Ipso substitution of aromatic bromine in chlorinated waters: Impacts on trihalomethane formation

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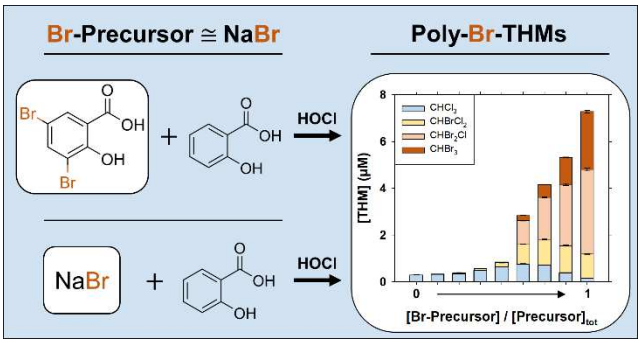
ABSTRACT

Parabens and salicylates were examined as disinfection byproduct (DBP) precursors to explore possible influence of ipso substitution (i.e., halogen exchange) on the yield and speciation of trihalomethanes (THMs) formed during water chlorination. Substoichiometric conversion of C–Br bonds into C–Cl bonds was confirmed for several parabens and salicylates. Co-occurrence of (mono)brominated and nonhalogenated precursors in the presence of free chlorine (but in the absence of added Br^-) generated polybrominated THMs, implicating ipso substitution. THM molar yield, bromine incorporation, and bromine recovery from brominated and nonhalogenated precursor mixtures were commensurate with those observed from equimolar additions of NaBr, indicating efficient displacement of aromatic bromine by free chlorine followed by reincorporation of liberated HOBr into DBP precursors. THM molar yield from brominated precursors was enhanced by up to a factor of 20 relative to nonhalogenated precursors. Trends in THM molar yields and bromine incorporation differed between brominated parabens and brominated salicylates, suggesting that the influence of ipso substitution on THM formation varies with the structure of the organic precursor. Collectively, these results provide new evidence of the often-overlooked role ipso substitution can play in promoting halogen exchange and bromine-enrichment among DBPs in chlorinated waters.

SYNOPSIS

In chlorinated water, ipso substitution is an underappreciated reaction pathway capable of influencing disinfection byproduct formation and speciation, including formation of trihalomethanes from parabens and salicylates.

47 **TOC Art**:


Br-Precursor ≅ NaBr
Poly-Br-THMs
HOCl
HOCl
NaBr
[THM] (µM)
[Br-Precursor] / [Precursor]tot

48

1. INTRODUCTION

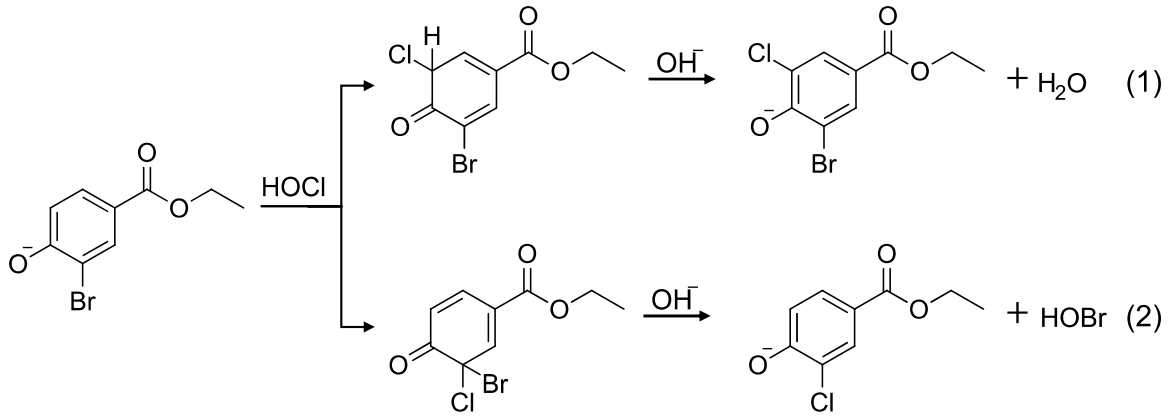
Activated aromatic moieties react readily with electrophilic halogens in solutions of free chlorine and free bromine.[1-3] The resulting halogenated aromatic compounds are estimated to contribute two-thirds of the total organic halogen concentration in chlorinated waters and are potentially more significant drivers of developmental toxicity than halogenated aliphatic compounds.[4] Hydroxy-substituted aromatic compounds are known precursors of the regulated disinfection byproduct (DBP) class trihalomethanes (THMs).[5] Compounds studied for their THM formation potential span a range of humic and fulvic substances,[6,7] aliphatic compounds,[8] and substituted alkyl and chlorophenols.[6] THM formation from hydroxybenzenes is strongly influenced by the identity and position of substituents relative to the hydroxyl group, ostensibly determining the reactivity of ketone-containing ring fragments believed to be the primary precursors of THMs. (**Scheme S1**).[9,10]

Chlorinated phenols have been evaluated as THM precursors relative to their nonhalogenated analogues; trichloromethane molar yields varied substantially depending on the number and position of chlorine substituents on the phenolic ring.[10] Prior studies of aromatic THM precursors have not, however, considered the impact of bromine substitution on THM yields and speciation. The greater reactivity of free bromine relative to free chlorine promotes bromination of aromatic compounds, even in the presence of excess free chlorine.[11] The resulting brominated DBPs are typically more genotoxic than their chlorinated counterparts.[12] Nevertheless, brominated aromatic compounds may be subject to further reactions, including ipso substitution, which involves the exchange of Br^+ with Cl^+ (**Scheme 1**).[11,13-15]

Despite its presence in the literature dating to 1903, ipso substitution appears scarcely with respect to DBP formation.[15] In 1988, the formation of dibrominated anilines and phenols was observed from the chlorination of para-bromoaniline and para-bromophenol, respectively.[14] A more recent study assessed substitutions of chloro-, bromo-, and iodo-substituted benzene, anisoles, and phenols in solutions of free chlorine and free bromine.[13] HOBr potentially released during ipso substitution could be rapidly reincorporated into DBP precursors.[16-18] Accordingly, contributions of HOBr liberated from brominated

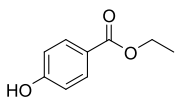
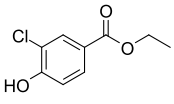
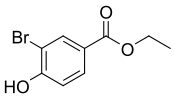
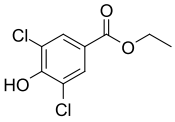
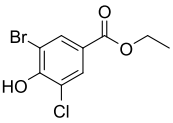
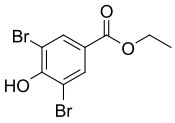
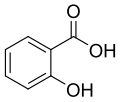
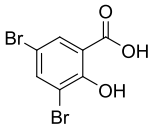
aromatic compounds by ipso substitution may provide a mechanism by which the bromine-enrichment of DBPs can occur.

Scheme 1. Transformation of 3-Bromoethylparaben by **(1)** Electrophilic Aromatic Substitution, Yielding 3-Bromo-5-chloroethylparaben or **(2)** Ipso Substitution, Yielding 3-Chloroethylparaben.



The purpose of this study was to elucidate the influence of ipso substitution on the formation of THMs from two classes of aromatic micropollutants: parabens and salicylates. Parabens (*para*-hydroxybenzoate esters) have been widely employed as antimicrobial preservatives in pharmaceutical and personal care products (PPCPs). Parabens remain ubiquitous contaminants that have been detected in surface water,[19,20] wastewater,[21-24] and sediment.[25] Increasing attention has been paid to the chlorination and bromination of methyl paraben[26,27] and its halogenated products,[28] which have been detected in rivers and swimming pools.[20,29] The potential for parabens to generate THMs upon reaction with free chlorine and free bromine has not been previously investigated. Salicylates were selected for study due to their structural similarity to parabens, previous detections in surface waters and wastewaters, well-characterized reactivity toward free chlorine and free bromine, and demonstrated ability to generate THMs.[16,30-32] Herein, eight ethylparabens and salicylates (**Table 1**) were reacted with solutions of free chlorine to (1) determine the THM yield of parabens and salicylates in the presence of free chlorine, (2) examine the effects of precursor halogenation on THM formation and distribution, (3) evaluate THM distribution from the ipso substitution of aromatic Br in Br-precursors relative to Br^- from NaBr, and (4) assess the influence of pH and chloride on THM formation in binary precursor systems.

Table 1. Structures, Names, and Abbreviations of Ethylparabens and Salicylic Acids Examined Herein

 ethylparaben (**EP**)	 3-chloroethylparaben (**CEP**)	 3-bromoethylparaben (**BEP**)	 3,5-dichloroethylparaben (**DCEP**)
 3-bromo-5-chloroethylparaben (**BCEP**)	 3,5-dibromoethylparaben (**DBEP**)	 salicylic acid (**SA**)	 3,5-dibromosalicylic acid (**DBSA**)

2. METHODS

A comprehensive list of reagents, standards, and their purities can be found in **Table S1** of the Supporting Information (**SI**). Most reagents were commercially available at high purities (>99%); 3-bromo-5-chloroethylparaben (BCEP) was synthesized from 3-chloroethylparaben (CEP) using molecular bromine (**Figure S1**). All aqueous solutions and standards were prepared in 18 MΩ·cm ultrahigh-purity (UHP) water. Solutions of free chlorine were prepared daily from laboratory-grade sodium hypochlorite (6 wt%), standardized by UV-vis spectrophotometry.[33] Glassware used in halogenation experiments were pre-rinsed with NaOCl (~0.5 M) to ensure reaction vessels were chlorine-demand free.

2.1 Time course reactions

Time course reactions were performed with selected brominated ethylparabens to elucidate possible formation of ipso substitution products (i.e., replacement of Br with Cl). All halogenation reactions were performed in 40 mL amber glass vials containing a phosphate buffer (20 mM, pH 6.0 – 8.0). Free chlorine was added as NaOCl. To promote pseudo-first-order conditions, NaOCl was added such that the initial concentration of NaOCl was at least in 10-fold molar excess relative to the initial concentration of the parent paraben. Parent paraben (20 μM) was added as a methanolic spike such that the final methanolic content of the reactor was <0.5 vol%. Reactors were capped and shaken by hand for at least 10 s and maintained at

20.0±0.1 °C in a circulating water bath. At predetermined time intervals designed to span approximately 2 reaction half-lives, 1.0 mL aliquots (minimum of 6 per reactor) were withdrawn and transferred to 2 mL HPLC sample vials pre-amended with at least a 40% molar excess of either sodium thiosulfate or 1,3,5-trimethoxybenzene (TMB) (i.e., [quencher] > 1.4$[FAC]_o$). HPLC sample vials were capped and shaken for 10 s. Volumes of added quencher were typically <30 µL. Quenched samples were refrigerated at 4 ºC and analyzed within 1 week via either an Agilent 1200 or 1260 series high-performance liquid chromatograph with a diode array detector (HPLC-DAD, see additional HPLC method details in the **SI**). EP transformation products were identified via retention-time matching with solutions of reference materials.

2.2 Haloform reactions

Haloform reactions were performed in volatile organic analysis (VOA) vials with PTFE-lined septa. Nominal concentrations of NaOCl, NaBr, and precursor organic compounds were verified gravimetrically for each reactor. For reactions controlling organic bromine, aliquots of methanolic stock solutions for each precursor organic compound ($[precursor]_o$ = 20 µM) were added to a 40 mL vial followed by 40 mL of phosphate buffer solution (20 mM, pH = 8.00, [NaCl] = 1.0 mM, $[NaNO_3]$ = 9.0 mM). For selected experiments, an aqueous stock of NaBr was added as the Br source instead of a brominated organic compound. The final methanolic content of each reactor was <1 vol%. At t = 0, NaOCl was spiked to reach 500 µM, and the vial was capped and inverted several times. A 20 mL amber glass vial was then filled to headspace free with reaction solution and kept at 20.0±0.1 °C in a recirculating water bath for 24 h.

For varied NaCl reactions, [NaCl] + $[NaNO_3]$ = 10 mM; NaCl and NaOCl were added prior to the parent compound to allow free chlorine species to equilibrate and to oxidize any Br^- present (e.g., as an impurity in NaCl).[33] To assess for trace Br^- as a contaminant of NaCl, 200 µL aliquots of reaction solution were quenched with 1,3,5-trimethoyxybenzene (TMB) and analyzed for 1-bromo-2,4,6-trimethoxybenzene (Br-TMB) via HPLC (see **SI**).[33,34] In reaction solutions with the highest examined [NaCl] of 10 mM, Br^- was below the detection limit (0.03 µM as Br-TMB).

2.3 Sample extraction, instrumental analysis, and quality assurance

After 24 h of incubation, four aliquots of reaction solution were transferred from each reactor to 8 mL vials pre-amended with ascorbic acid in 5-fold molar excess of $[NaOCl]_0$ and 1 mL MTBE containing 1,2-dibromopropane as an internal standard. Liquid-liquid extractions were performed by vortex mixing for 30 s; extraction efficiencies were within 100 ± 5% (n = 8). Extracted samples were refrigerated at 5 °C to promote phase separation, transferred via a glass, gas-tight syringe into 2 mL autosampler vials containing 150 µL glass inserts, stored at −20 °C, and analyzed within one week.

Extracts were analyzed using gas chromatography-mass spectrometry (GC-MS) with an Agilent 8890/5977 GC-MS in selected ion monitoring mode. Complete parameters for quantification of trihalomethanes by GC-MS are in the SI (**Table S2**). Blank samples were analyzed at least every 10 samples to verify the absence of carryover. Fresh aliquots of calibration standards were prepared for each sample batch, and calibration checks at the midpoint of the calibration range were analyzed at the middle and end of each analytical sequence.

3. RESULTS AND DISCUSSION

3.1 Detection of ipso substitution products

Reference materials were used to verify the formation of ipso substituted products during reactions of brominated ethylparabens with NaOCl. For example, chlorination of 3-bromoethylparaben (BEP) yielded 3,5-dichloroethylparaben (DCEP) and 3,5-dibromoethylparaben (DBEP) as minor products within 2 min (**Figure 1**). DCEP is the ipso substitution product. DBEP ostensibly results from the reaction of BEP with HOBr liberated via ipso substitution of another BEP molecule. Formation of DBEP from the chlorination of BEP demonstrates Br-enrichment of DBPs linked to ipso substitution. Ipso substitution products were also observed upon chlorination of BCEP (yielding DCEP, **Figure S2**) and DBEP (yielding BCEP, **Figure**

S3). At 50 mM ultrahigh-purity NaCl (99.99%), BEP formed up to 0.86 µM DBEP – more than could have been attributed to potential trace Br^- (<0.15 µM) originating from NaCl.

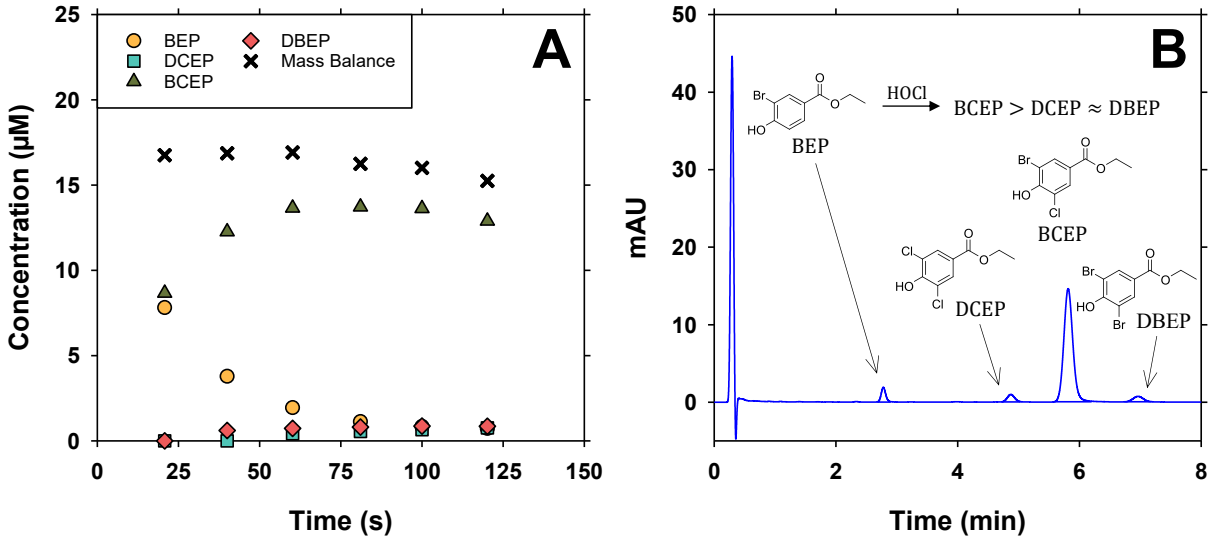


Figure 1. A) Example time course reaction of 20 µM BEP with 200 µM NaOCl; additional conditions: $[NaNO_3]$ = 10 mM, $[Na_3PO_4]$ = 20 mM, [NaCl] = 50 mM, pH = 6.99, and T = 20.0 °C. **B)** Sample HPLC-DAD chromatogram from the time course shown in frame A demonstrating formation of DCEP and DBEP from chlorination of BEP.

3.2 THM formation from ethylparabens

THM yield and speciation from the 24 h chlorination of each EP variant are shown in **Figure 2A**. THM molar yields (mol THM/mol EP variant) from ethylparabens ranged from 0.4% to 1.8% and were generally lower than those observed for other substituted phenols.[10] EP, CEP, and DCEP produced only trichloromethane (TCM). THM yields from DCEP were 40% lower than yields from EP and CEP. The major pathway to TCM from EP may not require (or may be impeded by) chlorination of both carbons *ortho* to the hydroxyl group, which contrasts with previous observations of similar THM yields from phenol, 2-chlorophenol, and 2,4,6-dichlorophenol.[10] A more modest decline in total THMs (TTHMs) was observed comparing BCEP to BEP, though DBEP produced overall more THMs than BEP (**Figure 2A**).

3.3 Formation of brominated THMs

Brominated THMs were detected whenever a brominated paraben served as the THM precursor

(**Figure 2A**). TTHMs from DBEP were approximately 24% greater than from BEP, indicating the bromination of both carbons *ortho* to the hydroxyl group does not impede THM formation in the same manner as when the *ortho* carbons are chlorinated. Polybrominated THM yields increased in the order BCEP < BEP < DBEP. Estimated yields of HOBr from ipso substitution of brominated ethylparabens are approximately 0.5 – 1.0 μM (**Figures 1, S2, S3**). Notably, [Br^-] as low as 0.6 μM have been shown previously to impact THM speciation in chlorinated systems,[35]

To investigate the influence of total added bromine, BCEP was varied as the source of bromine, with EP varied to maintain a uniform total added paraben concentration, $[P]_{tot}$ = 20 μM (**Figure 2B**). As added bromine was increased, THM distribution shifted towards polybrominated THMs. Tribromomethane (TBM) was below quantification limits at [BCEP] < 5 μM, but dibromochloromethane (DBCM) was quantifiable at [BCEP] as low as 1 μM. To the best of our knowledge, the formation of polybrominated THMs via chlorination of a monobrominated aromatic compound (in the absence of added inorganic bromide) has not been previously reported. Ipso substitution and subsequent re-incorporation of Br^+ into THM precursors may explain our results (**Scheme 1**).[13] Evidence of ipso substitution has been observed in reactions of halogenated aromatics with free chlorine, yielding chlorinated compounds from iodinated precursors, and polybrominated and mixed-halogenated products from brominated precursors.[13,14] Indeed, even 2,4,6-tribromophenol was detected after reactions of NaOCl with 2-bromophenol.[13]

3.4 THM relative yields with precursor mixtures

Experiments were conducted to determine how bromine source (organic bromine versus NaBr) influences THM formation. The sources of organic bromine included DBEP and 3,5-dibromosalicylate (DBSA). For the organic bromine systems, [dibrominated precursor] was varied while either [EP] or [SA] was adjusted to maintain equal organic carbon loadings (e.g., $[EP]_{tot} = [DBEP]_o + [EP]_o$ = 20 μM, **Figure 3**). The maximum achievable range of total added bromine was 0 (100% EP or SA) to approximately 40 μM total bromine (100% DBEP or DBSA). Parallel experiments were conducted to achieve concentrations of added inorganic bromide (as NaBr) ranging from 0 to 40 μM, with $[organic\ precursor]_{tot}$ fixed at 20 μM

(**Figure S4**). All contributions to [organic precursor]$_{tot}$ in varied [Br^-] experiments were from either EP or SA only.

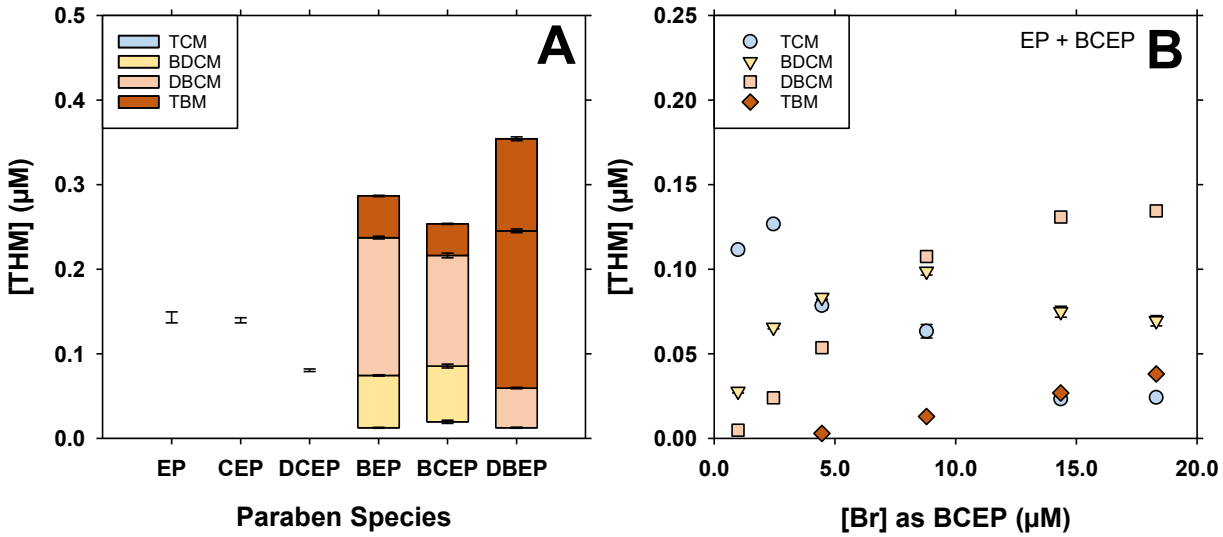


Figure 2. A) 24 h yields of THMs from each EP species (20 μM initial paraben concentration). **B)** 24 h yields of THMs from EP + BCEP ($[EP]_o$ + $[BCEP]_o$ = 20 μM) as a function of added Br as BCEP ($[Br]_o$ = $[BCEP]_o$, accomplished by varying $[BCEP]_o$ / $[EP]_o$. $[NaOCl]_o$ = 500 μM, [NaCl] = 1 mM, $[NaNO_3]$ = 9 mM, pH = 8.18±0.02. Error estimates represent 95% confidence intervals and are smaller than symbols if not shown.

From 100% EP to 100% DBEP, [TTHMs] increased by a factor of 2.8 (**Figure 3A**). Greater concentrations of polybrominated THMs were formed at higher proportions of DBEP. The relative proportion of TCM to TTHMs decreased from 100% at 0 μM Br as DBEP to <2% at 40 μM Br as DBEP (**Figure 3A**). TBM increased linearly with increasing DBEP. Molar yields of each THM were determined from reactions with EP, SA, DBEP, and DBSA alone (i.e., reacted individually with NaOCl) and used to calculate THM relative yield in binary precursor systems using **Eq. 1**.

$$\text{Relative yield} = \frac{[\text{THM}]_{\text{binary system}}}{\sum([\text{precursor}] \times \text{THM yield}_{\text{precursor only}})} \quad \textbf{[1]}$$

Relative yields of each THM for 100% EP ($[DBEP]/[P]_{tot}$ = 0) and 100% DBEP ($[DBEP]/[P]_{tot}$ = 1) were, by definition, equal to 1. Applications of **Eq. 1** assumed THM yields from EP and DBEP were constant; relative yields different than 1 indicated interactions between precursors in mixed systems. Relative yields of TCM decreased from 0.70 to 0.27 as $[DBEP]/[P]_{tot}$ increased from 0.03 to 0.75, indicating the TCM

yields decrease with added organic bromine (**Figure 3B**). Notably, at [DBEP]/$[P]_{tot}$ of 0.03, [BDCM] was nearly 20 times higher than predicted by data from single-precursor systems. DBCM relative yield reached a maximum of 2.76 at [DBEP]/$[P]_{tot}$ of 0.25. Both maxima in BDCM and DBCM relative yields occurred while EP was the dominant paraben in the mixture, suggesting a synergistic effect in the binary precursor systems. THM yields in experiments with added NaBr (**Figure S4A**) were similar to those observed in reactions with only DBEP as the source of bromine (**Figure 3A**), suggesting that DBEP and NaBr as bromine sources have similar effects on THM profiles.

3.5 Parallel experiments with salicylates

For the SA + DBSA system, [TTHMs] were <1 μM from 0 to 20 μM added bromine but increased to a maximum of approximately 8 μM [TTHMs] at 40 μM added bromine (**Figure 3C**). TTHM molar yield from the chlorination of DBSA was over 18 times higher than molar yields from EP or DBEP. With no added bromine, 20 μM SA produced comparable [TTHMs] (molar yield of 1.5%) to EP (0.9%). DBCM generated from chlorination of SA steadily increased with added bromine irrespective of source (DBSA or NaBr) (**Figure 3C, S5B**). TBM increased linearly with added [Br] but was below limits of quantification at [Br] < 10 μM. In contrast, TBM was quantifiable at [Br] ≥ 5 μM from NaBr or DBEP when parabens served as precursors.

In contrast with the paraben system, [TCM] yield was enhanced by increased proportions of DBSA relative to total SA (**Figure 3D**). Added bromine (as DBSA) ostensibly enhanced THM yield overall, including TCM. Enhanced THM formation as a function of added Br^- has been observed in previous studies;[36] organic bromine subject to ipso substitution could have presented similar effects.

Of the brominated THMs, only BDCM showed relative yields substantially greater than 1.0 in the SA system, reaching a maximum of 2.2. The maximum BDCM relative yield of approximately 2.2 at 20 μM added [Br] from SA+DBSA was in stark contrast with the relative yield of 20 (2000%) from EP+DBEP at 1 μM [Br]. Differences in precursor structure are likely the driver of the disparity between THM yield and speciation from parabens and salicylates. THMs have been postulated to form primarily from aromatic

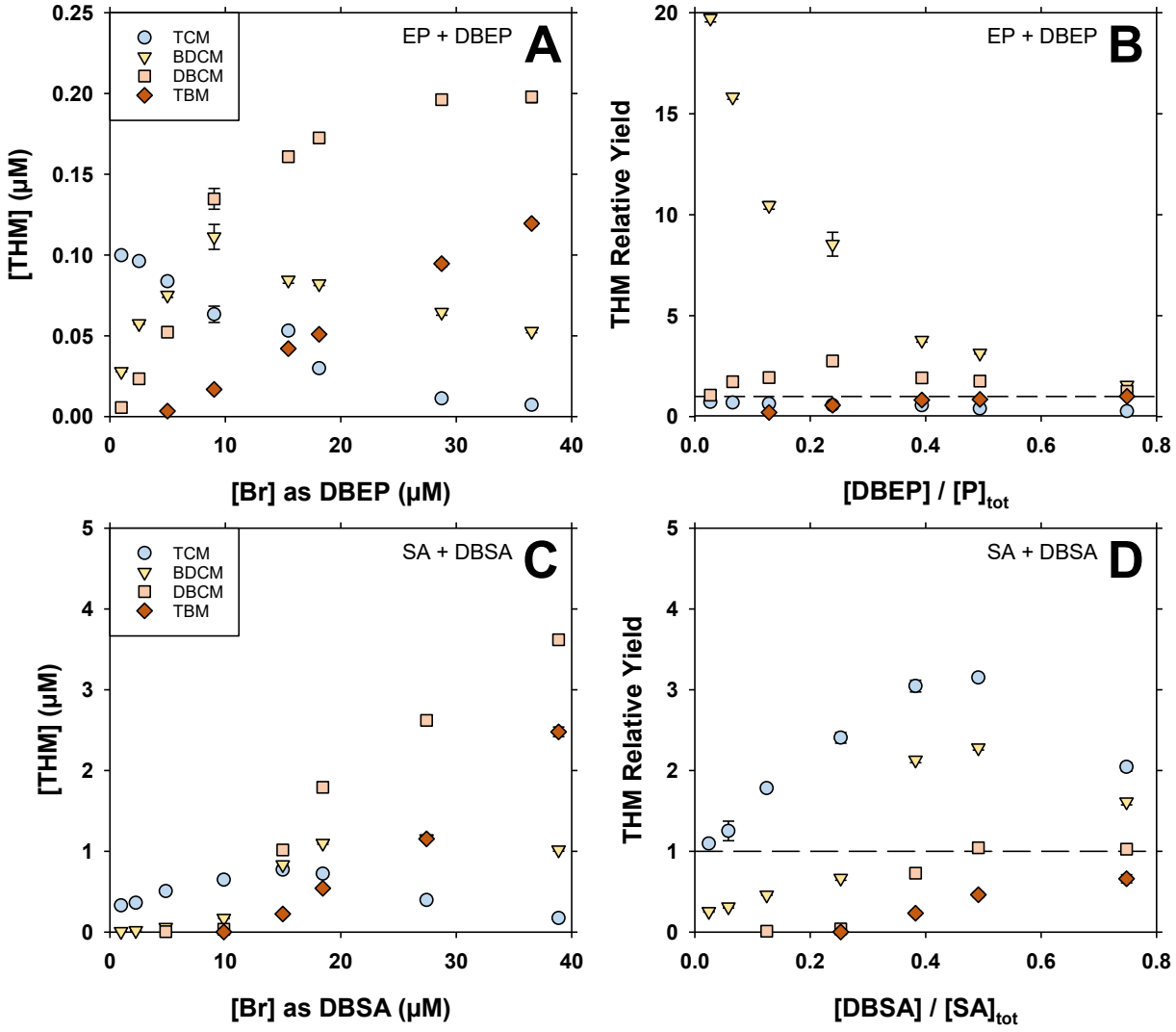


Figure 3. A) [THM] distribution from parabens as a function of added [Br] as DBEP from 1 to 40 μM. **B)** [THM] yields relative to those calculated from experimental THM molar yields of EP and DBEP (when reacted individually with NaOCl) as a function of the DBEP fraction of total parabens. **C)** [THM] distribution from salicylates as a function of added [Br] as DBSA from 1 to 40 μM. **D)** Measured [THM] relative to calculated [THM] from SA and DBSA (when reacted individually with NaOCl) as a function of DBSA fraction of total salicylates. Dashed lines represent relative yield of 1 for reference. **A)**, **B)** pH = 8.18 ± 0.02, $[P]_{tot}$ = [EP] + [DBEP] **C)**, **D)** pH = 8.15 ± 0.03, $[SA]_{tot}$ = [SA] + [DBSA]. All frames: $[P]_{tot} = [SA]_{tot}$ = 20 μM, $[NaOCl]_o$ = 500 μM, [NaCl] = 1 mM, $[NaNO_3]$ = 9 mM, 24 h chlorine contact time. Error estimates represent 95% confidence intervals and are smaller than symbols if not shown.

carbons *ortho* to a hydroxyl group.[37-40] For parabens, both carbons *ortho* to the hydroxyl group can be readily halogenated. For SA, one such carbon is substituted with a carboxylate group. Decarboxylation reactions in chlorinated systems have been reported for some hydroxybenzenes but not for salicylic acid.[39]

241 Accordingly, the degree of bromine substitution observed in THMs from parabens may not be possible
242 from SA at added bromine <15 μM.

243 **3.6 Bromine incorporation**

244 To further assess Br-THM speciation, bromine incorporation factor (*n*) was calculated using **Eq. 2.**[36,41]

245 $$n = \frac{[\text{BDCM}] + 2[\text{DBCM}] + 3[\text{TBM}]}{[\text{TTHM}]} \quad \textbf{[2]}$$

246 Bromine incorporation represents the relative concentration of Br-THMs normalized to TTHMs and can
247 possess a maximum value of 3, representing 100% TBM. Bromine incorporation values were calculated
248 for each data set independently (EP+DBEP, EP+NaBr, SA+DBSA, SA+NaBr). THM bromine
249 incorporation from EP increased with increasing [Br], with a maximum value of 2.3 occurring at the highest
250 added [Br] (**Figure 4A**). In the salicylate system, bromine incorporation also increased with added bromine
251 to a maximum value of 2.15. THM bromine incorporation from parabens generally exceeded that of
252 salicylates throughout the range tested, though the difference was greatest at low [Br] (**Figure 4A**). While
253 both precursors reached similar bromine incorporation maxima (representing primarily TBM), the
254 maximum [TTHMs] from salicylates exceeded parabens by a factor of approximately 20.

255 **Figure 4B** depicts a bromine incorporation cross-correlation between reactions amended with NaBr
256 as the bromine source and reactions amended with organic bromine (Br-Precursors) as the bromine source.
257 For both ethylparabens and salicylates as precursors, THM bromine incorporation from NaBr and from
258 organic bromine were strongly correlated (adjusted $R^2 \geq 0.98$, **Figure 4B**). These results imply that THM
259 bromine incorporation depended on the quantity of bromine added, not on the bromine source or on the
260 degree of precursor bromination. The slopes of both cross-correlations were near unity, suggesting that
261 bromine liberation by free chlorine is efficient for brominated parabens and salicylates.

262 **3.7 THM molar yield and bromine recovery**

263 TTHM molar yields were calculated as moles of THMs produced per mole of organic precursor
264 (**Figure 5A**). At the highest level of added bromine as DBSA or NaBr, the maximum TTHM molar yield

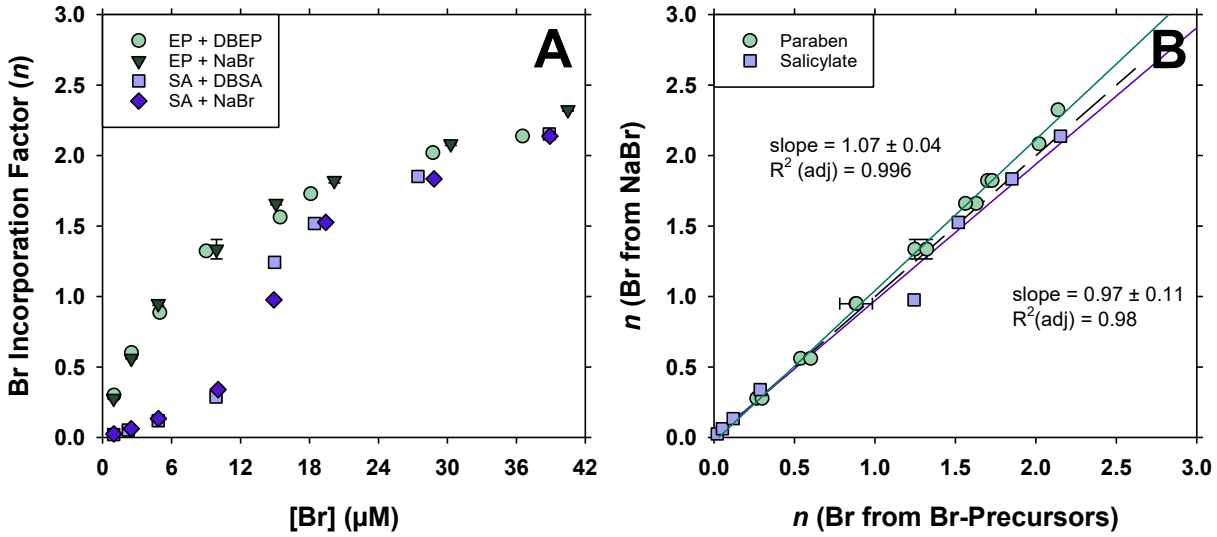


Figure 4. A) THM bromine incorporation factor (*n*, Eq. 2) as a function of added Br as organic Br (DBEP or DBSA) or inorganic Br^-. **B)** Cross-correlation of THM *n* values: Br added from NaBr as a function of Br added from organic Br-precursors. Paraben data include DBEP and BCEP data; salicylate data were from DBSA only. Error estimates represent 95% confidence intervals and are smaller than symbols if not shown.

of the salicylate system was over 10-times greater than that of the paraben system (37.5% and. 2.1%, respectively). The TTHM molar yield from both precursors increased with added bromine (as organic bromine or NaBr), though the total increase was greater from salicylate (22-fold) than from parabens (2.8-fold). For salicylates, the 20-fold increase in TTHM molar yield when comparing SA (1.7%) to DBSA (37.5%) is noteworthy and exceeds previously reported increases in TCM molar yield resulting from the halogenation of phenol (2% TCM molar yield) relative to 2-chlorophenol (10%) and 3-chlorophenol (32%).[40] Bromide-enhanced yields of THM have been attributed to superior nucleofugality (leaving group ability) of brominated relative to chlorinated methyl carbanions.[35] To our knowledge, such enhancements in THM molar yield resulting from the pre-bromination of a precursor have not previously been reported.

Bromine recovery as THMs was calculated as the quotient of total Br-THMs ([BDCM] + 2[DBCM] + 3[TBM]) divided by the total concentration of Br added to the system. Bromine recovery as Br-THMs derived from salicylates increased with added bromine as organic bromine or NaBr (**Figure 5B**). The inflection point where bromine recovery from salicylate began to increase corresponded to ratios of added

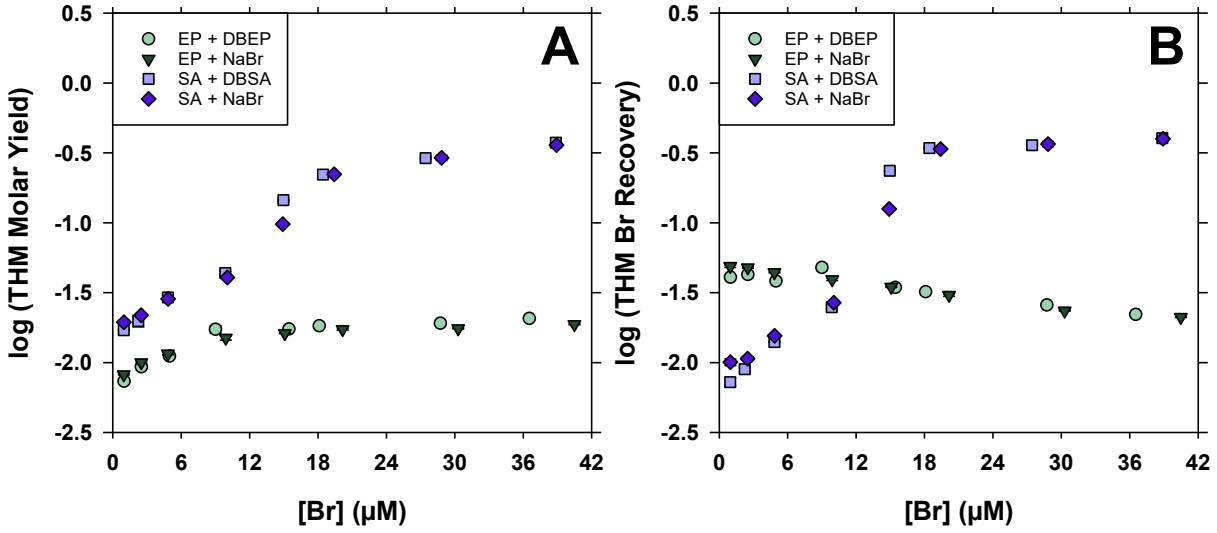


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Figure 5. A) Log of THM molar yield (mol THMs per mol precursor) and **B)** log of bromine recovery as THMs of ethylparaben (EP) and salicylate (SA) as a function of added bromine either as NaBr, DBEP, or DBSA (see legend). Bromine recovery was the total [Br] present as THMs calculated as [BDCM] + 2[DBCM] + 3[TBM] relative to added [Br] either as a precursor or NaBr. Error estimates represent 95% confidence intervals and are smaller than symbols if not shown.

281

282 [Br] to total precursor concentration greater than 0.5. Over the range of added [Br], bromine recovery as
283 THMs from paraben precursors declined by a factor of 2 while bromine recovery as THMs increased by a
284 factor of nearly 50 (**Figure 5B**). Precursors that readily undergo ring cleavage such as parabens may present
285 less evidence of ipso substitution if aromaticity is required for substitution to occur.[42] However, at added
286 [Br] less than 10 µM, bromine recovery as THMs from parabens exceeded that of salicylates. The average
287 bromine recovery from paraben precursors was 4.4% from 1 – 10 µM added [Br], while salicylate
288 precursors had an average bromine recovery of 1.5% over the same range.

289 Regioselectivity may influence Br-THM yields from salicylates. At pH 8, bromination of salicylic acid
290 para to the hydroxyl group proceeds ~3 times faster than bromination ortho to the hydroxyl group.[16] If THM
291 formation occurs primarily from positions ortho to the hydroxyl substituent, regioselectivity of
292 halogenation favoring the *para* position may limit bromine recovery from salicylate as THMs. The
293 inflection points in bromine recovery (**Figure 5B**) and THM bromine incorporation (**Figure 4A**) may have
294 represented a critical concentration of added Br where the bromination rate for THM active sites in salicylic

acid became competitive with that of free chlorine.

Each level of [Br] from BCEP, DBEP, and DBSA was paired with the approximately equivalent [Br^-] level from EP+NaBr or SA+NaBr, and paired t-tests were performed for each metric: [THM], [TTHM], THM bromine incorporation, THM molar yield, and THM bromine recovery (**Table 2**).[43] With the exception of bromine incorporation for BCEP paired with EP+NaBr, all pairs of metrics were not significantly different at the 95% confidence level (**Table 2**). For BCEP, the presence of an initial chlorine atom *ortho* to the hydroxyl group may have affected bromine incorporation in THMs relative to EP+NaBr. For the remaining 23 metrics, THM yield and distribution between organic bromine from parabens or salicylates by ipso substitution and by oxidation of NaBr were not significantly different ($p > 0.05$).

Table 2. Associated p Values from Paired Student's t-Tests Evaluating THM Concentrations, Bromine Incorporation (*n*), Bromine Recovery (Br Rec.), and THM Molar Yield When Br Originated from Brominated Organic Precursors Compared to When Br Originated from NaBr.[a]

Br Source	[TCM]	[BDCM]	[DBCM]	[TBM]	[TTHM]	*n*	Br Rec.	Molar Yield
BCEP	0.067	0.32	0.42	0.070	0.12	0.064	0.033[b]	0.11
DBEP	0.10	0.68	0.28	0.25	0.21	0.95	0.081	0.69
DBSA	0.10	0.83	0.81	0.81	0.50	0.76	0.43	0.38

[a] BCEP = 3-bromo-5-chloroethylparaben (6 data points); DBEP = 3,5-dibromoethylparaben (8 data points); DBSA = 3,5-dibromosalicylic acid (8 data points).
[b] Indicates statistically significant difference ($p < 0.05$) between Br originating from BCEP compared to Br originating from NaBr.

3.8 Effects of [Cl^-] and pH

No appreciable change in THM formation from ethylparabens was observed at pH 8 from 2 to 10 mM of added NaCl (**Figure S5A)**. However, [THMs] increased over the same [Cl^-] range at pH 6 when DBEP only or DBEP+EP served as precursors (**Figures S5B, S5C**), potentially implicating Cl_2 as a reactive species capable of promoting THM formation.[16,35,44-46] Under these conditions, [Cl_2] is proportional to both [H^+] and [Cl^-].[47] Aromatic halogenation was not rate-limiting for THM formation from phenols.[10] Thus, increased free halogen reactivity ostensibly contributes to other, subsequent halogenation steps requisite for THM formation. THM distribution shifted from primarily brominated at pH 8 to primarily chlorinated

312 at pH 6 for EP+DBEP mixtures, consistent with the participation of hydroxide as a nucleophile in ipso
313 substitution to abstract Br^+ (**Scheme 1**) and/or the weaker acidity of HOBr ($pK_a = 8.8$) relative to HOCl
314 ($pK_a = 7.5$). THM bromine recovery increased linearly as a function of [Cl^-] (**Figure S5D**). The slope for
315 EP+DBEP was greater than twice that of DBEP alone, indicating that Br-THM formation from ipso
316 substitution may be enhanced by larger proportions of more reactive chlorine species relative to HOCl (e.g.,
317 Cl_2), or by more reactive bromine species from liberated free bromine relative to HOBr (e.g., BrCl).[47]

318 **4. ENVIRONMENTAL SIGNIFICANCE**

319 Our results indicate that ipso substitution can influence the transformations and fate of parabens and
320 salicylates in chlorinated water. Our findings also demonstrate that bromination of these aromatic
321 compounds prior to subsequent reactions with free chlorine may enhance THM molar yields by up to a
322 factor of 20. This effect was more pronounced for salicylates than for parabens. Consequently, elevated
323 [Br^-] in source waters may result in a disproportionate increase in THMs beyond simply shifting THM
324 speciation toward increased bromine incorporation. For the compounds examined herein, aromatic bromine
325 proved to be comparably reactive as Br^- in generating brominated THMs. Ipso substitution could
326 conceivably impact the speciation of other DBPs beyond THMs.[48] Bromine-enrichment of DBPs associated
327 with ipso substitution may increase the toxicity of chlorinated drinking water and wastewater[49,50] via a
328 reaction mechanism that is generally overlooked in the environmental literature.[13,14] The extent to which
329 ipso substitution influences the formation of DBPs other than halogenated parabens, halogenated
330 salicylates, and THMs merits future investigation. Formation of ipso substitution products was observed
331 within 25 s at 20 °C (Figure 1A), suggesting that ipso substitution is likely to be relevant on timescales of
332 water disinfection. Effects of temperature on such reactions merit future study. The possible role of radical
333 intermediates in such reactions also warrants future study.

334 Interestingly, THM molar yield was not correlated with bromine incorporation or bromine recovery as
335 THMs. At lower, environmentally relevant concentrations of added Br (1 – 2 μM, surface waters; 8 μM,
336 desalinated seawater),[51] TTHM molar yield was on average 2.5 times higher from salicylates than parabens.

However, THM bromine recovery from parabens was several times higher than salicylates at the same [Br], irrespective of source. Therefore, for systems containing trace [Br^-], a precursor's THM molar yield may not be an adequate predictor of the overall toxicity of resulting DBPs.[50] Compounds with lower THM molar yields but a greater propensity for bromine incorporation could contribute more significantly to TTHMs (by mass) and may also contribute disproportionately towards the resulting toxicity of disinfected waters relative to those with higher molar yields and lower bromine incorporation.

Investigations of THM formation in systems containing Br^- have historically challenged researchers' attempts to predict the distribution and degree of bromination in the resulting products.[35,36,52,53] Our work highlights the pertinence of ipso substitution with respect to these challenges and reinforce Traynham's comments to chemists in 1983: "Omission of ipso substitutions from discussions of aromatic substitution reactions is, at best, misleading about the kinds of products that might be formed."[54]

ASSOCIATED CONTENT

Supporting Information. List of abbreviations, structures, reagent information, synthesis details of 3-bromo-5-chloroethylparaben, instrumental methods, and supplemental THM data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

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