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Chlorination of Phenols Revisited: Unexpected Formation of α,β-Unsaturated C_4-Dicarbonyl Ring Cleavage Products

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Abstract

Despite decades of research on the fate of phenolic compounds when water is disinfected with hypochlorous acid (HOCl), there is still considerable uncertainty regarding the formation mechanisms and identity of ring cleavage products, especially at higher chlorine doses. This study focuses on the formation of electrophilic ring cleavage products - a class of compounds that poses potential health risks at relatively low concentrations -from the reactions of phenols with chlorine. By monitoring the formation of products of reactions between ring cleavage products and the model nucleophile *N*-α-acetyl-lysine, we identified the α,β-unsaturated dialdehyde 2-butene-1,4-dial (BDA) and its chlorinated analogue chloro-2-butene-1,4-dial (Cl-BDA) after chlorination of phenol, para- and ortho-substituted chlorophenols (2-Cl, 4-Cl, 2,4-diCl-, 2,6-diCl and 2,4,6-triCl-phenol) and 3,5-di-Cl-catechol. Maximum yields of BDA were observed when chlorine was present in large excess (HOCl:phenol ratios of 30:1 to 50:1) with yields ranging from 18% for phenol to 46% for 3,5-diCl-catechol. BDA and Cl-BDA formation was also observed during chlorination of brominated phenols. For methyl-substituted phenols, the presence of methyl substituents in both positions ortho to the hydroxy group inhibited BDA and Cl-BDA formation, but chlorination of cresols and 2,3-dimethylphenol yielded methyl- and dimethyl-BDA species. This study provides new insights into the formation of reactive and toxic electrophiles during chlorine disinfection. It also provides evidence for the importance of phenoxy radicals produced by one-electron transfer reactions initiated by chlorine in the production of dicarbonyl ring cleavage products.

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Supporting Information

Additional information on detected NAL adducts including high-resolution mass spectrometry results showing isotope patterns of chlorinated and brominated BDA adduct species and MS^2 fragmentation data of identified NAL adducts, yields of BDA at high chlorine doses (PDF).

Introduction

The widespread adoption of chlorine disinfection in drinking water treatment resulted in significant decreases in the incidences of waterborne diseases such as cholera and typhoid fever.[1–3] Unfortunately, chlorine reacts with organic and inorganic water constituents to produce a variety of disinfection by-products (DBPs) that pose potential health risks.[4,5] More than 700 DBPs have been identified, including suspected and known carcinogens, including haloacetaldehydes and haloacetonitriles.[6–8] However, despite decades of research, researchers have only been able to account for 40% of the halogenated DBP mass balance.[9,10]

Among the chemical moieties that serve as DBP precursors, phenols are of particular importance due to their widespread occurrence in natural organic matter (NOM) and anthropogenic chemicals (e.g., consumer products such as triclosan, additives that are released by plastic pipes like bisphenols and nonylphenol) coupled with their relatively high reactivity with hypochlorous acid (HOCl).[10–13] The reaction of HOCl with phenolic compounds occurs through an electrophilic attack on an aromatic carbon to yield chlorine-substituted products.[14–16] The main initial products reported from the reaction between phenol and chlorine are 2- and 4-chlorophenol, which are produced as a result of the preferential attack of HOCl at the ortho and para positions.[17] Subsequent reactions with HOCl yield 2,4- and 2,6-dichlorophenol followed by 2,4,6-trichlorophenol.[14,18–20] Under conditions typically encountered during drinking water disinfection, chlorophenols are frequently detected at concentrations between 1 and 10 μg/L.[21–28] The presence of chlorophenol is primarily of concern due to their low taste and odor thresholds.[14,16,29] In addition, 2,4,6-triCl-phenol is a probable human carcinogen.[30,31]

To reduce concentrations of chlorophenols produced during drinking water treatment, plant operators often increase the initial chlorine concentration.[15,16] This process converts chlorinated phenols into ring cleavage products, including chloroform, trihalomethanes and chlorinated and non-chlorinated organic acids.[20,32–38] Despite substantial efforts to understand the mechanisms of ring cleavage and the products produced during extended chlorination of phenolic compounds, the chemistry involved in the process is only partially understood.[19] For example, researchers have reported that chlorination of meta-substituted phenols (e.g., resorcinol) results in their nearly quantitative conversion to chloroform.[20,36] In contrast, chlorination of ortho- and para-substituted phenols produces much smaller amounts of ring cleavage products, with chloroform yields ranging from approximately 1 to 10%.[20,36,37] This indicates the formation of other, so far unknown ring cleavage products. The importance of identifying these compounds is highlighted by inability of known transformation products to explain the mutagenicity observed with *in vitro* bioassays after phenol-containing water is chlorinated.[39–42]

Due to analytical challenges associated with the identification of low molecular weight aliphatic compounds, the ring cleavage products of phenolic compounds requires the development of more sensitive analytical methodologies. An approach that is increasingly used in toxicology to identify reactive and potentially toxic metabolites involves the detection of their reaction products (i.e., adducts) with biomolecules, such as DNA and

proteins.[43,44] *In vivo*, the reactions, which are referred to as direct molecular initiating events, have been associated with adverse outcome pathways, such as cancer and cardiovascular diseases.[45,46] Among the reactive metabolites produced during oxidative water treatment, reactive electrophiles (e.g., aldehydes and epoxides) are of particular importance due to their reactivity with nucleophilic moieties in proteins, including cysteine, lysine and histidine, and primary and secondary amines in DNA.[47–50] In toxicology, this has led to the development of *in chemico* methods to screen large numbers of chemicals for their binding to biomolecules.[51,52] In addition, this approach has recently been applied to identify reactive transformation products formed from the reactions of phenolic compounds with hydroxyl radical ($HO^{\bullet}$).[53]

To gain insight into the nature and potential toxicity of ring cleavage products associated with the chlorination of phenols, we applied conditions typically employed during drinking water chlorination and used the amino acid *N*-α-acetyl-lysine to detect reactive electrophiles. *N*-α-acetyl-lysine was chosen as a target biomolecule because its nucleophilicity makes it a preferred reaction partner for many electrophiles.[47,54] Experiments using various halogenated and non-halogenated phenols, alkylphenols and catechols and different chlorine doses were used to investigate the effect of phenol structure on reaction mechanisms and product yields.

Materials and Methods

Chemicals

Phenols and dichlorobenzoquinone were purchased from Sigma-Aldrich (St. Louis, MO) and Fisher Scientific (Fairlawn, NJ), respectively, at the highest available purity (>97%). *N*-α-acetyl-lysine (NAL) was purchased from Sigma-Aldrich (purity >98%). All other chemicals were obtained from Fisher Scientific. Working solutions of chlorine were prepared by diluting a commercial solution of sodium hypochlorite (NaOCl, 5% active chlorine, reagent grade, Fisher Scientific). Sodium hypochlorite was standardized by iodometry.[55] 2-Butene-1,4-dial (BDA) was synthesized in our laboratory as described below.

Chlorination experiments

Experiments to assess the transformation of phenols were conducted at different HOCl concentrations at a fixed initial phenol concentration of 0.1 mM (molar HOCl:phenol ratios varied from 1:10 to 40:1). To investigate the fate of ring cleavage products at very high HOCl doses, additional experiments were performed using HOCl:phenol ratios up to 200:1; SI Fig. S3). Experiments were performed in ultrapure water buffered at pH 8±0.1 using 50 mM borate. If not indicated otherwise, chlorination experiments were performed for 30 min, after which the remaining HOCl was quenched with excess thiosulfate (minimum HOCl:thiosulfate ratio 1:10). Afterwards the solutions were allowed to react for 15 min before NAL was added (100 μL, 1 mg mL^{-1}, 0.5 mM final conc.). Samples were stored in the dark at room temperature for 24h prior to analysis of NAL adducts using LC/MS/MS and LC-HRMS (discussed below). Control experiments were conducted in the absence of HOCl, phenols and/or NAL to verify that the observed products were attributable to the reactions of the ring cleavage products with NAL. Additional experiments with H_2O_2 as

alternative quenching agent gave similar results, indicating that thiosulfate had negligible impacts on the formation of transformation products. All experiments were performed at room temperature (20±3°C).

LC-MS/MS analysis

Analysis of NAL adducts was conducted using LC-MS/MS analysis as described previously.[53] Briefly, chromatographic separation was achieved using a Hydro-RP column using 0.1% acetic acid and methanol as eluents. Positive electrospray ionization (ESI+) mass spectrometry was used for detection of NAL adducts. Precursor ion scan mode was used (precursor ion: m/z 84) to facilitate adduct identification. BDA was quantified by using a standard addition method (5–7 levels; max. added concentration at least one order of magnitude above the sample concentration). The stock solution of BDA (1 M) was obtained by hydrolysis of 2,5-dimethoxy-2,5-dihydrofuran in water as reported previously.[53,56]

LC-HRMS analysis

For determination of accurate masses of observed adducts, a LTQ Orbitrap XL HRMS system (Thermo Scientific) was used. The Orbitrap was coupled to an Agilent 1260 HPLC system (quaternary pump, autosampler). Chromatographic separation was achieved using the same method as described for the LC-MS/MS. Mass ranges for full-scan MS experiments were set to 220–600 m/z, the injection volume was 50 μL. Internal calibration was used to ensure accurate mass determinations with a resolution of 100,000 (mass accuracy < 1 ppm). High Energy Collisional Dissociation (HCD) was used to obtain MS^2 spectra of the main adducts. An isolation window of 2 m/z was used for the precursor ion selection and normalized collision energy was set to 35%. Further details are provided in Prasse et al.[53]

Results & Discussion

Identification of N-α-acetyl-lysine adducts

For phenol, three NAL adducts were detected when chlorine was present in large excess relative to phenol (molar chlorine:phenol ratio > 10:1; Fig. 1; SI, Fig. S1). Two of the adducts had the same mass (m/z 255) while the third had a mass of m/z 289. Analysis by HRMS yielded the formula $C_{12}H_{19}O_4N_2$ for the two adducts with m/z 255 (255.13402; Δm = 0.33 ppm). These adducts, which have previously been observed in experiments in which phenol was exposed to UV light and hydroxyl radical, were confirmed to be BDA.[53] Quantification using standard addition indicated a maximum BDA yield of 18% under the investigated experimental conditions (chlorine-to-phenol ratio 30:1; Figs. 2 and 3A), thus demonstrating the important contribution of these previously unknown transformation products to the ring cleavage products produced when phenol reacts with chlorine. Analysis of adduct m/z 289 using HRMS indicated substitution of one hydrogen with a chlorine atom ($C_{12}H_{18}O_4N_2Cl$; exact mass: 289.09506; Δm = 0.35 ppm), which was also evident from the observed isotope pattern (SI, Fig. S2) and the loss of HCl in MS^2 fragmentation experiments (Fig. 1). Due to the high similarity of the fragmentation pattern with m/z 255, we conclude that the adduct with m/z 289 was most likely 2-chloro-2-butene-1,4-dial (Cl-BDA).

Our results indicate the existence of a previously unrecognized ring cleavage pathway that results in the formation of chlorinated and non-chlorinated C_4-unsaturated dicarbonyls from the reaction of phenol with chlorine. The yields of BDA increased up to a HOCl:phenol ratio of 50:1 after which concentrations decreased (SI, Fig. S3). A similar trend was observed for the formation of the ring cleavage product Cl-BDA, but the highest yield was observed at a HOCl:phenol ratio of 20:1 (Figure 2A). Cl-BDA formation at lower HOCl:phenol ratios compared to BDA suggests that BDA is formed from a reaction of Cl-BDA with HOCl (Figs. 2 and 3). In addition, the results also showed that BDA is eventually transformed by chlorine into products that are not detectable by this method. It is worth noting that the formation of Cl-BDA and BDA in kinetic experiments, which appears to occur simultaneously (Fig. 1), is likely attributable to Cl-BDA concentrations below the detection limit and/or transformation of Cl-BDA to BDA in the initial phase of the experiments when chlorine excess is highest.

Potential transformation pathways leading to the formation of α,β-unsaturated dicarbonyl compounds

To further elucidate the pathway through which phenols produce α,β-unsaturated ring cleavage products, additional experiments were conducted with chlorinated phenols. The results revealed that BDA and Cl-BDA are also formed when 2-Cl-, 4-Cl-phenol, 2,4-diCl-, 2,6-diCl-phenol and 2,4,6-triCl-phenol react with chlorine (Fig. 2). In contrast, reactions of 3-Cl-phenol, 2,3-diCl-phenol and 2,4,5-triCl-phenol with chlorine yielded little or no BDA or Cl-BDA, indicating that chlorine substituents in the meta position interfere with the reaction. In general, these results suggest that the formation of BDA and Cl-BDA involves a similar initial reaction in which electrophilic substitution produces o- and p-substituted chlorophenols with 2,4,6-triCl-phenol as the common precursor that reacts further with HOCl to produce ring cleavage products.[14] This is also supported by the dose dependent formation of BDA which increases in the order phenol < 2-/4-Cl-phenol < 2,4-/2,6-diCl-phenol < 2,4,6-triCl-phenol (Fig. 2).

Previous studies on the chlorination of 2,4,6-triCl-phenol indicated that 2,6-dichlorobenzoquinone (DCBQ) formed with yield up to 18% at pH ≤ 6.[57–59] In contrast, at circumneutral pH values (i.e., under conditions typical for drinking water disinfection), DCBQ yields were less than 0.5% for phenol and its chlorinated analogues.[60] To assess the possibility that DCBQ acted as an intermediate in the formation of BDA and Cl-BDA, we exposed DCBQ to varying concentrations of chlorine at pH 8 and did not detect any product (results not shown). Therefore, we conclude that the formation of BDA and Cl-BDA occurs via a different reaction pathway.

To gain insight into the role of substituents on the transformation pathway, experiments were conducted with various substituted phenolic and non-phenolic aromatic compounds (Table 1). The absence of BDA and Cl-BDA formation during chlorination of benzene, toluene and chlorobenzene under the same conditions as discussed for phenol revealed the critical role of the phenolic moiety and agrees with the low reactivity of these compounds with HOCl. Similarly, the results from experiments with p-methyl-anisole, which reacts rapidly with

HOCl,[61,62] also showed that the hydroxy group needs to be freely available (i.e., unsubstituted), for dicarbonyl compound production to occur.

For substituted phenols, the presence of methyl-substituents at both carbon atoms in the α-position relative to the hydroxy group (2,6-dimethyl- and 2,4,6-trimethyl-phenol) prevented the formation of BDA and Cl-BDA, indicating an involvement of the α-carbons in the reaction mechanism. In contrast, the presence of only one α-carbon methyl substituent (o-cresol) led to the formation of methyl-BDA (Table 1; SI, Fig. S4). The same adduct was previously observed in the reaction of cresols with hydroxyl radicals.[53] Although methyl-BDA was detected for all cresols, the formation of chlorinated methyl-BDA (Cl-methyl-BDA) was only observed for m-cresol (SI, Fig. S5 and S6; see below for mechanistic explanation). For 2,3-dimethylphenol the formation of an adduct with m/z 283, attributable to the presence of a dimethylated BDA species was observed (Table 1, SI, Fig. S7). Finally, the formation of BDA and Cl-BDA from p-hydroxy benzoic acid chlorination was consistent with previous studies showing that p-hydroxy benzoic acids react with HOCl by replacement of the carboxy group, yielding 2,4,6-triCl-phenol,[63,64] which subsequently underwent ring cleavage through reactions with chlorine. The presence of a second hydroxy group on the phenolic compound in either the meta (resorcinol) or the para position (hydroquinone) prevented the formation of BDA and Cl-BDA.

Both electrophilic ring cleavage products were detected in experiments with catechol (i.e., 1,2-dihydroxybenzene). Results from experiments with 3,5-diCl-catechol, the hydroxy-analogue of 2,4,6-triCl-phenol further revealed that the presence of a second hydroxy group in ortho position substantially promotes the formation of BDA and Cl-BDA with BDA yields up to 46% (Fig. 3A). The results further indicate that Cl-BDA could be a potential precursor of BDA as Cl-BDA is formed at lower chlorine doses compared to BDA (Fig. 3B).

Under conditions representative of drinking water treatment (i.e., circumneutral pH, high HOCl:phenol ratios), the distribution of ring cleavage products exhibits trends that suggest the existence of at least two main transformation pathways. For meta-substituted phenols (e.g., resorcinol, 3-chlorophenol) high yields of chloroform[20,36,65,66] along with low yields of α,β-unsaturated dicarbonyls are observed. In contrast, ortho- and para-substituted phenols exhibit lower yields of chloroform and higher yields of α,β-unsaturated dicarbonyls.

Implications for the underlying reaction mechanism

The formation of chlorinated and non-chlorinated α,β-unsaturated dicarbonyl compounds from the reactions of chlorine with phenolic compounds has not been previously reported and cannot be explained by reaction pathways postulated in literature.[65,67,68] However, a potentially relevant reaction pathway involving the formation of a radical intermediate via one-electron transfer has been indicated previously based on the detection of chlorinated phenyl-phenols when phenol and alkylphenols react with chlorine.[69–72] Furthermore, the formation of BDA has been reported previously for the reaction of phenol with hydroxyl radicals (•OH), which also suggests the potential involvement of phenoxy radical intermediates, which can form from BDA via an endoperoxide intermediate.[53,73] Even though the relevance of free radical intermediates in aqueous chlorination of phenolic compounds has not been studied in detail, several reaction mechanisms could potentially

contribute to their formation. In particular, the reaction of phenols with HOCl via single electron transfer can result in the formation of the $HOCl^{\bullet-}$ radical anion, which quickly decomposes into $^{\bullet}OH$ and chloride.[74] This process would likely be accelerated by the reaction of phenol with reactive intermediates, in particular $ClO^{\bullet}$, which is formed from the scavenging of $^{\bullet}OH$ by OCl^{-}.[75] However, the presence of the radical scavenger t-BuOH did not significantly influence the formation of BDA (results not shown). In addition, while $^{\bullet}OH$ production was demonstrated for the reaction of various hydroxyphenol species with chlorine,[76] $^{\bullet}OH$ yields in experiments with 2,4,6-triCl-phenol were only very low (results not shown). Alternatively, formation of phenoxy radical intermediates has also been postulated for the reaction with dichlorine monoxide (Cl_2O).[77] Cl_2O is formed in water via nucleophilic attack of OCl^{-} on HOCl and its formation is favorable at elevated HOCl concentrations as used in parts of this study.[78,79] In the case of Cl_2O, formation of phenoxy radical intermediates can be attributed to the decomposition of Cl_2O to $Cl^{\bullet}$ and $ClO^{\bullet}$.[77] However, these experiments have so far only been performed in organic solvents and the relevance of this mechanism is controversial as other studies were not able to detect the formation of radical intermediates.[77] Another mechanism that is supported by the high BDA yields observed for 3,5-diCl-catechol (Fig. 3 A) involves dihydroxyphenols, in particular catechol and hydroquinone, for which the formation of phenoxy-radicals is also possible via direct oxidation by HOCl. This would give rise to quinone species[80], which then react with a second catechol or hydroquinone molecule by comproportionation.[81,82] Overall, our results strongly suggest the involvement phenoxy radical intermediates that lead to the formation of Cl-BDA and BDA. However, additional studies are necessary to confirm the underlying reaction mechanisms.

Formation of α,β-unsaturated dicarbonyl compounds from chlorination of bromophenols

In order to investigate whether also the chlorination of bromophenols, which are of increasing concern as drinking water contaminants especially in coastal regions, results in the formation of α,β-unsaturated dicarbonyl compounds, additional chlorination experiments were performed with 2-Br, 4-Br, 2,4-diBr, 2,6-diBr-, 2,4,6-triBr-phenol (Fig. 4). Similar to their chlorinated analogues, formation of BDA was observed in chlorination experiments with all investigated bromophenols. In contrast, Cl-BDA formation was only observed for 2-Br, 4-Br-, 2,6-diBr-phenol. Furthermore, chlorination of 4-Br-, 2,4-diBr- and 2,4,6-triBr-phenol also gave rise to the formation of a brominated BDA species (Br-BDA; see SI, Figs. S8 and S9 for details).

The detection of Cl-BDA and Br-BDA in experiments with 4-Br-phenol suggests a reaction mechanism that involves the cleavage of the aromatic ring at different positions (Fig. 4). Chlorination of 4-bromophenol also led to the highest relative yields of both Cl-BDA and Br-BDA compared to the other brominated phenols (Fig. 4). The fact that BDA yields were substantially higher and the dose-dependent formation of all three carbonyl compounds exhibit similar behavior suggests the role of Cl-BDA and Br-BDA as BDA precursors. Furthermore, chlorination of 2-Br-phenol exclusively led to the formation of Cl-BDA whereas Br-BDA was the only halogenated BDA species observed for 2,4-diBr-phenol (Fig. 4). In addition, for 2,6-diBr-phenol (i.e., with bromine atoms in both o-positions), Br-BDA was detected in much lower yields compared to Cl-BDA. As such, the obtained results,

clearly demonstrate the relevance of α,β-unsaturated dicarbonyl compounds as important DBPs in the chlorination of bromophenols with the formation of halogenated BDA species strongly depending on the position of the Br substituents (Fig. 5).

Practical Implications

The results of this study indicate that BDA, Cl-BDA, Br-BDA and their methyl-substituted analogues are important ring cleavage products of the reactions of phenols with HOCl under conditions typical of water treatment systems, with maximum BDA yields of up to 46% for 3,5-diCl-catechol. BDA, which is also formed during the CYP450-mediated metabolism of furan, is acutely toxic to liver cells and is highly reactive towards proteins and DNA.[83–88] It exhibits a strong positive response in the Ames assay and induces strand breaks and cross-links in DNA.[88,89] Similar effects have also been observed for methylated BDA species.[90,91] The toxicity of the halogenated BDA compounds has not been studied. However, based on their reactivity with NAL, similar modes of action and toxicity are likely. Additional research is needed to assess the in vivo toxicity of these compounds from drinking water exposure.

Due to the widespread occurrence of phenolic compounds in drinking water sources, unsaturated C_4-dicarbonyl compounds are likely present in chlorinated drinking water. Additional research is needed to quantify the concentrations of these C_4-dicarbonyl compounds after water is disinfected with chlorine in drinking water treatment plants and in distribution systems. Phenol, chlorophenols and bromophenols occur in source waters and in finished drinking water at concentrations as high as 10 μg L^{-1}.[17,21,27,92–94] On the basis of results from this study, concentrations of α,β-unsaturated dialdehydes in a similar concentration range (i.e., several micrograms per liter) could occur when chlorine is employed for disinfection and to mitigate taste and odor issues associated with the presence of chlorophenols. The concentrations of these compounds will be affected by chlorine dose and the presence of organic and inorganic compounds that can react with dicarbonyls (e.g., nucleophilic compounds like proteins associated with biofilms). Additional research is needed on the biostability of α,β-unsaturated dicarbonyl compounds, their formation relative to other DBPs and the relevance of phenolic groups present in NOM as precursors of α,β-unsaturated dicarbonyl compounds formed during drinking water chlorination.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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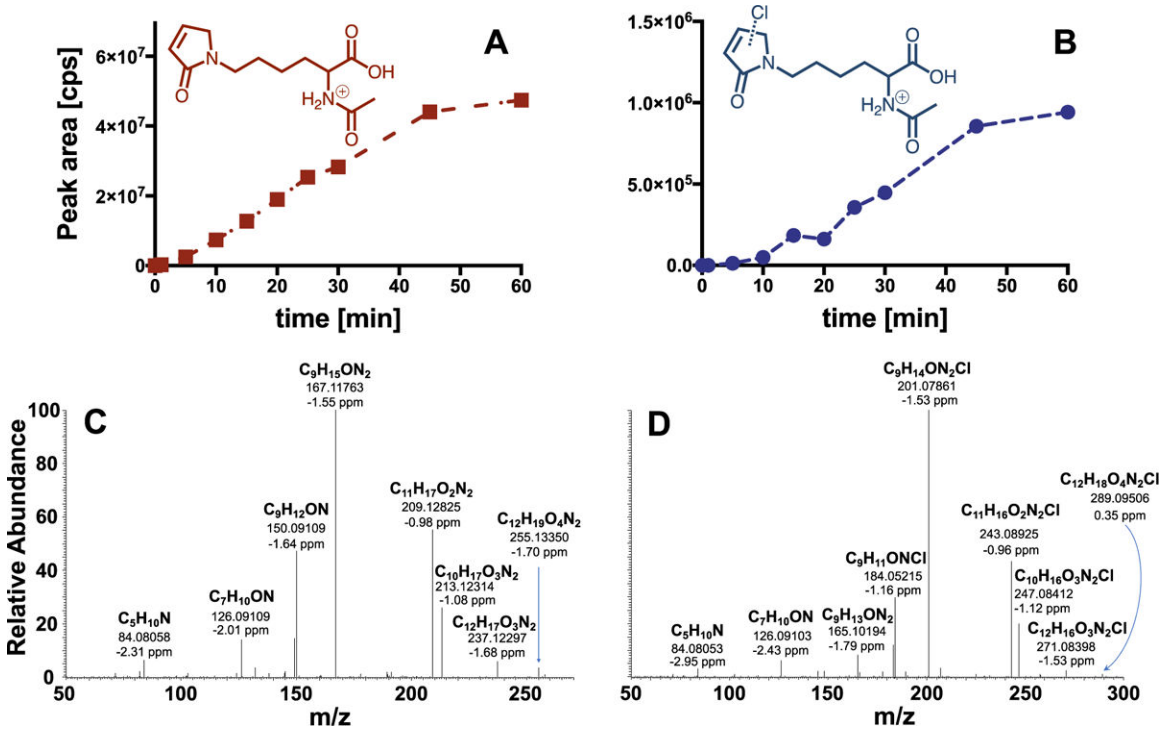


Fig. 1.

Kinetics of the formation of NAL-adducts (A) m/z 255 and (B) m/z 289 during reaction of phenol with chlorine (molar HOCl:phenol ratio 10:1; HOCl: 1 mM; phenol 0.1 mM). LC/MS/MS in precursor ion scan mode was used for identification of adducts while the chemical structures of the adducts were derived from HRMS analysis. Results of MS^2 experiments with (C) m/z 255 and (D) m/z 289 show cleavage of H_2O, cleavage of C_2H_2O and H_2CO_2. In addition, cleavage of NH_3 from m/z 201 and 165 in MS^2 spectrum of m/z 289 yielding m/z 184 and 148, respectively (i.e., before and after HCl elimination), and from m/z 167 in MS^2 spectrum of m/z 255 yielding m/z 150 was observed. See SI for Cl isotope pattern observed for m/z 289 (Fig. S2).

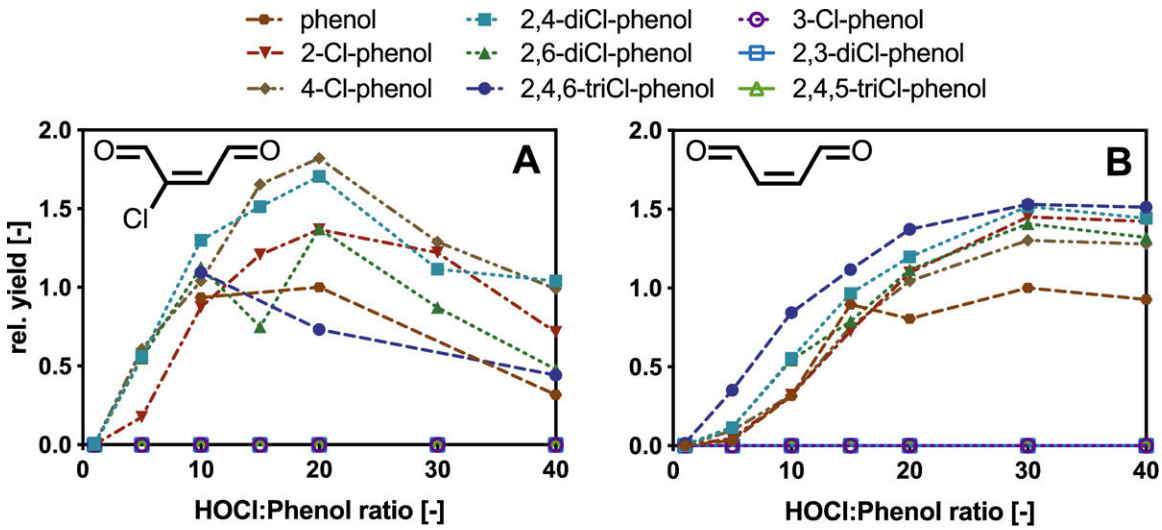


Fig. 2.

Yields of (A) Cl-BDA and (B) BDA in experiments with chlorinated phenols relative to those obtained for phenol (rel. yield). Conditions: borate buffer (50 mM); pH 8; incubation time: 30 min; initial phenol concentration = 0.1 mM. The lines are shown to guide the eye. Cl-BDA and BDA were absent in experiments with 3-Cl-phenol, 2,3-diCl-phenol and 2,4,5-triCl-phenol.

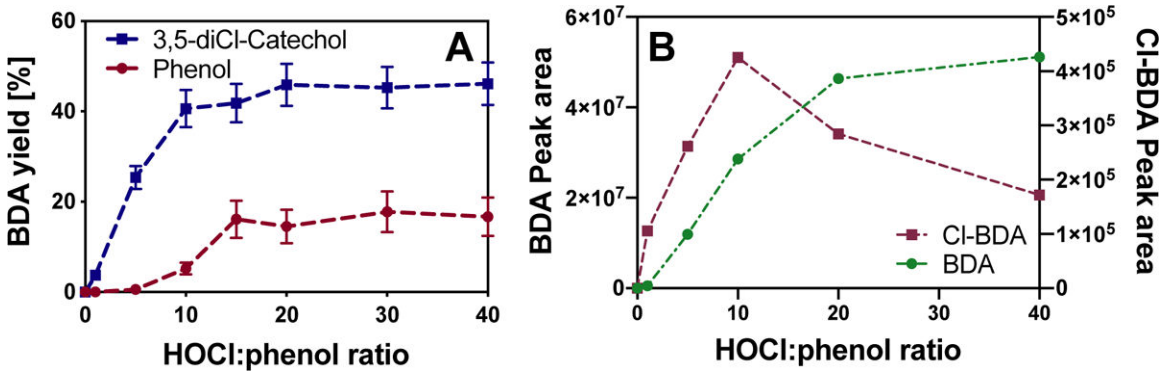


Fig. 3.

(A) BDA yields in experiments with phenol and 3,5-diCl-catechol at different molar HOCl:phenol ratios in borate buffer (50 mM) at pH 8 (incubation time: 30 min; initial concentration of phenol and 3,5-diCl-catechol: 0.1 mM). Error bars were derived from 95% confidence intervals of linear regressions obtained from standard addition method. (B) HOCl dose-dependent formation of BDA and Cl-BDA in chlorination experiments with 2,4,6-triCl-phenol.

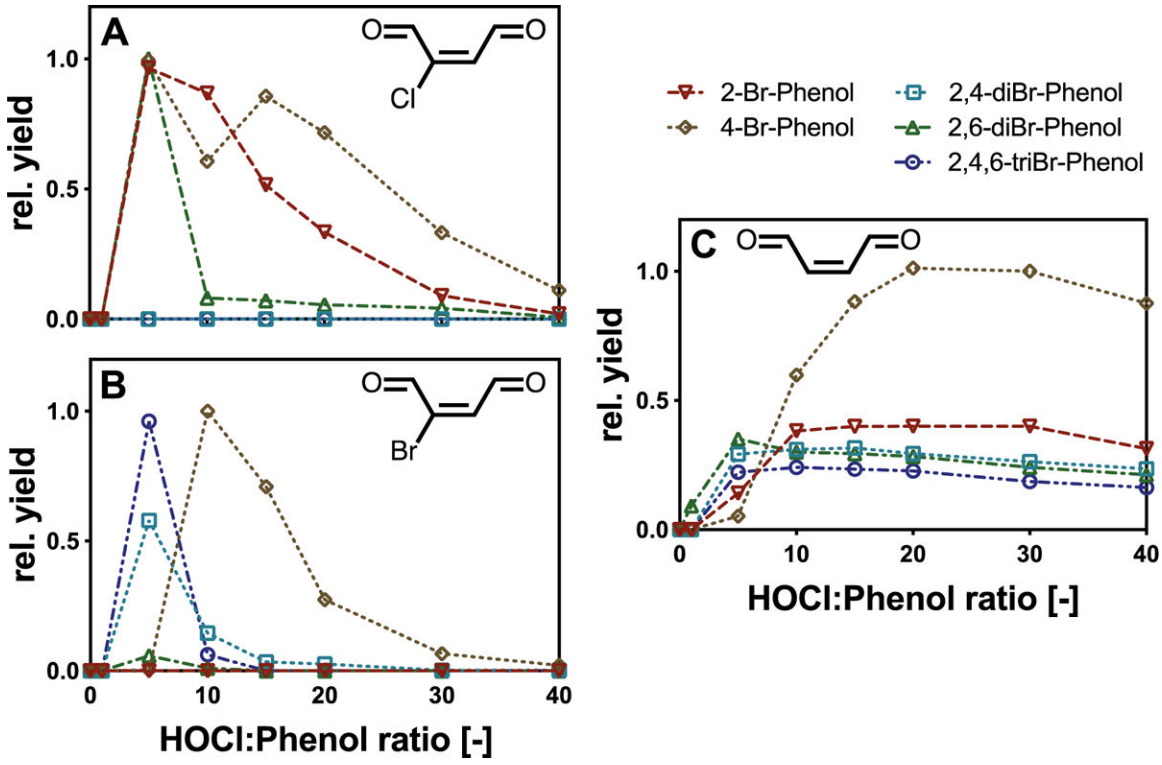
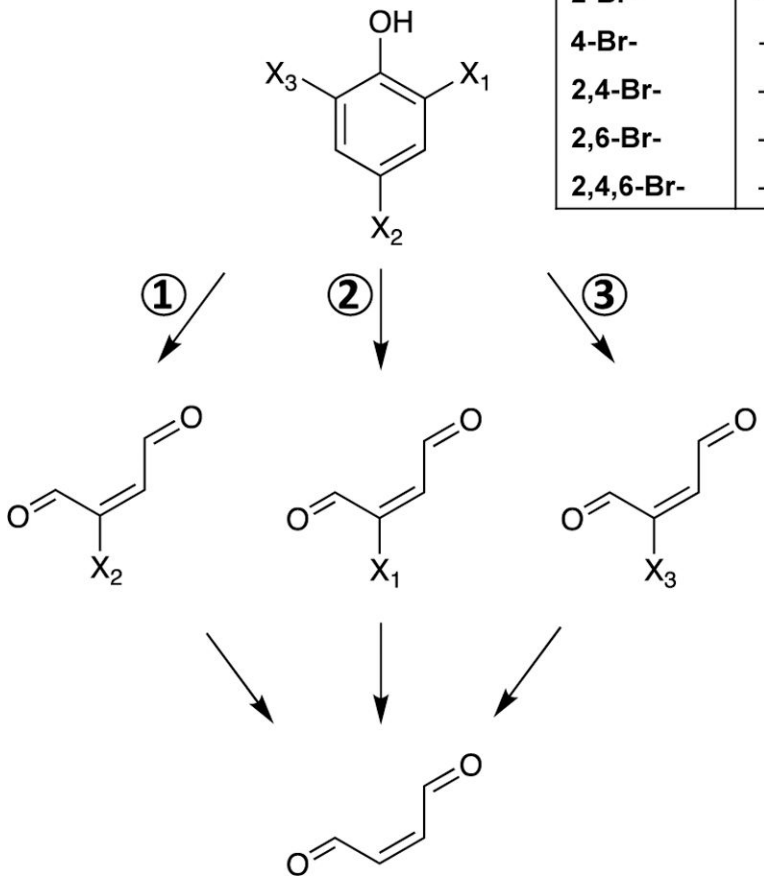


Fig. 4.

Yields of (A) Cl-BDA, (B) Br-BDA and (C) BDA in chlorination experiments with bromophenols at various molar HOCl:phenol ratios. Yields are given relative to the highest yields of all three compounds observed in experiments with 4-Br-phenol (rel. yield). Experimental conditions: 50 mM borate buffer, pH8; initial concentration of bromophenols: 0.1 mM; chlorination time: 30 min.



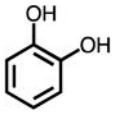
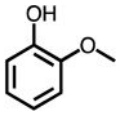
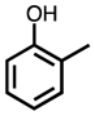
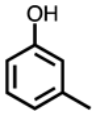
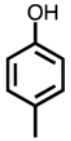
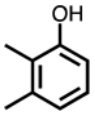
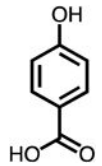
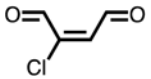
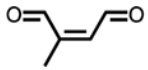
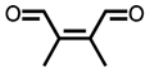
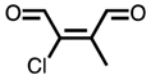
Br-phenol	X_1	X_2	X_3
2-Br-	-Br	-Cl	-Cl
4-Br-	-Cl	-Br	-Cl
2,4-Br-	-Br	-Br	-Cl
2,6-Br-	-Br	-Cl	-Br
2,4,6-Br-	-Br	-Br	-Br

Figure 5:

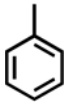
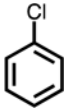
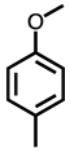
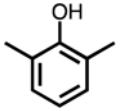
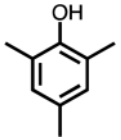
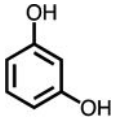
General transformation pathway of 2,4,6-trihalophenols during chlorination of bromophenols and subsequent formation of halogenated BDA and BDA. The results indicate the involvement of pathway 1 for all bromophenols while pathways 2 and 3 were not observed for 2-Br- and 2,4-diBr-phenol, respectively.

Table 1.

Formation of C_4-dicarbonyl compounds during chlorination of various substituted phenols and non-phenolic aromatic compounds.

C_4-dialdehyde	catechol 	guaiacol 	o-cresol 	m-cresol 	p-cresol 	2,3-CH_3-phenol 	p-OH-benzoic acid 
BDA 	✓	✓	×	×	×	×	✓
Cl-BDA 	✓	✓	×	×	×	×	✓
methyl-BDA 	×	×	✓	✓	✓	×	×
dimethyl-BDA 	×	×	×	×	×	✓	×
methyl-Cl-BDA 	×	×	×	✓	×	×	×

Monoaromatic and phenolic compounds for which no C_4- or methyl-C_4-dicarbonyl formation was observed:

benzene 	toluene 	Cl-benzene 	p-CH_3-anisole 	2,6-CH_3-phenol 	2,4,6-CH_3-phenol 	resorcinol 	hydroquinone