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Structural effects on the bromination rate and selectivity of alkylbenzenes and alkoxybenzenes in aqueous solution†

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Abstract

Aqueous free bromine species (e.g., HOBr, BrCl, Br_2, BrOCl, Br_2O, and H_2OBr^+) can react with activated aromatic compounds via electrophilic aromatic substitution to generate products with industrial applications, environmental consequences, and potentially adverse biological effects. The relative contributions of these brominating agents to overall bromination rates can be calculated via nonlinear regression analyses of kinetic data collected under a variety of solution conditions, including variations in parameters (e.g., $[Cl^-]$, $[Br^-]$, and pH) known to influence free bromine speciation. Herein, kinetic experiments conducted in batch reactors were employed to evaluate the contributions of steric and electronic effects on bromination of monosubstituted alkylbenzenes (ethyl, isopropyl, *tert*-butyl) and alkoxybenzenes (ethoxy, isopropoxy, *tert*-butoxy) and to elucidate the inherent reactivities of aqueous brominating agents towards these aromatic compounds. For bromination at the *para* position of alkylbenzenes, overall reactivity increased from *tert*-butyl < ethyl ≈ isopropyl. For bromination at the *para* position of alkoxybenzenes, reactivity increased from *tert*-butoxy < ethoxy < isopropoxy. In going from ethyl to *tert*-butyl and ethoxy to isopropoxy, unfavorable steric effects attenuated the favorable electronic effects imparted by the substituents. When comparing unsubstituted benzene, alkyl-, and alkoxybenzenes, the structure of the substituent has a significant effect on bromination rates, nucleophile regioselectivity, and electrophile chemoselectivity. Hirshfeld charges were useful predictors of reactivity and regioselectivity. The experimental results were also modeled using Taft equations. Collectively, these findings indicate that steric effects, electronic effects, and brominating agents other than HOBr can influence aromatic compound bromination in solutions of free bromine.

1. Introduction

Bromination of aromatic compounds typically involves covalent bond formation between a nucleophilic carbon atom and an electropositive bromine atom.[1] Aromatic bromination is an essential step in the synthesis of commercially-important specialty chemicals, including selected pharmaceuticals,[2–4] pesticides,[5–8] flame retardants,[9–11] and dyes.[12–15] Bromination of aromatic moieties is also associated with the unintentional formation of organobromine compounds in drinking water,[16–21] wastewater,[22,23] and recreational waters (e.g., pools and spas).[24–27] Some of these organobromine compounds (e.g., brominated methanes and acetates) are disinfection byproducts (DBPs) whose concentrations are regulated in drinking water in the United States and elsewhere.[28–31] Brominated DBPs are of concern due to their potential cytotoxic[32,33] and genotoxic effects.[34–36]

In addition to generating potentially-toxic DBPs, bromine substitution at aromatic moieties may also contribute to the antimicrobial properties of bromine disinfectants in recreational waters[20,37,38] and in household cleaners.[39] Electrophilic bromine species are also generated in vivo via enzyme-mediated oxidation of bromide by H_2O_2 within specific mammalian leukocytes.[40,41] In addition to killing invading pathogens, these bromine species can also transform endogenous biomolecules (e.g., via bromination of aromatic compounds)[42–44] and potentially contribute to inflammatory diseases such as asthma,[45] Alzheimer's,[46] and COVID-19.[47]

Bromide is a nearly omnipresent constituent of natural waters, including precipitation, groundwater, freshwater lakes, and seawater.[48,49] Naturally-occurring bromide can be rapidly and stoichiometrically oxidized (**eq 1**) in the presence of the common water disinfectant hypochlorous

acid, (HOCl, pK_a = 7.50, 20 °C)[50] to form a mixture of bromine species in the 0 or +I oxidation states (**Table 1**), collectively referred to as free (available) bromine.

$$HOCl(aq) + Br^- \rightleftharpoons HOBr(aq) + Cl^- \quad (1)$$

$$\log K_1 = 5.18 \text{ (20 °C)}[51]$$

Likewise, the sum of all the chlorine species in the 0 or +I oxidation states (e.g., HOCl, OCl^-, Cl_2, and Cl_2O) is referred to as free available chlorine (FAC). In addition to oxidation of bromide by FAC, free bromine can form through oxidation of bromide in waters treated with ozone[55,56] and chloroamines.[57,58,59]

Table 1. Equilibria involving free available bromine species.[a]

Reaction	*Equilibrium Constant*[a]	*Equation Number*
$HOBr(aq) + Cl^- + H^+ \rightleftharpoons BrCl(aq) + H_2O$	$\log K_2 = 4.09$[52]	2
$Br_2(aq) + H_2O \rightleftharpoons HOBr(aq) + Br^- + H^+$	$\log K_3 = -8.40$[53]	3
$2HOBr(aq) \rightleftharpoons Br_2O(aq) + H_2O$	$\log K_4 = 0.80$[54] (25 °C)	4
$HOCl(aq) + HOBr(aq) \rightleftharpoons BrOCl(aq) + H_2O$	$\log K_5 = -0.46$[54] (25 °C)	5
$HOBr(aq) + H^+ \rightleftharpoons H_2OBr^+(aq)$	not available	6

[a] Unless stated otherwise, all equilibrium constants are at 0 M ionic strength and 20 °C.[50]

All bromine species in **Table 1** can conceivably serve as electrophilic brominating agents of aromatic compounds.[60,61] Nevertheless, hypobromous acid (HOBr, **eq 7**) is widely assumed to be the only kinetically relevant brominating agent because it is the most abundant form of free available bromine in aqueous solutions at near-neutral pH.

$$HOBr \rightleftharpoons BrO^- + H^+ \quad (7)$$

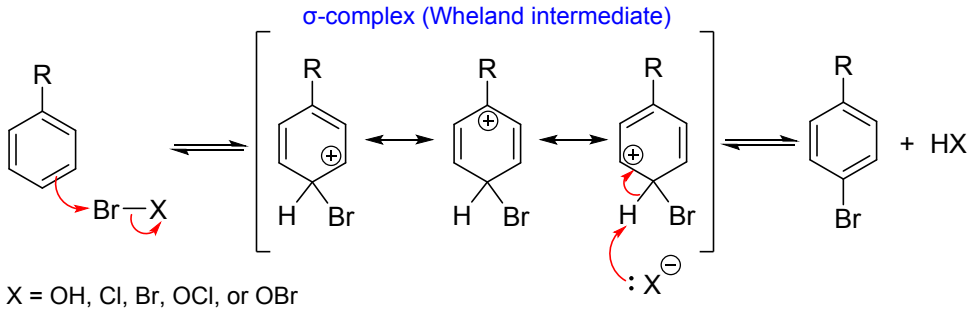
$$pK_a = 8.70 \text{ (20 °C, ref 11)}$$

While typically present at lesser concentrations, BrCl, Br_2, Br_2O, BrOCl (**eqs 2 – 5**), are inherently more reactive brominating agents than HOBr.[54,62,63] Second-order rate constants for bromination of anisole,[62] dimethenamid (a substituted thiophene),[54] and salicylic acid[63] by BrCl, Br_2, Br_2O, and BrOCl are at least 2×10^3 (and up to 8×10^6) times greater than the corresponding second-order rate constants for HOBr. Similar ranges of second-order rate constants were reported for bromination of *p*-xylene by BrCl, Br_2, and HOBr.[60] That the inherent reactivity of BrCl, Br_2, Br_2O, and BrOCl can exceed that of the (more abundant) HOBr by several orders of magnitude suggests that these less-abundant electrophiles may be kinetically competent, particularly in reactions involving modestly nucleophilic organic substrates.[61] Notably, in addition to influencing overall bromination rates, brominating agent speciation can also affect the regioselectivity of bromine substitution during reactions with compounds possessing more than one nonequivalent reactive position (e.g., anisole and salicylic acid).[62,63] Nevertheless, a systemic evaluation of how aromatic compound structure influences selectivity toward the aforementioned aqueous brominating agents has not been previously reported.

For bromination of *p*-xylene, H_2OBr^+ was postulated to be an active brominating agent at low pH.[60] Bromination studies of anisole,[62] dimethenamid,[54] and salicylic acid[63] did not need to invoke H_2OBr^+ (**eq 6**) as an active brominating agent in order to model the influence of pH on bromine substitution rates. Instead, rate enhancements at low pH were ascribed to BrCl. Nevertheless, data in these studies do not preclude the possible influence of H_2OBr^+, particularly in solutions with low concentrations of chloride ion (noting that [BrCl], but not [H_2OBr^+], is proportional to [Cl^-], **Table 1**).

Bromination of aromatic compounds by free bromine species has been postulated to occur via electrophilic aromatic substitution (**Scheme 1**).[62,64] A recent computational study determined

that the activated complex associated with electrophilic aromatic bromination has an energy and structure similar to that of the σ-complex.[65] Computational models also indicate that reaction rate and regioselectivity of bromination are strongly dependent on the substituent(s) associated with the aromatic substrate.[65–67] However, laboratory studies investigating structure-reactivity effects involving aromatic nucleophiles and aqueous brominating agents are largely absent from the literature.[62]



Scheme 1. Electrophilic aromatic bromination mechanism of monosubstituted benzenes; R denotes an activating substituent (e.g., an alkyl or alkoxy group).

The purpose of this study is to investigate how steric and electronic effects influence the rate and selectivity of monosubstituted benzene bromination and to determine regiospecific second-order rate constants associated with each kinetically competent electrophile-nucleophile (i.e., bromine species-aromatic compound) pair. The reactivity of each electrophilic bromine species can be elucidated by systematically varying solution conditions known to influence free bromine speciation (e.g., [Cl^-], [FAC], [Br^-], and pH)[62] and monitoring the effects of such changes on overall bromination rates. The organic nucleophiles examined in this study include benzene (as a reference compound), three monosubstituted alkylbenzenes (ethyl-, isopropyl- and *tert*-butylbenzene), and three monosubstituted alkoxybenzenes (ethoxy-, isopropoxy-, and *tert*-butoxybenzene). These organic compounds were selected for study due to their systematic structural variations, which are anticipated to exert differing steric and electronic effects on

aromatic bromination rates and selectivity. The absence of ionizable groups simplifies reactivity models such that only the speciation of brominating agents (and not of organic nucleophiles) is anticipated to vary with pH.

The presence of an alkyl or alkoxy substituent is predicted to increase bromination rates (relative to benzene) and to direct bromination to the *para* and *ortho* positions of the alkyl- and alkoxybenzenes.[68] In addition to exerting favorable electronic effects on rates of bromine substitution, all substituents examined herein are postulated to exert differing and ostensibly rate-slowing steric effects relative to (unsubstituted) benzene. The relative influence of steric and electronic effects is anticipated to vary depending on the identity of the brominating agent.[62] Collectively, the suite of aromatic compounds examined herein permits us to quantify the relative importance of steric versus electronic effects on aromatic bromination across a range of aqueous solution conditions. This work represents one of the most comprehensive evaluations to date of the interplay between structural effects and electrophile speciation on the kinetics of aromatic bromination in aqueous systems.

2. Experimental

2.1 Method Overview. The kinetic experiments described below employed aqueous batch reactors containing free available bromine (prepared by oxidizing bromide with NaOCl). Solution conditions known to influence bromine speciation (e.g., pH, $[Br^-]$, $[Cl^-]$, [FAC], temperature) were carefully controlled. Reactors were initiated via addition of an organic substrate (benzene, alkylbenzene, or alkoxybenzene) to reaction solutions pre-amended with a pH buffer, NaBr, NaOCl (as the source of FAC), NaCl (to fix $[Cl^-]$), and $NaNO_3$ (to fix ionic strength). Aliquots from reaction solutions were periodically obtained, quenched with excess thiosulfate (to eliminate

active halogens), and extracted into an organic solvent. Extracts were analyzed by gas chromatography-mass spectrometry (GC-MS) to monitor the loss of organic substrates and formation of brominated products.

A list of reagents is provided in **Table S1** of the electronic supplementary information (ESI). Unless noted otherwise, all aqueous solutions were prepared in deionized water that was further purified to a resistivity of ≥18 MΩ cm (NANOpure, Thermo Scientific). All pH adjustments were performed using NaOH or HNO_3. The pH of reaction solutions was measured at the conclusion of each kinetic experiment. All pH measurements were obtained using a Fisher Accumet AB 150 pH meter with an automatic temperature compensation glass electrode that was calibrated daily using certified buffers of pH 4.00, 7.00, and 10.00.

2.2 Bromination of Benzene with Varied [NaCl]. Among the free bromine species listed in **Table 1**, BrCl was previously shown to be the most inherently reactive toward modestly nucleophilic organic compounds.[54,62,63] Due to the anticipated low reactivity of benzene toward aqueous free bromine, we hypothesized that BrCl would be the only brominating agent sufficiently reactive to brominate benzene under the conditions examined herein. Accordingly, experiments were designed to interrogate the influence of BrCl by varying [NaCl], noting that [BrCl] is proportional to $[Cl^-]$ (**eq 2**). Buffer solution (containing $[phosphate]_{tot}$ = 25 mM, [NaBr] = 55 mM, [NaCl] = 0 to 300 mM, and $[NaNO_3]$ = 300 mM – [NaCl]) was adjusted to pH 6.3 and diluted to 100.0 mL with water in a glass volumetric flask. NaOCl (0.7 mL of 900 mM aqueous stock) was added (giving a diluted $[NaOCl]_o$ = 6.0 mM), and the flask was placed into a circulating water bath at 20.00 ± 0.02 °C for 5 min. Thereafter, a solution of benzene (985 μL of 10.3 mM in methanol) was added to initiate the reaction with $[benzene]_o$ = 0.10 mM, and the flask was shaken manually for 10 s. Reaction solutions contained ≤1 vol% of methanol. The solution was then rapidly

transferred into six amber glass vials (8-mL capacity) so that there was no headspace (to prevent volatilization of benzene or bromobenzene). Vials were capped and placed into the water bath. Every 30 min over 3 h, one 8-mL vial was sacrificed; a 2.0-mL aliquot from each 8-mL vial was transferred into a waste container to permit addition of sodium thiosulfate (500 µL of 300 mM stock in water) and 800 µL of MTBE (containing 10.2 µM 2-chlorobenzonitrile, CBN, as an internal standard) to quench and extract the aliquot, respectively. Reaction solution and aliquot volumes were determined gravimetrically (weighing by difference to ± 0.01 mg, Mettler Toledo Excellence XA). After vigorously shaking the vials for 30 s, approximately 190 µL of the MTBE layer was transferred into a 2-mL autosampler vial containing a 200-µL glass insert. Extracted samples were analyzed via GC-MS (see Section 2.5).

2.3 Bromination of Alkylbenzenes. Unlike benzene, alkylbenzenes were anticipated to be reactive toward a wider range of brominating agents due to their activating alkyl substituent. Accordingly, a greater number of independent variables were investigated for kinetic experiments involving alkylbenzenes so as to more comprehensively characterize reactive brominating agents in these reactions. Reactors included a pH buffer solution containing sodium salts of phosphate or borate (typically 20 mM formal concentration), $NaNO_3$ (typically 95 mM), NaCl (typically 5 mM), and NaBr (typically 1 mM) in water. The effects of several independent variables on bromination rates were examined, including formal concentration of buffers (10 – 40 mM), $[Cl^-]$ (5.60 – 61.7 mM), $[FAC]_o$ (1.20 – 10.2 mM), $[Br^-]_o$ (5.87 – 9.74 mM), and pH (5.31 – 7.92). For most experiments, FAC was added in excess of Br^- to promote stoichiometric oxidation of Br^- into free bromine. For selected experiments, Br^- was added in excess of FAC; such excess Br^- concentrations are denoted herein as $[Br^-]_{xs}$ (= $[Br^-]_o - [FAC]_o$) and ranged from 1.00 – 5.01 mM. In experiments where $[Cl^-]$ was varied, $[NaNO_3]$ was adjusted to maintain approximately uniform

ionic strength such that $[NaNO_3]$ + [NaCl] = 100 mM. For experiments in which $[FAC]_o$ was varied, stock NaOCl solutions subjected to liquid-liquid extractions (to remove Cl^-) served as the source of FAC to minimize the variability of $[Cl^-]$ (noting that reagent-grade NaOCl solutions are generally equimolar in Cl^-); see Section S2 in the ESI for additional details.

Reactors were prepared by adding pH buffer solution (40.0 mL) to 40-mL amber glass vials (to minimize headspace). A mixed, methanolic stock solution (containing ~1.5 mM each of ethylbenzene, isopropylbenzene, and *tert*-butylbenzene) was added to reactors to achieve initial concentrations of each alkylbenzene at 16 μM. Reaction solutions contained ≤1.3 vol% methanol. After a 5 min equilibration period in a water bath (20.00 ± 0.02 °C), FAC was added as aqueous NaOCl. For reactors in which $[Br^-]$ was varied in the presence of excess FAC, $[FAC]_o = [Br^-]$ + 0.5 mM; for all other experiments, $[FAC]_o$ = 1.15 mM. Vials were capped, shaken manually for 10 s, and returned to the water bath. Reactor aliquots (0.900 mL each) were periodically transferred to 4-mL amber glass vials pre-amended with excess $Na_2S_2O_3$ ($[Na_2S_2O_3]/[FAC]_o \approx 1.4$ mol:mol). Isooctane (0.500 mL, containing 10.0 μM CBN as the internal standard) was added to the 4-mL vials as the extraction solvent. Vials were vigorously shaken for 30 s, and 190 μL of the isooctane layer was transferred to a 2-mL autosampler vial containing a 200-μL glass insert. Extracted samples were analyzed via GC-MS (see Section 2.5).

2.4 Bromination of Alkoxybenzenes. Kinetic experiments examining bromination rates of alkoxybenzenes were similar to those described above for alkylbenzenes, with key differences described below. Reactors included a pH buffer solution (sodium bicarbonate or sodium borate, typically 20 mM formal concentration), $NaNO_3$ (typically 90 mM), NaCl (typically 10 mM), and NaBr (typically 350 μM) in water. Independent variables included buffer salt formal concentration (10 – 50 mM), $[NaNO_3]$ (45 – 215 mM), $[Cl^-]$ (10 – 50 mM), $[FAC]_o$ (400 – 800 μM), $[Br^-]$ (150

– 350 μM), $[Br^-]_{xs}$ (400 – 750 μM), and pH (6.5 – 10.0). For each reactor, buffer solution (25.0 mL) was transferred into a 40-mL amber glass vial, and FAC was added as aqueous NaOCl to achieve $[FAC]_o$ = 0.400 mM. After a 5 min equilibration period in a water bath (20.00 ± 0.02 °C) to allow for oxidation of bromide, a mixed, methanolic spike (containing ~2 mM each of ethoxybenzene, isopropoxybenzene, and *tert*-butoxybenzene) was added to reactors to achieve initial concentrations of each alkoxybenzene at 10 μM. Quenching and extraction procedures were the same as for the alkylbenzene reactions, except for the use of toluene (0.500 mL, containing 10.2 μM CBN as the internal standard) as the extraction solvent instead of isooctane. Extracted samples were analyzed via GC-MS (see Section 2.5).

2.5 Analysis of Reactants and Products. Concentrations of benzene, alkyl-, alkoxybenzenes, and their monobrominated products were analyzed via gas chromatography (GC, Agilent 7890A) with mass spectrometry (MS, Agilent 5975C) operated in selective ion monitoring mode. Additional GC-MS method details are provided in the ESI (Section S3).

2.6 Calculation of Rate Constants.

Pseudo-First-Order Rate Constants. For bromination of benzene and alkylbenzenes, pseudo-first-order rate constants (k_{obs}, s^{-1}) were calculated by monitoring brominated-product formation as a function of time.

$$\text{rate of brominated product formation} = \frac{\mathrm{d[Br-product]}}{\mathrm{dt}} = k_{\mathrm{obs}}[\text{(alkyl)benzene}]_{\mathrm{o}} \qquad (8)$$

where the rate of brominated product formation is obtained from linear regressions of [Br-product] versus time plots (**Figure S1**). To ensure pseudo-first-order conditions, ratios of $[HOBr]_{tot,o}$ to $[(alkyl)benzene]_o$ were always greater than 50, where $[HOBr]_{tot,o}$ denotes the total free bromine concentration at t = 0. Sampling times were selected such that initial parent concentrations

decreased by <5% over the course of the experiments. Benzene was unable to be quantified via our GC-MS method due to its co-elution with the solvent (MTBE); therefore, $[benzene]_o$ was assumed to equal the nominal concentration achieved following the addition of benzene to the reaction solution. Initial concentrations of ethyl-, isopropyl-, and *tert*-butylbenzene were assumed to equal those obtained from a control experiment involving no added FAC and no added $Na_2S_2O_3$. For such experiments, the methanolic spike containing all parent compounds was added to the 40-mL amber glass vial (containing 40.0-mL of buffer solution), vials were capped, shaken for 10 s (t = 0), aliquots (0.900 mL) were obtained after 1 and 2 hours, and extracted into isooctane as described in Section 2.3. Because concentrations of each alkylbenzene were not significantly different (at the 95% confidence level) between the 1-h and 2-h incubation times, concentrations were averaged for both incubation times and used to calculate k_{obs} via **eq 8**. Alkoxybenzenes are substantially more reactive toward brominating agents than are (alkyl)benzenes. Therefore, losses of alkoxybenzenes were monitored during time course reactions (**Figure S2A**) and pseudo-first-order rate constants were calculated from the slopes of ln[alkoxybenzene] versus time plots (**Figure S2B**).

Alkyl- and alkoxybenzenes react with aqueous brominating agents predominantly at the carbon atoms *ortho* and *para* to the alkyl or alkoxy substituent. Assuming that additional reaction pathways contribute negligibly to overall rates of parent compound loss, rate constants corresponding to net bromination are equal to the sum of regiospecific rate constants (i.e., $k_{obs,net} = k_{obs,orhto} + k_{obs,para}$). Pseudo-first-order rate constants corresponding to bromination at the *ortho* ($k_{obs,ortho}$) and *para* ($k_{obs,para}$) positions were calculated using **eq 9 and 10**, respectively.

$$k_{obs,ortho} = k_{obs,net}\frac{[\text{ortho Br product}]}{[\text{ortho Br product}] + [\text{para Br product}]} \quad (9)$$

$$k_{\text{obs,para}} = k_{\text{obs,net}} \frac{[\text{para Br product}]}{[\text{ortho Br product}] + [\text{para Br product}]} \quad (10)$$

Concentration ratios of *ortho* and *para* brominated products for each time course were obtained by averaging the measured ratios in each reactor at each sampling time. All solution conditions and measured pseudo-first-order rate constants are compiled in **Table S5-S14**.

Second-Order Rate Constants. Due to the sluggish reactivity of benzene toward aqueous brominating agents, BrCl is anticipated to be the only kinetically competent brominating species, noting that BrCl has been shown to have the highest inherent reactivity towards aromatic compounds among the putative aqueous brominating agents.[69] Therefore, the second-order rate constant, k_{BrCl} (M^{-1} s^{-1}), for bromination of benzene was calculated from the linear regression of k_{obs} as a function of [Cl^-]

$$k_{obs} = k_{BrCl} K_2 [\text{HOBr}][\text{H}^+][\text{Cl}^-] + j \quad (11)$$

where *j* corresponds to the y-intercept (see ref 54 for additional details).

Brominating-agent-specific second-order rate constants corresponding to the formation of each regioisomeric product of alkyl- and alkoxybenzene bromination were calculated through nonlinear least-squares regression (*Scientist 3.0*, Mircomath) of **eq 12**.

$$k_{\text{obs}} = k_{\text{HOBr}}[\text{HOBr}] + k_{\text{BrCl}}[\text{BrCl}] + k_{\text{Br}_2\text{O}}[\text{Br}_2\text{O}] + k_{\text{H}_2\text{OBr}^+}[\text{H}_2\text{OBr}^+] + k_{\text{Br}_2}[\text{Br}_2] \quad (12)$$

Experimentally determined k_{obs} values (**Tables S5-S14**) and calculated equilibrium concentrations of bromine species (**eq 1 – 6**) under the various conditions employed in kinetic experiments were used as input values. Brominating-agent-specific second-order rate constants (e.g., k_{HOBr}) served as fitting parameters. A data binning process involving iterative fitting was used to increase the precision of the calculated second-order rate constants; see ESI Section S6 for additional details.

2.7 Data Modeling of Taft Parameters. To quantify how electronic and steric effects exerted by substituents impact bromination rates, the polar sensitivity factor, ρ^*, and the steric sensitivity factor, δ, were determined via the Taft equation (**eq 13**)

$$\log\left(\frac{k_s}{k_H}\right) = \rho^* \sigma^* + \delta E_s \quad (13)$$

where $\log\left(\frac{k_s}{k_H}\right)$ is the ratio of the rate constant of a substituted benzene undergoing bromination relative to that of benzene, σ^* is the polar substituent constant, and E_s is the steric substituent constant.[70,71] Values of σ^* and E_s for bromination of the alkyl- and alkoxybenzenes were normalized to that of benzene (**Table S17**). Taft parameters for bromination of alkyl- and alkoxybenzenes were determined via nonlinear regression analysis of **eq 13**, which were performed using SigmaPlot 13.0. Literature values of steric substituent constants are not reported for isopropoxy and *tert*-butoxy substituents; therefore, Taft parameters were not calculated for isopropoxybenzene and *tert*-butoxybenzene; see ESI Section S7 for more details.

3. Results and discussion

Kinetics of alkyl- and alkoxybenzene bromination were examined to evaluate the influence of steric and electronic effects on bromine substitution rates and selectivity. Reactivity toward brominating agents generally increased in the order benzene < *tert*-butyl < isopropyl < ethyl << *tert*-butoxy < ethoxy < isopropoxy, with greater reactivity at the *para*-positions compared to the *ortho*-positions. Below, the effects of various solution conditions and of organic nucleophile structure on bromination kinetics are discussed.

3.1 Effect of Buffer Concentration and Ionic Strength. The formal concentration of buffer salts containing phosphate, bicarbonate, or borate (10 – 50 mM) did not appreciably influence rates of

alkyl- and alkoxybenzene bromination (data not shown). Rates of alkoxybenzene bromination were not appreciably influenced by changes in ionic strength (data not shown). Nevertheless, ionic strength was kept approximately constant for all reactions herein (e.g., by fixing the value of [NaCl] + [$NaNO_3$]).

3.2 Effect of Chloride Concentration. Plots of k_{obs} values for the formation of brominated benzenes as a function of $[Cl^-]_{tot}$ (the total concentration of Cl^- from all sources, including added NaCl, added FAC, and Cl^- generated from oxidation of Br^- by FAC) revealed a positive linear relationship (**Figure 1**). These results suggest that bromination of the examined aromatic compounds is subject to chloride catalysis.[49,61]

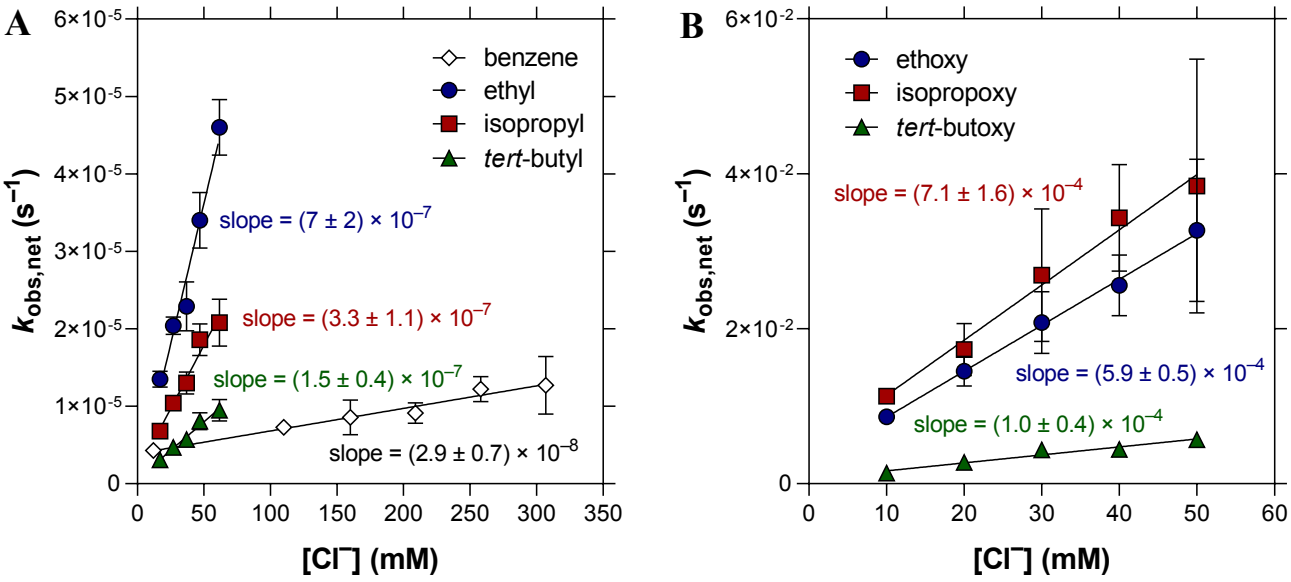


Figure 1. Pseudo-first-order rate constants for bromination of (**A**) benzene, alkyl-, and (**B**) alkoxybenzenes as a function of total chloride concentration. Solution conditions: T = 20.00 °C, (**A, benzene**) $[FAC]_o$ = 6.0 mM, phosphate (25 mM) as pH buffer, pH = 6.30, $[benzene]_o$ = 100 μM, $[Br^-]$ = 55 mM, and [NaCl] + [$NaNO_3$] = 300 mM; (**A, alkylbenzenes**) $[FAC]_o$ = 1.16 mM, phosphate (20 mM) as pH buffer, pH = 6.30, $[alkylbenzene]_o$ = 16 μM, $[Br^-]$ = 0.99 mM, and [NaCl] + [$NaNO_3$] = 100 mM; (**B**) $[FAC]_o$ = 0.4 mM, phosphate (20 mM) as pH buffer, pH = 7.0, $[alkoxybenzene]_o$ = 10 μM, $[Br^-]$ = 0.35 mM, and [$NaNO_3$] = 90 mM . Graphed $[Cl^-]$ represents $[Cl^-]_{tot}$ (which is the contribution from all sources of Cl^-, including NaCl, added FAC, and generation of Cl^- during oxidation of Br^- by FAC). Error estimates denote 95% confidence intervals; error bars are smaller than symbols when not shown.

The slopes of the linear regressions in **Figure 1** indicate how susceptible each nucleophile is to catalysis of bromination by chloride under the stated conditions. The slopes increase from benzene < alkylbenzenes << alkoxybenzenes and, within those subgroups, generally decrease with increasing substituent size, suggesting that chloride catalysis is influenced by a combination of electronic and steric effects. Increasing chloride concentration in the presence of free bromine favors BrCl formation (**eq 2**). Accordingly, the observed increased reactivity with increasing $[Cl^-]_{tot}$ is consistent with BrCl as a reactive brominating agent. Because BrCl is ostensibly the only brominating agent whose concentration is proportional to $[Cl^-]$, the net contribution of brominating agents other than BrCl (e.g., HOBr, BrOCl, Br_2O) are reflected in the y-intercepts of **Figure 1**.

Due to the sluggish reactivity of benzene, it was anticipated that only the most reactive brominating agent, BrCl, would contribute to overall bromination rates; however, the y-intercept of the benzene linear regression (**Figure 1A**) is significantly greater than zero, suggesting that other brominating agents contribute to the net bromination rate of benzene. (Herein, all tests for statistical significance are evaluated with respect to the 95% confidence level.) The y-intercepts of the linear regressions associated with the alkylbenzenes and the alkoxybenzenes were several orders of magnitude lower than the measured $k_{obs,net}$ values (**Figure 1**), indicating that BrCl is the major contributor to overall bromination rates under the examined conditions.

The ratio $k_{obs,para}/k_{obs,ortho}$ can be used to quantify the regioselectivity of bromination of monosubstituted benzenes. If the para and ortho positions are equally reactive, $k_{obs,para}/k_{obs,ortho}$ will equal 0.5. Regioselectivity (quantified as $k_{obs,para}/k_{obs,ortho}$) did not vary appreciably as a function of $[Cl^-]$ for all compounds except *tert*-butyl, for which $k_{obs,para}/k_{obs,ortho}$ increased up to 63 and then decreased to 47 with increasing $[Cl^-]$ from 17 to 62 mM (**Figure S9**). Average $k_{obs,para}/k_{obs,ortho}$ values across all examined $[Cl^-]$ were 0.65 ± 0.08 (ethyl), 6.1 ± 0.3 (isopropyl), 51 ± 12 (*tert*-

butyl), 4.44 ± 0.09 (ethoxy), 4.18 ± 0.13 (isopropoxy), and 1.70 ± 0.16 (*tert*-butoxy). These values suggest that the regioselectivity of bromine substitution is more sensitive to substituent effects for alkylbenzenes than for alkoxybenzenes.

3.3 Effect of Excess Free Chlorine. Previous studies have demonstrated that the FAC concentration can influence bromination rates in solutions of free bromine by promoting the formation of BrOCl (**eq 5**), which has been shown to be a more inherently reactive brominating agent than HOBr.[49,61] Accordingly, experiments were performed herein in which the initial concentration of FAC ($[FAC]_o$) was varied to determine whether bromination rates of monosubstituted benzenes were influenced by $[FAC]_o$. For bromination of alkylbenzenes, no discernible trend was observed between k_{obs} values and $[FAC]_o$ (**Figure S3**). Despite attempts at modifying reaction conditions to favor reactivity toward BrOCl (e.g., by extracting Cl^- from FAC spiking solutions to minimize the influence of BrCl), slopes for all alkylbenzene k_{obs} versus $[FAC]_o$ plots were not significantly different than zero. A previous study of *p*-xylene bromination[60] similarly concluded that BrOCl did not appreciably influence bromination rates. Alkylbenzenes and *p*-xylene may be insufficiently nucleophilic to react appreciably with BrOCl in the solution conditions examined in these studies.

Conversely, for bromination of alkoxybenzenes, plots of k_{obs} as a function of $[FAC]_o$ revealed a positive, linear relationship (**Figure 2**), suggesting that BrOCl is a relevant brominating agent (**eq 5**).

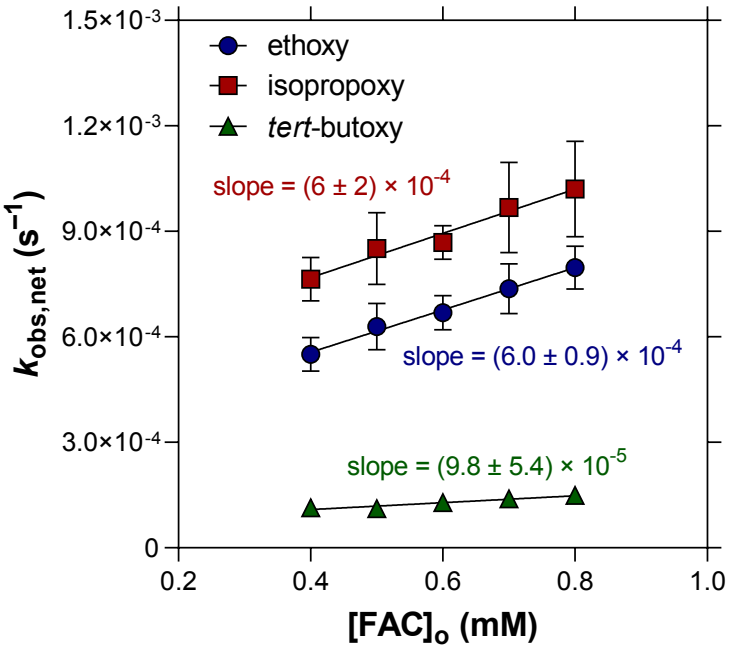


Figure 2. Pseudo-first-order rate constants for bromination of alkoxybenzenes as a function of initial free available chlorine (FAC) concentration. Solution conditions: T = 20.00 °C, [Br^-] = 350 μM, borate (20 mM) as pH buffer, pH = 8.2, [alkoxybenzene]$_o$ = 10 μM, [NaCl] = 10 mM, [$NaNO_3$] = 90 mM. Slopes have units of s^{-1} mM^{-1}. Error estimates denote 95% confidence intervals; error bars are smaller than symbols when not shown.

Alkoxybenzenes have lower (more negative) Hirshfeld charges calculated for their ortho and para positions relative to their alkylbenzene analogues.[72] The increased electron density at the ortho and para positions of alkoxybenzenes renders them more nucleophilic and thus potentially more susceptible to reactions with BrOCl (compared to alkylbenzenes), noting that BrOCl is less inherently reactive via electrophilic aromatic substitution than is BrCl.[60] For this set of experiments in which [FAC]$_o$ was the independent variable, net reactivity increased from *tert*-butyl < isopropyl < ethyl << *tert*-butoxy < ethoxy < isopropoxy. Regioselectivity ($k_{obs,para}/k_{obs,ortho}$) did not vary appreciably as a function of [FAC]$_o$ (**Figure S10**). Average $k_{obs,para}/k_{obs,ortho}$ values were 0.63 ± 0.06 (ethyl), 6.6 ± 0.5 (isopropyl), 82 ± 9 (*tert*-butyl), 7.5 ± 0.8 (ethoxy), 7.4 ± 0.6 (isopropoxy), and 3.1 ± 0.2 (*tert*-butoxy). For all three alkoxybenzenes and for *tert*-butylbenzene, $k_{obs,para}/k_{obs,ortho}$ values obtained from experiments performed with varied [FAC]$_o$ were somewhat greater than

those obtained from varied $[Cl^-]_{tot}$ experiments. These results suggest that BrOCl is more selective than BrCl for substitution at the *para* position of these monosubstituted benzenes.

3.4 Effect of Bromide in the Presence of Excess FAC. Plots of log k_{obs} values corresponding to formation of brominated alkylbenzenes as a function of the initial bromide concentration (as log $[Br^-]_o$) revealed approximately linear relationships with slopes ≥1 (**Figure 3A**), consistent with a greater-than-first-order dependence on the total free bromine concentration. Increasing $[Br^-]_o$ (in the presence of excess FAC) increases the total concentration of free bromine species, including HOBr (**eq 1**). Two equivalents of HOBr can participate in a dehydration reaction to form Br_2O (**eq 4**). Br_2O is the only bromine species anticipated to produce reaction orders in [HOBr] greater than 1.0 because $[Br_2O]$ has a second-order dependence on [HOBr].[49,54] For a number of organic compounds examined previously (e.g., anisole,[62] salicylic acid,[63] and dimethenamid[54]), the brominating reactivity of Br_2O is several orders of magnitude greater than HOBr. The positive, linear dependence of $\log(k_{obs})$ on $\log([Br^-]_o)$ in the presence of excess FAC suggests that Br_2O is influencing overall bromination rates of alkylbenzenes.[49] Reactivity of alkoxybenzenes also increased as a function of $[Br^-]_o$ but did not exhibit a greater-than-first-order dependence on $[Br^-]_o$ (**Figure 3B**), suggesting that Br_2O exerts a lesser influence on overall bromination rates of alkoxybenzenes relative to alkylbenzenes under the examined conditions.

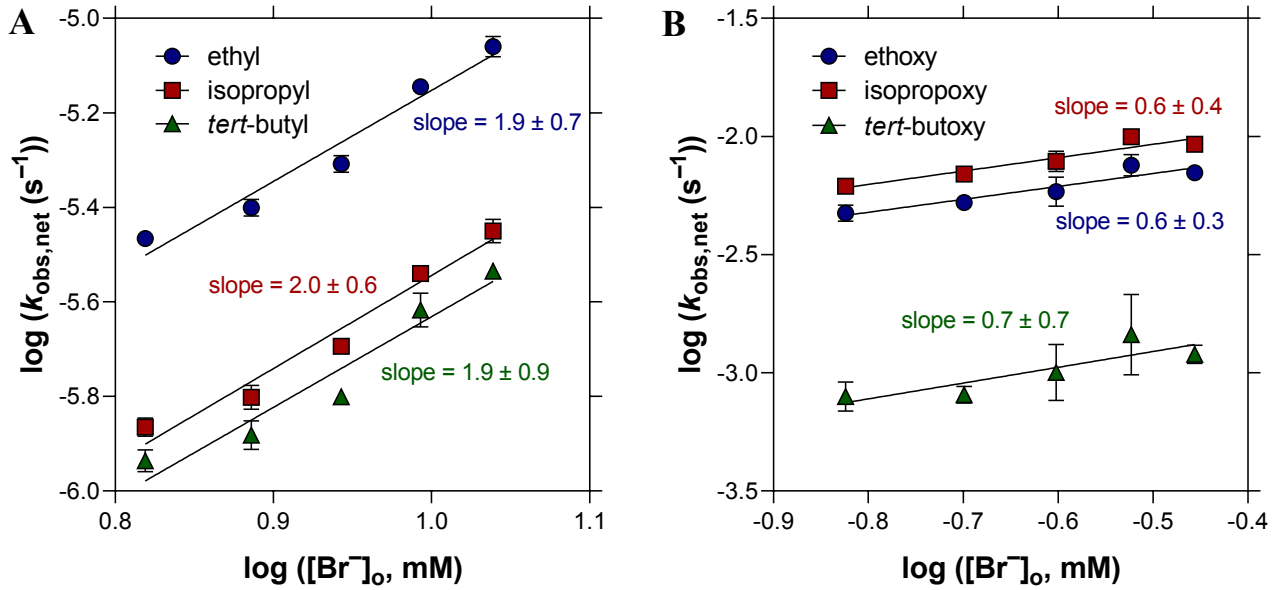


Figure 3. Pseudo-first-order rate constants for bromination of (**A**) alkylbenzenes and (**B**) alkoxybenzenes as a function of the initial bromide concentration in the presence of excess FAC. Solution conditions: T = 20.00 °C, (**A**) $[FAC]_o = [Br^-]_o + 0.5$ mM, borate (20 mM) as pH buffer, pH = 8.00, $[alkylbenzene]_o$ = 50 µM, [NaCl] = 5.00 mM, and $[NaNO_3]$ = 95 mM; (**B**) $[FAC]_o$ = 0.4 mM, phosphate (20 mM) as pH buffer, pH = 7.0, $[alkoxybenzene]_o$ = 10 µM, [NaCl] = 10.0 mM, $[NaNO_3]$ = 90 mM. Slopes have units of s^{-1} mM^{-1}. Error estimates denote 95% confidence intervals; error bars are smaller than symbols when not shown.

For the set of experiments in which $[Br^-]_o$ was the independent variable (**Figure 3**), net reactivity increased from *tert*-butyl < isopropyl < ethyl << *tert*-butoxy < ethoxy < isopropoxy. Regioselectivity ($k_{obs,para}/k_{obs,ortho}$) did not vary significantly as a function of $[Br^-]_o$ (**Figure S11**). Average $k_{obs,para}/k_{obs,ortho}$ values were 0.73 ± 0.03 (ethyl), 6.8 ± 0.3 (isopropyl), 124 ± 18 (*tert*-butyl), 4.73 ± 0.12 (ethoxy), 4.50 ± 0.05 (isopropoxy), and 1.87 ± 0.02 (*tert*-butoxy). The wider range of $k_{obs,para}/k_{obs,ortho}$ values for the alkylbenzenes (0.73 – 124) compared to the alkoxybenzenes (1.87 – 4.73) suggests that the regioselectivity of bromine substitution is more sensitive to substituent effects for alkylbenzenes than for alkoxybenzenes, as was also observed in the variable $[Cl^-]$ experiments discussed above.

3.5 Effect of Excess Bromide. Excess bromide ($[Br^-]_{xs}$) is defined as the difference between the initial bromide concentration and initial FAC concentrations (i.e., $[Br^-]_{xs} = [Br^-]_o - [FAC]_o$). Previous reports have shown that $[Br^-]_{xs}$ can influence bromination rates in solutions of free bromine by promoting the formation of Br_2 (**eq 3**), which has been shown to be a more inherently reactive brominating agent than HOBr.[49,61] Br_2 formation is favored by the co-occurrence of FAC and unoxidized Br^-; the concentration of Br_2 increases as $[Br^-]_{xs}$ increases (**eq 3**). For alkylbenzenes and alkoxybenzenes, a positive correlation was observed between k_{obs} and $[Br^-]_{xs}$ (**Figure S4**), consistent with Br_2 serving as an active brominating agent.

For this set of experiments in which $[Br^-]_{xs}$ was the independent variable, net reactivity increased from *tert*-butyl < isopropyl < ethyl << *tert*-butoxy < ethoxy < isopropoxy. The $k_{obs,para}/k_{obs,ortho}$ values generally increased with increasing $[Br^-]_{xs}$, indicating Br_2 is selective for bromination at the *para* positions (**Figure S12**). Average $k_{obs,para}/k_{obs,ortho}$ values were 1.22 ± 0.12 (ethyl), 7.4 ± 0.7 (isopropyl), 51 ± 14 (*tert*-butyl), 13 ± 4 (ethoxy), 12 ± 3 (isopropoxy), and 4.6 ± 0.9 (*tert*-butoxy). Slopes of k_{obs} versus $[Br^-]_{xs}$ plots (**Figure S4**) increase in the order *tert*-butyl < isopropyl < ethyl << *tert*-butoxy < ethoxy < isopropoxy, indicating that the degree of bromide catalysis is dependent on substituent structure.

3.5 Effect of pH. Solution pH can have a profound influence on free bromine speciation and, by extension, on rates of bromine substitution.[1,62] Reactivity of alkylbenzenes and alkoxybenzenes decreased as pH increased over the examined pH ranges (**Figure 4**).

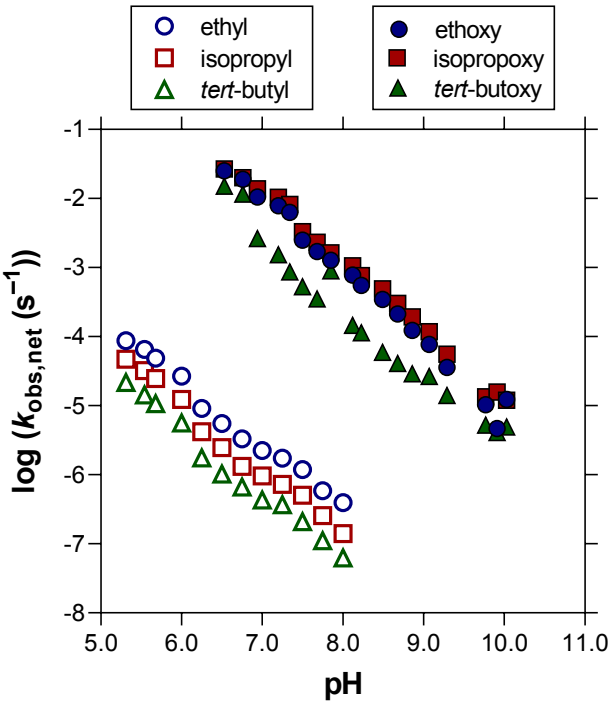


Figure 4. Pseudo-first-order rate constants for bromination of alkyl- and alkoxybenzenes as a function of pH. Solution conditions alkylbenzenes: $[FAC]_o$ = 1.50 mM, $[Br^-]_o$ = 1.00 mM, phosphate (20 mM) as pH buffer, $[alkylbenzene]_o$ = 50 μM, [NaCl] = 5.00 mM, $[NaNO_3]$ = 95 mM, and T = 20.00 °C. Solution conditions alkoxybenzenes: $[FAC]_o$ = 400 μM, $[Br^-]_o$ = 350 μM, borate and phosphate (20 mM each) as pH buffer, $[alkoxybenzene]_o$ = 10 μM, [NaCl] = 10 mM, $[NaNO_3]$ = 90 mM, and T = 20.00 °C. For clarity, 95% confidence intervals are not shown but are provided in Tables S13 and S14.

The decrease in k_{obs} values with increasing pH can be explained by the decrease in concentration of BrCl as pH increases. At pH < 8.0, concentrations of HOBr and Br_2O are comparatively unchanged, whereas concentration of BrCl (**eq 2**) and H_2OBr^+ (**eq 6**) decrease by an order of magnitude for each unit increase in pH. We posit that BrCl more likely accounts for this reactivity trend than H_2OBr^+ due to the presence of chloride ion at 5.0 and 10 mM for alkyl- and alkoxybenzenes, respectively. Notably, Br_2 is unlikely to exist in appreciable amounts in these systems because FAC was added in excess of bromide.

The general decrease in reactivity as pH increases (**Figure 4**) is consistent with bromination data reported previously for anisole, salicylic acid, and dimethenamid.[54,62,63] Inclusion of H_2OBr^+

did not improve the accuracy of model fits for studies of bromination of dimethenamid and salicylic acid, and similar trends in k_{obs} values at pH < 8.0 were attributed solely to BrCl.[54,63] We cannot, however, rule out possible contributions by H_2OBr^+ to k_{obs} values shown in **Figure 4**.

As pH decreases below ~7.0, the concentration of HOBr (pK_a = 8.70)[51] is generally constant from pH 4 – 7.[54] Thus, a kinetic model that only considers HOBr to be a reactive bromine species cannot account for the reactivity trend shown in **Figure 4**. These results are, however, consistent with BrCl and (potentially) H_2OBr^+ serving as active brominating agents. As pH increases, the contributions of BrCl and H_2OBr^+ to overall bromination rates is expected to decreases.[54,62]

Across the entire examined pH range, reactivity generally increased among the monosubstituted benzenes as: *tert*-butyl < isopropyl < ethyl << *tert*-butoxy < ethoxy < isopropoxy. The electron donating ability of the substituents is reported by March[73] to increases in the order ethyl < isopropyl < *tert*-butyl < ethoxy < isopropxy < *tert*-butoxy. However, computational studies of Hirshfeld charges suggest that electron density at the *ortho* and *para* positions increases in the order: tert-butyl < isopropyl ≈ ethyl < *tert*-butoxy < ethoxy < isopropoxy.[72] Notably, this trend in Hirshfeld charges aligns precisely with the experimental reactivity toward free bromine reported herein.

Regioselectivity of alkylbenzene bromination did not change significantly with pH (**Figure S13**). For alkoxybenzenes, values of $k_{obs,para}/k_{obs,ortho}$ remained approximately constant up to pH 7.5, increased from pH 7.5 to 9.3, then decreased at pH > 9.3 (**Figure S13**). Since the speciation of alkoxybenzenes is invariant under the examined pH range, the change in regioselectivity is likely due to changes in which brominating agent is predominant. For the experimental data set in which pH was the independent variable, average $k_{obs,para}/k_{obs,ortho}$ values were 0.59 ± 0.04 (ethyl),

6.1 ± 0.3 (isopropyl), 38 ± 8 (*tert*-butyl), 6.5 ± 1.0 (ethoxy), 6.4 ± 1.4 (isopropoxy), and 2.7 ± 0.5 (*tert*-butoxy).

3.6 Second-Order Rate Constants. Second-order rate constants corresponding to each brominating agent/nucleophilic site pair were calculated through nonlinear least-squares regression (*Scientist 3.0*) of **eq 12**. The calculated second-order rate constants are listed in **Table 2**. Previously reported rate constants for methoxybenzene (anisole) are also provided in **Table 2**.[62] The relative reactivity toward the *para* carbon atoms of each organic nucleophile followed the trend $Br_2O < Br_2 < BrCl$ for all alkylbenzenes and $HOBr < Br_2O < Br_2 < BrOCl < BrCl$ for all alkoxybenzenes excluding methoxybenzene, for which BrOCl was slightly less reactive than Br_2. The same reactivity trend was observed when comparing second-order rate constants for bromination at the *ortho* carbon atoms of each organic nucleophile. A second-order rate constant for bromination of alkylbenzenes involving H_2OBr^+ cannot be determined because a reliable estimate for the first acid-dissociation constant (pK_{a1}) of H_2OBr^+ has not been reported; therefore, the reactivity of H_2OBr^+ cannot be directly compared to the other brominating agents.[60]

For bromination of benzene, plots of k_{obs} as a function of $[Cl^-]$ yielded y-intercepts that were significantly different than zero (**Figure 1A**). Accordingly, brominating agents other than BrCl (e.g., Br_2 and BrOCl) are ostensibly relevant to the bromination of benzene. Upper limits for the second-order rate constants of Br_2, HOBr, and Br_2O in reactions with benzene are provided in **Table S18**.

Table 2. Second-order rate constants (M^{-1} s^{-1}) for the aqueous bromination of benzene, alkylbenzenes, and alkoxybenzenes at 20.0 °C.

Parent Nucleophile	Organic Product	k_{HOBr}	k_{BrCl}	k_{BrOCl}	k_{Br_2O}	k_{Br_2}
benzene	bromobenzene	ND [a]	5.7 ± 1.3	ND	ND	ND
ethylbenzene	*p*-bromo-ethylbenzene	ND	24 ± 3	ND	$(9.0 \pm 0.6) \times 10^{-3}$	0.028 ± 0.005
	o-bromo-ethylbenzene	ND	33 ± 5	ND	$(9.6 \pm 1.2) \times 10^{-3}$	0.013 ± 0.008
isopropylbenzene	*p*-bromo-isopropylbenzene	ND	26 ± 3	ND	$(5.6 \pm 0.7) \times 10^{-3}$	0.020 ± 0.002
	o-bromo-isopropylbenzene	ND	4.2 ± 0.8	ND	$(6.7 \pm 1.2) \times 10^{-4}$	$(2.8 \pm 0.4) \times 10^{-3}$
tert-butylbenzene	*p*-bromo-*tert*-butylbenzene	ND	13.3 ± 1.6	ND	$(6.7 \pm 0.6) \times 10^{-3}$	0.0100 ± 0.0011
	o-bromo-*tert*-butylbenzene	ND	0.27 ± 0.05	ND	$(1.8 \pm 0.8) \times 10^{-5}$	$(2.0 \pm 1.8) \times 10^{-3}$
methoxybenzene	*p*-bromo-methoxybenzene	0.070 ± 0.016	$(5.9 \pm 0.2) \times 10^{5}$	$(1.77 \pm 0.17) \times 10^{4}$	$(2.9 \pm 0.3) \times 10^{2}$	$(2.23 \pm 0.14) \times 10^{4}$
	o-bromo-methoxybenzene [b]	$(3.0 \pm 0.8) \times 10^{-3}$	$(9.0 \pm 0.5) \times 10^{4}$	$(1.50 \pm 0.07) \times 10^{3}$	15 ± 2	$(5.4 \pm 0.6) \times 10^{2}$
ethoxybenzene	*p*-bromo-ethoxybenzene [b]	0.48 ± 0.11	$(5.1 \pm 0.4) \times 10^{5}$	$(3.4 \pm 0.8) \times 10^{4}$	$(4.3 \pm 1.0) \times 10^{2}$	$(1.6 \pm 0.4) \times 10^{4}$
	o-bromo-ethoxybenzene	0.07 ± 0.03	$(1.0 \pm 0.6) \times 10^{5}$	$(1.90 \pm 0.10) \times 10^{3}$	12.0 ± 1.3	$(3.6 \pm 0.5) \times 10^{2}$
isopropoxybenzene	*p*-bromo-isopropoxybenzene	0.74 ± 0.12	$(6 \pm 2) \times 10^{5}$	$(3.5 \pm 1.5) \times 10^{4}$	$(1.8 \pm 0.7) \times 10^{2}$	$(2.3 \pm 0.3) \times 10^{4}$
	o-bromo-isopropoxybenzene	0.08 ± 0.03	$(1.3 \pm 0.8) \times 10^{5}$	$(1.9 \pm 0.7) \times 10^{3}$	40 ± 30	$(1.09 \pm 0.14) \times 10^{2}$
tert-butylbenzene	*p*-bromo-*tert*-butoxybenzene	0.07 ± 0.05	$(8 \pm 2) \times 10^{4}$	$(5 \pm 2) \times 10^{3}$	47 ± 6	$(2.7 \pm 0.5) \times 10^{3}$
	o-bromo-*tert*-butoxybenzene	0.028 ± 0.010	$(4 \pm 2) \times 10^{4}$	$(9 \pm 4) \times 10^{2}$	4 ± 2	$(4 \pm 1) \times 10^{2}$

[a] not determined
[b] ref 62

The relative reactivity of brominating agents is anticipated to depend on several factors, including the leaving group ability (nucleofugality), the charge on the electrophilic bromine atom(s), as well as the lowest unoccupied molecular orbital energy (E_{LUMO}), size and polarizability of the brominating agent.[54] For example, the greater reactivity of BrCl compared to BrOCl may result from the lower E_{LUMO} and lower Br–nucleofuge homolytic bond dissociation energy of BrCl compared to BrOCl (assuming that homolytic bond energies are proportional to heterolytic bond energies).[62] Similarly, the greater reactivity of BrOCl compared to Br_2 and Br_2O can be explained by the higher positive charge on the bromine atom and the greater polarizability of BrOCl.[62] The poor leaving group ability of OH^- from HOBr can explain why second-order rate constants were not quantifiable for HOBr for the bromination of alkylbenzenes or benzene. However, a second-order rate constant for HOBr was reported for the bromination of *p*-xylene,[60] anisole,[62] and the alkoxybenzenes examined herein, presumably due to greater nucleophilicity of these compounds compared to alkylbenzenes and benzene.

To evaluate the environmental relevance of alkylbenzene and alkoxybenzene bromination, half-lives ($t_{1/2}$) were calculated under typical drinking water treatment conditions ($[FAC]_o = 2.80 \times 10^{-5}$ M, $[Br^-]_o = 1.25 \times 10^{-6}$ M, $[Cl^-]_o = 3.00 \times 10^{-4}$ M, pH = 7.00, and T = 20.0 °C).[48,74] Estimated $t_{1/2}$ of bromination of alkylbenzenes (and benzene) all exceed 1000 y. The $t_{1/2}$ values calculated for bromination of alkoxybenzenes, however, range from 5 to 125 d. Chlorinated municipal drinking water has a typical residence time of several hours to several days prior to reaching a consumer.[19] Consequently, in contrast to alkylbenzenes, alkoxybenzenes may be sufficiently reactive so as to serve as precursors of brominated DBPs in chlorinated drinking water. Notably, in drinking water sources, sorption of aromatic compounds to natural organic matter may also affect rates of electrophilic substitution.[75]

497 *Reactivity of H_2OBr^+ Toward Alkylbenzenes.* Motivation to investigate the contribution of
498 H_2OBr^+ to alkylbenzene bromination stemmed from inadequate model fits when k_{obs} was plotted
499 against k_{calc} without accounting for the possible influence of H_2OBr^+ (**Figure S14**). Few previous
500 investigations have determined H_2OBr^+ to be an active brominating agent, including studies
501 involving *p*-xylene and acetanilide as nucleophiles.[60,76] Two kinetically indistinguishable methods
502 have been postulated for the participation of H_2OBr^+ during electrophilic bromination: one in
503 which H_2OBr^+ is preformed (e.g., via pre-equilibrium with HOBr (**eq 6**)) and another in which
504 HOBr and the organic nucleophile generate a π complex that is subsequently protonated.[60] To
505 determine if H_2OBr^+ was an active brominating agent, k_{obs} was plotted as a function of $[Cl^-]$ when
506 pH = 5.30, 5.50, 5.70, and 5.90. The y-intercept for each linear regression represents k_{obs}
507 extrapolated $[Cl^-] = 0$; these y-intercepts were plotted as a function of $[H^+]$ (**Figure S15**). The
508 equilibrium concentration of BrCl is anticipated to be negligible when $[Cl^-] = 0$ (**eq 2**). Therefore,
509 under low pH conditions at $[Cl^-] = 0$, H_2OBr^+ is more likely to be an active brominating agent than
510 is BrCl.

511 Slopes of k_{obs} (extrapolated to $[Cl^-] = 0$) versus $[H^+]$ for the formation of *para*-brominated
512 alkylbenzenes were not significantly different than zero (**Figure S15**), suggesting that H_2OBr^+ is
513 not an active brominating agent at this regioselective site. However, slopes of k_{obs} (extrapolated to
514 $[Cl^-] = 0$) versus $[H^+]$ for the formation of *ortho*-brominated alkylbenzenes were significantly
515 different than zero (**Figure S15**). A nonzero slope signifies that when $[Cl^-] = 0$, (and BrCl is
516 therefore negligible) some other brominating agent(s) must be involved. Therefore, data collected
517 at low pH values was binned during regression analyses to calculate if a rate constant for H_2OBr^+
518 could adequately fit the observed data. Model fits of k_{obs} versus calculated pseudo-first-order rate
519 constants, k_{calc}, that consider the reactivity of H_2OBr^+ for formation of *ortho*-brominated

alkylbenzenes had lower residuals (% differences) than those not accounting for H_2OBr^+ (**Figure S14**). For reactions postulated to involve H_2OBr^+ and the *ortho* positions of alkylbenzenes, third-order rate constants ($k_{H^+,HOBr}$, M^{-2} s^{-1}) were calculated to be (4.8 ± 1.0) × 10^3 (ethyl), (4.7 ± 0.9) × 10^2 (isopropyl), and 43 ± 13 (*tert*-butyl); these calculations assume $k_{H^+,HOBr}[HOBr][H^+] = k_{H_2OBr^+}[H_2OBr^+]$ in **eq 12.** For reactions involving *p*-xylene, Voudrias and Reinhard[60] proposed that H_2OBr^+ was a reactive brominating agent. As with our current examination of the formation of *ortho*-brominated alkylbenzenes, bromination of *p*-xylene (possible only at positions *ortho* to an alkyl group) could not be fully explained without invoking the reactivity of H_2OBr^+.[60]

Comparing the Contributions of BrCl to H_2OBr^+ to the Bromination of Alkylbenzenes. Although the reactivity of H_2OBr^+ cannot be directly compared to that of the other bromine species due to uncertainties associated with the pK_{a1} of H_2OBr^+, the [Cl^-] where the reactivities of BrCl and H_2OBr^+ contribute equally to overall bromination rates can be determined. Assuming that at low pH (i.e., pH < 6) only BrCl and/or H_2OBr^+ are kinetically relevant, k_{obs} can be expressed as:

$$k_{obs} = k_{H^+,HOBr}[H^+][HOBr] + k_{BrCl}[BrCl] \quad (14)$$

If BrCl and H_2OBr^+ contribute equally:

$$k_{H^+,HOBr}[H^+][HOBr] = k_{BrCl}[BrCl] \quad (15)$$

Substituting an expression for [BrCl] that includes K_{BrCl} (**eq 2**):

$$k_{H^+,HOBr}[H^+][HOBr] = k_{BrCl}K_{BrCl}[H^+][HOBr][Cl^-] \quad (16)$$

Solving for [Cl^-] in **eq 14** yields:

$$[Cl^-] = \frac{k_{H^+,HOBr}}{k_{BrCl}K_{BrCl}} \quad (17)$$

The [Cl^-] corresponding to equal contributions of BrCl and H_2OBr^+ was calculated using **eq 17** for *ortho* substituted alkylbenzenes where reactivity of H_2OBr^+ was shown to contribute to overall bromination rates. The results show that BrCl and H_2OBr^+ are calculated to make equal contributions to overall bromination rates at the *ortho* positions of ethyl-, isopropyl-, and *tert*-butyl-benzene when [Cl^-] = 12 mM, 91 mM, and 13 mM, respectively. At greater concentrations of chloride, the contribution of BrCl to the overall bromination rate will exceed that of H_2OBr^+. For example, in alkylbenzene experiments performed herein as a function of pH (**Figure 4**), [Cl^-] ≈ 5 mM, which is below the [Cl^-] at which the fractional contribution of H_2OBr^+ equals that of BrCl. Therefore, both BrCl and H_2OBr^+ ostensibly to serve as active brominating agents, particularly under acidic conditions in the absence of unoxidized bromide when contributions of other brominating agents (e.g., Br_2O and Br_2) are minor.

3.7 Contributions of Individual Brominating Agents to Overall Bromination Rates. To better visualize how each brominating agent contributes to overall bromination rates, the fractional contribution of each brominating agent to overall bromination rates can be calculated via **eq 18** and plotted as a function of various solution conditions (e.g., [Cl^-], [Br^-], and pH).

$$\text{fraction of } k_{\text{calc}} = \frac{k_{\text{Br agent}}\,[\text{Br agent}]}{k_{\text{calc}}} \tag{18}$$

Influence of Bromide. The influence of [Br^-] on fraction of k_{calc} for the *para* and *ortho* bromination of ethyl- and ethoxybenzene is depicted in **Figure 5** (similar plots for the other examined compounds are provided in **Figures S16** and **S17**).

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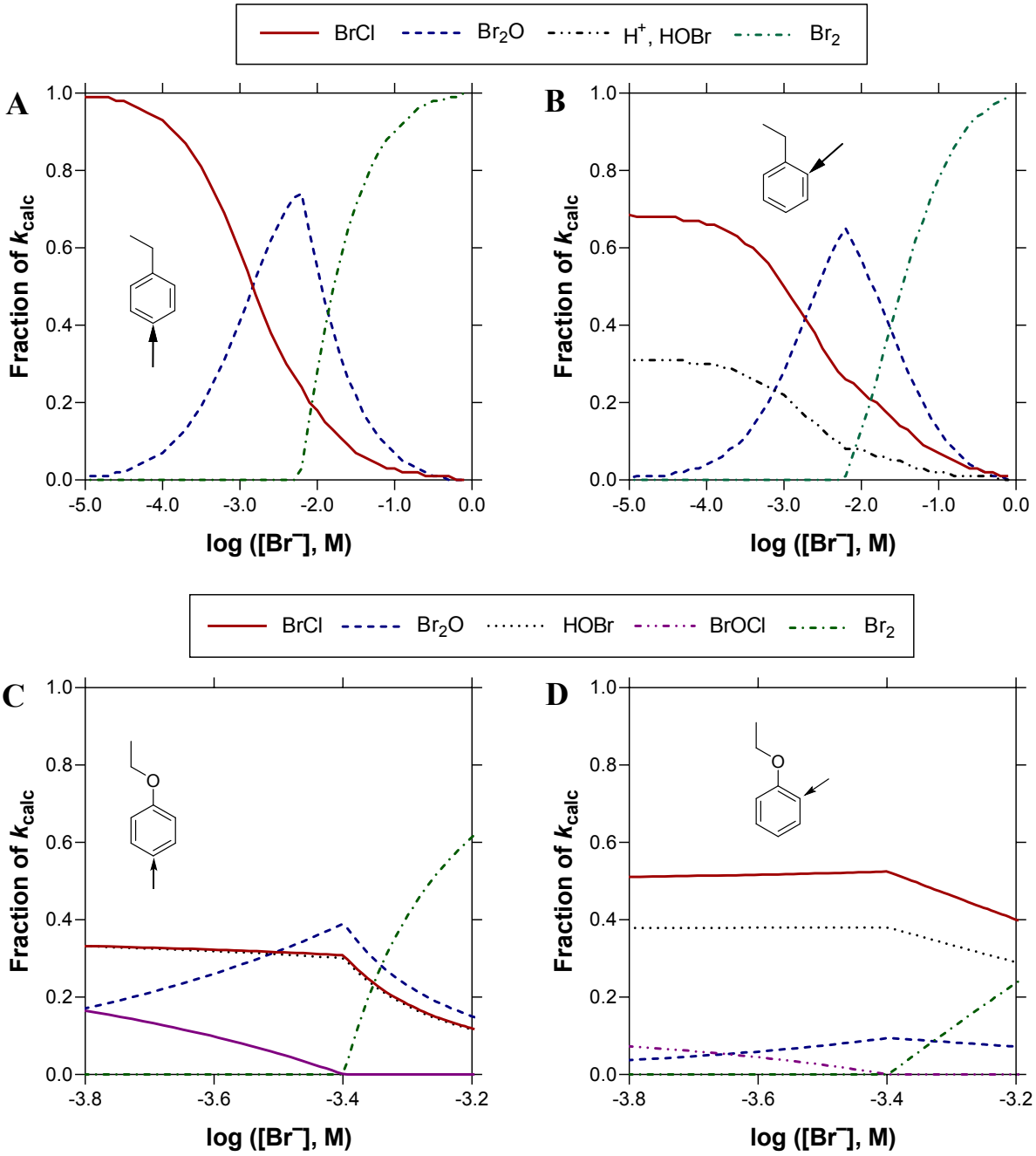


560

561 **Figure 5.** Contributions of brominating agents (as fraction of k_{calc} at 20 °C, where $k_{calc} = k_{BrCl}[BrCl] + k_{Br_2O}$
562 $[Br_2O] + k_{H^+,HOBr}[H_2OBr^+] + k_{Br_2}[Br_2] + k_{HOBr}[HOBr] + k_{BrOCl}[BrOCl]$) as a function of $[Br^-]$ for
563 bromination of ethylbenzene at the (**A**) *para* and (**B**) *ortho* positions and ethoxybenzene at the (**C**) *para* and
564 (**D**) *ortho* positions. All k_{calc} values assume stoichiometric oxidation of Br^- by excess FAC. Conditions for
565 frames (**A**) and (**B**): $[FAC]_o$ = 6.00 mM, [NaCl] = 10.00 mM, pH = 8.30, T = 20.0 °C. Conditions for frames
566 (**C**) and (**D**): $[FAC]_o$ = 0.40 mM, [NaCl] = 10.00 mM, pH = 8.46, T = 20.0 °C. Data for (H^+, HOBr) does
567 not appear in frames (**A**), (**C**), and (**D**) because the contribution of H_2OBr^+ to the formation of *para*-
568 brominated alkyl- and alkoxybenzenes and *ortho*-brominated alkoxybenzenes was negligible.

Because BrCl was the most inherently reactive of the examined brominating agents for all alkylbenzenes, its contribution was observed at the lower concentrations of bromide (**Figure 5**). As [Br^-] increases, the relative importance of bromine species other than BrCl (e.g., Br_2O and Br_2) increases. For example, when [Br^-] reaches 6.3 mM (log [Br^-] = –2.2), the contribution of Br_2O is maximal. At log [Br^-] > –2.2, the contribution of Br_2 steadily increased with increasing [Br^-], noting that the reactivity of Br_2 is negligible until bromide is present in excess of FAC.

For all alkoxybenzenes (**Figure 5C and 5D**), the contributions of HOBr and BrCl decreased with increasing [Br^-]. The contribution of Br_2 was negligible at [Br^-] ≤ 0.42 mM, above which the contribution of Br_2 increased with increasing [Br^-]. For all alkoxy substituents and all reactive positions, reactivity of Br_2O reached a maximum at 0.4 mM Br^-, then subsequently decreased at greater [Br^-].The influence of [Cl^-], [FAC], and pH on fraction of k_{calc} are described in the ESI (Section S11, **Figures S18 – S22**).

3.8 BrCl Reactivity Trends. The reactivity of BrCl (as log k_{BrCl}) at the *para* and *ortho* positions of monosubstituted benzenes is plotted against the molar volume of the substituent group[68] in **Figure 6**. Increasing molar volume of alkylbenzenes is associated with a significant decrease in k_{BrCl} at the *ortho* position, but no appreciable effect was observed at the *para* position. Ratios of Hirshfeld charges at the *ortho* and *para* positions (as a surrogate for the electronic effects on regioselectivity) vary only modestly (<8%) among ethyl-, isopropyl- and *tert*-butylbenzene.[72] Collectively, these results suggest that steric effects influence bromine substitution rates at the *ortho* positions (but perhaps not at the *para* positions) of alkylbenzenes. We note, however, that all such interpretations must be caveated by the potential covariance of electronic and steric effects.

For alkoxybenzenes, k_{BrCl} values for bromination at the *para* positions were greater than those at the *ortho* positions, but trends were similar: k_{BrCl} remained approximately equal from methoxy to ethoxy to isopropoxy, then slightly decreased for *tert*-butoxybenzene for both the *para* and *ortho* positions This trend suggests that, for alkoxybenzenes, steric effects on bromine substitution exert similar influences at both substitution positions.

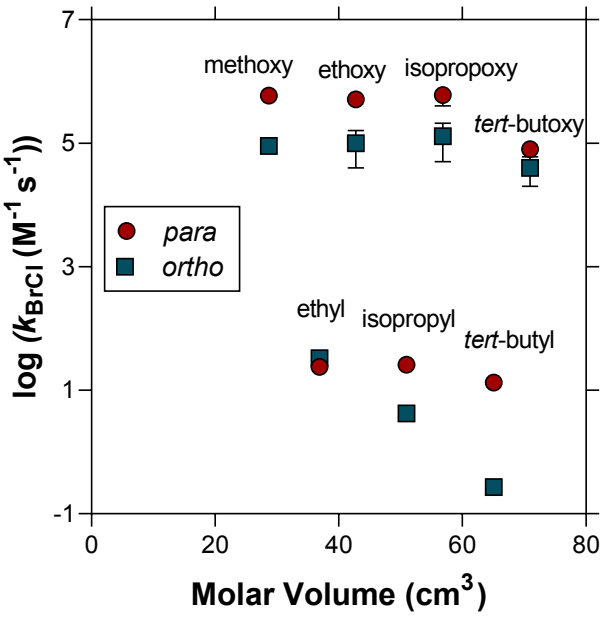
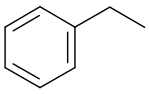
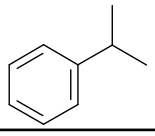
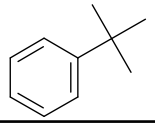
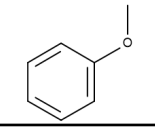
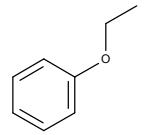
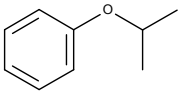
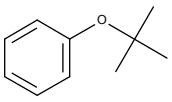


Figure 6. Second-order rate constants of BrCl (log scale) for bromination at the *para* and *ortho* positions as a function of the molar volume of each alkyl or alkoxy substituent. Error bars denote 95% confidence intervals (smaller than symbols when not shown).

Regiospecific rate constants of BrCl were normalized to that of benzene to illustrate how functional groups and substitution patterns impact reactivity (**Table 3**). The alkoxybenzenes were several orders of magnitude more reactive than the alkylbenzenes toward BrCl. Generally, as the size of the benzene substituent group increased, bromination at the *para* position was increasingly favored over bromination at the *ortho* position (i.e., increasing $k_{para,BrCl}/k_{ortho,BrCl}$). Bromination at the *ortho* positions of isopropyl- and *tert*-butylbenzene was less facile than bromination of

benzene. Reactivity increased from ethyl and ethoxy to isopropyl and isopropoxy, but then decreased for *tert*-butyl and *tert*-butoxy, respectively.

Table 3. Regiospecific second-order rate constants for the bromination of benzene and monosubstituted benzenes by BrCl.

Parent Nucleophile	Organic Product	k_{BrCl} (M^{-1} s^{-1})	Normalized k_{BrCl}	$k_{para,BrCl}/k_{ortho,BrCl}$
	bromobenzene	5.7 ± 1.3	1.0	not applicable
	*p*-bromoethylbenzene	24 ± 3	4	0.73
	o-bromoethylbenzene	33 ± 5	6	
	*p*-bromoisopropylbenzene	26 ± 3	5	6.2
	o-bromoisopropylbenzene	4.2 ± 0.8	0.7	
	*p*-bromo-*tert*-butylbenzene	13.3 ± 1.6	2.3	49
	o-bromo-*tert*-butylbenzene	0.27 ± 0.05	0.05	
	*p*-bromomethoxybenzene [a]	(5.9 ± 0.2) × 10^5	1.0 × 10^5	6.6
	o-bromomethoxybenzene [a]	(9.0 ± 0.5) × 10^4	1.6 × 10^4	
	*p*-bromoethoxybenzene	(5.1 ± 0.4) × 10^5	8.9 × 10^4	5.1
	o-bromoethoxybenzene	(1.0 ± 0.6) × 10^5	1.8 × 10^4	
	*p*-bromoisopropoxybenzene	(6 ± 2) × 10^5	1.1 × 10^5	5
	o-bromoisopropoxybenzene	(1.3 ± 0.8) × 10^5	2.3 × 10^4	
	*p*-bromo-tert-butoxybenzene	(8 ± 2) × 10^4	1.4 × 10^4	2
	o-bromo-tert-butoxybenzene	(4 ± 2) × 10^4	7 × 10^3	

[a] Data from ref 62

The ratio of the second-order rate constant of BrCl at the *para* position relative to that at the *ortho* position should be 0.5 if the *para* and *ortho* positions are equally reactive; however, the measured regioselectivity ($k_{para,BrCl}/k_{ortho,BrCl}$) ratio is greater than 0.5 for all of the alkyl- and alkoxybenzenes. Values of $k_{para,BrCl}/k_{ortho,BrCl}$ increased in the order methoxy < ethyl < *tert*-butoxy

611 < isopropoxy ≈ ethoxy < isopropyl < *tert*-butyl. For *tert*-butylbenzene, $k_{para,BrCl}/k_{ortho,BrCl}$ is 25 times
612 greater than that of *tert*-butoxybenzene, demonstrating that steric effects seem to have a greater
613 influence on regioselectivity for alkylbenzenes than for alkoxybenzenes.

614 Recent computational studies have estimated the nucleophilicity of monosubstituted
615 benzenes via calculation of Hirshfeld charges.[72,77] Replacing a hydrogen atom on benzene with an
616 alternative substituent redistributes electron density throughout the aromatic system. Electrophilic
617 aromatic substitution has been hypothesized to proceed preferentially at the position with the most
618 negative Hirshfeld charge.[72,78] Hirshfeld charges at the *para* carbons increase from isopropoxy
619 (most negative) < ethoxy < methoxy < *tert*-butoxy < isopropyl = ethyl < *tert*-butyl (**Figure 7**); a
620 similar trend was reported for Hirshfeld charges at the *ortho* positions.[72] Second-order rate
621 constants determined herein for reactions with BrCl generally increased as Hirshfeld charges
622 became more negative, although this relationship was more pronounced for alkylbenzenes than for
623 alkoxybenzenes (**Figure 7**). Previously calculated barrier heights (activation energies) for
624 electrophilic aromatic substitution revealed a positive, linear relationship between Hirshfeld
625 charge and barrier height, reinforcing the utility of Hirshfeld charges as predictors of reactivity
626 toward bromine substitution.[77,78]

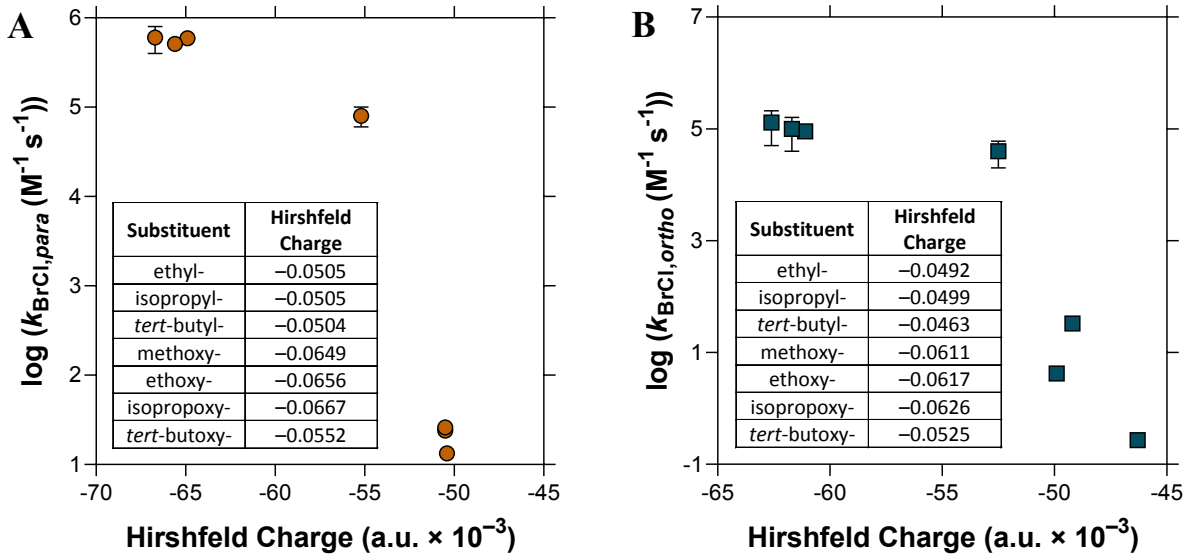


Figure 7. Second-order rate constants of BrCl as a function of Hirshfeld charge[72] for bromination at the (A) *para* and (B) *ortho* positions of alkyl- and alkoxybenzenes. Error bars represent 95% confidence intervals (smaller than symbols when not shown).

3.9 Determination of Taft Parameters. Polar sensitivity (ρ) and steric sensitivity (δ) factors were calculated based on **eq 13** for a variety of subgroups of the alkyl- and alkoxybenzenes of interest (**Table 4** and **Figures S5 – S8**). Subgroups permitted comparisons of *para*- and *ortho*-bromination as well as alkylbenzenes and alkoxybenzenes.

Table 4. Calculated Taft parameters (± 95% confidence intervals) for bromination at the *para* and *ortho* positions of alkylbenzenes and alkoxybenzenes.

Subgroup	ρ*	δ
para bromination	–7.8 ± 1.0	2.4 ± 0.4
ortho bromination	–7.1 ± 0.5	2.6 ± 0.2
alkylbenzenes	–4 ± 2	1.2 ± 0.7
alkoxybenzenes	–6 ± 2	–2 ± 5
para bromination (alkyl only)	–2.1 ± 0.1	0.47 ± 0.03
ortho bromination (alkyl only)	–5.2 ± 1.8	–2.0 ± 0.5
para bromination (alkoxy only)	–6.3 [a]	–2.1 [a]
ortho bromination (alkoxy only)	–5.0 [a]	–2.7 [a]

[a] 95% confidence intervals could not be calculated due to the small size (n = 2) of the data set, noting that steric substituent constants are not available for the isopropoxy and *tert*-butoxy groups.

A negative ρ^* indicates the reaction intermediate accumulates positive charge.[68] The ρ^* values for all of the subgroups were negative, suggesting that bromination rates should increase as the ability of substituent groups to increase electron density at the *ortho* and *para* positions increases. This result is consistent with the inverse relationship between reactivity to BrCl and Hirshfeld charges (**Figure 7**). Notably, recent computational studies determined that alkyl and alkoxy groups (as well as other *ortho*/*para* directing groups) do not donate electron density to adjacent aromatic systems. Such *ortho*/*para* directing groups are, in fact, inherently electron withdrawing yet concurrently serve to redistribute the electron density remaining in the aromatic ring to the *ortho* and *para* positions,[72] which is consistent with negative ρ^* values.

A positive δ indicates that the reaction rate is attenuated as steric bulk increases; a negative δ suggests the reaction rate increases as steric bulk increases.[68] When alkyl- and alkoxybenzenes were grouped together, δ values for *para* (2.4 ± 0.4) and *ortho* bromination (2.6 ± 0.2) were not significantly different. When alkylbenzenes were compared to alkoxybenzenes, δ was positive (1.2 ± 0.7) for alkylbenzenes (suggesting that as substituent size increases, reactivity of alkylbenzenes decreases), and, for alkoxybenzenes, δ was not significantly different than zero (indicating that substituent size does not appreciably impact reactivity). For alkylbenzenes, δ values switched from positive (0.47 ± 0.03) for reactions at *para* positions to negative (-2.0 ± 0.5) for reactions at *ortho* positions. For alkoxybenzenes, δ values were negative for reactions at both the *ortho* and *para* positions. Importantly, interpreting the polar and steric sensitivity factors independently does not permit accurate predictions of reactivity trends for bromination of alkyl- and alkoxybenzenes. Nevertheless, the calculated Taft parameters illustrate the importance of considering both the electronic and steric effects imparted by substituents when predicting reactivity of monosubstituted benzenes.

To compare the relative importance of electronic and steric effects, percent contributions of $\rho^*\sigma^*$ and δE_s to the overall Taft parameters (**eq 13**) were calculated (**Figure 8**). Steric and electronic effects were determined to have similar contributions to the Taft parameters for alkylbenzenes. The contribution of steric effects increases modestly as the size of the alkyl substituent increases from ethyl to isopropyl to *tert*-butyl. For alkoxybenzenes, electronic effects have a notably larger influence on reactivity than for alkylbenzenes. There does not appear to be a substantial difference in the relative contributions between *para* (**Figure 8A**) and *ortho* (**Figure 8B**) bromination. Overall, the Taft parameters indicate that electronic effects have a greater influence than steric effects on reactivity of monosubstituted benzenes, but both exert appreciable influence on overall reactivity.

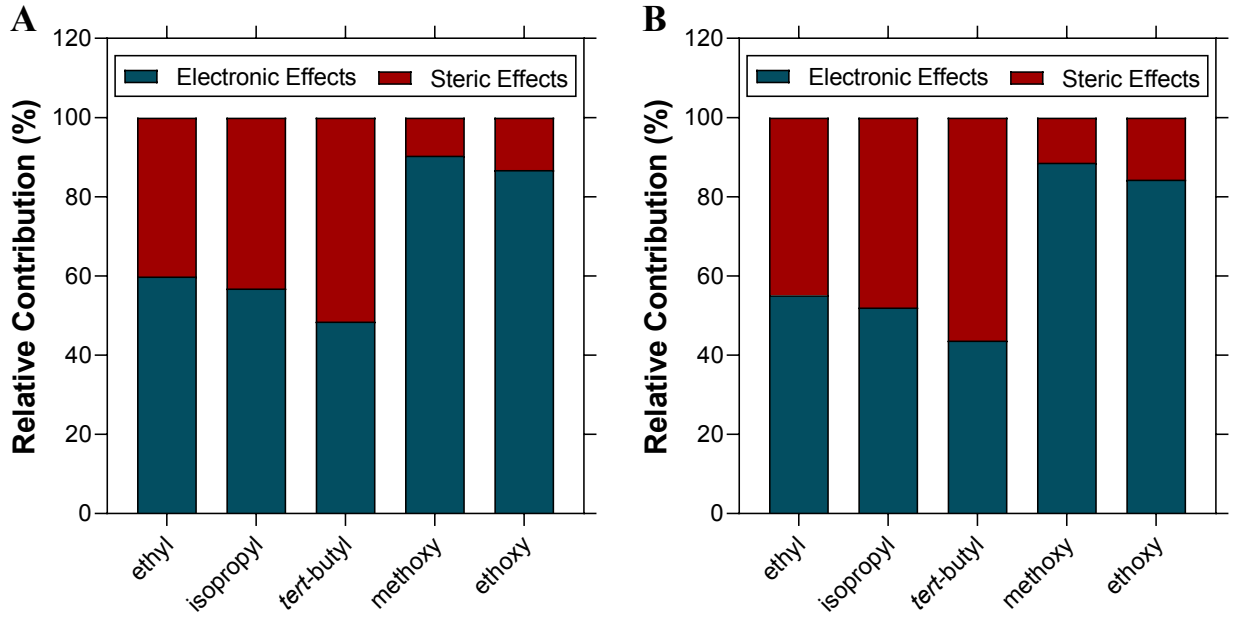


Figure 8. Percent relative contributions of electronic and steric effects for each alkyl- and alkoxybenzene for bromination at the (A) *para* and (B) *ortho* positions. Relative contributions of electronic effects = $\frac{|\rho^*\sigma^*|}{|\rho^*\sigma^*| + |\delta E_s|}$ and of steric effects = $\frac{|\delta E_s|}{|\rho^*\sigma^*| + |\delta E_s|}$.

673 **Comparisons to Previous Computational Studies**. Experimental findings from investigations of
674 alkyl- and alkoxybenzene bromination reported herein and computational findings from previous
675 studies support the idea that replacing hydrogen atoms on benzene with alkyl or alkoxy groups
676 results in nonhomogeneous reactivity at the *ortho* and *para* carbon atoms due to the changes in
677 nucleophilicity imparted by the substituents.[72] Computational work suggests that reactivity at the
678 *para* position of monosubstituted benzenes is greater than reactivity at the *ortho* positions because
679 the *para* position possesses a more negative Hirshfeld charge (i.e., increased local electron
680 density).[72] This computational findings generally agrees with the results reported herein for
681 bromination of monosubstituted benzenes in aqueous solutions of free bromine, excepting
682 bromination of ethylbenzene, for which the *para* position was less reactive than the *ortho*
683 positions. The computational model of Liu[72] did not, however, directly consider how steric effects
684 from the substituent group or the identity of the electrophile might influence reaction rates.
685 Another computational model from Liljenberg et al.[65] reported that the bromination rate and
686 positional selectivity of monosubstituted benzenes is strongly substituent-dependent; however,
687 only one brominating agent (Br_2) was considered.[65] For the experiments examined herein, several
688 brominating agents beyond Br_2 contributed to bromination of alkyl- and alkoxybenzenes. Our
689 examination of alkyl- and alkoxybenzene bromination revealed that the charge at the substitution
690 positions on the aromatic ring, and identities of both the substituent group and brominating agent,
691 can influence overall reactivity.

692 # Conclusions

693 Bromination of aromatic substrates is a key step in the production of several classes of
694 specialty chemicals[66] and in the generation of toxic byproducts during water disinfection.[34] When
695 such reactions proceed in aqueous systems, conventional wisdom typically assumes HOBr to be

696 the only relevant bromination agent; however, other electrophiles (BrCl, BrOCl, Br_2, Br_2O) have
697 been shown to be orders of magnitude more inherently reactive than HOBr.[54,62,63] This work
698 demonstrated the reactivity of such overlooked brominating agents toward benzene and several
699 monosubstituted analogues.

700 For bromination of alkylbenzenes, overall reactivity increased in the order $Br_2O < Br_2 <<$
701 BrCl. HOBr and BrOCl did not contribute appreciably to overall bromination rates of
702 alkylbenzenes. For *ortho*-brominated alkylbenzenes, H_2OBr^+ was shown to be kinetically
703 competent, but second-order rate constants could not be calculated because pK_{a1} of H_2OBr^+ is
704 poorly characterized. For bromination of alkoxybenzenes, overall reactivity increased in the order
705 $HOBr < Br_2O < Br_2 < BrOCl < BrCl$; H_2OBr^+ did not appear to influence bromination rates of
706 alkoxybenzenes. Among all brominating agents, overall reactivity generally increased in the order
707 *tert*-butyl < isopropyl < ethyl << *tert*-butoxy < ethoxy < isopropoxy. Reactivity at each
708 nucleophilic position toward BrCl was inversely proportional to the Hirshfeld charge, suggesting
709 that Hirshfeld charges are useful predictors of halogenation kinetics in aqueous systems.
710 Calculated Taft parameters revealed that electronic effects appear to dominate reactivity of alkyl-
711 and alkoxybenzenes toward BrCl, but both electronic and steric effects substantially influence
712 overall reactivity. The bromination reactions explored herein are postulated to involve closed-shell
713 electrophiles (Scheme 1). Nevertheless, the potential influence of open-shell electrophiles[61] cannot
714 be ruled out and merits future investigation.

715

Author contributions

Conceptualization, funding acquisition, methodology, investigation, writing (original draft): all authors; writing (review & editing): Schammel and Sivey; supervision: Sivey.

Conflicts of interest

There are no conflicts to declare.

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