Environmental Science
Water Research & Technology

PAPER

View Article Online
View Journal

Cite this: DOI: 10.1039/c7ew00491e

Emerging investigators series: comparing the inherent reactivity of often-overlooked aqueous chlorinating and brominating agents toward salicylic acid†

Matthew A. Broadwater,‡[a] Tyler L. Swanson[a] and John D. Sivey *[ab]

Chlorinated and brominated forms of salicylic acid (SA) have recently been identified as a new class of disinfection byproducts (DBPs) in drinking water. Herein, we report the inherent reactivity of several aqueous halogenating agents toward hydrogen salicylate, the predominant species of salicylic acid under environmental conditions. Using synthetic waters, halogenation rates associated with the formation of 3-chloro, 5-chloro, 3-bromo, and 5-bromosalicylate were measured as a function of pH, [Cl^-], [Br^-], free chlorine dose, and the initial concentration of SA. Halogenating-agent specific second-order rate constants were determined and decrease in the order: BrCl > BrOCl > Br_2 > Br_2O > Cl_2 > Cl_2O > HOBr > HOCl. Chloride is capable of enhancing rates of bromination and chlorination, ostensibly by promoting the formation of BrCl and Cl_2, both of which are several orders of magnitude more inherently reactive than HOBr and HOCl, respectively. Kinetic data also support the participation of salicyloyl hypochlorite as a chlorination intermediate capable of influencing chlorination rates at pH >8. Experiments in which buffer concentrations were varied indicate that phosphate buffers can enhance rates of SA bromination but not chlorination; carbonate and borate buffers did not appreciably influence rates of bromination or chlorination. Under conditions representative of chlorinated drinking water, rates of SA bromination will generally exceed rates of SA chlorination. The results discussed herein demonstrate the importance of considering halogenating agents beyond HOBr and HOCl when developing kinetic models to describe and predict halogenation rates and selectivity in waters containing free chlorine.

Received 14th November 2017,
Accepted 22nd December 2017

DOI: 10.1039/c7ew00491e

rsc.li/es-water

Water impact

When bromide-containing waters are chlorinated, a mixture of halogenating agents can form (including HOCl, Cl_2, Cl_2O, HOBr, BrCl, BrOCl) and can influence halogenation rates of salicylic acid, a precursor of an emerging class of disinfection byproducts (halosalicylates). By quantifying the inherent reactivity of these halogenating agents, relative rates of chlorination *versus* bromination can be predicted under a variety of conditions.

1. Introduction

Free chlorine (*e.g.*, HOCl and ClO^-) is a widely-used disinfectant in a variety of aqueous solutions, including drinking water, wastewater, and recreational water.[1–3] Concurrent with the deactivation of pathogens, free chlorine can chlorinate electron-rich sites of organic compounds.[4] When organic compounds are chlorinated in solutions of free chlorine, HOCl (eqn (1)) is often assumed to be the principal chlorinating agent.[1]

$$\mathrm{HOCl} \rightleftharpoons \mathrm{H^+} + \mathrm{ClO^-} \quad \mathrm{p}K_a = 7.58\ (20\ ^\circ\mathrm{C}, \text{ref. } 5) \qquad (1)$$

Additional free chlorine species can also exist in chlorinated waters, including Cl_2 and Cl_2O:

$$\mathrm{HOCl} + \mathrm{Cl^-} + \mathrm{H^+} \rightleftharpoons \mathrm{Cl_2} + \mathrm{H_2O} \quad \log K_2 = -3.00\ (\text{ref. } 6, \text{corrected to } 20\ ^\circ\mathrm{C}, \text{ref. } 7) \qquad (2)$$

$$2\mathrm{HOCl} \rightleftharpoons \mathrm{Cl_2O} + \mathrm{H_2O} \quad \log K_3 = -2.06\ (\text{ref. } 8, \text{corrected to } 20\ ^\circ\mathrm{C}, \text{ref. } 9) \qquad (3)$$

In aqueous systems disinfected with free chlorine, Cl_2 and Cl_2O typically exist at concentrations several orders of magnitude lower than that of HOCl; nevertheless, the greater electrophilicity of Cl_2 and Cl_2O renders these species capable of

[a] Department of Chemistry, Towson University, Towson, Maryland, USA. E-mail: jsivey@towson.edu; Tel: +1 410 704 6087
[b] Urban Environmental Biogeochemistry Laboratory, Towson University, Towson, Maryland, USA

† Electronic supplementary information (ESI) available. See DOI: 10.1039/c7ew00491e

‡ Current affiliation: Eshelman School of Pharmacy, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA.

influencing chlorination rates of compounds such *p*-xylene,[10,11] aromatic ethers,[12] phenols,[13] and pharmaceuticals.[14–16]

When solutions containing bromide are chlorinated, bromide can be oxidized into free bromine species, including HOBr.

$$\begin{aligned} &HOCl(aq) + Br^- \rightleftharpoons HOBr(aq) + Cl^- \\ &\log K_4 = 5.18\ (25\ ^\circ C,\ \text{ref. } 17) \end{aligned} \quad (4)$$

Free bromine can also form *via* oxidation of bromide in waters treated with ozone[18–20] or chloramines.[21–23] Bromide concentrations in drinking water influent typically range from 50–200 μg L^{-1};[24] somewhat higher bromide levels (100–250 μg L^{-1}) occur in municipal wastewater influent.[2] Bromide concentrations can exceed these ranges, however, particularly in waters affected by seawater intrusion[25,26] and by hydraulic fracturing operations.[27–30]

HOBr is the most abundant free bromine species in aqueous solutions at near-neutral pH:

$$\begin{aligned} &HOBr(aq) \rightleftharpoons H^+ + BrO^- \\ &pK_a = 8.70\ (20\ ^\circ C,\ \text{ref. } 31) \end{aligned} \quad (5)$$

As with free chlorine, free bromine can react with natural organic matter (NOM) to form disinfection byproducts (DBPs). HOBr is often assumed to be the only brominating agent that appreciably contributes to bromination rates of aromatic compounds in solutions disinfected with free chlorine.[32] There are, however, additional brominating agents that can form in solutions of free bromine, including Br_2, BrCl, Br_2O, and BrOCl (Table 1).

A comprehensive set of second-order rate constants for chlorination (HOCl, Cl_2, and Cl_2O) and bromination (HOBr, Br_2, BrCl, Br_2O, and BrOCl) have only been previously reported for one organic compound (the herbicide dimethenamid[35,36]). Rate constants for halogenation of *p*-xylene (by BrCl, Br_2, HOBr, Cl_2, and Cl_2O)[10,11] and for bromination of anisole (by BrCl, Br_2, BrOCl, Br_2O, and HOBr)[37] have also been reported. Dimethenamid, *p*-xylene, and anisole are all non-ionizable. The extent to which commonly-overlooked halogenating agents (*e.g.*, BrCl, BrOCl) might influence bromination rates of ionizable compounds is currently unknown.

The objective of this work is to quantify the inherent reactivity of chlorinating (Cl_2, Cl_2O, HOCl) and brominating (Br_2, BrCl, BrOCl, Br_2O, HOBr) agents toward salicylic acid (SA, Scheme 1). Under virtually all environmentally-relevant conditions, the most abundant form of SA (pK_{a1} = 2.97 and $pK_{a2} \approx$ 13.4)[38] is the monovalent anion, hydrogen salicylate (Fig. S1 in the ESI;† for a discussion of the uncertainty associated with pK_{a2}, see Table S1†). SA was selected for study because it contains ionizable functional groups, including a phenolic moiety, which is a known constituent of NOM with demonstrated reactivity toward free chlorine and free bromine.[39,40] SA can enter the environment through its use as a food preservative, pharmaceutical precursor, and keratolytic (skin-peeling) agent.[41] SA is also a human metabolite of aspirin[42] that is primarily excreted from the body *via* urine.[43,44] SA has been detected in wastewater influent and effluent,[45–48] as well as in surface waters.[41,46,49]

SA can react with aqueous chlorine to generate 3-chlorosalicylate (3-ClSA), 5-chlorosalicylate (5-ClSA), and 3,5-dichlorosalicylate (3,5-diClSA) (Scheme 1).[50–52] Similarly, SA can react with aqueous bromine to give 3-bromosalicylate (3-BrSA), 5-bromosalicylate (5-BrSA), and 3,5-dibromosalicylate (3,5-diBrSA).[50,51] Halogenated products of SA have been identified as an emerging class of DBPs in drinking water and wastewater.[50,52–54] Monohalogenated salicylates have toxicities comparable to those of haloacetic acids based on growth inhibition of a marine alga (*Tetraselmis marina*).[55]

Herein, we report regiospecific rate constants associated with SA halogenation by HOCl, Cl_2, Cl_2O, HOBr, Br_2, BrCl, Br_2O, and BrOCl. This work represents one of the first direct comparisons of chlorination and bromination rate constants that consider halogenating agents other than HOCl/Cl_2 and HOBr/Br_2.[10,11,35] Such a direct reactivity comparison between chlorinating and brominating agents can inform models of chlorine and bromine incorporation into organic compounds. A more robust understanding of the reactivity of free chlorine relative to free bromine is also significant because brominated DBPs are generally more cytotoxic and more genotoxic than their chlorinated analogues.[56–59]

Table 1 Additional brominating agents and associated equilibrium constants

Eqn	Reaction	Equilibrium Constant[a]
6	$Br_2(aq) + H_2O \rightleftharpoons HOBr(aq) + Br^- + H^+$	$\log K_6 = -8.40$ (20 °C)[33]
7	$HOBr(aq) + Cl^- + H^+ \rightleftharpoons BrCl(aq) + H_2O$	$\log K_7 = 4.09$ (20 °C)[34]
8	$2HOBr(aq) \rightleftharpoons Br_2O(aq) + H_2O$	$\log K_8 = 0.80$ (25 °C)[35]
9	$HOCl(aq) + HOBr(aq) \rightleftharpoons BrOCl(aq) + H_2O$	$\log K_9 = -0.46$ (25 °C)[35]

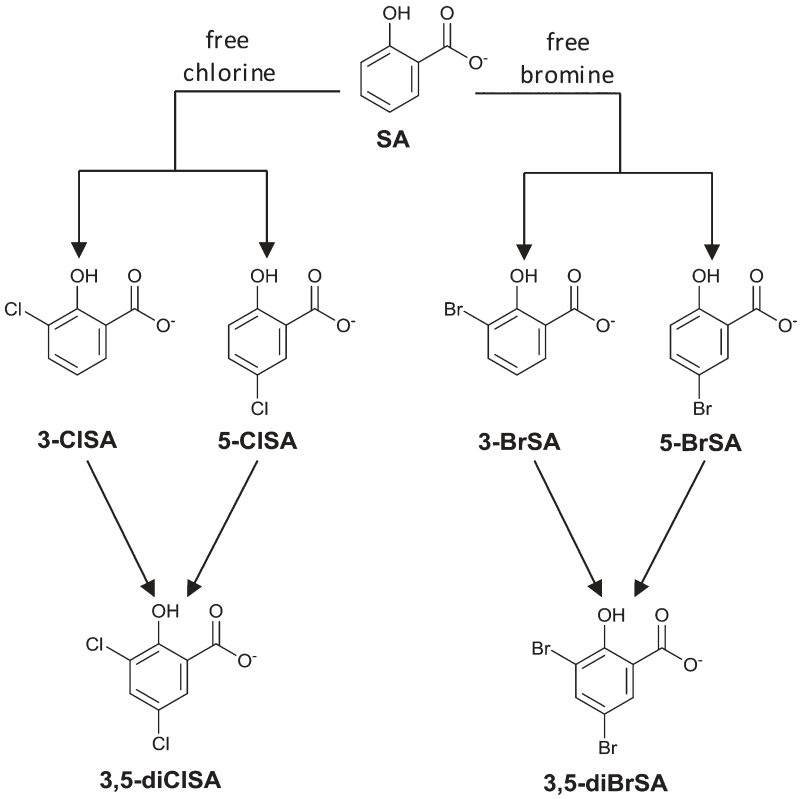
[a] Unless indicated otherwise, all equilibrium constants herein correspond to 0 M ionic strength.

2. Methods

Descriptions of all reagents are available in the ESI† (Table S2). For reactors to which NaCl was added as a source of Cl^-, ultra high-purity sodium chloride (99.999%, Sigma-Aldrich) was used to minimize unintentional introduction of bromide, which is a possible contaminant in lower-purity grades of sodium chloride.[13,36]

2.1 Kinetic experiments

Halogenation rates of SA were determined *via* batch kinetic experiments. Reactions were carried out in a circulating water bath at 20.00 ± 0.02 °C. Reactions were performed in 40 mL amber glass vials fitted with PTFE-lined caps; vials were treated with NaOCl (~5 mM) and rinsed with 18 MΩ cm water (Nanopure, Thermo Scientific) prior to use. Total solution volumes of reactors were ~25 mL. Aqueous solutions used for kinetic experiments were prepared in 18 MΩ cm water



Scheme 1 Reaction pathways and product formation for chlorination and bromination of hydrogen salicylate, the principal species of salicylic acid at near-neutral pH.

and contained a pH buffer (sodium phosphate, sodium borate, or sodium carbonate, typically 20 mM), $NaNO_3$ (typically 95 mM), and NaCl (typically 5 mM). Nitric acid and sodium hydroxide were used to adjust the pH of buffered solutions. To maintain a uniform ionic strength in experiments where $[Cl^-]$ was varied, $[NaNO_3]$ was adjusted such that $[NaNO_3]$ + [NaCl] = 100 mM. Time course data from >110 experiments were collected. Single experiments were performed for most conditions, for which the associated uncertainties reported herein correspond to 95% confidence intervals for the time course regressions from which rate constants were calculated. For selected conditions, kinetic experiments were performed in triplicate, for which relative standard deviations were <3% for the measured chlorination and bromination rate constants.

Chlorination reactions. Chlorination reactors included NaOCl as the source of free chlorine. NaOCl stock solutions were standardized by iodometric titration.[60] NaOCl working solutions were standardized daily at pH > 10 using a Cary 60 (Agilent) UV-vis spectrophotometer (ε_{ClO^-} = 366 L mol^{-1} cm^{-1}, λ = 295 nm). Pseudo-first-order conditions were employed in which the initial molar concentration of free chlorine was at least 10× greater than that of SA (*i.e.*, $[HOCl]_{tot,o}/[SA]_{tot,o}$ >10). After all components except SA were added, reactors were capped, shaken, and placed in a water bath for ~5 min to permit thermal equilibration. SA was delivered into reactors as a methanolic spike at t = 0; final concentrations of methanol in reactors were ≤1 vol%. Methanol was selected as a carrier solvent due to the low reactivity of primary alcohols toward free chlorine[4] and free bromine.[32] Reactors were capped, manually shaken for 10 s, and returned to the water bath. Reactor aliquots (0.900 mL) were taken periodically and transferred into 2 mL glass HPLC autosampler vials containing excess thiosulfate ($[Na_2S_2O_3] \approx 1.4 \times [HOCl]_{tot,o}$) to quench residual free chlorine; vials were immediately capped and shaken. Vial caps contained PTFE-lined septa. After the last aliquot was obtained, the pH of reactors was measured using a Fisher Accumet AB 150 pH meter with automatic temperature compensation (calibrated daily using certified buffers at pH 4.0, 7.0, and 10.0).

Sets of reactors were used to determine the influence of several independent variables on the kinetics of SA chlorination. Examined independent variables included pH, $[SA]_{tot,o}$, $[HOCl]_{tot,o}$, [NaCl], $[PO_4^{3-}]_{tot}$, $[CO_3^{2-}]_{tot}$, and $[borate]_{tot}$. The effects of ionic strength were also assessed by varying $[NaNO_3]$. Specific solution conditions for each chlorination reactor are listed in Tables S3–S5.† An example time course of a chlorination reaction of SA is shown in Fig. S2.†

Bromination reactions. Bromination experiments of SA followed the same method as described above for the chlorination experiments except as noted below. Reactors contained NaBr (typically 20 μM) and NaOCl (typically 27 μM). An incubation time ≥5 min was employed to permit oxidation of bromide by free chlorine to give free bromine. In the presence of a

large excess of free bromine relative to SA (*i.e.*, under pseudo-first-order conditions), bromination of SA was generally too rapid to permit quantification of rate constants using our aliquot-quenching method. Therefore, second-order conditions (such that $[HOBr]_{tot,o}$ = $[SA]_{tot,o}$ = typically 20 μM) were employed for all bromination reactors except those used to determine the reaction order in $[SA]_{tot,o}$, for which $[SA]_{tot,o}$ ranged from 6–10 μM and $[HOBr]_{tot,o}$ = 100 μM.

Sets of reactors were used to elucidate the effects of several independent variables on the kinetics of SA bromination. The independent variables that were tested included pH, $[HOCl]_{tot,o}$, [NaCl], $[NaBr]_o$ in the presence of excess free chlorine, [excess Br^-], and $[PO_4^{3-}]_{tot}$. The effects of ionic strength were also examined by varying $[NaNO_3]$. In most reactors, free chlorine was added in excess of bromide (on a molar basis) to permit stoichiometric oxidation of bromide into free bromine. In reactors where excess Br^- was the independent variable, bromide was added in excess of free chlorine. Excess Br^- is defined as $[Br^-]_o - [HOCl]_{tot,o}$. Specific solution conditions for each bromination reactor are provided in Tables S6–S10.† An example time course from a bromination reactor is shown in Fig. S3.†

2.2 Analysis of reactants and products

SA, 3-ClSA, 5-ClSA, 3,5-diClSA, 3-BrSA, 5-BrSA, 3,5-diBrSA were analyzed in quenched samples *via* a Shimadzu high-performance liquid chromatograph with a diode array detector. Additional details about the HPLC method are provided in the ESI.†

2.3 General comments on kinetic modeling

Under all examined solution conditions, hydrogen salicylate (HSA^-) is the most abundant SA species (*i.e.*, the fraction of $[SA]_{tot}$ existing as HSA^- ≈1 and therefore $[SA]_{tot} \approx [HSA^-]$). Based on the findings of previous halogenation studies involving phenolic compounds,[4,13,32] the nucleophilicity of SA species is anticipated to increase in the order: salicylic acid (H_2SA) < hydrogen salicylate (HSA^-) < salicylate (SA^{2-}). Despite the anticipated greater reactivity of SA^{2-} (relative to HSA^-) toward free chlorine and free bromine, the kinetic results herein (ranging from pH 6–11) can be modeled assuming HSA^- as the only reactive nucleophile, excepting chlorination reactions postulated to involve salicyloyl hypochlorite (discussed below). Accordingly, unless otherwise noted, all rate constants herein assume hydrogen salicylate as the reactive nucleophile.

All values of [NaCl] reported herein denote concentrations of added NaCl. This value is distinct from the total concentration of Cl^- present in reactors, noting that NaOCl (the source of free chlorine) is approximately equimolar in Cl^-.[13] In addition, oxidation of bromide by free chlorine generates a stoichiometric amount of Cl^- (eqn (4)). When calculating the speciation of free chlorine and free bromine in individual reactors, the total concentration of Cl^- was used, which accounts for all of the aforementioned sources of Cl^-.

2.4 Calculation of chlorination rate constants

For chlorination experiments, rate constants were calculated by monitoring the loss of SA and the formation of monochlorinated products. Plots of the natural logarithm of $[SA]_{tot}$ as a function of time were linear (R^2 typically >0.99) with negative slopes equal to pseudo-first-order rate constants ($k_{SA,obs}$, s^{-1}) corresponding to the loss of SA. Regiospecific pseudo-first-order rate constants corresponding to the formation of 3-ClSA ($k_{3\text{-ClSA,obs}}$) and 5-ClSA ($k_{5\text{-ClSA,obs}}$) were calculated *via*:

$$k_{3\text{-ClSA,obs}} = \left(k_{SA,obs}\right)\frac{[3\text{-ClSA}]_f}{[3\text{-ClSA}]_f + [5\text{-ClSA}]_f} \quad (10)$$

$$k_{5\text{-ClSA,obs}} = \left(k_{SA,obs}\right)\frac{[5\text{-ClSA}]_f}{[3\text{-ClSA}]_f + [5\text{-ClSA}]_f} \quad (11)$$

$[3\text{-ClSA}]_f$ and $[5\text{-ClSA}]_f$ denote the final measured concentration (in the last sample collected) of 3-ClSA and 5-ClSA, respectively. The dichlorinated product of SA (3,5-diClSA) was also monitored to ensure that ≤2% of $[SA]_o$ (on a molar basis) was converted into 3,5-diClSA such that $k_{SA,obs} \approx k_{3\text{-ClSA,obs}} + k_{5\text{-ClSA,obs}}$.

2.5 Calculation of bromination rate constants

For bromination experiments, loss of SA and formation of monobrominated products were monitored as a function of time. For reactions in which $[NaBr]_o$ (in the presence of excess free chlorine) was the independent variable, Scientist 3.0 (MicroMath Scientific Software) was used to fit concentration *versus* time data for SA and for the two monobrominated products according to the following set of differential rate equations:

$$\frac{d[SA]_{tot}}{dt} = -\left(k_{3\text{-BrSA,app}} + k_{5\text{-BrSA,app}}\right)[SA]_{tot}[HOBr]_{tot}^n \quad (12)$$

$$\frac{d[3\text{-BrSA}]_{tot}}{dt} = k_{3\text{-BrSA,app}}[SA]_{tot}[HOBr]_{tot}^n - k'_{3\text{-BrSA,app}}[3\text{-BrSA}]_{tot}[HOBr]_{tot}^n \quad (13)$$

$$\frac{d[5\text{-BrSA}]_{tot}}{dt} = k_{5-\text{BrSA,app}}[SA]_{tot}[HOBr]_{tot}^n - k'_{5-\text{BrSA,app}}[5\text{-BrSA}]_{tot}[HOBr]_{tot}^n \quad (14)$$

$$\frac{d[HOBr]_{tot}}{dt} = -\left(k_{3-BrSA,app} + k_{5-BrSA,app}\right)[SA]_{tot}[HOBr]_{tot}^{n} - k'_{3-BrSA,app}[3\text{-BrSA}]_{tot}[HOBr]_{tot}^{n} - k'_{5-BrSA,app}[5\text{-BrSA}]_{tot}[HOBr]_{tot}^{n} \quad (15)$$

where $k_{3\text{-BrSA,app}}$ and $k_{5\text{-BrSA,app}}$ denote rate constants (M^{-n} s^{-1}) corresponding to the formation of 3-BrSA and 5-BrSA, respectively; n is the reaction order in $[HOBr]_{tot}$; $k'_{3\text{-BrSA,app}}$ and $k'_{5\text{-BrSA,app}}$ are rate constants (M^{-n} s^{-1}) corresponding to the loss of 3-BrSA and 5-BrSA, respectively, due to subsequent bromination. To improve the precision of the determined rate constants, an iterative fitting method was employed (see ESI† for details). In most reactors, the extent to which 3-BrSA and 5-BrSA underwent subsequent bromination to give 3,5-diBrSA was sufficiently minor so as to preclude the determination of values for $k'_{3\text{-BrSA,app}}$ and $k'_{5\text{-BrSA,app}}$ that were significantly different than 0 (at the 95% confidence level). To minimize possible over-parameterization, the kinetic model represented by eqn (12)–(15) was constrained such that the same n value was assumed for all bromination reactions in any given reactor. Values of n between 1.0 and 1.2 were observed for experiments in which $[NaBr]_o$ was the independent variable. The bromination reactions associated with eqn (12)–(15) are assumed to be first-order with respect to the organic compound undergoing bromination, which is consistent with the results of experiments in which $[SA]_{tot,o}$ was varied. The results of reaction order experiments are discussed further in section 3.2.

For experiments in which n is approximately equal to 1.0 (and recalling that $[SA]_{tot,o} = [HOBr]_{tot,o}$ for most of the bromination experiments herein), eqn (12) simplifies to:

$$\frac{d[SA]_{tot}}{dt} = -\left(k_{3\text{-BrSA,app}} + k_{5\text{-BrSA,app}}\right)[SA]_{tot}^{2} \quad (16)$$

Replacing ($k_{3\text{-BrSA,app}}$ + $k_{5\text{-BrSA,app}}$) with $k_{SA,app}$ (a rate constant corresponding to the net loss of SA, units M^{-1} s^{-1}) and integrating yields:

$$\frac{1}{[SA]_{tot}} = k_{SA,app}t + \frac{1}{[SA]_{tot,o}} \quad (17)$$

For bromination experiments in which pH, $[Cl^-]$, $[HOCl]_{tot,o}$, [excess Br^-], $[NaNO_3]$, and $[PO_4^{3-}]_{tot}$ were the independent variables, plots of $\frac{1}{[SA]_{tot}}$ as a function of time were linear (R^2 typically >0.99) and were used to determine $k_{SA,app}$ based on eqn (17). For these reactions, apparent second-order rate constants ($k_{3\text{-BrSA,app}}$ and $k_{5\text{-BrSA,app}}$, units M^{-1} s^{-1}) were calculated *via*:

$$k_{3\text{-BrSA,app}} = \left(k_{SA,app}\right)\frac{[3\text{-BrSA}]_f}{[3\text{-BrSA}]_f + [5\text{-BrSA}]_f} \quad (18)$$

$$k_{5\text{-BrSA,app}} = \left(k_{SA,app}\right)\frac{[5\text{-BrSA}]_f}{[3\text{-BrSA}]_f + [5\text{-BrSA}]_f} \quad (19)$$

$[3\text{-BrSA}]_f$ and $[5\text{-BrSA}]_f$ denote the final, measured concentration of 3-BrSA and 5-BrSA, respectively, in the last sample obtained. The dibrominated product of SA (3,5-diBrSA) was also monitored in all bromination experiments. Appreciable formation of 3,5-diBrSA can limit the applicability of eqn (18) and (19) due to anticipated differences in the transformation rates of 3-BrSA and 5-BrSA to give 3,5-diBrSA. Accordingly, sampling times for these reactions were selected such that generally ≤2% of $[SA]_o$ (molar basis) was converted into 3,5-diBrSA during the period of observation. To facilitate calculations of rate constants specific to individual brominating agents, apparent second-order rate constants ($k_{3\text{-BrSA,app}}$ and $k_{5\text{-BrSA,app}}$, units of M^{-n} s^{-1}) were converted into the corresponding apparent first-order rate constants ($k_{3\text{-BrSA,obs}}$ and $k_{5\text{-BrSA,obs}}$ units of s^{-1}) by multiplying the former by $[HOBr]_{tot}^{n}$ (units of M^n).

3. Results and discussion

For most solution conditions examined herein, 5-ClSA was the major chlorination product of SA and 5-BrSA was the major bromination product. 3-ClSA and 3-BrSA were also detected (typically as the minor product) in all chlorination and bromination experiments, respectively. These products are consistent with previous reports of aqueous halogenation occurring at the *para* and *ortho* positions (relative to the hydroxyl group) of SA.[48,50–52,61] Under some solution conditions favoring elevated halogenation rates (*e.g.*, low pH), 3,5-diClSA and 3,5-diBrSA were also detected in chlorination and bromination reactors, respectively. Carbon mass balances on SA generally did not fall below $[SA]_o$, which suggests that unmonitored products (*e.g.*, 3-chloro-5-bromosalicylate or 3-bromo-5-chlorosalicylate) did not form in appreciable amounts. For bromination and chlorination, changes in ionic strength (imparted by varying $[NaNO_3]$ from 0.035–0.15 M) did not appreciably influence reaction rates (data not shown). The effects of additional solution conditions on rates of SA chlorination and bromination are discussed below.

3.1 Chlorination of SA

Effects of buffer concentration. Pseudo-first-order rate constants corresponding to formation of 3-ClSA and 5-ClSA increase as the formal concentration of phosphate increases (Fig. S4†), suggesting that catalysis by one or more phosphate species may be occurring. Similar experiments performed as a function of the formal concentration of borate (Fig. S5†)

and carbonate (Fig. S6†) do not show an appreciable influence of these buffers on chlorination rate constants. Chlorination rate constants of SA were also measured as a function of pH using phosphate, borate, or a mixture of borate + carbonate as pH buffers (Fig. S7†). Chlorination rate constants determined from reactors containing phosphate are greater than those measured in the other buffer systems. This discontinuity between the buffer systems provides additional evidence that phosphate can affect chlorination rates of SA. The rate enhancement in the presence of phosphate buffer appears to increase as pH increases from 6.2 to 7.8 (Fig. S7†). These results can be rationalized in at least two ways: (1) HPO_4^{2-} is of greater importance than is $H_2PO_4^-$ (pK_a = 7.2)[62] to the observed buffer catalysis; and/or (2) chlorinating agents participating in reaction pathways catalyzed by phosphate species become more important as pH increases from 6.2 to 7.8. To avoid the possible influence of phosphate catalysis, borate and carbonate were used as pH buffers for experiments involving chlorination of SA from which halogenating-agent-specific rate constants were calculated.

Influence of pH. Pseudo-first-order rate constants corresponding to formation of 3-ClSA and 5-ClSA decrease as pH increases over the range 6.2–8.6 (Fig. 1A); an increase in reactivity is observed from pH 8.6–10.2, followed by a plateau in reactivity from pH 10.2–11.1.

Despite the presence of a phenolic moiety on SA, the reactivity profile of SA differs from that of phenol.[13,63] Between pH 6 and 12, the reactivity of phenol toward free chlorine reaches a maximum near pH 8.6,[13] which approximately corresponds to the midpoint between the pK_a of HOCl (7.58)[5] and the pK_a of phenol (9.95).[64] The reactivity maximum of phenol in solutions of free chlorine can be rationalized by the greater electrophilicity of HOCl relative to ClO^- coupled with the greater nucleophilicity of phenolate relative to phenol. Despite the weaker acidity of hydrogen salicylate (pK_{a2} = 13.4)[38] compared to phenol, an analogous model (in which SA^{2-} reacts with HOCl) does not adequately explain the reactivity profile of SA due to the inability of such a model to capture the depression observed between pH 8 and 10 (see additional discussion below).

The regioselectivity of SA chlorination can be quantified as the ratio of pseudo-first-order rate constants corresponding to formation of 5-ClSA and 3-ClSA. As pH increases from 6 to 11, the regioselectivity ratio decreases from approximately 2 to 0.8 (Fig. 1B). The shift in regioselectivity as the pH increases suggests that more than one chlorinating agent and/or more than one SA species contribute to overall chlorination rates in these systems.

Effects of chloride. The effects of $[Cl^-]$ on pseudo-first-order chlorination rate constants were tested by varying [NaCl] while maintaining uniform ionic strength (*i.e.*, [NaCl] + $[NaNO_3]$ = 100 mM) (Fig. 2). The positive, linear correlation between $[Cl^-]$ and k_{obs} suggests that Cl_2 is affecting chlorination rates, attributable to the dependence of $[Cl_2]$ on $[Cl^-]$ (eqn (2)). The results shown in Fig. 2 suggest that Cl^- can catalyze chlorination of SA to similar extents at both the 3- and 5-positions. In addition to SA, other organic compounds have also been shown to be susceptible to chloride-catalyzed chlorination,[65] including several ionizable[13–16,66,67] and nonionizable[10,12,36] compounds.

Effects of free chlorine. In order to determine the reaction order in free chlorine, experiments were performed in which the initial concentration of free chlorine ($[HOCl]_{tot,o}$) was varied. The reaction order in $[HOCl]_{tot,o}$ is equal to the slope of the resulting log k_{obs} *versus* log $[HOCl]_{tot,o}$ plots (Fig. 3). The formation of 5-ClSA (Fig. 3A) and 3-ClSA (Fig. 3B) have reaction orders in $[HOCl]_{tot,o}$ between 1 and 2, which suggests that there are multiple chlorinating agents influencing overall chlorination rates under the examined conditions. These reaction orders are best viewed as average reaction orders in $[HOCl]_{tot,o}$, noting that such reaction orders may not be constant if the relative contribution of individual chlorinating agents changes over the range of examined $[HOCl]_{tot,o}$ values.

If only HOCl were influencing chlorination rates, the reaction order in $[HOCl]_{tot,o}$ is anticipated to equal 1. If only Cl_2O

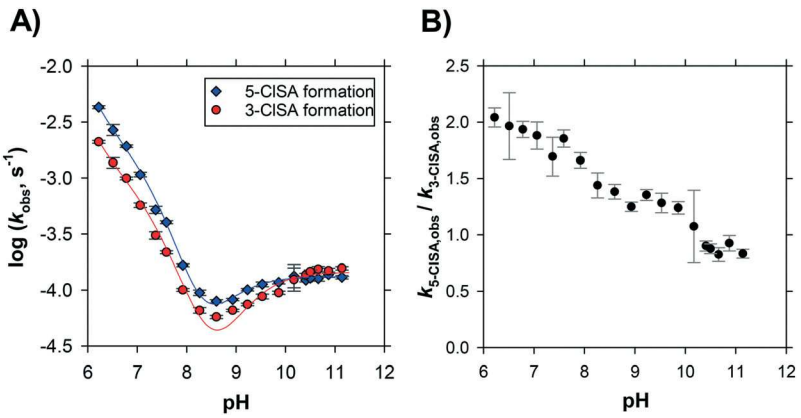


Fig. 1 (A) Log of pseudo-first-order rate constants and (B) regioselectivity ratios for chlorination of SA (yielding 5-chlorosalicylate (5-ClSA) and 3-chlorosalicylate (3-ClSA)) as a function of pH. Solid lines in frame (A) denote model fits based on eqn (24). All error bars denote 95% confidence intervals (smaller than symbols if not shown). Conditions for both frames: $[HOCl]_{tot,o}$ = 5.0 mM, borate (19 mM) + carbonate (19 mM) as a mixed pH buffer, $[SA]_{tot,o}$ = 20 μM, [NaCl] = 4.9 mM, $[NaNO_3]$ = 92 mM, T = 20.0 °C.

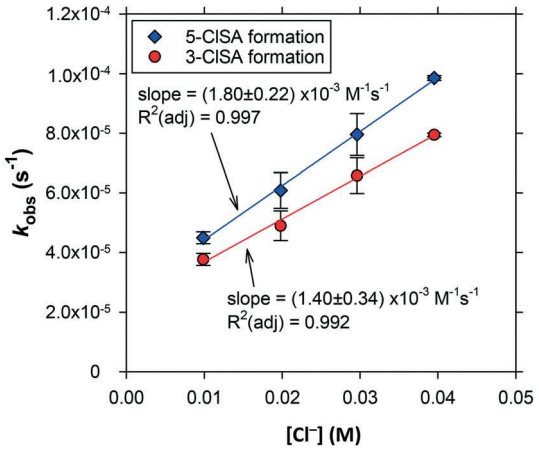


Fig. 2 Pseudo-first-order rate constants for chlorination of SA (yielding 5-chlorosalicylate (5-ClSA) and 3-chlorosalicylate (3-ClSA)) as a function of chloride concentration. Error bars denote 95% confidence intervals (smaller than symbols if not shown). Conditions: $[HOCl]_{tot,o}$ = 0.46 mM, phosphate (20 mM) as a pH buffer, pH = 7.0, $[SA]_{tot,o}$ = 15 μM, [NaCl] + [$NaNO_3$] = 100 mM, T = 20.0 °C.

were influencing chlorination rates, the reaction order in $[HOCl]_{tot,o}$ is anticipated to equal 2 (noting that $[Cl_2O]$ is proportional to $[HOCl]^2$ *vis-à-vis* eqn (3)). If Cl_2 were influencing chlorination rates, the reaction order in $[HOCl]_{tot,o}$ could conceivably range from 1 to 2 due to the approximately equimolar concentration of Cl^- and free chlorine in NaOCl stock solutions.[13] In reactors containing low background levels of Cl^-, doubling the dosage of free chlorine can result in an approximately 4-fold increase in $[Cl_2]$ due to the dependence of $[Cl_2]$ on both [HOCl] and [Cl^-] (eqn (2)). Accordingly, rates exhibiting a greater-than-first-order dependence on free chlorine dose can be attributed to Cl_2O, Cl_2, or a combination of the two.

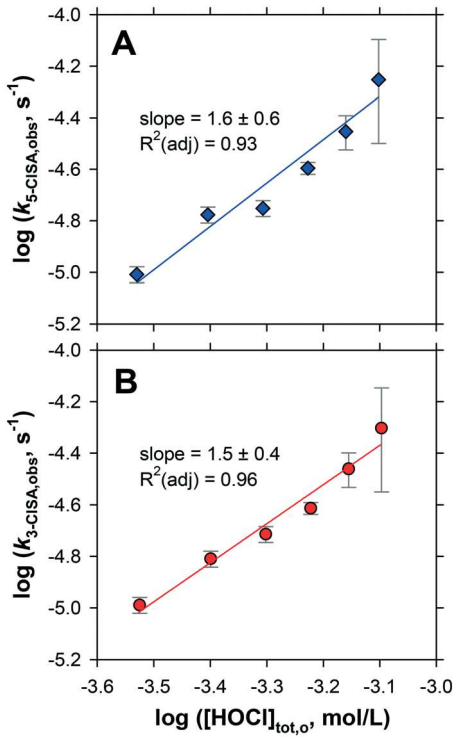


Fig. 3 Pseudo first-order rate constant for chlorination of SA yielding (A) 5-chlorosalicylate (5-ClSA, $k_{5\text{-ClSA,obs}}$) and (B) 3-chlorosalicylate (3-ClSA, $k_{3\text{-ClSA,obs}}$) as a function of the initial concentration of free chlorine ($[HOCl]_{tot,o}$). Uncertainties denote 95% confidence intervals. Conditions: pH = 7.5, phosphate (20 mM) as a pH buffer, $[SA]_{tot,o}$ = 15 μM, [NaCl] = 9.9 mM, [$NaNO_3$] = 89 mM, T = 20.0 °C.

To isolate the possible influence of Cl_2O, a sufficient amount of NaCl (9.9 mM) was added to the variable free chlorine reactors (Fig. 3) so as to attenuate the influence of Cl^- (≤0.8 mM) derived from addition of free chlorine. That reaction orders in $[HOCl]_{tot,o}$ between 1 and 2 were determined in the presence of a 9.9 mM Cl^- background suggests that Cl_2O contributes to net chlorination rates in these systems. As with Cl_2, Cl_2O has been previously shown to influence chlorination rates of both ionizable[13–16] and nonionizable[10,12,36] organic compounds.

Influence of the initial concentration of SA. All chlorination reactions reported herein were performed under conditions such that $[HOCl]_{tot,o} \gg [SA]_{tot,o}$. Nevertheless, chlorination rates of SA could conceivably be limited by the formation rates of active chlorinating agents (*e.g.*, Cl_2, Cl_2O) whose equilibrium concentrations are low relative to $[SA]_{tot,o}$. To assess whether formation of chlorinating agents is rate-limiting, experiments were performed as a function of $[SA]_{tot,o}$ at pH 7.0 and 9.9. Log–log plots of initial chlorination rate *versus* $[SA]_{tot,o}$ were linear with slopes not significantly different than 1 at the 95% confidence level (Fig. 4); these slopes correspond to the reaction order in $[SA]_{tot,o}$. That reaction orders in $[SA]_{tot,o}$ are not significantly different than 1 suggests that formation of active chlorinating agents is not rate-limiting under the examined conditions.

3.2 Bromination of SA

Effects of buffer concentration and pH. The formal concentration of phosphate buffer (ranging from 20 to 50 mM) does not appreciably influence bromination rates of SA (Fig. S8†). Thus, unlike chlorination of SA, buffer catalysis by one or more phosphate species does not appear to affect bromination of SA. In addition, no discontinuities are evident in plots of pseudo-first-order bromination rate constants (Fig. 5) at pH values corresponding to changes in the composition of the pH buffer (*i.e.*, phosphate at pH < 8, borate at 8 ≤ pH < 9.5, carbonate at pH ≥ 9.5). Accordingly, buffer identity does not appear to influence bromination rates under the examined conditions.

Pseudo-first-order rate constants corresponding to formation of 3-BrSA and 5-BrSA generally decrease across the examined pH range (6–10), although a shoulder (and, for 3-BrSA, a depression) is evident between pH 7.0–8.5 (Fig. 5A). Unlike the reactivity profile for chlorination of SA (Fig. 1A), k_{obs} values for bromination of SA do not increase at pH > 8.6. This suggests that nucleophiles other than hydrogen salicylate (*e.g.*, dibasic salicylate) are not influencing bromination rates in these systems.

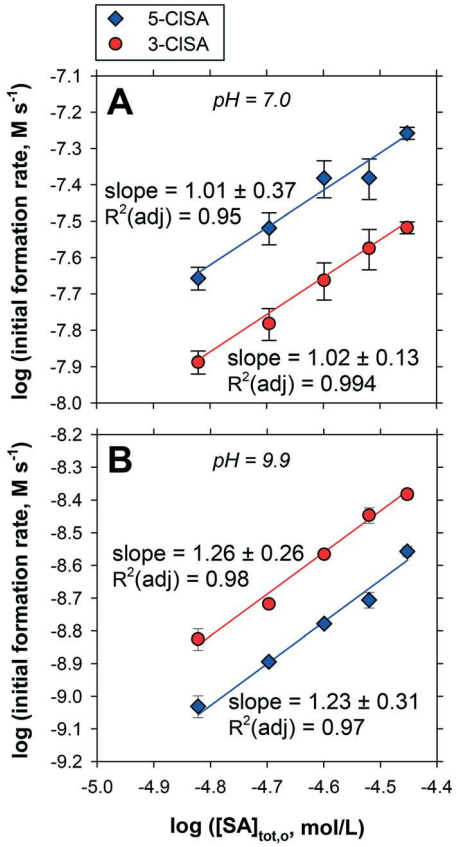


Fig. 4 Initial rates of formation of 5-chlorosalicylate (5-ClSA) and 3-chlorosalicylate (3-ClSA) as a function of the total initial concentration of SA at (A) pH 7.0 and (B) pH 9.9. Uncertainties denote 95% confidence intervals (smaller than symbols if not shown). Additional uniform conditions: $[HOCl]_{tot,o}$ = 5.0 mM, [NaCl] = 9.7 mM, $[NaNO_3]$ = 91 mM, borate (19 mM) + carbonate (19 mM) as a mixed pH buffer, T = 20.0 °C.

The reactivity profile for bromination of SA as a function of pH differs from that of phenol reported by Gallard *et al.*[68] Apparent rate constants for bromination of phenol (measured in solutions of free bromine generated *via* ozonation of bromide) reach a maximum at pH ≈ 9.3 and decrease continually at lower (to pH 4) and higher (to pH 12) pH values.[68] That bromination rate constants of phenol do not increase with decreasing pH at pH < 7 (as observed for SA) likely results from the absence of added free chlorine and chloride in the phenol experiments, which (as discussed below) can enhance bromination rates of SA.

The regioselectivity of SA bromination exhibits a strong dependence on pH (Fig. 5B). Formation of 5-BrSA is approximately 9 times faster than is formation of 3-BrSA at pH < 6.5 and approximately 3 times faster at pH > 8.0. This shift in regioselectivity is likely due to pH-dependent changes in bromine speciation. Under all examined pH values, regioselectivity favoring halogenation at the 5-position is greater for bromination (Fig. 5B) than for chlorination (Fig. 1B). Brominating agents have larger molar volumes relative to their chlorinated analogues (Table 2); therefore, steric effects could explain (at least in part) the greater regioselectivity of bromination compared to chlorination. Electronic effects (*e.g.*, polarizability) could also contribute to differences in halogenation rates and regioselectivity between bromination and chlorination.

Effects of chloride. The concentration of chloride was varied for a series of reactions performed at pH 7.0 and uniform ionic strength (0.1 M). A plot of k_{obs} values for both brominated products as a function of $[Cl^-]$ is approximately linear with slopes >0 (Fig. 6). Of the possible brominating agents shown in Table 1, only the concentration of BrCl is influenced by $[Cl^-]$ under otherwise uniform conditions. These results support the role of BrCl as an active brominating agent in these solutions. The relationship between $[Cl^-]$ and enhanced rates of bromination (*via* formation of BrCl) has been previously reported for reactions of other aromatic compounds, including *p*-xylene,[10] (bromo)anisoles,[37] dimethenamid,[35] and nalidixic acid (a quinolone antibiotic).[70]

Effects of free chlorine. The initial concentration of free chlorine ($[HOCl]_{tot,o}$) was varied in experiments performed at pH 7.0 such that $[HOCl]_{tot,o} > [Br^-]_o$. As $[HOCl]_{tot,o}$ increases, k_{obs} values also increase (Fig. 7).

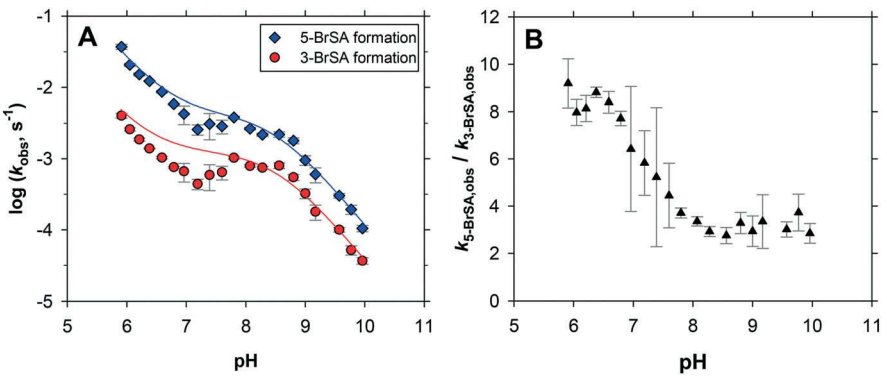


Fig. 5 (A) Log of pseudo-first-order rate constants and (B) regioselectivity ratios for bromination of SA (yielding 5-bromosalicylate (5-BrSA) and 3-bromosalicylate (3-BrSA)) as a function of pH. Solid lines in frame (A) denote model fits based on eqn (25). Error bars in both frames denote 95% confidence intervals (smaller than symbols if not shown). Conditions for both frames: $[NaBr]_o$ = $[SA]_{tot,o}$ = 20 μM, $[HOCl]_{tot,o}$ = 27 μM, a pH buffer (20 mM formal concentration of phosphate, borate, or carbonate), [NaCl] = 4.9 mM, $[NaNO_3]$ = 94 mM, T = 20.0 °C.

Table 2 Physical properties of halogenating agents[a]

Halogenating agent	Normalized molar volume	Normalized polarizability
HOCl	1.00	1.00
HOBr	1.05	1.36
Cl_2	1.37	1.39
BrCl	1.42	1.76
Br_2	1.47	2.09
Cl_2O	1.54	1.61
BrOCl	1.59	1.97
Br_2O	1.64	2.30

[a] Property estimates determined *via* ACD/ChemSketch.[69] All property values normalized to those of HOCl.

The ability of free chlorine (added in excess of bromide) to enhance bromination rates has been previously reported for experiments involving dimethenamid[35] and (bromo)anisoles.[37] As in these previous studies, the ability of excess free chlorine to increase rates of bromination can be explained by the formation of BrOCl, whose concentration is proportional to [HOCl] (eqn (9)). In systems containing reducing agents (*e.g.*, natural waters), the ability of excess free chlorine to enhance rates of bromination could also result from re-oxidation of Br^- by free chlorine.[32] Such redox-cycling of bromine is not anticipated to be significant in the synthetic waters employed herein.

Effects of excess bromide. When the dose of free chlorine is insufficient to effect stoichiometric oxidation of bromide, systems can contain non-trivial amounts of unoxidized (*i.e.*, "excess") bromide. Such systems in which $[HOCl]_{tot,o} < [Br^-]_o$ are experimentally useful because these systems favor the formation of Br_2 and are not anticipated to contain a detectable free chlorine residual (thereby precluding the influence of BrOCl). Values of k_{obs} corresponding to formation of 5-BrSA and 3-BrSA generally increase with increasing [excess Br^-] (Fig. S9†). These results are consistent with the participation of Br_2 as an active brominating agent, noting that $[Br_2]$ is proportional to [excess Br^-] (eqn (6)). Previous studies reported that the inherent reactivity of Br_2 toward a variety of organic compounds[32,37] (including phenol[68,71]) exceeds that of HOBr, often by several orders of magnitude.

Effects of initial concentration of free bromine. When the initial concentration of free bromine ($[HOBr]_{tot,o}$) was varied from 20–60 μM, k_{obs} values for bromination of SA increased in a curvilinear fashion (Fig. 8A), indicative of a greater-than-first-order dependence of bromination rates on $[HOBr]_{tot,o}$. The reaction order in $[HOBr]_{tot,o}$ (n) associated with each examined $[HOBr]_{tot,o}$ was determined using nonlinear regression analysis of eqn (12)–(15) with concentration *versus* time data serving as input. As $[HOBr]_{tot,o}$ increases from 20 to 60 μM, n increases from 1.01 ± 0.03 to 1.22 ± 0.05 (Fig. 8B). The equilibrium concentrations of all brominating agents shown in Table 1 are proportional to $[HOBr]_{tot,o}$, except Br_2O, whose concentration is proportional to $[HOBr]^2_{tot,o}$. The results shown in Fig. 8 suggest that Br_2O can contribute to overall bromination rates of SA, particularly at the higher end of the examined $[HOBr]_{tot,o}$ range.

Effects of initial concentration of SA. As with chlorination of SA, formation of active halogenating agents could conceivably limit bromination rates of SA. To determine whether formation of brominating agents influences measured rates of SA bromination, experiments were performed in which the initial concentration of SA was varied. For both the major (5-BrSA) and minor (3-BrSA) products, log–log plots of initial rate of product formation *versus* $[SA]_o$ are linear with slopes not significantly different than 1.0 (Fig. S10†). These results indicate that reactions of SA with free bromine are first-order in [SA] and suggest that formation of brominating agents is

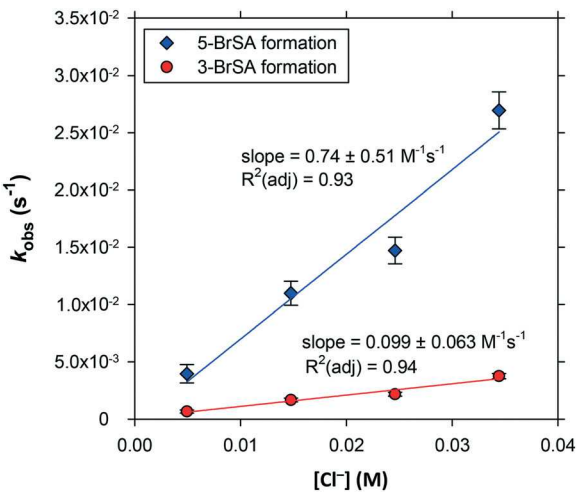


Fig. 6 Pseudo-first-order bromination rate constants as a function of chloride concentration. Error bars denote 95% confidence intervals (smaller than symbols if not shown). Conditions: $[NaBr]_o$ = $[SA]_{tot,o}$ = 20 μM, $[HOCl]_{tot,o}$ = 27 μM, phosphate (20 mM) as a pH buffer, pH = 7.0, [NaCl] + $[NaNO_3]$ = 100 mM, T = 20.0 °C.

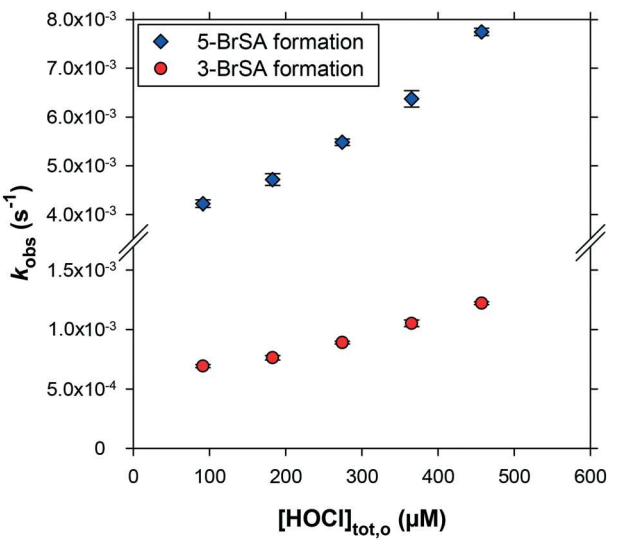


Fig. 7 Pseudo-first-order rate constants (k_{obs}) as a function of initial concentration of free chlorine ($[HOCl]_{tot,o}$). Error bars denote 95% confidence intervals (smaller than symbols if not shown). Conditions: $[NaBr]_o$ = $[SA]_{tot,o}$ = 20 μM, phosphate (20 mM) as a pH buffer, pH = 7.0, [NaCl] = 4.9 mM, $[NaNO_3]$ = 93 mM, T = 20.0 °C.

not rate-limiting, consistent with previous bromination studies involving anisole[37] and dimethenamid.[35]

3.3 Reaction mechanisms and rate constants for individual halogenating agents

Evidence discussed above indicates that Cl_2 and Cl_2O, in addition to HOCl, can serve as chlorinating agents of SA *via* electrophilic aromatic substitution. It is also conceivable that ClO^- could participate in chlorination reactions, although the formal negative charge is anticipated to attenuate the electrophilicity of ClO^-. Attempts to model the chlorination data collected as a function of pH using combinations of these four chlorinating agents (Cl_2, Cl_2O, HOCl, and/or ClO^-) and assuming only hydrogen salicylate (HSA^-) as the reactive nucleophile failed to provide reasonable fits to the experimental data across the entire examined pH range of 6–11 (Fig. S11†). Inclusion of dibasic salicylate (SA^{2-}) as a possible reactive nucleophile did not, however, improve the model fits (Fig. S12†). A common shortcoming of each of these models is their inability to concurrently capture the minimum in the log k_{obs} data at pH 8.5 and the plateau at pH > 10.

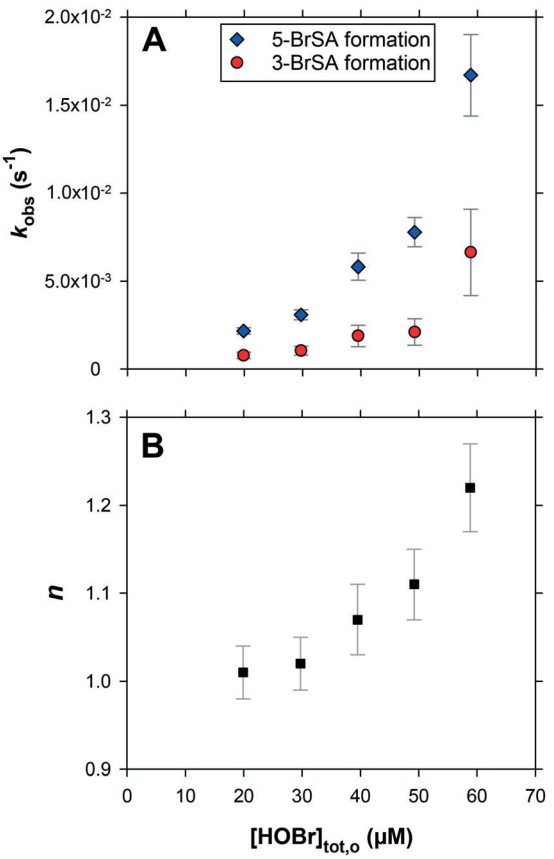
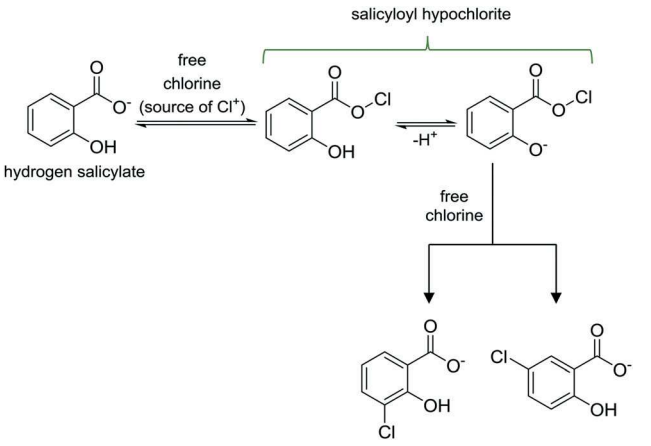


Fig. 8 (A) Pseudo-first-order bromination rate constants (k_{obs}) and (B) reaction order in total free bromine (n) as a function of the initial concentration of free bromine ($[HOBr]_{tot,o}$). All uncertainties denote 95% confidence intervals (smaller than symbols if not shown). Conditions for both frames: $[HOCl]_{tot,o} = [NaBr]_o + 7$ μM, $[SA]_{tot,o} = [NaBr]_o$, borate (20 mM) as a pH buffer, pH = 8.8, [NaCl] = 4.9 mM, $[NaNO_3]$ = 94 mM, T = 20.0 °C.

The best model fit (shown as solid lines in Fig. 1) was obtained when Cl_2, Cl_2O, and HOCl were assumed as chlorinating agents of HSA^- and, in a parallel pathway, HSA^- was assumed to be capable of forming salicyloyl hypochlorite, a postulated intermediate leading to the formation of 3-ClSA and 5-ClSA following chlorination of salicyloyl hypochlorite by free chlorine (Scheme 2).

Previous studies involving compounds with structural motifs similar to SA have discussed the ability of organic hypochlorites, including acetyl hypochlorite and benzoyl hypochlorite, to serve as reaction intermediates and/or chlorinating agents.[72–75] Cl^+ transfer to carboxylate moieties has also been proposed as an intermediate step in reactions of free chlorine with low-molecular-weight carboxylic acids and carbohydrates.[76] To our knowledge, this is the first report of salicyloyl hypochlorite as a putative reaction intermediate. Attempts to identify salicyloyl hypochlorite *via* UV-vis spectrophotometry did not yield absorbance bands distinct from the reactants (HSA^- and free chlorine), perhaps due to the modest differences in chromophoric structure between HSA^- and salicyloyl hypochlorite and/or the low relative abundance of salicyloyl hypochlorite. The free chlorine doses employed herein were greater than those typical of chlorinated drinking water. As such, whether or not salicyloyl hypochlorite influences chlorination rates under conditions more typical of chlorinated drinking water merits further investigation.

The phenolic moiety of salicyloyl hypochlorite is anticipated to be more acidic than HSA^- (pK_{a2} = 13.4). Bonding of Cl^+ to the carboxylate group disrupts the ability of the carboxylate group to participate in a bidentate-style complexation of the acidic proton in HSA^-, which can account for the increased acidity predicted for salicyloyl hypochlorite relative to HSA^-. From this perspective, the acid–base chemistry of salicyloyl hypochlorite is predicted to be similar to that of methyl salicylate (pK_a = 9.8).[77] Results from our reactivity models (discussed below) provide pK_a estimates of ~9.0 for salicyloyl hypochlorite. The increased acidity of



Scheme 2 Postulated pathway for the chlorination of hydrogen salicylate proceeding through salicyloyl hypochlorite as an intermediate under alkaline conditions.

salicyloyl hypochlorite (relative to HSA^-) results in an increased fraction of salicyloyl hypochlorite existing in the more nucleophilic phenolate form. Chlorination of salicyloyl hypochlorite by free chlorine to give 3-ClSA and 5-ClSA is anticipated to be more facile when salicyloyl hypochlorite exists predominantly in the phenolate form. As such, the postulated participation of salicyloyl hypochlorite as a chlorination intermediate could affect the reactivity and regioselectivity of SA chlorination, particularly at pH > 8. The reaction order in [SA] of approximately 1 at pH 9.9 (Fig. 4) is consistent with formation of salicyloyl hypochlorite (*e.g.*, from reaction of HSA^- with HOCl) prior to presumably rate-determining ring chlorination of salicyloyl hypochlorite (phenolate form) by free chlorine.

The rate equation corresponding to the best-fit model for the chlorination data is:

$$-\frac{d[SA]_{tot}}{dt} = \left(k_{Cl_2}[Cl_2] + k_{Cl_2O}[Cl_2O] + k_{HOCl}[HOCl]\right)[HSA^-] + k_{SAOCl}[HOCl]_{tot}[SAOCl^-] \quad (20)$$

where k_{SAOCl} is a second-order rate constant (M^{-1} s^{-1}) corresponding to chlorination of salicyloyl hypochlorite in the phenolate form by free chlorine; $[SAOCl^-]$ denotes the molar concentration of salicyloyl hypochlorite (phenolate form). Assuming that $[SAOCl^-]$ is proportional to both $[HOCl]_{tot}$ and $[HSA^-]$, the concentration of salicyloyl hypochlorite in the phenolate form can be expressed as:

$$[SAOCl^-] = \frac{K_{a,SAOCl}}{K_{a,SAOCl} + 10^{-pH}} K_{assoc}[HOCl]_{tot}[HSA^-] \quad (21)$$

where $K_{a,SAOCl}$ is the acid-dissociation constant of the phenolic form of salicyloyl hypochlorite and K_{assoc} is a concentration-based equilibrium constant (M^{-1}) for the association of free chlorine with HSA^- to give salicyloyl hypochlorite. Substituting eqn (21) into eqn (20) gives:

$$-\frac{d[SA]_{tot}}{dt} = \left(k_{Cl_2}[Cl_2] + k_{Cl_2O}[Cl_2O] + k_{HOCl}[HOCl]\right)[HSA^-] + k_{SAOCl}\frac{K_{a,SAOCl}}{K_{a,SAOCl} + 10^{-pH}} K_{assoc}[HOCl]_{tot}^2[HSA^-] \quad (22)$$

The value of K_{assoc} is unknown, which precludes a determination of k_{SAOCl}; however, the product of $k_{SAOCl}K_{assoc}$ (defined as J, units M^{-2} s^{-1}) can be calculated using the modeling approach employed herein. If estimates of K_{assoc} become available in the future, back-calculation of k_{SAOCl} is straightforward. Substituting J into eqn (22) and rearranging gives:

$$-\frac{d[SA]_{tot}}{dt} = \left(k_{Cl_2}[Cl_2] + k_{Cl_2O}[Cl_2O] + k_{HOCl}[HOCl] + J\frac{K_{a,SAOCl}}{K_{a,SAOCl} + 10^{-pH}}[HOCl]_{tot}^2\right)[HSA^-] \quad (23)$$

The terms within the parentheses in eqn (23) are equal to the pseudo-first-order chlorination rate constant ($k_{Cl,obs}$):

$$k_{Cl,obs} = k_{Cl_2}[Cl_2] + k_{Cl_2O}[Cl_2O] + k_{HOCl}[HOCl] + J\frac{K_{a,SAOCl}}{K_{a,SAOCl} + 10^{-pH}}[HOCl]_{tot}^2 \quad (24)$$

For the bromination experiments, results shown above indicate that HSA^- is the only kinetically-relevant nucleophile under the conditions examined herein. In contrast to the modeling efforts associated with the chlorination data, invoking a salicyloyl hypohalite intermediate did not improve model fits for the bromination data, particularly with respect to the minimum in rate constants at near-neutral pH (Fig. 5). The increased reactivity of brominating agents relative to their chlorinated analogs could preclude the need for bromination to proceed *via* a salicyloyl hypohalite intermediate. A reactivity model assuming HOBr as the only active brominating agent provides a reasonable fit to the experimental data at pH > 7.2 but substantially underestimates the experimental data at pH < 7.2 (Fig. S13†). Inclusion of BrCl provides improved model fits at pH < 7.2 (Fig. S13†). The results discussed above indicate that BrOCl, Br_2O, HOBr, and Br_2 can also serve as brominating agents, depending on the solution conditions. As such, the following reactivity model was employed for the bromination experiments:

$$k_{Br,obs} = k_{BrCl}[BrCl] + k_{Br_2}[Br_2] + k_{BrOCl}[BrOCl] + k_{Br_2O}[Br_2O] + k_{HOBr}[HOBr] \quad (25)$$

Second-order rate constants specific to individual chlorinating and brominating agents were calculated through iterative least-squares regression (Scientist 3.0, MicroMath Scientific Software) of eqn (24) and (25), respectively. Experimental k_{obs} values and calculated equilibrium concentrations of the chlorine and bromine species were used as inputs; second-order rate constants (k_{Cl_2} *et al.*), $K_{a,SAOCl}$, and J were treated as fitting parameters. A data binning procedure was used to increase the precision of the calculated second-order rate constants (see Tables S11 and S12† for more details).

The results of the modeling efforts are listed in Table 3. The model fits to the experimental data for chlorination (eqn (24)) and bromination (eqn (25)) of SA as a function of pH are shown as solid lines in Fig. 1 and 5, respectively. For both chlorination and bromination, the kinetic models provide a somewhat better fit to the data associated with 5-ClSA and 5-BrSA (typically the major products) compared to the data associated with 3-ClSA and 3-BrSA (typically the minor products). Inclusion of terms for H_2OCl^+ and H_2OBr^+ in our

models was not necessary in order to provide good agreement with the experimental data at pH < 7.

The normalized rate constants shown in Table 3 are relative to reactions involving HOCl + hydrogen salicylate. The overall reactivity trend of chlorinating agents toward HSA^- is $HOCl < Cl_2O < Cl_2$. That Cl_2 is the most reactive species can be explained by the trend in nucleofugality (leaving-group ability) associated with the three chlorinating species: OH^- (from HOCl) < OCl^- (from Cl_2O) < Cl^- (from Cl_2).[12] Other factors that might affect the order of reactivity of these chlorinating agents include polarizability and electropositivity of the Cl atom(s). The same reactivity trend observed with HSA^- ($HOCl < Cl_2O < Cl_2$) was also reported for three aromatic ethers (3-methylanisole, 1,3-dimethoxybenzene, and 1,3,5- trimethoxybenzene).[12] For dimethenamid[36] and *p*-xylene,[10] Cl_2 and Cl_2O were shown to have approximately equal inherent reactivity. Consistent with previous studies,[12,36] Cl_2 and Cl_2O were five to seven orders of magnitude more inherently reactive toward HSA^- relative to HOCl.

The overall reactivity trend of brominating agents for reactions generating 5-BrSA and 3-BrSA (Table 3) is $HOBr < Br_2O \approx Br_2 < BrOCl < BrCl$. The relatively high inherent reactivity of BrCl and BrOCl can be explained by the greater partial positive charge on the bromine atom in each of these mixed halogen species ($BrCl > Br_2$, $BrOCl > Br_2O$).[37] Other factors that can potentially contribute to the reactivity trend among the brominating agents include nucleofugality, bond dissociation energies, polarizability, and (particularly for sterically-hindered reaction sites) molar volume.[37]

The reactivity trend for bromination of *p*-xylene,[10] dimethenamid,[35] and the *para* position of anisole[37] is $HOBr < Br_2O < BrOCl < Br_2 < BrCl$ (for *p*-xylene, rate constants were not reported for Br_2O and BrOCl). Anisole, dimethenamid, and *p*-xylene lack ionizable groups. Such differences in structure likely influence the order of reactivity toward free bromine species.

3.4 Competition between chlorination and bromination

When bromide-containing waters are chlorinated with excess chlorine, the resulting solution can contain a mixture of free chlorine and free bromine. Free chlorine and free bromine species are both capable of reacting with nucleophilic moieties within NOM, resulting in the formation of chlorinated and brominated DBPs. Understanding the mechanisms influencing the rate and extent of chlorine incorporation *versus* bromine incorporation into NOM is important because (1) brominated DBPs are generally more toxic than their chlorinated counterparts[56–59] and (2) preferential incorporation of Br into regulated DBPs can make it more difficult for water treatment utilities to comply with mass-based DBP regulations due to the greater atomic weight of Br relative to Cl.[78]

Competition between free chlorine and free bromine for reactive sites on organic compounds (including NOM) can conceivably be influenced by several factors, including: (1) the concentration of free chlorine relative to free bromine; (2) the reactivity of free chlorine relative to free bromine; (3) the concentration, identity, and accessibility of reactive sites on organic nucleophiles; (4) the concentration and identity of reductants (inorganic and organic) capable of reducing free halogens; and (5) solution conditions (*e.g.*, pH, $[Cl^-]$, $[Br^-]_o$, $[NH_3]_{tot}$, chlorine dose, temperature) known to affect the speciation and reactivity of free halogens and/or organic nucleophiles. With halogenating-agent-specific rate constants in hand (Table 3), the relative rate of bromination to chlorination (*i.e.*, $k_{Br,obs}/k_{Cl,obs}$, from eqn (24) and (25)) can be estimated for hypothetical solution conditions. These ratios are best viewed as the relative initial rate of bromination to chlorination, noting that such ratios can change over the course of a reaction as reactants are consumed.

Under conditions typical of chlorinated drinking water, half-times predicted for SA halogenation (chlorination + bromination) are generally < 1.5 h (Fig. 9). Half-times typically

Table 3 Regiospecific second-order chlorination and bromination rate constants for reactions with hydrogen salicylate (HSA^-) and salicyloyl hypochlorite (phenolate form, $SAOCl^-$) at the 3- ($k_{3\text{-XSA}}$) and 5- ($k_{5\text{-XSA}}$) positions[a]

Reagents	$k_{3\text{-XSA}}$ (M^{-1} s^{-1})	$k_{5\text{-XSA}}$ (M^{-1} s^{-1})	$k_{5\text{-XSA}}/k_{3\text{-XSA}}$	Normalized $k_{3\text{-XSA}}$	Normalized $k_{5\text{-XSA}}$
BrCl + HSA^-	$(1.15 \pm 0.10) \times 10^6$	$(9.0 \pm 2.0) \times 10^6$	7.8 ± 1.9	2.1×10^7	1.5×10^8
BrOCl + HSA^-	$(3.0 \pm 0.8) \times 10^5$	$(1.4 \pm 0.4) \times 10^6$	4.7 ± 1.8	5.4×10^6	2.4×10^7
Br_2 + HSA^-	$(9.1 \pm 1.6) \times 10^4$	$(5.1 \pm 1.3) \times 10^5$	5.6 ± 1.7	1.6×10^6	8.6×10^6
Br_2O + HSA^-	$(9.0 \pm 5.2) \times 10^4$	$(4.5 \pm 2.1) \times 10^5$	5.0 ± 3.7	1.6×10^6	7.6×10^6
Cl_2 + HSA^-	$(3.9 \pm 0.6) \times 10^4$	$(8.3 \pm 1.1) \times 10^4$	2.1 ± 0.4	7.0×10^5	1.4×10^6
Cl_2O + HSA^-	$(2.6 \pm 0.7) \times 10^3$	$(5.9 \pm 1.5) \times 10^3$	2.3 ± 0.8	4.6×10^4	1.0×10^5
HOBr + HSA^-	50 ± 7	154 ± 28	3.1 ± 0.7	8.9×10^2	2.6×10^3
HOCl + HSA^-	0.056 ± 0.027	0.059 ± 0.013	1.1 ± 0.6	1.0	1.0

Reagents	J (M^{-2} s^{-1})[b]		$pK_{a,SAOCl}$[c]		$J_{5\text{-XSA}}/J_{3\text{-XSA}}$
	3-ClSA	5-ClSA	3-ClSA	5-ClSA	
$SAOCl^-$ + free chlorine	5.8 ± 0.6	5.3 ± 0.2	9.2 ± 0.3	8.7 ± 0.2	0.91 ± 0.12

[a] X = Cl or Br; T = 20.0 °C; uncertainties denote 95% confidence intervals. [b] $J_{3\text{-ClSA}}$ and $J_{5\text{-ClSA}}$ denote reactivity coefficients that account for the equilibrium constant describing the formation of salicyloyl hypochlorite (from the reaction of hydrogen salicylate + free chlorine) and subsequent ring chlorination of the phenolate form of salicyloyl hypochlorite by free chlorine to give 3-ClSA or 5-ClSA. As the equilibrium constant describing the formation of salicyloyl hypochlorite is unknown, $J_{3\text{-ClSA}}$ and $J_{5\text{-ClSA}}$ do not represent true third-order rate constants. [c] $pK_{a,SAOCl}$ denotes the acid-dissociation constant of salicyloyl hypochlorite (phenolic form).

decrease with decreasing pH, increasing [Br^-], increasing [Cl^-], and increasing $[HOCl]_{tot,o}$. Values of $k_{Br,obs}/k_{Cl,obs}$ for reactions involving SA under conditions representative of chlorinated drinking water are predicted to range from 10^1–10^3 (Fig. 9), excepting conditions where $[Br^-]_o/[HOCl]_{tot,o}$ approaches or exceeds 1.0. This range of $k_{Br,obs}/k_{Cl,obs}$ is consistent with previous studies demonstrating that free bromine is commonly 2-to-3 orders of magnitude more inherently reactive as a halogenating agent compared to free chlorine.[4,32,35] As pH values increase above 7, $k_{Br,obs}/k_{Cl,obs}$ values decrease substantially (Fig. 9A) due to the participation of salicyloyl hypochlorite as a chlorination intermediate (see Fig. S14† for fractional contributions of individual halogenating agents). Results shown in Fig. 9B suggest that changes in $[Br^-]_o$ across ranges typical of drinking water sources can have a large effect on rates of SA bromination relative to chlorination. At pH 7, changes in [Cl^-] are predicted to have a minor influence (if any) on $k_{Br,obs}/k_{Cl,obs}$ (Fig. 9C), which suggests that Cl^- can catalyze bromination and chlorination to similar degrees. Free chlorine is also capable of enhancing rates of bromination and chlorination (Fig. 9D), although the effects of changes in $[HOCl]_{tot,o}$ appear to be more modest than those attributable to changes in [Cl^-].

The rate constants reported in Table 3 can also be used to estimate yields of monochlorinated and monobrominated products of SA under conditions typical of chlorinated drinking water. The results of these calculations are shown in Table 4 and indicate that yields of monobrominated products are anticipated to exceed those of the monochlorinated products by 57-fold (molar basis) in the effluent of a simulated chlorine contact basin (pH 7, 0.5 h residence time). Quantitative conversion of SA into halogenated products is predicted to occur after approximately 3 h in the distribution system (pH 8), at which time the yields of monobrominated products are estimated to exceed those of the monochlorinated products by a factor of 17 (molar basis). These predictions do not account for the ability of monohalogenated products of SA to undergo subsequent halogenation or for the consumption of halogenating agents by nucleophiles other than SA. Overall, these findings, along with the data shown in Fig. 9, suggest that timescales of SA halogenation in chlorinated drinking water are on par with the formation of trihalomethanes and haloacetic acids from so-called "slow" reacting sites within natural organic matter.[79–81]

3.5 Additional implications for chlorinated waters

Many previous halogenation studies commonly assume that HOCl and/or HOBr are the only kinetically-relevant halogenating agents in chlorinated waters.[4,32] Models that discount

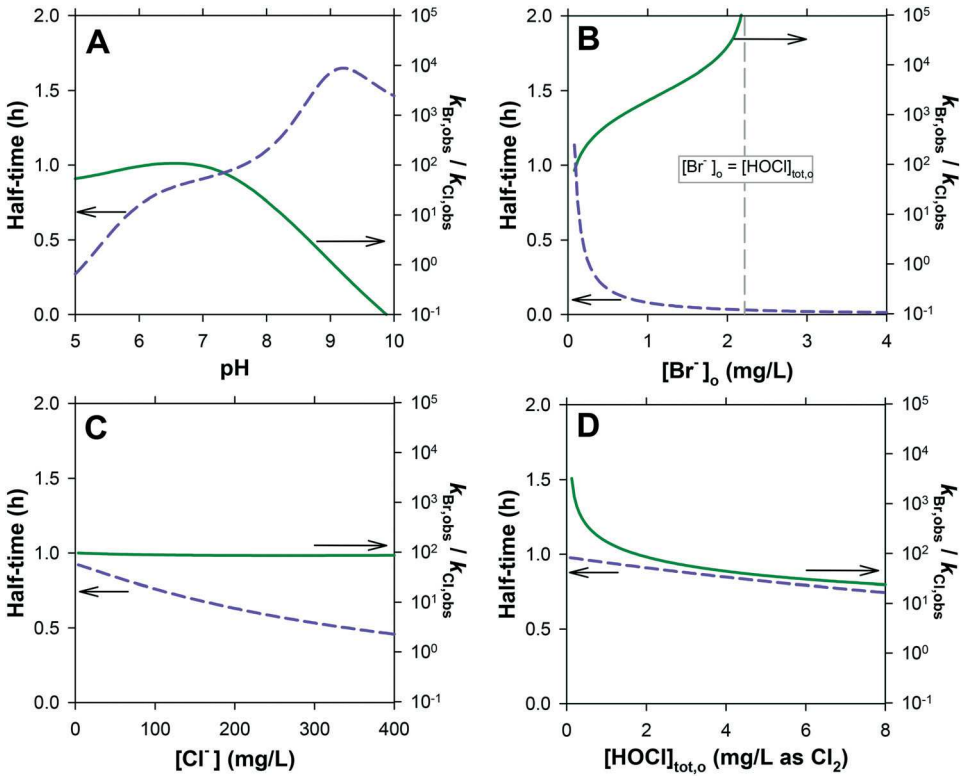


Fig. 9 Half-times for net halogenation (chlorination + bromination) of SA (dashed purple lines) and ratios of pseudo-first-order rate constants for bromination and chlorination ($k_{Br,obs}/k_{Cl,obs}$, solid green lines) as a function of (A) pH, (B) $[Br^-]_o$, (C) [Cl^-], and (D) $[HOCl]_{tot,o}$. All data refer to reactions leading to the formation of 5-ClSA and 5-BrSA, which represent the major halogenation products of SA under most conditions. Unless otherwise indicated on the x-axes, conditions are typical of chlorinated drinking water: pH = 7.0, $[Br^-]_o$ = 0.10 mg L^{-1} (1.25 μM), [Cl^-] = 11 mg L^{-1} (0.30 mM), $[HOCl]_{tot,o}$ = 2.0 mg L^{-1} as Cl_2 (28 μM), and T = 20 °C. The results shown assume that the speciation of free chlorine and free bromine is thermodynamically-controlled.

Table 4 Predicted concentrations of monohalogenated salicylates formed from SA during simulated drinking water chlorination[a]

System	Monochlorinated products of SA ($\mu g\ L^{-1}$)	(nM)	Monobrominated products of SA ($\mu g\ L^{-1}$)	(nM)
Chlorine contact basin (pH 7, 0.5 h residence time)	0.002	0.01	0.12	0.57
Distribution system[b] (pH 8, 3 h residence time)	0.014	0.08	0.3	1.37

[a] Assumed conditions: $[SA]_o$ = 0.20 $\mu g\ L^{-1}$ = 1.45 nM (median concentration reported in rivers and streams by ref. 41), $[Br^-]_o$ = 0.10 mg L^{-1} = 1.25 μM, $[Cl^-]$ = 11 mg L^{-1} = 0.30 mM, $[HOCl]_{tot,o}$ = 2.0 mg L^{-1} as Cl_2 = 28 μM, T = 20 °C. [b] Product yields denote net yields of monohalogenated products formed in the chlorine contact basin and in the distribution system under the stated conditions and timescales. These values do not account for (1) consumption of halogenating agents by nucleophiles other than SA or (2) the ability of monohalogenated products of SA to undergo subsequent halogenation.

the roles of halogenating agents other than HOCl and HOBr are unlikely to capture the effects of, for example, $[Cl^-]$ on halogenation rates, particularly for organic compounds whose nucleophilicities are on par with or less than that of SA. Chloride catalysis may be particularly significant in drinking water impacted by road salt,[82–85] seawater intrusion,[26,86] and oil/gas exploration.[27,87–89] Chloride in municipal wastewater,[90] saline sewage,[54] salt water swimming pools,[91,92] ballast water,[93,94] and desalination plants[95–98] is also likely to enhance halogenation rates.

Conventional halogenation models that assume HOCl and/or HOBr are the only relevant halogenating agents run the risk of over-estimating the inherent reactivity of these hypohalous acids. For example, our results indicate that the second-order rate constant corresponding to the overall reactivity of HOBr toward SA (calculated as $k_{3\text{-BrSA,HOBr}} + k_{5\text{-BrSA,HOBr}}$ at 20 °C) equals $(2.0 \pm 0.3) \times 10^2\ M^{-1}\ s^{-1}$. A previous investigation[99] of salicylic acid bromination reported a value of $4.03 \times 10^4\ M^{-1}\ s^{-1}$ for k_{HOBr} (at 25 °C) based on a reactivity model that assumed HOBr was the only active brominating agent. By not accounting for additional brominating agents, the previous investigation appears to overestimate the inherent reactivity of HOBr by a factor of ~200.

4. Conclusions

Several conclusions can be drawn from this work, including:

- Kinetic models that only account for HOCl and HOBr cannot adequately explain the reactivity of SA toward free chlorine and free bromine, respectively.
- Kinetic evidence supports the participation of additional halogenating agents, including Cl_2, Cl_2O, BrCl, BrOCl, Br_2, and Br_2O, when bromide-containing synthetic waters are treated with free chlorine.
- Under the majority of solution conditions, halogenation is anticipated to proceed *via* bimolecular reactions at the 3- and 5-positions of hydrogen salicylate (HSA^-); however; under alkaline conditions, salicyloyl hypochlorite appears to serve as a chlorination intermediate.
- Solution conditions known to influence the speciation of free chlorine and free bromine (including pH, $[Br^-]_o$, $[Cl^-]$, $[HOCl]_{tot,o}$) can substantially influence the rate and bromine-to-chlorine selectivity of SA halogenation.
- Phosphate as a pH buffer is capable of enhancing rates of SA chlorination (but not bromination). As such, when performing halogenation experiments, care should be taken to evaluate the possible influence of buffers.

Conflicts of interest

There are no conflicts of interest to declare.

Acknowledgements

The authors thank Drs. Keith Reber and Kathryn Kautzman (Towson University) for fruitful discussions related to this manuscript. The authors also acknowledge the anonymous reviewers for their insightful comments. Funding from the U.S. National Science Foundation (CBET-1651536), the American Chemical Society Petroleum Research Fund (Grant 54560-UNI4), Towson University's Office of Undergraduate Research, and the Fisher College of Science and Mathematics (including a Fisher Endowed Professorship to J. D. S.) is gratefully acknowledged. Any opinions, findings, and conclusions or recommendations expressed herein are those of the authors and do not necessarily reflect the views of the National Science Foundation or of the American Chemical Society Petroleum Research Fund.

References

1 J. C. Crittenden, R. R. Trussell, D. W. Hand, K. J. Howe and G. Tchobanoglous, *Water Treatment Principles and Design*, Wiley, Hoboken, NJ, 2005.
2 G. Tchobanoglous, H. D. Stensel, R. Tsuchihashi, F. Burton, M. Abu-Orf, G. Bowden and W. Pfrang, *Wastewater Engineering: Treatment and Resource Recovery*, McGraw Hill Education, New York, 5th edn, 2014.
3 Black & Veatch Corporation, *White's Handbook of Chlorination and Alternative Disinfectants*, Wiley, Hoboken, NJ, 5th edn, 2010.
4 M. Deborde and U. von Gunten, *Water Res.*, 2008, **42**, 13–51.
5 J. C. Morris, *J. Phys. Chem.*, 1966, **70**, 3798–3805.
6 M. W. Beach and D. W. Margerum, *Inorg. Chem.*, 1990, **29**, 1225–1232.
7 R. Connick and Y.-T. Chia, *J. Am. Chem. Soc.*, 1959, **81**, 1280–1284.
8 W. A. Roth, *Z. Phys. Chem., Abt. A*, 1929, **145**, 289–297.

9 M. Reinhard, G. D. Redden and E. A. Voudrias, *Water Chlorination: Environmental Impact and Health Effects*, ed. R. L. Jolley, et al., Ann Arbor Science, Ann Arbor, MI, 1990, pp. 859–870.
10 E. A. Voudrias and M. Reinhard, *Environ. Sci. Technol.*, 1988, **22**, 1049–1056.
11 E. A. Voudrias and M. Reinhard, *Environ. Sci. Technol.*, 1988, **22**, 1056–1062.
12 J. D. Sivey and A. L. Roberts, *Environ. Sci. Technol.*, 2012, **46**, 2141–2147.
13 S. S. Lau, S. M. Abraham and A. L. Roberts, *Environ. Sci. Technol.*, 2016, **50**, 13291–13298.
14 M.-Q. Cai, L. Feng, J. Jiang, F. Qi and L.-Q. Zhang, *Water Res.*, 2013, **47**, 2830–2842.
15 M. Soufan, M. Deborde, A. Delmont and B. Legube, *Water Res.*, 2013, **47**, 5076–5087.
16 H. Cheng, D. Song, Y. Chang, H. Liu and J. Qu, *Chemosphere*, 2015, **141**, 282–289.
17 A. Bard, R. Pearson and J. Jordan, *Standard Potentials in Aqueous Solution*, Marcel Dekker, New York, 1985.
18 U. Pinkernell and U. von Gunten, *Environ. Sci. Technol.*, 2001, **35**, 2525–2531.
19 W. R. Haag and J. Hoigne, *Environ. Sci. Technol.*, 1983, **17**, 261–267.
20 T. P. Bonacquisti, *Toxicology*, 2006, **221**, 145–148.
21 A. Bousher, P. Brimblecombe and D. Midgley, *Water Res.*, 1989, **23**, 1049–1058.
22 T. W. Trofe, G. W. Inman and J. D. Johnson, *Environ. Sci. Technol.*, 1980, **14**, 544–549.
23 M. Gazda, L. E. Dejarme, T. K. Choudhury, R. G. Cooks and D. W. Margerum, *Environ. Sci. Technol.*, 1993, **27**, 557–561.
24 P. Westerhoff, M. Siddiqui, J. Debroux, W. Zhai, K. Ozekin and G. Amy, in *Critical Issues in Water and Wastewater Treatment: Proceedings of the 1994 National Conference on Environmental Engineering*, ed. J. N. Ryan and M. Edwards, American Society of Civil Engineers, New York, 1994, pp. 670–677.
25 D. Andreasen and W. Fleck, *Hydrogeol. J.*, 1997, **5**, 17–26.
26 A. D. Werner, M. Bakker, V. E. A. Post, A. Vandenbohede, C. Lu, B. Ataie-Ashtiani, C. T. Simmons and D. A. Barry, *Adv. Water Resour.*, 2013, **51**, 3–26.
27 J. S. Harkness, G. S. Dwyer, N. R. Warner, K. M. Parker, W. A. Mitch and A. Vengosh, *Environ. Sci. Technol.*, 2015, **49**, 1955–1963.
28 N. R. Warner, C. A. Christie, R. B. Jackson and A. Vengosh, *Environ. Sci. Technol.*, 2013, **47**, 11849–11857.
29 J. M. Wilson and J. M. Van Briesen, *Environ. Sci. Technol.*, 2013, **47**, 12575–12582.
30 M. L. Hladik, M. J. Focazio and M. Engle, *Sci. Total Environ.*, 2014, **466**, 1085–1093.
31 M. Eigen and K. Kustin, *J. Am. Chem. Soc.*, 1962, **84**, 1355–1361.
32 M. B. Heeb, J. Criquet, S. Zimmermann-Steffens and U. von Gunten, *Water Res.*, 2014, **48**, 15–42.
33 H. A. Liebhafsky, *J. Am. Chem. Soc.*, 1934, **56**, 1500–1505.
34 Q. Liu and D. W. Margerum, *Environ. Sci. Technol.*, 2001, **35**, 1127–1133.
35 J. D. Sivey, J. S. Arey, P. R. Tentscher and A. L. Roberts, *Environ. Sci. Technol.*, 2013, **47**, 1330–1338.
36 J. D. Sivey, C. E. McCullough and A. L. Roberts, *Environ. Sci. Technol.*, 2010, **44**, 3357–3362.
37 J. D. Sivey, M. A. Bickley and D. A. Victor, *Environ. Sci. Technol.*, 2015, **49**, 4937–4945.
38 *Handbook of Chemistry and Physics*, ed. D. Lide, CRC Press, Boca Raton, 1996.
39 P. Westerhoff, P. Chao and H. Mash, *Water Res.*, 2004, **38**, 1502–1513.
40 J. Hanna, W. Johnson, R. Quezada, M. Wilson and L. Xiao-Qiao, *Environ. Sci. Technol.*, 1991, **25**, 1160–1164.
41 T. A. Ternes, *Water Res.*, 1998, **32**, 3245–3260.
42 J. O. Miners, *Clin. Pharmacokinet.*, 1989, **17**, 327–344.
43 C. R. Macpherson, M. D. Milne and B. M. Evans, *Br. J. Pharmacol. Chemother.*, 1955, **10**, 484–489.
44 C. J. Needs and P. M. Brooks, *Clin. Pharmacokinet.*, 1985, **10**, 164–177.
45 H.-B. Lee, T. E. Peart and M. L. Svoboda, *J. Chromatogr. A*, 2005, **1094**, 122–129.
46 T. Heberer, *J. Hydrol.*, 2002, **266**, 175–189.
47 C. Hignite and D. L. Azarnoff, *Life Sci.*, 1977, **20**, 337–341.
48 D. N. Bulloch, E. D. Nelson, S. A. Carr, C. R. Wissman, J. L. Armstrong, D. Schlenk and C. K. Larive, *Environ. Sci. Technol.*, 2015, **49**, 2044–2051.
49 B. Kasprzyk-Hordern, R. M. Dinsdale and A. J. Guwy, *Talanta*, 2008, **74**, 1299–1312.
50 Y. Pan and X. Zhang, *Environ. Sci. Technol.*, 2013, **47**, 1265–1273.
51 J. B. Quintana, R. Rodil, P. López-Mahía, S. Muniategui-Lorenzo and D. Prada-Rodríguez, *Water Res.*, 2010, **44**, 243–255.
52 Y. Pan, Y. Wang, A. Li, B. Xu, Q. Xian, C. Shuang, P. Shi and Q. Zhou, *Water Res.*, 2017, **112**, 129–136.
53 M. Yang and X. Zhang, *Trends Environ. Anal. Chem.*, 2016, **10**, 24–34.
54 G. Ding, X. Zhang, M. Yang and Y. Pan, *Water Res.*, 2013, **47**, 2710–2718.
55 J. Liu and X. Zhang, *Water Res.*, 2014, **65**, 64–72.
56 M. J. Plewa, E. D. Wagner, S. D. Richardson, A. D. Thruston, Y.-T. Woo and A. B. McKague, *Environ. Sci. Technol.*, 2004, **38**, 4713–4722.
57 S. D. Richardson, M. J. Plewa, E. D. Wagner, R. Schoeny and D. M. DeMarini, *Mutat. Res.*, 2007, **636**, 178–242.
58 S. Echigo, S. Itoh, T. Natsui, T. Araki and R. Ando, *Water Sci. Technol.*, 2004, **50**, 321–328.
59 Y. Komaki, J. Pals, E. D. Wagner, B. J. Mariñas and M. J. Plewa, *Environ. Sci. Technol.*, 2009, **43**, 8437–8442.
60 *Standard Methods for the Examination of Water and Wastewater*, ed. E. W. Rice, R. B. Baird, L. S. Clesceri and A. D. Eaton, American Public Health Association, American Water Works Association, Water Environment Federation, Washington, D.C., 2012.
61 W. Prütz, *Arch. Biochem. Biophys.*, 1998, **357**, 265–273.
62 D. C. Harris, *Quantitative Chemical Analysis*, W. H. Freeman, New York, 8th edn, 2010.

63 H. Gallard and U. von Gunten, *Environ. Sci. Technol.*, 2002, **36**, 884–890.
64 R. Schwarzenbach, P. Gschwend and D. Imboden, *Environmental Organic Chemistry*, John Wiley & Sons, Hoboken, NJ, 2nd edn, 2003.
65 J. D. Sivey, M. A. Bickley and D. A. Victor, in *Recent Advances in Disinfection By-Products*, American Chemical Society, Washington, DC, 2015, pp. 251–269.
66 M. C. Dodd and C.-H. Huang, *Water Res.*, 2007, **41**, 647–655.
67 P. Wang, Y.-L. He and C.-H. Huang, *Water Res.*, 2011, **45**, 1838–1846.
68 H. Gallard, F. Pellizzari, J. P. Croue and B. Legube, *Water Res.*, 2003, **37**, 2883–2892.
69 *ACD/ChemSketch v. 2016.2*, Advanced Chemistry Development, Inc., 2016.
70 Z. Wu, K. Guo, J. Fang, X. Yang, H. Xiao, S. Hou, X. Kong, C. Shang, X. Yang, F. Meng and L. Chen, *Water Res.*, 2017, **126**, 351–360.
71 O. Tee, M. Paventi and J. Bennett, *J. Am. Chem. Soc.*, 1989, **111**, 2233–2240.
72 Z. Jia, D. W. Margerum and J. S. Francisco, *Inorg. Chem.*, 2000, **39**, 2614–2620.
73 N. Bunce and D. D. Tanner, *J. Am. Chem. Soc.*, 1969, **91**, 6096–6102.
74 N. Bunce and L. Urban, *Can. J. Chem.*, 1971, **49**, 821–827.
75 P. B. D. De la Mare, *Electrophilic halogenation: Reaction pathways involving attack by electrophilic halogens on unsaturated compounds*, Cambridge University Press, Cambridge, 1976.
76 Z. Zhou, A. Jaaskelainen and T. Vuorinen, *J. Pulp Pap. Sci.*, 2008, **34**, 212.
77 F. E. Scully and J. Hoigné, *Chemosphere*, 1987, **16**, 681–694.
78 G. Hua and D. A. Reckhow, *Water Res.*, 2012, **46**, 4208–4216.
79 R. Larson and E. Weber, *Reaction Mechanisms in Environmental Organic Chemistry*, Lewis Publishers, Boca Raton, 1994.
80 X. Zhu and X. Zhang, *Water Res.*, 2016, **96**, 166–176.
81 H. Gallard and U. von Gunten, *Water Res.*, 2002, **36**, 65–74.
82 E. E. Huling and T. C. Hollocher, *Science*, 1972, **176**, 288–290.
83 S. S. Kaushal, P. M. Groffman, G. E. Likens, K. T. Belt, W. P. Stack, V. R. Kelly, L. E. Band and G. T. Fisher, *Proc. Natl. Acad. Sci. U. S. A.*, 2005, **102**, 13517–13520.
84 V. R. Kelly, G. M. Lovett, K. C. Weathers, S. E. G. Findlay, D. L. Strayer, D. J. Burns and G. E. Likens, *Environ. Sci. Technol.*, 2008, **42**, 410–415.
85 S. R. Corsi, D. J. Graczyk, S. W. Geis, N. L. Booth and K. D. Richards, *Environ. Sci. Technol.*, 2010, **44**, 7376–7382.
86 T. Oki and S. Kanae, *Science*, 2006, **313**, 1068–1072.
87 J. M. Wilson and J. M. VanBriesen, *Environ. Pract.*, 2012, **14**, 288–300.
88 M. L. Hladik, M. Focazio and M. Engle, *Sci. Total Environ.*, 2014, **466–467**, 1085–1093.
89 K. M. Parker, T. Zeng, J. Harkness, A. Vengosh and W. A. Mitch, *Environ. Sci. Technol.*, 2014, **48**, 11161–11169.
90 G. Tchobanoglous, F. L. Burton and H. D. Stensel, *Wastewater Engineering: Treatment and Reuse*, McGraw-Hill, Boston, 2003.
91 J. Parinet, S. Tabaries, B. Coulomb, L. Vassalo and J.-L. Boudenne, *Water Res.*, 2012, **46**, 828–836.
92 T. Manasfi, M. De Méo, B. Coulomb, C. Di Giorgio and J.-L. Boudenne, *Environ. Int.*, 2016, **88**, 94–102.
93 B. Werschkun, S. Banerji, O. C. Basurko, M. David, F. Fuhr, S. Gollasch, T. Grummt, M. Haarich, A. N. Jha and S. Kacan, *Chemosphere*, 2014, **112**, 256–266.
94 A. D. Shah, Z.-Q. Liu, E. Salhi, T. Höfer, B. Werschkun and U. von Gunten, *Environ. Sci.: Water Res. Technol.*, 2015, **1**, 465–480.
95 J. Le Roux, N. Nada, M. T. Khan and J.-P. Croué, *Desalination*, 2015, **359**, 141–148.
96 E. Agus, N. Voutchkov and D. L. Sedlak, *Desalination*, 2009, **237**, 214–237.
97 D. Kim, G. L. Amy and T. Karanfil, *Water Res.*, 2015, **81**, 343–355.
98 R. Padhi, M. Sowmya, A. Mohanty, S. Bramha and K. Satpathy, *Water Environ. Res.*, 2012, **84**, 2003–2009.
99 V. F. Ximenes, N. H. Morgon and A. R. de Souza, *J. Inorg. Biochem.*, 2015, **146**, 61–68.

