products, but only 2,4-dichlorophenol and 2,4,6-trichlorophenol were detected. Both chlorophenols were detected when triclosan reacted under excess free-chlorine conditions. 2,4-Dichlorophenol was identified on the basis of its elution time and its molecular ion at m/z 342 and fragment ion at m/z 161 (M^+−PFB). 2,4,6-Trichlorophenol was identified using its elution time as well as the molecular ion at m/z 376 and fragment ion at m/z 197 (M^+−PFB).

Analytical standards are unavailable for compounds A−C, and thus they have not been quantified at this time. The formation and decay of these intermediates, however, is a strong function of the solution pH (Figure 4). All three species form to the greatest extent at pH 7, with intermediates A and B forming and then decaying. Within the time scale of these measurements, however, the concentration of intermediate C continually rises. Over longer time scales, intermediate C eventually decays (Supporting Information Figure S6). The delayed rate at which intermediate C is degraded indicates that this compound is relatively stable compared to triclosan and intermediates A and B.

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 4D). This behavior is consistent with the known reactivity of 2,4-dichlorophenol at acidic pH values. At a pH of 4, only 0.014% of 2,4-dichlorophenol exists in the reactive phenolate ion form, and thus once 2,4-dichlorophenol is formed it is relatively stable at low pH values. The formation of 2,4-dichlorophenol is believed to occur via oxidative cleavage of the carbon−oxygen bond between the phenol ring and the chlorobenzene ring in triclosan. Production of 2,4,6-trichlorophenol is delayed relative to 2,4-dichlorophenol formation and is pH dependent (Figure 4E). Experiments examining the reactivity

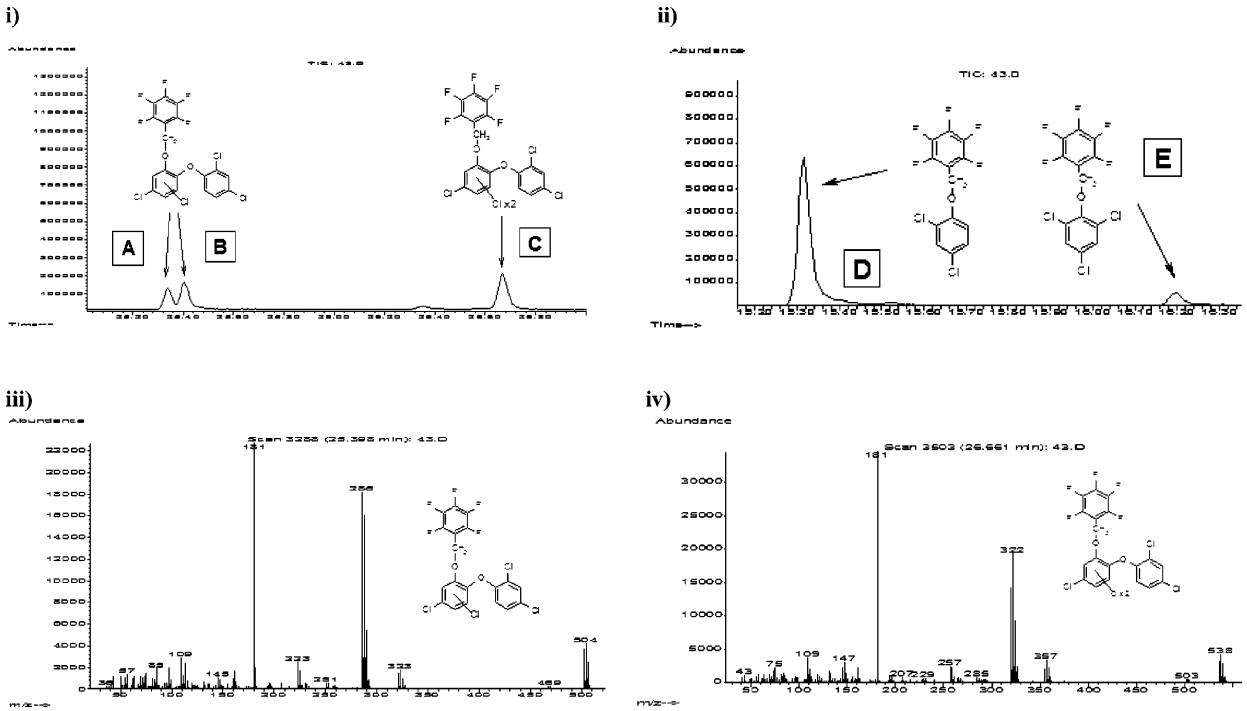

FIGURE 3. (i) GC chromatogram of PFB-derivatized chlorophenoxyphenol intermediates A, B, and C; (ii) GC chromatogram of PFB-derivatized chlorophenol intermediates D and E; (iii) mass spectrum of PFB-derivatized monochlorinated triclosan intermediate (intermediate A or B); (iv) mass spectrum of PFB-derivatized dichlorinated triclosan intermediate (intermediate C).

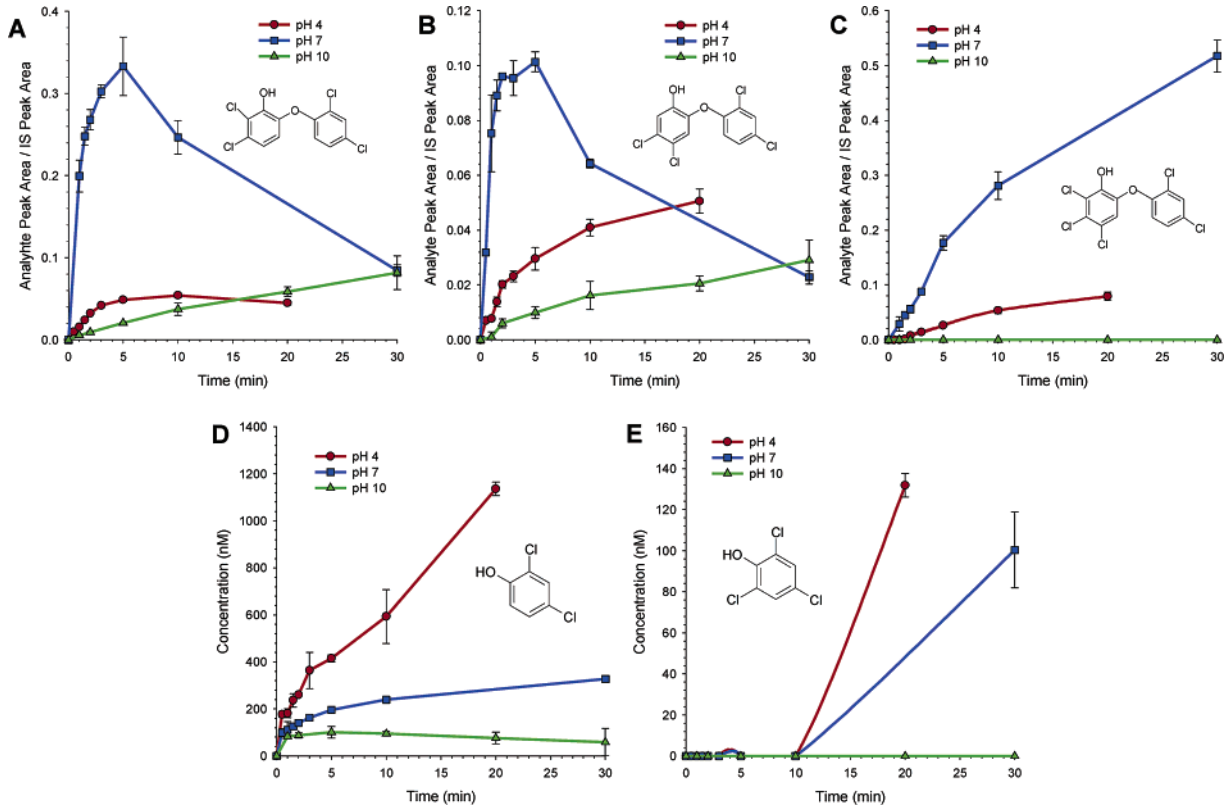

FIGURE 4. Formation and decay of A: 5,6-dichloro-2-(2,4-dichlorophenoxy)phenol, B: 4,5-dichloro-2-(2,4-dichlorophenoxy)phenol, C: 4,5,6-trichloro-2-(2,4-dichlorophenoxy)phenol, D: 2,4-dichlorophenol, E: 2,4,6-trichlorophenol for pH 4, 7, and 10. Reaction conditions: $[triclosan]_0 = 5.05\ \mu M$; $[free\ chlorine]_0 = 14.2\ \mu M$; $[NaHCO_3] = 2$ mM. Note that the *y*-axes vary considerably.

of 2,4-dichlorophenol toward free chlorine confirmed previously reported results (*38*, *40*) that indicated 2,4,6-trichlorophenol forms via chlorination of 2,4-dichlorophenol (Supporting Information Figure S7).

Other than 2,4-dichlorophenol and 2,4,6-trichlorophenol, no additional dichlorophenols or trichlorophenols were detected in the reaction solutions. On the basis of the structures of intermediates A, B, and C 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 in this system. Since none of these chlorophenols were detected, however, it appears likely that either

(1) the phenol ring of triclosan is cleaved immediately before or after scission of the ether bond or (2) these chlorophenols react too quickly to be detected. To address this second possibility, a set of experiments was conducted to examine the reactivity of 2,3-dichlorophenol, 3,4-dichlorophenol, and 2,3,4-dichlorophenol with free chlorine under pseudo-first-order conditions with a 10× chlorophenol molar excess at pH 7. Under these conditions, k_{obs} values for 3,4-dichlorophenol (=2.04 × 10^{-3} s^{-1}) and 2,3,4-trichlorophenol (=1.75 × 10^{-3} s^{-1}) are similar to the measured k_{obs} value for 2,4-dichlorophenol (=1.83 × 10^{-3} s^{-1}) at this pH. This observation suggests that if these species were formed as intermediates that they should be detectable like 2,4-dichlorophenol. Although 2,3-dichlorophenol reacts faster (k_{obs} = 9.70 × 10^{-3} s^{-1}) than the other three chlorophenols, the reaction rate is still 1.5× slower than that of triclosan, and thus this species should also be detectable if it were formed. These observations suggest that cleavage of the phenol ring of triclosan occurs at or near the same time as the breaking of the ether linkage between the phenol ring and the formation of 2,4-dichlorophenol.

Onodera et al. (*42*) reported the formation of 2,3,4-trichlorophenol and 2,4-dichlorophenol when triclosan reacted with free chlorine. These authors, however, did not detect 2,4,6-trichlorophenol. On the basis of their observations, Onodera et al. suggested that the dichlorinated triclosan intermediate (intermediate C in this paper) undergoes ether cleavage resulting in two chlorophenols: 2,4-dichlorophenol from the 2,4-dichlorophenoxy ring of triclosan and 2,3,4-trichlorophenol from the 4,5,6-trichlorophenol ring. Unfortunately, it is difficult to compare the results obtained in the present study with those reported by Onodera et al. because their paper does not fully describe their experimental conditions. Furthermore, as 2,3,4-trichlorophenol and 2,4,6-trichlorophenol have identical mass spectra and similar retention times, it is possible that 2,4,6-trichlorophenol was mistakenly identified as 2,3,4-trichlorophenol. This hypothesis seems likely given that Onodera et al. did not detect 2,4,6-trichlorophenol, a well-known product of the chlorination of 2,4-dichlorophenol (*38*, *40*).

Linear Free-Energy Relationship. A linear free-energy relationship (LFER) correlating the rate of electrophilic substitution of chlorinated phenols by hypochlorous acid (described by k_{ArO^-}) to the Hammett σ^+ substituent constant was developed. Although other Hammett parameters (i.e., σ, σ^-) have previously been used to correlate phenol reactivity (*37*, *49*−*51*), electrophilic substitution by HOCl is most appropriately described using Brown−Okamoto parameters (σ^+; ref *52*). This scale accounts for through-resonance between the chloro ring substituents and the electron-deficient reaction center of the aromatic ring (*49*, *50*, *52*). For each compound in Table 1, the sum $\Sigma\sigma^+_{o,m,p}$ was obtained using literature values for σ^+_m and σ^+_p (*52*). Values for σ^+_o were estimated on the basis of the following (*53*): σ^+_o = 0.66σ^+_p. For triclosan, the σ^+_o value was determined using this approximation and by assuming that the literature value for a $-OC_6H_5$ group in the para position (*54*) is representative of $-OC_6H_3Cl_2$. Figure 5 shows the correlation between $\Sigma\sigma^+_{o,m,p}$ and k_{ArO^-} for HOCl. The resulting linear regression for the chlorophenols is

$$\log k_{ArO^-} = -(10.7 \pm 2.2)\Sigma\sigma^+_{o,m,p} + 4.43\ (\pm 0.35) \qquad R^2 = 0.96,\ n = 8 \quad (7)$$

The negative sign for the Hammett slope (ρ) reflects an increased deactivating effect as additional chlorine substituents are added to the phenol ring. By using this LFER and by calculating the appropriate Brown−Okamoto parameters (Table 1), $k_{ArO^-,i}$ values were determined for 5,6-dichloro-2-(2,4-dichlorophenoxy)phenol (k_{ArO^-} = 600 $M^{-1}s^{-1}$), 4,5-dichloro-2-(2,4-dichlorophenoxy)phenol (k_{ArO^-} = 300 $M^{-1}s^{-1}$), and 4,5,6-trichloro-2-(2,4-dichlorophenoxy)phenol (k_{ArO^-} = 40 $M^{-1}s^{-1}$). As shown, the predicted reactivity of the chlorinated triclosan intermediates decreases with the addition of chlorine substituents. This result is consistent with the reactivity trends depicted in Figure 4.

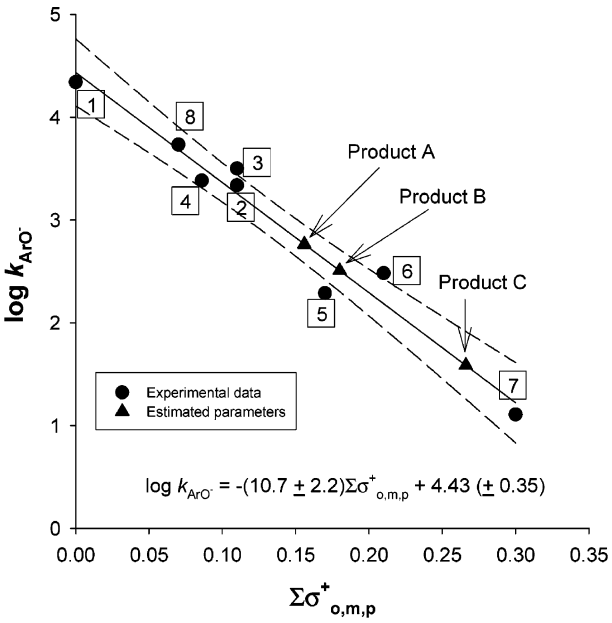

FIGURE 5. Linear free-energy relationship correlating the reactivity of a series of chlorophenols toward hypochlorous acid. The numbers in boxes refer to the compounds listed in Table 1.

Using the appropriate k_{ArO^-} values, half-lives for triclosan and its daughter products were estimated for pH 7 under excess free-chlorine conditions (Table 1). Under these conditions, similar to those found for treated drinking water, both 4,5,6-trichloro-2-(2,4-dichlorophenoxy)phenol and 2,4,6-trichlorophenol are relatively unreactive ($t_{1/2}$ > 20 min), and thus these compounds would be expected to form and be fairly stable over the course of a given experiment, a result experimentally observed.

Formation of Chloroform. Prior studies have shown that chlorinated phenols can act as precursors to chloroform (*37*, *55*). To assess the potential for triclosan to act similarly, we conducted experiments employing a 10× excess of free chlorine and measured chloroform production as a function of pH. Figure 6 shows that chloroform is readily produced when free chlorine reacts with triclosan at pH 5, 6, 8, and 9. Chloroform yields were greatest at circumneutral pH and lower under acidic or basic conditions. This pH trend is consistent with prior studies of chloroform formation when phenolic species react with free chlorine (*56*, *57*) and reflects the pH sensitive speciation of the reactants. After 48 h, 1.53 μM (183 μg/L) of chloroform had formed at pH 8 for an initial triclosan concentration of 2.5 μM (data not shown). This molar yield of chloroform (=0.612 μM chloroform/μM triclosan) is considerably larger than the yields observed for other chlorophenol species chlorinated under similar pH conditions (*37*) and suggests that the *ortho*-$OC_6H_3Cl_2$ and meta-Cl functional groups in triclosan strongly activate this compound toward chloroform production. Prior studies have shown that chloroform production is enhanced when the phenol ring is chlorinated in the meta-position (*37*, *55*); however, this is the first work to suggest that the *ortho*-$OC_6H_3Cl_2$ group enhances production of chloroform. This finding suggests that the ether linkages prevalent in humic materials (*58*) could affect the formation of several disinfection byproducts (DBPs) observed when humic-containing waters are chlorinated.

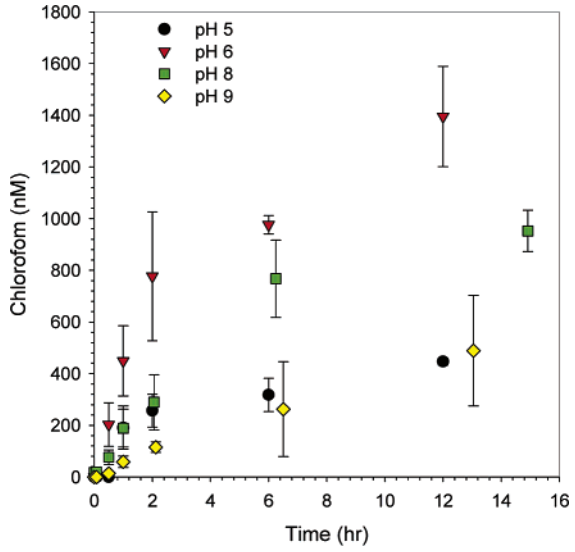

FIGURE 6. Chloroform formation as a function of solution pH. Reaction conditions: $[triclosan]_0 = 2.5\ \mu M$; $[free\ chlorine]_0 = 25\ \mu M$; $[NaHCO_3] = 2$ mM.

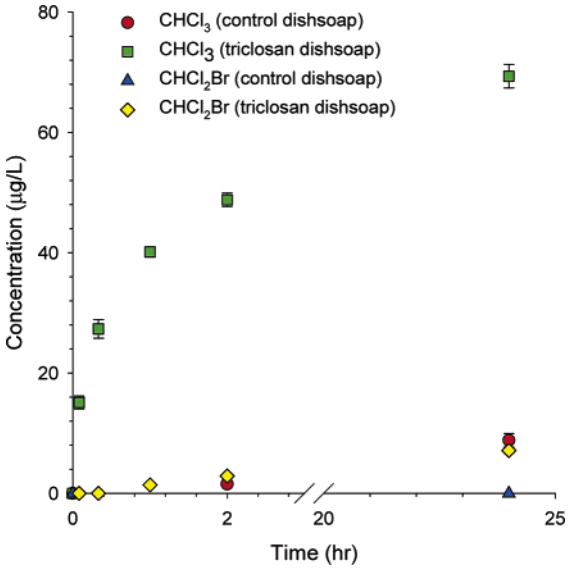

FIGURE 7. Formation of trihalomethanes when dish soap brand X reacts with chlorinated water. Reactions conditions: $[free\ chlorine]_0 = 84.9\ \mu M$; [dish soap] = 0.25 g/L; pH = 7; triclosan concentration in antibacterial soap was measured at 1.4 mg/g. At 24 h, the molar concentration of $CHCl_3$ is 581 nM and the $CHCl_2Br$ molar concentration is 44 nM for the triclosan dishsoap samples.

Chloroform production in the free chlorine–triclosan reactions could result from cleavage of the phenol ring in triclosan or could result from cleavage of the 2,4-dichlorophenol intermediate. To assess which pathway predominates in this system, an experiment examining chloroform production when 2,4-dichlorophenol reacts with free chlorine was performed (Supporting Information Figure S8). Under similar reaction conditions to those used in the triclosan experiments, the concentrations of chloroform formed when 2,4-dichlorophenol and free chlorine react are an order of magnitude lower than the concentrations of chloroform formed during the triclosan/free chlorine reactions. This finding suggests that the majority of $CHCl_3$ produced in this system originates from oxidation and ring cleavage of the phenol moiety of triclosan and not from reactions involving the 2,4-dichlorophenol produced via ether cleavage.

Hypothesized Reaction Pathway. On the basis of the kinetic experiments presented herein (Figures 4 and S6), it is possible to develop a reaction pathway for this system. In this pathway, triclosan can either undergo ether cleavage resulting in production of 2,4-dichlorophenol and products not detected via PFBBr derivatization-GC/MS analysis (e.g., quinones) or it can be chlorinated to produce one of two chlorophenoxyphenol intermediates: 5,6-dichloro-2-(2,4-dichlorophenoxy)phenol or 4,5-dichloro-2-(2,4-dichlorophenoxy)phenol. The chlorophenoxyphenol intermediates then either are further chlorinated to produce 4,5,6-trichloro-2-(2,4-dichlorophenoxy)phenol or can undergo ether cleavage to produce 2,4-dichlorophenol and products not detected via GC/MS. The 2,4-dichlorophenol produced during these interactions can either be further chlorinated to produce 2,4,6-trichlorophenol or can undergo ring cleavage as documented elsewhere (*37*, *55*).

The authors' contend that triclosan, 5,6-dichloro-2-(2,4-dichlorophenoxy)phenol, 4,5-dichloro-2-(2,4-dichlorophenoxy)phenol, and 4,5,6-trichloro-2-(2,4-dichlorophenoxy)-phenol all serve as precursors to 2,4-dichlorophenol. This contention is supported by the fact that 2,4-dichlorophenol can be detected under conditions when no chlorinated triclosan intermediates are present (Figure 4, pH 10) and 2,4-dichlorophenol production continues to occur after triclosan, 5,6-dichloro-2-(2,4-dichlorophenoxy)phenol, and 4,5-dichloro-2-(2,4-dichlorophenoxy)phenol are no longer present (Figure S6). The former observation indicates that triclosan can undergo ether cleavage to produce 2,4-dichlorophenol and the latter observation indicates that 4,5,6-trichloro-2-(2,4-dichlorophenoxy)phenol can do the same. It therefore is reasonable to conclude that the dichlorinated triclosan intermediates (5,6-dichloro-2-(2,4-dichlorophenoxy)phenol and 4,5-dichloro-2-(2,4-dichlorophenoxy)phenol) also undergo ether cleavage.

Reaction pathways in addition to ring chlorination and ether cleavage may exist and may result in intermediates or products that could not be detected and identified with the procedures employed in this project. However, as shown in Figure S6, the molar yield for the two chlorophenols at 120 min is ~45% and a substantial amount of 4,5,6-trichloro-2-(2,4-dichlorophenoxy)phenol is still present. These observations suggest that the pathway described here is a significant reaction pathway, if not the most important pathway describing triclosan reactivity toward free chlorine.

Engineering and Health Significance of Results. The reactions between triclosan and free chlorine are rapid at pH values typically encountered in drinking waters and lead to the production of several deleterious products. Under our reaction conditions, when only 2.5 μM (750 μg/L) triclosan reacts with an excess of free chlorine, significant quantities of chloroform are produced. Although the ng/L quantities of triclosan measured in source waters suggest that the importance of these reactions toward DBP formation within drinking water treatment plants and distribution systems is minor, they could have great significance within consumers' homes.

"Antimicrobial" cleaning agents currently on the market often contain triclosan at concentrations of 0.1−1%. To assess the potential for chloroform formation during household use of triclosan-containing antibacterial products, an experiment was conducted in which two dish soaps of brand X, one formulation containing triclosan (quantified as 1.4 mg triclosan/g soap) and one without, were added to chlorinated water at a concentration of 0.25 g/L. Trihalomethane formation in these samples was then monitored with time (Figure 7). Under these test conditions, the measured chloroform level was 15 μg/L after 5 min and 49 μg/L within 120 min. Over this same time frame, the chloroform levels for the nontriclosan formulation were near the detection limit. Given the rapid kinetics of chloroform production under

these test conditions, the potential exists for substantial chloroform production to occur via daily household use of triclosan-containing products. The importance of dermal and inhalational exposures to triclosan-mediated production of chloroform (and other trihalomethanes) needs to be critically assessed.

In addition to chloroform, the reactions between triclosan and free chlorine result in the production of 2,4-dichlorophenol, 2,4,6-trichlorophenol, and several chlorinated triclosan intermediates. Although the health implications of the chlorinated triclosan intermediates are currently unknown, 2,4-dichlorophenol is a known source of taste and odor problems (*40*). In the reactions where 2,4-dichlorophenol was monitored (Figure 4D), concentrations (~300 nM in pH 7 experiment) were typically 1 to 2 orders of magnitude higher than the average threshold odor concentration of 2 μg/L (~12 nM; ref *40*). These yields resulted from an initial triclosan concentration of 5.05 μM (1.46 mg/L). For soap concentrations similar to those employed in the chloroform formation experiment and for a solution pH of 7, one could expect to produce ~12 μg/L of 2,4-dichlorophenol, and thus the possibility definitely exists for odor problems to develop.

This study also has application to the wastewater treatment industry. Free chlorine is often employed during wastewater treatment to disinfect the final effluent. The kinetic results obtained herein would appear to suggest that triclosan should be rapidly removed via this chlorination process. However, when wastewater effluent is chlorinated, the high levels of ammonia present effectively cause formation of inorganic and organic chloramines. In general, chloramines are weaker oxidants than free chlorine and it is expected that they react with triclosan at a much slower rate. The lower reactivity of chloramines could explain why triclosan has been detected in wastewater treatment effluents. Research is currently underway to characterize the reaction rates and the products formed when triclosan reacts with chloramines. The results of these studies will help further characterize triclosan's fate during wastewater effluent chlorination.

Acknowledgments

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Supporting Information Available

Tables of chlorine decay percentages, chlorine isotope MS analysis, and molecular weights for PFBBr functionalized triclosan and its daughter products; figures illustrating reaction orders with respect to free chlorine and triclosan; figure depicting chlorine isotope MS spectra; figures illustrating triclosan and free-chlorine decay and subsequent product formation; a figure illustrating chloroform production when 2,4-dichlorophenol reacts with free chlorine. This material is available free of charge via the Internet at http://pubs.acs.org.

Literature Cited

(1) Jones, R. D.; Jampani, H. B.; Newman, J. L.; Lee, A. S. Triclosan: A review of effectiveness and safety in health care settings. *Am. J. Infect. Control* **2000**, *28*, 184−196.

(2) Meincke, B. E.; Kranz, R. G.; Lynch, D. L. Effect of Irgasan on bacterial growth and its adsorption into the cell wall. *Microbios* **1980**, *1980*, 133−147.

(3) McMurry, L. M.; Oethinger, M.; Levy, S. B. Overexpression of *marA*, *soxS* or *acrAB* produces resistance to triclosan in *Escherichia coli*. *FEMS Microbiol. Lett.* **1998**, *166*, 305−309.

(4) McMurry, L. M.; McDermott, P. F.; Levy, S. B. Genetic evidence that InhA of *Mycobacterium smegmatic* is a target for triclosan. *Antimicrob. Agents Chemother.* **1999**, *43*, 711−713.

(5) Slayden, R. A.; Lee, R. E.; Clifton E. Barry, R. Isoniazid affects multiple components of the type II fatty acid synthase system of *Mycobacterium tuberculosis*. *Mol. Microbiol.* **2000**, *38*, 514−525.

(6) McDonnell, G. D. P. Action and targets of triclosan. *ASM News* **1998**, *64*, 670−671.

(7) Schweizer, H. P. Triclosan: a widely used biocide and its link to antibiotics. *FEMS Microbiol. Lett.* **2001**, *202*, 1−7.

(8) Lindstrom, A.; Buerge, I. J.; Poiger, T.; Bergqvist, P.-A.; Muller, M. D.; Buser, H.-R. Occurrence and environmental behavior of the bactericide triclosan and Its methyl derivative in surface waters and in wastewater. *Environ. Sci. Technol.* **2002**, *36*, 2322−2329.

(9) McAvoy, D. C.; Schatowitz, B.; Jacob, M.; Hauk, A.; Eckhoff, W. S. Measurement of triclosan in wastewater treatment systems. *Environ. Toxicol. Chem.* **2002**, *21*, 1323−1329.

(10) Kanda, R.; Griffin, P.; James, H. A.; Fothergill, J. Pharmaceutical and personal care products in sewage treatment works. *J. Environ. Monit.* **2003**, *5*, 823−830.

(11) Bester, K. Triclosan in a sewage treatment process-balances and monitoring data. *Water Res.* **2003**, *37*, 3891−3896.

(12) Sabaliunas, D.; Webb, S. F.; Hauk, A.; Jacob, M.; Eckhoff, W. S. Environmental fate of triclosan in the River Aire basin, UK. *Water Res.* **2003**, *37*, 3145−3154.

(13) Singer, H.; Muller, S.; Tixier, C.; Pillonel, L. Triclosan: Occurrence and fate of a widely used biocide in the aquatic environment: Field measurements in wastewater treatment Plants, Surface Waters, and Lake Sediments. *Environ. Sci. Technol.* **2002**, *36*, 4998−5004.

(14) Federle, T. W.; Kaiser, S. K.; Nuck, B. A. Fate and effects of triclosan in activated sludge. *Environ. Toxicol. Chem.* **2002**, *21*, 1330−1337.

(15) Lopez-Avila, V.; Hites, R. A. Organic compounds in an industrial wastewater. Their transport into sediments. *Environ. Sci. Technol.* **1980**, *14*, 1382−1390.

(16) Aguera, A.; Fernandez, A. R.; Piedra, L.; Mezcua, M.; Gomez, M. J. Evaluation of triclosan and biphenylol in marine sediments and urban wastewaters by pressurized liquid extraction and solid phase extraction followed by gas chromatography mass spectrometry and liquid chromatography mass spectrometry. *Anal. Chim. Acta* **2003**, *480*, 193−205.

(17) Boyd, G. R.; Palmeri, J. M.; Zhang, S.; Grimm, D. A. Pharmaceuticals and personal care products (PPCPs) and endocrine disrupting chemicals (EDCs) in stormwater canals and Bayou St. John in New Orleans, Louisiana, USA. *Sci. Total Environ.* **2004**, *333*, 137−148.

(18) Kolpin, D. W.; Furlong, E. T.; Meyer, M. T.; Thurman, E. M.; Zaugg, S. D.; Barber, L. B.; Buxton, H. T. Pharmaceuticals, hormones, and other organic wastewater contaminants in U.S. streams, 1999-2000: A national reconnaissance. *Environ. Sci. Technol.* **2002**, *36*, 1202−1211.

(19) McBain, A. J.; Bartolo, R. G.; Catrenich, C. E.; Charbonneau, D.; Ledder, R. G.; Price, B. B.; Gilbert, P. Exposure of sink drain microcosms to triclosan: Population dynamics and antimicrobial susceptibility. *Appl. Environ. Microbiol.* **2003**, *69*, 5433−5442.

(20) Hay, A. G.; Dees, P. M.; Sayler, G. S. Growth of a bacterial consortium on triclosan. *FEMS Microbiol., Ecol.* **2001**, *36*, 105−112.

(21) Latch, D. E.; Packer, J. L.; Arnold, W. A.; McNeill, K. Photochemical conversion of triclosan to 2,8-dichlorodibenzo-*p*-dioxin in aqueous solution. *J. Photochem. Photobiol., A: Chem.* **2003**, *158*, 63−66.

(22) Tixier, C.; Singer, H. P.; Canonica, S.; Muller, S. R. Phototransformation of triclosan in surface waters: A relevant elimination process for this widely used biocide-Laboratory studies, field measurements, and modeling. *Environ. Sci. Technol.* **2002**, *36*, 3482−3489.

(23) Morrall, D.; McAvoy, D.; Schatowitz, B.; Inauen, J.; Jacob, M.; Hauk, A.; Eckhoff, W. A field study of triclosan loss rates in river water (Cibolo Creek, TX). *Chemosphere* **2004**, *54*, 653−660.

(24) Zhang, H.; Huang, C.-H. Oxidative transformation of triclosan and chlorophene by manganese oxides. *Environ. Sci. Technol.* **2003**, *37*, 2421−2430.

(25) Stackelberg, P. E.; Furlong, E. T.; Meyer, M. T.; Zaugg, S. D.; Hendersen, A. K.; Reissman, D. B. Persistence of pharmaceutical

compounds and other organic wastewater contaminants in a conventional drinking-water-treatment plant. *Sci. Total Environ.* **2004**, *329*, 99−113.
(26) Boyd, G. R.; Reemtsma, H.; Grimm, D. A.; Mitra, S. Pharmaceuticals and personal care products (PPCPs) in surface and treated waters of Louisiana, USA and Ontario, Canada. *Sci. Total Environ.* **2003**, *311*, 135−149.
(27) Snyder, S. A.; Westerhoff, P.; Yoon, Y.; Sedlak, D. L. Pharmaceuticals, personal care products, and endocrine disruptors in water: Implications for the water industry. *Environ. Eng. Sci.* **2003**, *20*, 449−469.
(28) Heberer, T.; Fuhrmann, B. *Occurrence of Pharmaceutical Residues in Sewage, River, Ground, and Drinking Water in Greece and Berlin (Germany)*; American Chemical Society: Washington, DC, 2001; Vol. 791.
(29) Frick, E. A.; Henderson, A. K.; Moll, D. M.; Furlong, E. T.; Meyer, M. T. Presence of Pharmaceuticals in Wastewater Effluent and Drinking Water, Metropolitan Atlanta, Georgia, July-September 1999. In *Proceedings of the 2001 Georgia Water Resources Conference*; Hatcher, K. J., Ed.; The University of Georgia: Atlanta, 2001.
(30) Henderson, A. K.; Moll, D. M.; Frick, E. A.; Zaugg, S. Presence of Wastewater Tracers and Endocrine Disrupting Chemicals in Treated Wastewater Effluent and in Municipal Drinking Water, Metropolitan Atlanta, 1999. In *Proceedings of the 2nd International Conference on Pharmaceuticals and Endocrine Disrupting Chemicals in Water*, National Ground Water Association: Minneapolis, MN, 2001.
(31) Adams, C.; Wang, Y.; Loftin, K.; Meyer, M. Removal of antibiotics from surface and distilled water in conventional water treatment processes. *J. Environ. Eng. (N.Y.)* **2002**, *128*, 253−260.
(32) Ternes, T. A.; Meisenheimer, M.; McDowell, D.; Sacher, F.; Brauch, H.-J.; Haist-Gulde, B.; Preuss, G.; Wilme, U.; Zulei-Seibert, N. Removal of pharmaceuticals during drinking water treatment. *Environ. Sci. Technol.* **2002**, *36*, 3855−3863.
(33) Hu, J. Y.; Cheng, S. J.; Aizawa, T.; Terao, Y.; Kunikane, S. Products of aqueous chlorination of 17 beta-estradiol and their estrogenic activities. *Environ. Sci. Technol.* **2003**, *37*, 5665−5670.
(34) Onodera, S.; Yamada, K.; Yamaji, Y.; Ishikura, S.; Suzuki, S. Chemical changes of organic compounds in chlorinated water X. Formation of polychlorinated methylphenoxymethylphenols (Prediоxins) during chlorination of methylphenols in dilute aqueous solution. *J. Chromatogr.* **1986**, *354*, 293−303.
(35) Onodera, S.; Iino, N.; Matsuda, M.; Ishikura, S. Chemical changes of organic compounds in chlorinated water VI. Gas chromatographic and mass spectrometric studies of the reactions of phenylphenols with hypochlorite in dilute aqueous solution. *J. Chromatogr.* **1983**, *265*, 201−213.
(36) Onodera, S.; Tabata, M.; Suzuki, S.; Ishikura, S. Gas chromatographic identification and determination of chlorinated quinones formed during chlorination of dihydric phenols with Hypochlorite in Dilute Aqueous Solution. *J. Chromatogr.* **1980**, *200*, 137−144.
(37) Gallard, H.; von Gunten, U. Chlorination of phenols: Kinetics and formation of chloroform. *Environ. Sci. Technol.* **2002**, *36*, 884−890.
(38) Lee, G. F.; Morris, J. C. Kinetics of chlorination of phenol-chlorophenolic tastes and odors. *Int. J. Air Water Pollut.* **1962**, *6*, 419−431.
(39) Soper, F. G.; Smith, G. F. The halogenation of phenols. *J. Chem. Soc.* **1926**, *6*, 1582−1591.
(40) Burttschell, R. H.; Rosen, A. A.; Middleton, F. M.; Ettinger, M. B. Chlorine derivatives of phenol causing taste and odor. *J.—Am. Water Works Assoc.* **1959**, *51*, 205−214.
(41) Gallard, H.; von Gunten, U. Chlorination of natural organic matter: kinetics of chlorination and of THM formation. *Water Res.* **2002**, *36*, 65−74.
(42) Onodera, S.; Ogawa, M.; Suzuki, S. Chemical changes of organic compounds in chlorinated water XIII. Gas chromatographic-mass spectrometric studies of the reactions of Irgasan DP 300 [5-chloro-2-(2,4-dichlorophenoxy)phenol] with chlorine in dilute aqueous solution. *J. Chromatogr.* **1987**, *392*, 267−275.
(43) Kanetoshi, A.; Ogawa, H.; Katsura, E.; Kaneshima, H. Chlorination of Irgasan DP300 and formation of dioxins from its chlorinated derivatives. *J. Chromatogr.* **1987**, *389*, 139−153.
(44) Clesceri, L. S., Ed. *4500Cl- G. DPD Colorimetric Method*; American Water Works Association, American Public Health Association, Water Pollution Control Federation: Washington, DC, 1989.
(45) Schwarzenbach, R. P.; Gschwend, P. M.; Imboden, D. M. *Environmental Organic Chemistry*, 2nd ed.; John Wiley & Sons: Hoboken, NJ, 2003.
(46) Jensen, J. N.; Johnson, J. D. Interferences by monochloramine and organic chloramines in free available chlorine methods. 2. N, N-Diethyl-P-Pheynylenediamine. *Environ. Sci. Technol.* **1990**, *24*, 935−900.
(47) Nakamura, S.; Takino, M.; Daishima, S. Trace level determination of phenols as pentafluorobenzyl derivatives by gas chromatography-negative-ion chemical ionization mass spectrometry. *Analyst* **2001**, *126*, 835−839.
(48) Rebenne, L. M.; Gonzalez, A. C.; Olson, T. M. Aqueous chlorination kinetics and mechanism of substituted dihydroxybenzenes. *Environ. Sci. Technol.* **1996**, *30*, 2235−2242.
(49) Canonica, S.; Tratnyek, P. G. Quantitative structure-activity relationships for oxidation reactions of organic chemicals in water. *Environ. Toxicol. Chem.* **2003**, *22*, 1743−1754.
(50) Hansch, C.; Leo, A. *Exploring QSAR: Fundamentals and Applications in Chemistry and Biology*; American Chemical Society: Washington, DC, 1995.
(51) Gallard, H.; Pellizzari, F.; Croue, J. P.; Legube, B. Rate constants of reactions of bromine with phenols in aqueous solution. *Water Res.* **2003**, *37*, 2883−2892.
(52) Li, C.; Hoffman, M. Z. One-electron redox potentials of phenols in aqueous solution. *J. Phys. Chem. B* **1999**, *103*, 6653−6656.
(53) Jonsson, M.; Lind, J.; Eriksen, T. E.; Merenyi, G. O-H bond strengths and one-electron reduction potentials of multisubstituted phenols and phenoxyl radicals - Predictions using free-energy relationships. *J. Chem. Soc., Perkin Trans. 2* **1993**, 1567−1568.
(54) Hansch, C.; Leo, A.; Taft, W. A survey of hammett substituent constants and resonance and field parameters. *Chem. Rev.* **1991**, *91*, 165−195.
(55) Hirose, Y.; Okitsu, T. Formation of trihalomethanes by reaction of halogenated phenols or halogenated anilines with sodium-hypochlorite. *Chemosphere* **1982**, *11*, 81−87.
(56) de Laat, J.; N., M.; Dore, M. Chlorination of organic compounds: Chlorine demand and reactivity in relationship to the trihalomethane formation. *Water Res.* **1982**, *16*, 1437−1450.
(57) Boyce, S. D.; Hornig, J. F. Reaction pathways of trihalomethane formation from the halogenation of dihydroxyaromatic model compounds for humic-acid. *Environ. Sci. Technol.* **1983**, *17*, 202−211.
(58) Leenheer, J. A.; Wershaw, R. L.; Reddy, M. M. Strong Acid, Carboxyl-Group Structures in Fulvic Acid from the Suwannee River, Georgia. 2. Major Structures. *Environ. Sci. Technol.* **1995**, *29*, 399−405.

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