SUPPORTING INFORMATION

Contributions of BrCl, Br_2, BrOCl, Br_2O, and HOBr to regiospecific bromination rates of anisole and bromoanisoles in aqueous solution

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33 pages, 17 figures, and 17 tables

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Speciation Diagrams for Aqueous Free Bromine

A simplified speciation diagram for free bromine (representative of the solution conditions employed for several of the reactors herein) is shown in **Figure S1**.

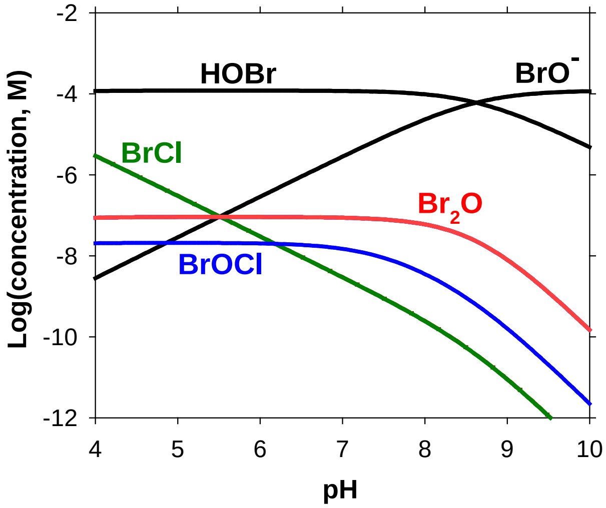


Figure S1. Example speciation diagram for a solution of free bromine at 20 °C. Composition: $[Br(I)]_{tot} = 1.2 \times 10^{-4}$ M, $[HOCl]_{tot} = 5.0 \times 10^{-4}$ M, [NaCl] = 0.010 M, ionic strength = 0.10 M (achieved via addition of 0.090 M $NaNO_3$). For clarity, additional anionic free bromine species (e.g., $BrCl_2^-$) are omitted (see discussion below).

Six free bromine species (HOBr, BrO^-, Br_2, BrCl, BrOCl, Br_2O) are described in eqs 2 – 6 of the main text. Depending on solution conditions, three additional species ($BrCl_2^-$, Br_2Cl^-, and Br_3^-) and can also form in solutions of free bromine. For example, $BrCl_2^-$ can exist in equilibrium with BrCl (**Figure S2A**).

$$\mathbf{BrCl(aq) + Cl^- \rightleftharpoons BrCl_2^-} \qquad \text{(S1)}$$
$$(\log K_{S1} = 0.58, 25\ °C, \text{ref } 1)$$

When unoxidized bromide coexists with free bromine, Br_2 can form (eq 3, main text) along with Br_2Cl^- and Br_3^-:

$$\mathbf{Br_2(aq) + Cl^- \rightleftharpoons Br_2Cl^-} \qquad \text{(S2)}$$
$$(\log K_{S2} = 0.11, 25\ °C, \text{ref } 1)$$

$$\mathbf{Br_2(aq) + Br^- \rightleftharpoons Br_3^-} \qquad \text{(S3)}$$
$$(\log K_{S3} = 1.21, 25\ °C, \text{ref } 2)$$

An example speciation diagram of free bromine in the presence of unoxidized bromide is shown in **Figure S2B**.

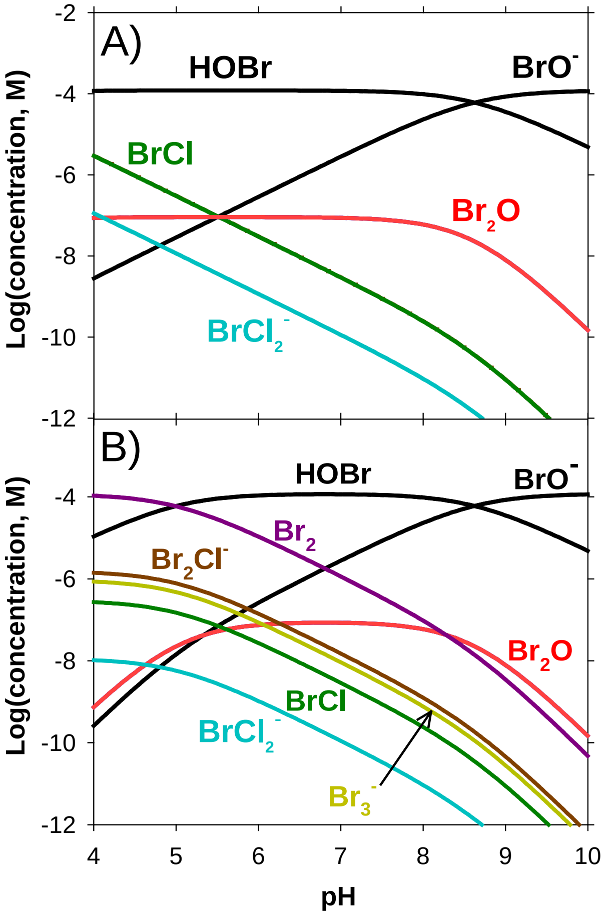


Figure S2. Aqueous free bromine speciation diagrams at 20 °C in the absence (**A**) and presence (**B**) of excess (unoxidized) bromide. Frame A: $[Br(I)]_{tot}$ = 1.2 x 10^{-4} M, $[HOCl]_{tot}$ = 0 M, [NaCl] = 0.010 M. Frame B: $[Br(I)]_{tot}$ = 1.2 x 10^{-4} M, $[HOCl]_{tot}$ = 0 M, [NaCl] = 0.010 M, [NaBr] = 5.0 x 10^{-4} M. Both frames assume an ionic strength of 0.10 M (achieved via addition of 0.090 M $NaNO_3$).

Due to their formal negative charge, $BrCl_2^-$, Br_2Cl^-, and Br_3^- are anticipated to be rather unreactive electrophiles (relative to neutral species such as BrCl, Br_2, BrOCl, and Br_2O). Indeed, as discussed in the main text and below, model results assuming BrCl, Br_2, BrOCl, Br_2O, and HOBr as the active brominating agents agree well with measured kinetic data, suggesting that additional bromine species (e.g., Br_3^-, Br_2Cl^-, and $BrCl_2^-$) do not appreciably influence observed bromination rates. Nevertheless, to improve accuracy when calculating concentrations of individual brominating agents, $BrCl_2^-$, Br_2Cl^-, and Br_3^- were included in the free bromine mass balance equation employed herein (eq S4):

$$\mathbf{[Br(I)]_{tot} = [HOBr] + [OBr^-] + [BrCl] + [Br_2] + [BrOCl] + 2[Br_2O] + [Br_3^-] + [Br_2Cl^-] + [BrCl_2^-]} \quad \text{(S4)}$$

Although the oxidation state of both bromine atoms in Br_2 is 0, this molecule can behave as Br^{-I}–Br^{+I} when participating in electrophilic aromatic substitution reactions and when hydrolyzing to yield HOBr + Br^- + H^+ (eq 3, main text). Accordingly, it is appropriate to consider Br_2 as a constituent of free bromine. For additional discussions of free bromine speciation, including a summary of alternative pathways capable of generating the aforementioned bromine species, we recommend the review by Heeb *et al.*[3]

Reagents

All aqueous solutions were prepared using deionized water further purified to 18 MΩ•cm resistivity with a Nanopure Analytical UV system (Thermo Scientific). Stock solutions of NaOCl (~6% w/w, Fisher Scientific) were standardized colorimetrically (via iodometric titration).[4] Working solutions of free chlorine were prepared fresh daily by diluting NaOCl stock with 18 MΩ•cm water and were standardized spectrophotometrically.[5] Solutions of free bromine were prepared *in situ* via oxidation of bromide by free chlorine. Free bromine can undergo slow disproportionation.[6] Rates of disproportionation are greater for HOBr than BrO^-.[6] To minimize the influence of disproportionation, total reaction times were ≤60 min for reactions conducted at pH < 8.8; reaction times were ≤6.2 h for reactions conducted at pH ≥ 8.8. Calculated decreases in $[Br(I)]_{tot}$ due to disproportionation (including general-base catalysis by carbonate)[6] during the course of reactions were <1% for most (<3% for all) solution conditions employed herein.

Additional reagents are compiled in **Table S1**. All reagents were used as received.

Table S1. List of Reagents and Their Associated Purity and Vendor Information

Reagent	Purity	Vendor
2,4-dibromoanisole	98%	Acros Organics
2,6-dibromoanisole	95+%	Ark Pharm
2-bromoanisole	97%	Sigma-Aldrich
2-chlorobenzonitrile	99%	Acros Organic
4-bromoanisole	99%	Sigma-Aldrich
anisole	99.7%	Sigma-Aldrich
methanol	99.9%	Fisher Scientific
nitric acid	70%	Fisher Scientific
sodium bicarbonate	99.7+%	Acros Organics
sodium bromide	99.5%	Acros Organics
sodium chloride	99.999%	Acros Organics
sodium hydroxide (aqueous)	50%	Ricca Chemical Company
sodium hypochlorite (aqueous)	5.65-6%	Fisher Scientific
sodium nitrate	>99%	Acros
sodium tetraborate decahydrate	99.5%	Acros Organics
sodium thiosulfate	≥98%	Fisher Scientific
toluene	99.9%	Fisher Scientific

Reactor Compositions and Measured Rate Constants: Bromination of Anisole

Solution compositions and pseudo-first-order rate constants for bromination of anisole as a function of pH (**Table S2**), added bromide (**Table S3**), added sodium chloride (**Table S4**), free chlorine (**Table S5**), and added *excess* bromide (**Table S6**) are compiled below.

Table S2. Pseudo-First-Order Rate Constants for *Para* ($k_{I,obs}$) and *Ortho* ($k_{II,obs}$) Bromination of Anisole as a Function of pH at 20 °C[a]

pH	**log ($k_{I,obs}$ s^{-1})**	**log ($k_{II,obs}$ s^{-1})**
5.33	-1.085	-1.906
5.52	-1.236	-2.053
5.67	-1.372	-2.185
5.78	-1.496	-2.301
5.86	-1.570	-2.380
5.97	-1.696	-2.524
6.08	-1.784	-2.594
6.21	-1.952	-2.766
6.32	-2.005	-2.808
6.63	-2.249	-3.094
6.83	-2.463	-3.336
7.09	-2.711	-3.572
7.25	-2.879	-3.805
7.42	-3.011	-3.961
7.73	-3.290	-4.281
7.87	-3.493	-4.477
8.18	-3.831	-4.896
8.38	-4.082	-5.173
8.56	-4.312	-5.389
8.73	-4.581	-5.656
8.87	-4.808	-5.947
8.93	-4.878	nq[b]
9.05	-5.075	-6.247
9.11	-5.160	nq
9.24	-5.385	-6.612
9.29	-5.489	nq
9.45	-5.720	nq
9.65	-6.116	nq
9.84	-6.480	nq

[a] All reactors contained: $[NaBr]_o$ = 1.2×10^{-4} M, $[HOCl]_{tot,o}$ = 5.7×10^{-4} M, bicarbonate (20 mM) or borate (20 mM) as a pH buffer, $[anisole]_o$ = 10 µM, [NaCl] = 9.8 mM, $[NaNO_3]$ = 88 mM.

[b] nq denotes not quantified

Table S3. Pseudo-First-Order Rate Constants for *Para* ($k_{I,obs}$) and *Ortho* ($k_{II,obs}$) Bromination of Anisole as a Function of Added Bromide in the Presence of Excess Free Chlorine at 20 °C[a]

$[NaBr]_o$ (M)	**pH**	**log ($k_{I,obs}$ s^{-1})**	**log ($k_{II,obs}$ s^{-1})**
2.74×10^{-4}	8.80	-4.359	-5.487
3.12×10^{-4}	8.81	-4.296	-5.449
3.51×10^{-4}	8.81	-4.243	-5.386
3.90×10^{-4}	8.81	-4.172	-5.364
4.28×10^{-4}	8.83	-4.121	-5.289
2.66×10^{-4}	9.40	-5.180	-6.381
3.04×10^{-4}	9.40	-5.138	-6.350
3.41×10^{-4}	9.42	-5.065	-6.310
3.79×10^{-4}	9.40	-5.018	-6.256
4.16×10^{-4}	9.42	-4.943	-6.189

[a] All reactors contained: $[HOCl]_{tot,o}$ = 5.6×10^{-4} M, borate (20 mM) as a pH buffer, $[anisole]_o$ = 20 µM, [NaCl] = 2.9 mM, $[NaNO_3]$ = 95 mM.

Table S4. Pseudo-First-Order Rate Constants for *Para* ($k_{I,obs}$) and *Ortho* ($k_{II,obs}$) Bromination of Anisole as a Function of Chloride Concentration at 20 °C[a]

[NaCl] (M)	**log ($k_{I,obs}$ s^{-1})**	**log ($k_{II,obs}$ s^{-1})**
5.97×10^{-3}	-2.567	-3.360
1.39×10^{-2}	-2.287	-3.034
2.19×10^{-2}	-2.138	-2.877
2.98×10^{-2}	-2.027	-2.763

[a] All reactors contained: $[NaBr]_o$ = 1.1×10^{-4} M, carbonate (20 mM) as a pH buffer, pH = 6.8, $[anisole]_o$ = 10 µM, $[HOCl]_{tot,o}$ = 5.1×10^{-4} M, $[NaNO_3]$ + [NaCl] = 100 mM.

Table S5. Pseudo-First-Order Rate Constants for *Para* ($k_{I,obs}$) and *Ortho* ($k_{II,obs}$) Bromination of Anisole as a Function of Excess Free Chlorine at 20 °C[a]

$[HOCl]_{tot,o}$ (M)	pH	log ($k_{I,obs}$ s^{-1})	log ($k_{II,obs}$ s^{-1})
5.88×10^{-4}	8.48	-4.112	-5.149
6.87×10^{-4}	8.49	-4.079	-5.123
7.84×10^{-4}	8.49	-4.043	-5.103
8.82×10^{-4}	8.50	-4.012	-5.096
9.81×10^{-4}	8.50	-3.976	-5.068

[a] All reactors contained: $[NaBr]_o = 2.30 \times 10^{-4}$ M, borate (20 mM) as a pH buffer, $[anisole]_o$ = 19 µM, [NaCl] = 2.9 mM, $[NaNO_3]$ = 93 mM.

Table S6. Pseudo-First-Order Rate Constants for *Para* ($k_{I,obs}$) and *Ortho* ($k_{II,obs}$) Bromination of Anisole as a Function of Excess Bromide at 20 °C[a]

$[NaBr]_o$ (M)	pH	log ($k_{I,obs}$ s^{-1})	log ($k_{II,obs}$ s^{-1})
1.97×10^{-4}	7.33	-2.756	-4.144
2.96×10^{-4}	7.29	-2.292	-3.894
3.94×10^{-4}	7.28	-2.155	-3.745
4.90×10^{-4}	7.32	-2.036	-3.666
5.88×10^{-4}	7.34	-1.987	-3.601

[a] All reactors contained: $[HOCl]_{tot,o} = 1.2 \times 10^{-4}$ M, borate (20 mM) as a pH buffer, $[anisole]_o$ = 10 µM, $[NaNO_3]$ = 98 mM, no added NaCl.

Reactor Compositions and Measured Rate Constants: Bromination of 4-Bromoanisole

Solution compositions and pseudo-first-order rate constants for bromination of 4-bromoanisole as a function of pH (**Table S7**), added bromide (**Table S8**), added free chlorine (**Table S9**), and added *excess* bromide (**Table S10**) are compiled below.

Table S7. Pseudo-First-Order Rate Constants for Bromination of 4-Bromoanisole to give 2,4-Dibromoanisole ($k_{\mathrm{III,obs}}$) as a Function of pH at 20 °C[a]

pH	log ($k_{\mathrm{III,obs}}$ s^{-1})
5.96	-4.148
6.01	-4.248
6.16	-4.402
6.42	-4.642
6.66	-4.887
6.93	-5.116
7.42	-5.631

[a] All reactors contained: $[NaBr]_o$ = 5.5 x10^{-4} M, $[HOCl]_{tot,o}$ = 5.7 x10^{-4} M, bicarbonate (20 mM) as a pH buffer, $[\text{4-bromoanisole}]_o$ = 30 µM, [NaCl] = 2.8 mM, $[NaNO_3]$ = 92 mM.

[b] nq denotes not quantified

Table S8. Pseudo-First-Order Rate Constants for Bromination of 4-Bromoanisole to give 2,4-Dibromoanisole ($k_{\mathrm{III,obs}}$) as a Function of Added Bromide in the Presence of Excess Free Chlorine at 20 °C[a]

$[NaBr]_o$ (M)	$[HOCl]_{tot,o}$ (M)	pH	log ($k_{\mathrm{III,obs}}$ s^{-1})
6.96 x10^{-4}	8.79 x10^{-4}	7.80	-5.712
9.96 x10^{-4}	1.16 x10^{-3}	7.83	-5.484
1.30 x10^{-3}	1.45 x10^{-3}	7.85	-5.244
1.60 x10^{-3}	1.73 x10^{-3}	7.88	-5.134
1.90 x10^{-3}	2.00 x10^{-3}	7.89	-4.951

[a] All reactors contained: borate (20 mM) as a pH buffer, $[\text{4-bromoanisole}]_o$ = 59 µM, $[NaNO_3]$ = 49 mM, no added NaCl. The amount of added free chlorine was varied to maintain a uniform amount of excess free chlorine ($[HOCl]_{tot,o}$ – $[NaBr]_o$) in each reactor.

Table S9. Pseudo-First-Order Rate Constants for Bromination of 4-Bromoanisole to give 2,4-Dibromoanisole ($k_{\mathrm{III,obs}}$) as a Function of Excess Free Chlorine at 20 °C[a]

$[HOCl]_{tot,o}$ (M)	pH	log ($k_{\mathrm{III,obs}}$ s^{-1})
5.88 x10^{-4}	7.61	-5.899
6.87 x10^{-4}	7.58	-5.690
7.84 x10^{-4}	7.56	-5.584
8.82 x10^{-4}	7.54	-5.463
9.81 x10^{-4}	7.52	-5.389

[a] All reactors contained: $[NaBr]_o$ = 4.06 x10^{-4} M, borate (20 mM) as a pH buffer, $[\text{4-bromoanisole}]_o$ = 60 µM, $[NaNO_3]$ = 49 mM, no added NaCl.

Table S10. Pseudo-First-Order Rate Constants for Bromination of 4-Bromoanisole to give 2,4-Dibromoanisole ($k_{\mathrm{III,obs}}$) as a Function of Excess Bromide at 20 °C[a]

$[NaBr]_o$ (M)	pH	log ($k_{\mathrm{III,obs}}$ s^{-1})
7.11 x10^{-4}	6.89	-4.833
7.63 x10^{-4}	6.86	-4.749
8.12 x10^{-4}	6.87	-4.701
8.61 x10^{-4}	6.86	-4.660
9.13 x10^{-4}	6.88	-4.669

[a] All reactors contained: $[HOCl]_{tot,o}$ = 4.05 x10^{-4} M, bicarbonate (20 mM) as a pH buffer, $[\text{4-bromoanisole}]_o$ = 40 µM, $[NaNO_3]$ = 98 mM, no added NaCl.

Reactor Compositions and Measured Rate Constants: Bromination of 2-Bromoanisole

Solution compositions and pseudo-first-order rate constants for bromination of 2-bromoanisole as a function of pH (**Table S11**), added bromide (**Table S12**), added free chlorine (**Table S13**), and added *excess* bromide (**Table S14**) are compiled below.

Table S11. Pseudo-First-Order Rate Constants for Bromination of 2-Bromoanisole to give 2,4-Dibromoanisole ($k_{IV,obs}$) and 2,6-Dibromoanisole ($k_{V,obs}$) as a Function of pH at 20 °C[a]

pH	log ($k_{IV,obs}$ s^{-1})	log ($k_{V,obs}$ s^{-1})
5.97	-2.685	-4.809
6.34	-3.017	-5.165
6.64	-3.314	-5.416
6.87	-3.562	-5.699
7.04	-3.747	-5.883
7.26	-3.983	-6.134
7.48	-4.253	-6.452
7.64	-4.391	-6.516
7.86	-4.644	-6.855
7.98	-4.782	-6.887
8.15	-4.972	-7.136
8.38	-5.240	-7.817
8.60	-5.520	-7.592
8.77	-5.792	-8.121
8.98	-6.098	-8.363
9.32	-6.653	-8.800
9.48	-6.912	-8.851

[a] All reactors contained: $[NaBr]_o$ = 4.0 x10^{-4} M, $[HOCl]_{tot,o}$ = 5.0 x10^{-4} M, bicarbonate (20 mM) or borate (20 mM) as a pH buffer, $[\text{2-bromoanisole}]_o$ = 25 µM, [NaCl] = 9.7 mM, $[NaNO_3]$ = 87 mM.

Table S12. Pseudo-First-Order Rate Constants for Bromination of 2-Bromoanisole to give 2,4-Dibromoanisole ($k_{IV,obs}$) and 2,6-Dibromoanisole ($k_{V,obs}$) as a Function of Added Bromide in the Presence of Excess Free Chlorine at 20 °C[a]

$[NaBr]_o$ (M)	pH	log ($k_{IV,obs}$ s^{-1})	log ($k_{V,obs}$ s^{-1})
5.01 x10^{-4}	9.01	-6.262	-8.615
6.01 x10^{-4}	9.01	-6.169	nq[b]
7.01 x10^{-4}	9.02	-6.100	-8.511
8.01 x10^{-4}	9.02	-6.038	-8.467
9.01 x10^{-4}	9.03	-5.943	-8.407

[a] All reactors contained: $[HOCl]_{tot,o}$ = 1.10 x10^{-3} M, borate (20 mM) as a pH buffer, $[\text{2-bromoanisole}]_o$ = 20 µM, [NaCl] = 3.0 mM, $[NaNO_3]$ = 94 mM.

[b] nq denotes not quantified

Table S13. Pseudo-First-Order Rate Constants for Bromination of 2-Bromoanisole to give 2,4-Dibromoanisole ($k_{IV,obs}$) and 2,6-Dibromoanisole ($k_{V,obs}$) as a Function of Excess Free Chlorine at 20 °C[a]

$[HOCl]_{tot,o}$ (M)	pH	log ($k_{IV,obs}$ s^{-1})	log ($k_{V,obs}$ s^{-1})
6.50 x10^{-4}	7.28	-4.746	-6.961
7.50 x10^{-4}	7.35	-4.687	-7.091
8.50 x10^{-4}	7.30	-4.631	-6.927
1.00 x10^{-3}	7.38	-4.572	-6.721

[a] All reactors contained: $[NaBr]_o$ = 4.40 x10^{-4} M, bicarbonate (20 mM) as a pH buffer, $[\text{2-bromoanisole}]_o$ = 20 µM, no added NaCl, $[NaNO_3]$ = 94 mM.

Table S14. Pseudo-First-Order Rate Constants for Bromination of 2-Bromoanisole to give 2,4-Dibromoanisole ($k_{IV,obs}$) and 2,6-Dibromoanisole ($k_{V,obs}$) as a Function of Excess Bromide at 20 °C[a]

$[NaBr]_o$ (M)	**pH**	**log ($k_{IV,obs}$ s^{-1})**	**log ($k_{V,obs}$ s^{-1})**
5.51 $\times 10^{-4}$	6.87	-3.401	-6.527
6.50 $\times 10^{-4}$	6.88	-3.252	-6.547
7.51 $\times 10^{-4}$	6.85	-3.070	-6.449
8.51 $\times 10^{-4}$	6.90	-3.035	-6.434
1.00 $\times 10^{-3}$	6.88	-2.961	-6.416

[a] All reactors contained: $[HOCl]_{tot,o}$ = 4.40 $\times 10^{-4}$ M, bicarbonate (20 mM) as a pH buffer, $[2\text{-bromoanisole}]_o$ = 20 µM, $[NaNO_3]$ = 94 mM, no added NaCl.

GC-MS Method Details

Quantitation of parent compounds and brominated products was achieved via gas chromatography with a mass selective detector (GC-MS). Separations were achieved on a DB-5MS+DG column (Agilent, length = 30 m + 10 m DuraGuard, diameter = 0.250 mm, film thickness = 0.25 µm). Toluene samples (1.0 µL) were injected into an inlet (280 °C) operated in splitless mode. The initial oven temperature (80 °C) was held for 2 min, followed by a ramp at 5 °C/min to 125 °C (no hold) and a second ramp at 32 °C/min to 285 °C (no hold); the total analysis time was 16 min. The selected ion monitoring parameters are listed in **Table S15**.

Table S15. Details of GC-MS Selected Ion Monitoring Method

Analyte	*Retention time (min)*	*Quantitation Ion*	*Monitoring Ion*
anisole	5.20	108 $M^{+\bullet}$	none[a]
2-chlorobenzonitrile (internal standard)	10.13	137 $M^{+\bullet}$	102 $(M - CH_3)^+$
4-bromoanisole	10.81	186 $M^{+\bullet}$	171 $(M - CH_3)^+$
2-bromoanisole	10.95	186 $M^{+\bullet}$	171 $(M - CH_3)^+$
2,6-dibromoanisole	13.34	266 $M^{+\bullet}$	251 $(M - CH_3)^+$
2,4-dibromoanisole	14.07	266 $M^{+\bullet}$	251 $(M - CH_3)^+$
2,4,6-tribromoanisole	14.95	346[b] $M^{+\bullet}$	331 $(M - CH_3)^+$

[a] As appreciable levels of background ions (likely originating from the solvent toluene) were detected with mass-to-charge ratios identical to the major daughter ions of anisole, no monitoring ions were recorded for this analyte. Background ions did not, however, interfere with quantitation of the molecular ion (m/z = 108) of anisole.

[b] Ion with m/z = 346 corresponds to 2,4,6-tribromoanisole possessing two ^{79}Br isotopes and one ^{81}Br isotope. This ion was monitored to confirm that no detectable 2,4,6-tribromoanisole formed during the experiments described herein.

Example Time Courses

Representative time courses for the bromination of anisole (**Figure S3**), 4-bromoanisole (**Figure S4**), and 2-bromoanisole (**Figure S5**) are shown below.

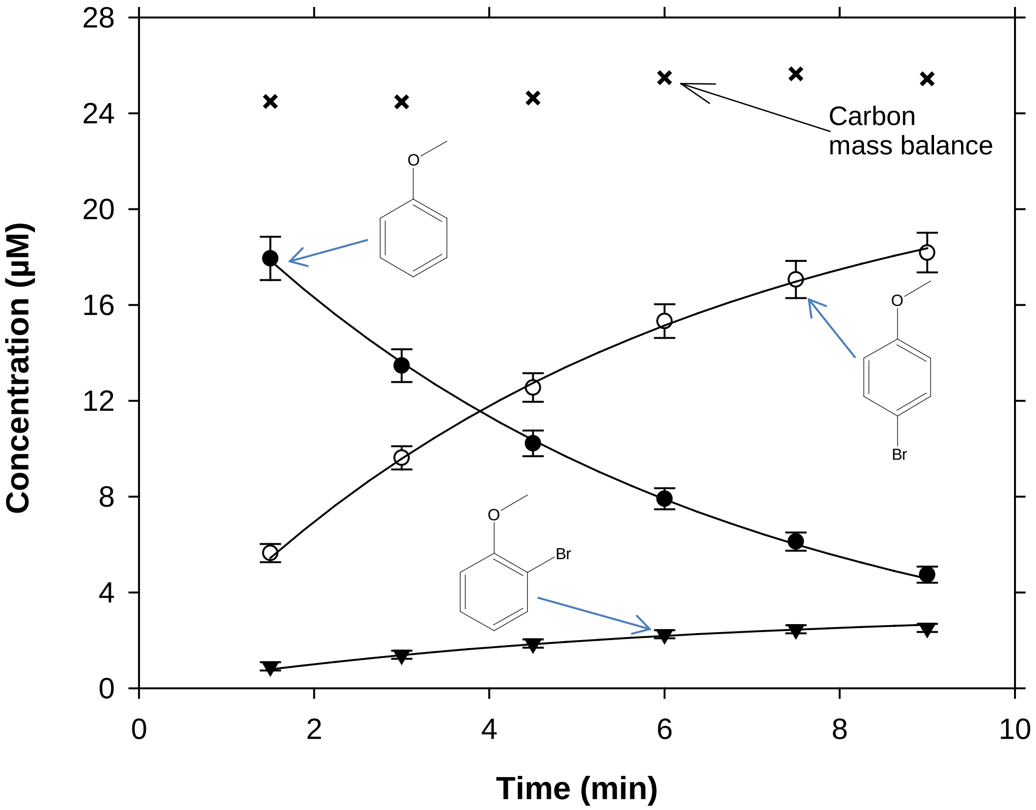


Figure S3. Example time course for the bromination of anisole (closed circles) to give 4-bromoanisole (open circles) and 2-bromoanisole (triangles). Carbon mass balance (X) calculated as [anisole] + [4-bromoanisole] + [2-bromoanisole]. Solid lines denote model fits (eqs 9 – 11 in main text) to the data. Error bars denote 95% confidence intervals. Conditions: $[NaBr]_o$ = 116 μM, $[HOCl]_{tot,o}$ = 652 μM, [NaCl] = 9.6 mM, $[NaNO_3]$ = 87 mM, pH = 6.85 (20 mM bicarbonate buffer), T = 20.0 °C.

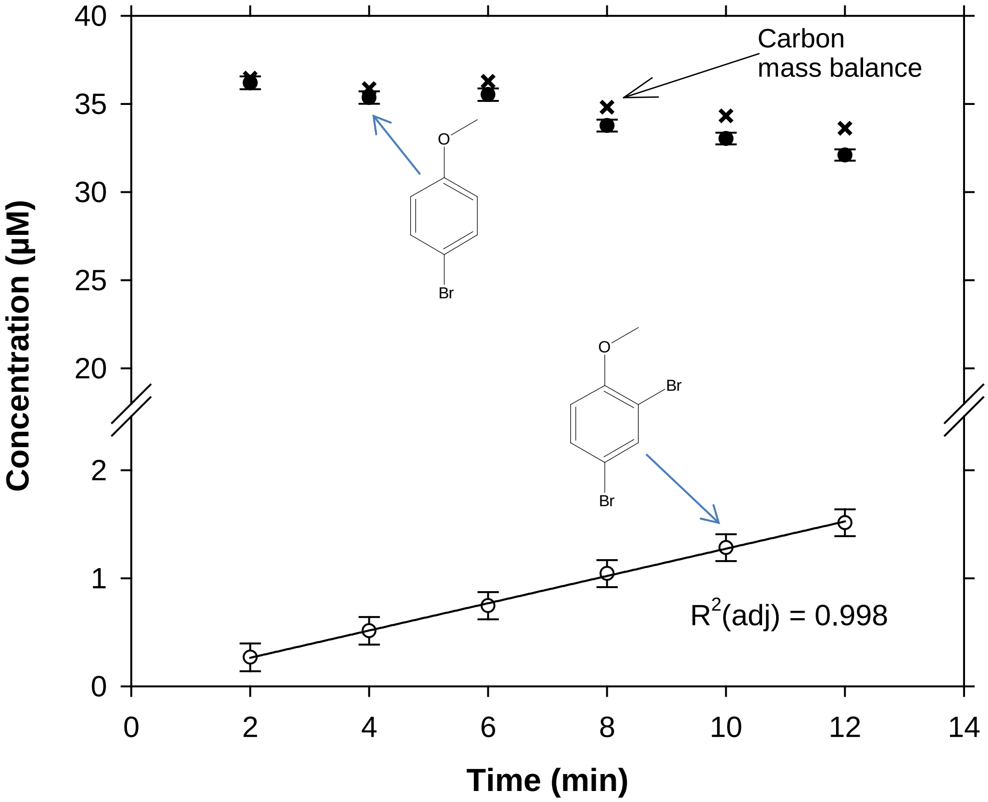


Figure S4. Example time course for the bromination of 4-bromoanisole (closed circles) to give 2,4-dibromoanisole (open circles). Carbon mass balance (X) calculated as [4-bromoanisole] + [2,4-dibromoanisole]. Solid line denotes linear fit to the data. Error bars denote 95% confidence intervals. Conditions: $[NaBr]_o$ = 550 µM, $[HOCl]_{tot,o}$ = 570 µM, [NaCl] = 2.8 mM, $[NaNO_3]$ = 92 mM, pH = 5.96 (20 mM bicarbonate buffer), T = 20.0 °C.

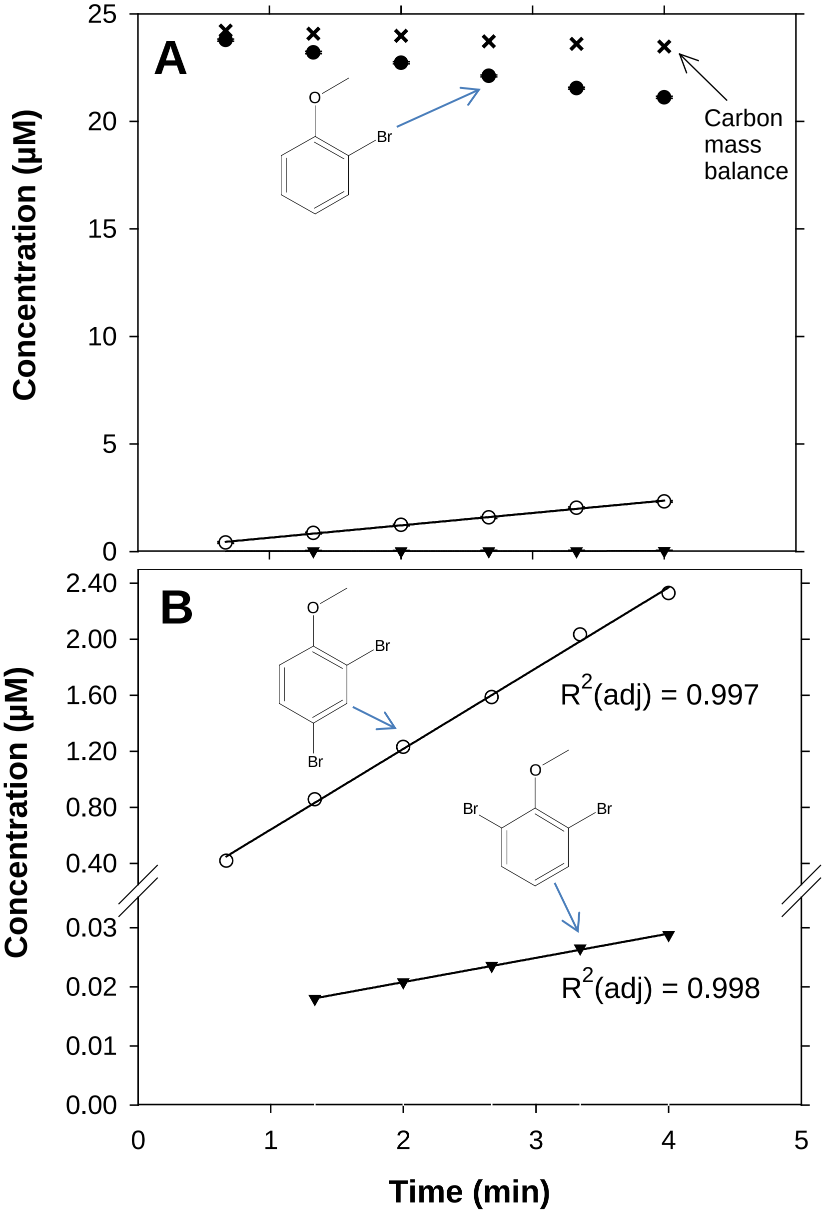


Figure S5. (**A**) Example time course for the bromination of 2-bromoanisole (closed circles) to give 2,4-dibromoanisole (open circles) and 2,6-dibromoanisole (triangles). Carbon mass balance (X) calculated as [2-bromoanisole] + [2,4-dibromoanisole] + [2,6-dibromoanisole]. Solid lines denote linear fits to the data. Error bars denote 95% confidence intervals (smaller than symbols when not shown). (**B**) Enlarged depiction of product formation data (identical data as in frame A). Conditions: $[NaBr]_o$ = 400 µM, $[HOCl]_{tot,o}$ = 500 µM, [NaCl] = 9.7 mM, $[NaNO_3]$ = 87 mM, pH = 6.34 (20 mM bicarbonate buffer), T = 20.0 °C.

Calculation of Second-Order Rate Constants

Second-order rate constants for each brominating agent/regioisomeric product pair were determined via nonlinear least-squares regression analysis of eq S5:

$$k_{\mathrm{obs}} = k_{\mathrm{BrCl}}[\mathrm{BrCl}] + k_{\mathrm{Br2}}[\mathrm{Br_2}] + k_{\mathrm{BrOCl}}[\mathrm{BrOCl}] + k_{\mathrm{Br2O}}[\mathrm{Br_2O}] + k_{\mathrm{HOBr}}[\mathrm{HOBr}] \qquad \text{(S5)}$$

where k_{obs}, a pseudo-first-order rate constant (s^{-1}), is equal to the sum of second-order rate constants (M^{-1} s^{-1}) multiplied by molar concentrations of each brominating agent. Concentrations of each brominating agent were calculated by simultaneously solving eqs 1 – 6 and eq S4. Most experiments herein were conducted at 0.1 M ionic strength. Accordingly, speciation calculations included activity coefficients calculated via the Davies equation.[7] That bromination rates were shown to be first-order in the concentration of anisole (the most reactive aromatic compound examined herein; see **Figure S8** below) suggests formation of brominating agents was not rate-limiting.

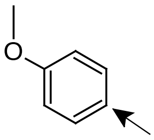
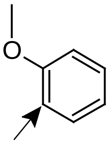
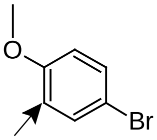
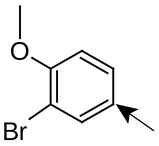
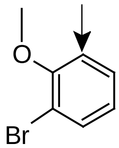
To afford robust calculations of second-order bromination rate constants, (regiospecific) reactivity data for anisole, 4-bromoanisole, and 2-bromoanisole were divided into bins (**Table S16**) according to which brominating agent was anticipated to predominate. The bin corresponding to BrCl typically included reactors amended with NaCl and adjusted to pH < 7 (noting that the concentration of BrCl is proportional to [Cl^-] and [H^+]; see eq 4 in the main text). For all reactors in the Br_2 bin, NaBr was added in excess of free chlorine to promote formation of Br_2(aq) via eq 3 (main text). The BrOCl bin included reactors in which the concentration of (excess) free chlorine was systematically varied (noting that BrOCl is proportional to [HOCl]; eq 6, main text). The Br_2O bin typically included reactors in which the concentration of HOBr was varied (noting that Br_2O is proportional to $[\mathrm{HOBr}]^2$; eq 5, main text); in these reactors, [HOBr] was adjusted by varying the amount of NaBr added in the presence of excess free chlorine.

Reactors similar to those assigned to the Br_2O bin can also be used to determine second-order rate constants for HOBr, particularly if [HOBr] is varied at pH > pK_a of HOBr, noting that the concentration of Br_2O decreases to a greater degree with increasing pH than does HOBr due to the second-order dependence of [Br_2O] on [HOBr].

During nonlinear regression analyses (performed via *Scientist 3.0*®, MicroMath®), second-order rate constants were fit iteratively in the order described in **Table S16**. In all cases, k_{Br2} was calculated using the Br_2 bin data and previously optimized values k_{BrCl}, k_{BrOCl}, k_{Br2O}, and k_{HOBr} as input. The results are shown in **Table 1** (main text).

Including a term for hypobromite (i.e., $k_{BrO-}[BrO^-]$) in eq S5 did not improve model fits. Indeed, the reactivity of hypobromite toward the parental anisoles examined herein was too small to quantify. Hypobromite was previously determined to be sufficiently unreactive toward dimethenamid[8] and *p*-xylene[9] so as to preclude determination of a second-order rate constant for this free bromine species. The presence of a formal negative charge on hypobromite, together with the requisite expulsion of a poor leaving group (O^{2-}) is anticipated to attenuate the electrophilicity of this free bromine species relative to the brominating agents included in eq S5. Previous studies of bromination of phenolic compounds and primary amines did, however, report second-order rate constants for reactions involving hypobromite (ref 3 and references therein). The increased nucleophilicity of phenols and primary amines (relative to anisoles) may explain their reactivity toward hypobromite, particularly in solutions at high pH.

Table S16. Bins Used When Performing Nonlinear Regression Analyses to Determine Second-Order Rate Constants[a]

Brominating Agent	k_{I} [b] 	k_{II} [c] 	k_{III} [d] 	k_{IV} [e] 	k_{V} [f] 
BrCl	Table S2 ($pH<7.0$ only)	Table S2 ($pH<6.1$ only)	Table S7	Table S11 ($pH<7.1$ only)	Table S11 ($pH<7.1$ only)
BrOCl	Table S2 ($8.0<pH<9.3$) + Table S3 ($pH\approx8.8$ only) + Table S5	Table S5[b]	Table S9	Table S13	Table S13
Br_2O		Table S3 ($pH\approx8.8$ only)	Table S8	Table S12	Table S12
HOBr	Table S2 ($9.2<pH<9.7$) + Table S3 ($pH\approx9.4$ only)	Table S3 ($pH\approx9.4$ only)	not quantified[g]	Table S11 ($pH>9.3$ only)	not quantified[g]
Br_2	Table S6	Table S6	Table S10	Table S14	Table S14

[a] Arrows denote site of bromination; see Scheme 1 (main text) for complete reaction pathway.

[b] Order of optimization: BrCl, BrOCl concurrent with Br_2O, HOBr, Br_2

[c] Order of optimization: BrCl, Br_2O, HOBr, BrOCl, Br_2

[d] Order of optimization: BrCl, BrOCl, Br_2O, Br_2

[e] Order of optimization: HOBr, Br_2O, BrOCl, BrCl, Br_2

[f] Order of optimization: BrCl, Br_2O, BrOCl, Br_2

[g] The contribution of HOBr to the overall regiospecific bromination rate was sufficiently small as to preclude calculation of k_{HOBr} based on our data sets.

Second-order rate constants for bromination of anisole by BrCl can also be determined from the slopes of k_{obs} versus $[Cl^-]$ plots (**Figure 1A**). As derived by Sivey *et al.*,[8] the slope of such plots is equal to $k_{BrCl}K_4[HOBr][H^+]$, where K_4 is the equilibrium constant for the formation of BrCl (eq 4, main text). Using the slopes reported in **Figure 1A**, $k_{\mathrm{I,BrCl}}$ and $k_{\mathrm{II,BrCl}}$ are calculated as $(6.4 \pm 0.5)\mathrm{x}10^5$ M^{-1} s^{-1} and $(1.22 \pm 0.14)\mathrm{x}10^5$ M^{-1} s^{-1}, respectively, where uncertainties denote 95% confidence intervals. These rate constants are in agreement with those reported in **Table 1** (main text).

Influence of Buffer Concentration on Bromination Rates

A previous investigation discovered evidence of buffer catalysis by phosphate during bromination of dimethenamid.[8] To avoid the potential catalytic effects of phosphate, the current work employed bicarbonate and borate as pH buffers. The concentration of bicarbonate and borate did not appreciably influence initial rates of 4-bromoanisole formation during reactions of anisole with free bromine (**Figure S6**).

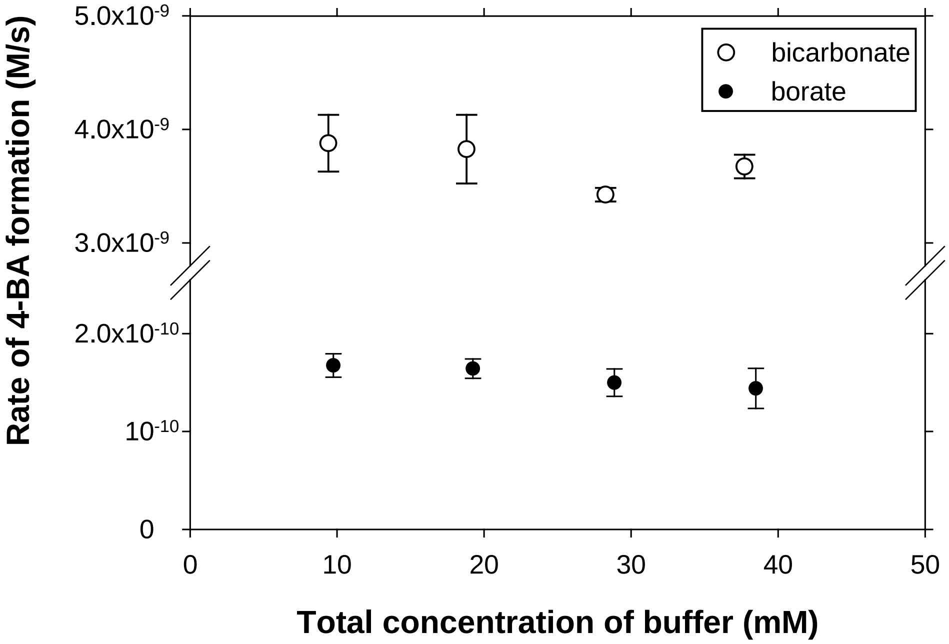


Figure S6. Initial rates of 4-bromoanisole (4-BA) formation (from the reaction of anisole with free bromine) as a function of buffer concentration: bicarbonate (open circles) and borate (filled circles). Uniform conditions: $[NaBr]_o$ = 120 µM, $[NaNO_3]$ = 90 mM, T = 20.0 °C. Bicarbonate conditions: $[HOCl]_{tot,o}$ = 560 µM, pH 7.35, $[anisole]_o$ = 8.8 µM. Borate conditions: $[HOCl]_{tot,o}$ = 550 µM, pH 8.95, $[anisole]_o$ = 9.6 µM.

Influence of Ionic Strength on Bromination Rates

Ionic strength can conceivably influence bromination rates of aromatic compounds either directly (e.g., by altering the stabilities of activated complexes in the rate-determining step[10]) or indirectly (e.g., by altering equilibrium concentrations of free bromine species). To assess the potential effects of ionic strength on the bromination reactions examined herein, initial rates of *para* bromination of anisole were measured as a function of $NaNO_3$ concentration (30 – 120 mM, **Figure S7**). Measured bromination rates did not differ significantly across the examined range of ionic strengths. Nevertheless, ionic strengths for all other experiments performed herein were fixed such that concentrations of added $NaNO_3$ and NaCl typically totaled 100 mM.

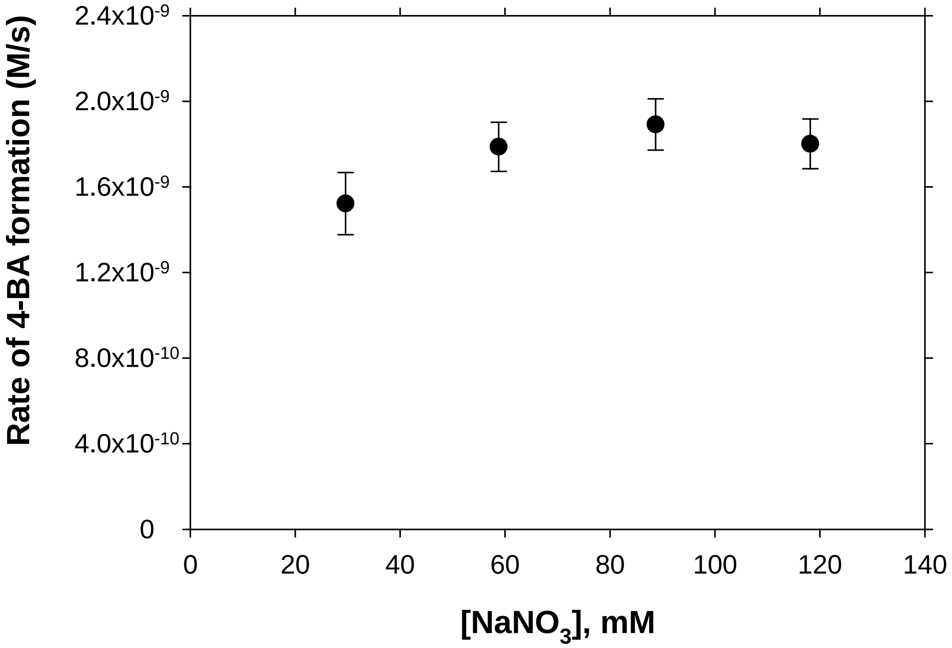


Figure S7. Influence of ionic strength (adjusted by varying the concentration of $NaNO_3$) on initial rates of 4-bromoanisole (4-BA) formation from the reaction of anisole with free bromine. Conditions: $[NaBr]_o$ = 115 µM, $[HOCl]_{tot,o}$ = 640 µM, [NaCl] = 9.6 mM, pH 8.20 (20 mM borate buffer), $[anisole]_o$ = 8.2 µM, T = 20.0 °C.

Effects of Initial Concentration of Anisole

The reaction order in [anisole] was determined by varying the initial concentration of added anisole in the presence of a sufficient excess of free bromine (formed via NaBr + excess free chlorine) to maintain pseudo-first-order conditions. The reaction order in [anisole] with respect to 4-BA formation can be derived beginning with the rate equation for 4-BA formation (eq S6):

$$\frac{d[\text{4−BA}]}{dt} = k_{\text{I,obs}}[\text{anisole}]^n \qquad \text{(S6)}$$

where *n* is the reaction order in [anisole]. Taking common logarithms yields:

$$\log\left(\frac{d[\text{4−BA}]}{dt}\right) = n(\log[\text{anisole}]) + \log(k_{\text{I,obs}}) \qquad \text{(S7)}$$

Accordingly, a plot of $\log\left(\frac{d[\text{4−BA}]}{dt}\right)$ versus log[anisole] will have a slope equal to *n* (**Figure S8**). Similarly, the reaction order in [anisole] for the formation of the minor product (2-BA) is equal to the slope of $\log\left(\frac{d[\text{2−BA}]}{dt}\right)$ versus log[anisole].

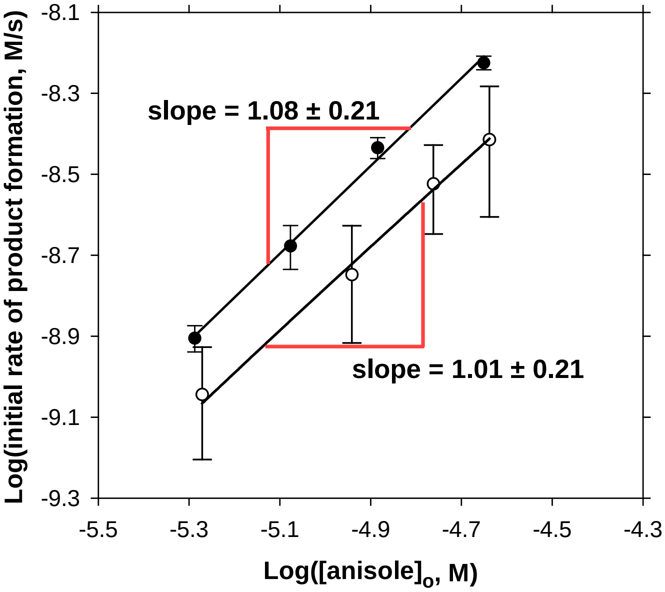


Figure S8. Initial rate of 4-bromoanisole (closed circles) and 2-bromoanisole (open circles) formation as a function of initial concentration of anisole. Note logarithmic scale on both axes. Uncertainties denote 95% confidence intervals. Conditions: $[\text{NaBr}]_o$ = 120 µM, $[\text{HOCl}]_{\text{tot,o}}$ = 660 µM, [NaCl] = 9.8 mM, pH 6.83 (20 mM bicarbonate buffer), T = 20.0 °C.

Rate Constants for the Formation of Free Bromine Species

Reactors were prepared by combining NaBr and (typically excess) free chlorine and allowing these components to react for sufficient time to permit >99% oxidation of bromide prior to addition of a parental anisole. The goal of this experimental design is to maximize the likelihood that free bromine speciation can be accurately described via equilibrium constants (eqs 1 – 6). Such an approach is necessitated by the unavailability of rate constants for the formation of all reactive brominating agents. Specifically, formation rate constants have not been reported for BrOCl (aq) and Br_2O (aq). Formation rate constants are shown in **Table S17** for the other brominating agents whose reactivity toward anisole is quantified herein.

Table S17. Formation Rate Constants for Brominating Agents

Reaction	*Rate constant*		*Conditions*	*Ref*
	forward reaction	*reverse reaction*		
$HOCl + Br^- \rightleftharpoons HOBr + Cl^-$	1.55×10^3 M^{-1} s^{-1}	1.0×10^{-2} M^{-1} s^{-1} [a]	25 °C, $\mu = 1$ M	11
$HOBr(aq) + Br^- + H^+ \rightleftharpoons Br_2(aq) + H_2O$	1.6×10^{10} M^{-2} s^{-1}	110 s^{-1}	20 °C, $\mu = 0.1$ M	12
$HOBr(aq) + Cl^- + H^+ \rightleftharpoons BrCl(aq) + H_2O$	2.3×10^{10} M^{-2} s^{-1}	$(3.0 \pm 0.4) \times 10^6$ s^{-1}	25 °C, $\mu = 1$ M	1

[a] Calculated from equilibrium constant (K_{eq}) reported in reference 11, noting that $K_{eq} = k_+/k_–$, where k_+ and $k_–$ are rate constants for the forward and reverse reactions, respectively.

The rate constant for formation of Br_2 ($k_+ = 1.6 \times 10^{10}$ M^{-2} s^{-1}, **Table S17**) corresponds to a half-life ($t_{1/2} = \frac{\ln 2}{k_+[H^+][Br^-]_{xs}}$) of 2 s under conditions representative of reactions performed herein in the presence of excess bromide ($p[H^+] = 7.17$, $[Br^-]_{xs} = 2.8 \times 10^{-4}$ M, $[HOCl]_{tot,o} = 1.2 \times 10^{-4}$ M, no added NaCl). The experimental half-life for overall bromination of anisole under the same conditions is 100 s. Similarly, the rate constant for formation of BrCl ($k_+ = 2.2 \times 10^{10}$ M^{-2} s^{-1}, adjusted to $\mu = 0.1$ M via the Truesdell-Jones equation[13]) corresponds to a half-life ($t_{1/2} = \frac{\ln 2}{k_{+}[\mathrm{H}^{+}][\mathrm{Cl}^{-}]}$) of 0.02 s under conditions representative of reactions performed herein in the presence of added NaCl (p[H^{+}] = 6.98, [Cl^{-}] = 0.01 M, [Br^{-}]$_{o}$ = 1.2 x 10^{-4} M, [HOCl]$_{tot,o}$ = 5.7 x 10^{-4} M). The experimental half-life corresponding to the overall bromination of anisole under the same conditions is 300 s. These findings suggest formation rates of BrCl and Br$_2$ are fast relative to rates of anisole bromination under the conditions examined herein, consistent with the finding of reactions that are first-order in [anisole] (**Figure S8**).

Effects of Initial Concentration of Free Bromine

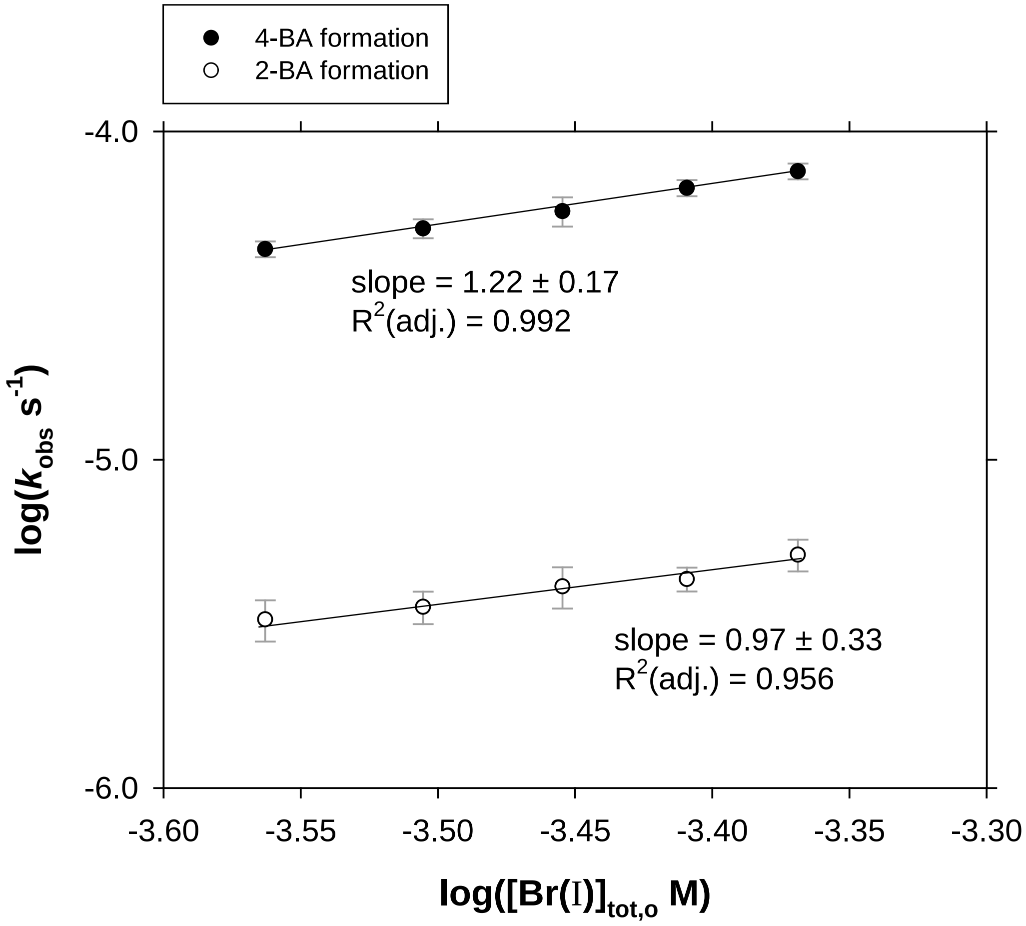


Figure S9. Pseudo-first-order rate constants corresponding to the formation of 4-bromoanisole (4-BA, filled circles) and 2-bromoanisole (2-BA, open circles) as a function of total initial free bromine concentration. Note log scale on both axes. Conditions: pH 8.81, borate buffer (20 mM), $[NaBr]_o$ = 274 – 428 µM, $[HOCl]_{tot,o}$ = 560 µM, $[anisole]_o$ = 20 µM, $[NaNO_3]$ = 95 mM, T = 20.0 °C.

Reactions in the Presence of Excess Bromide

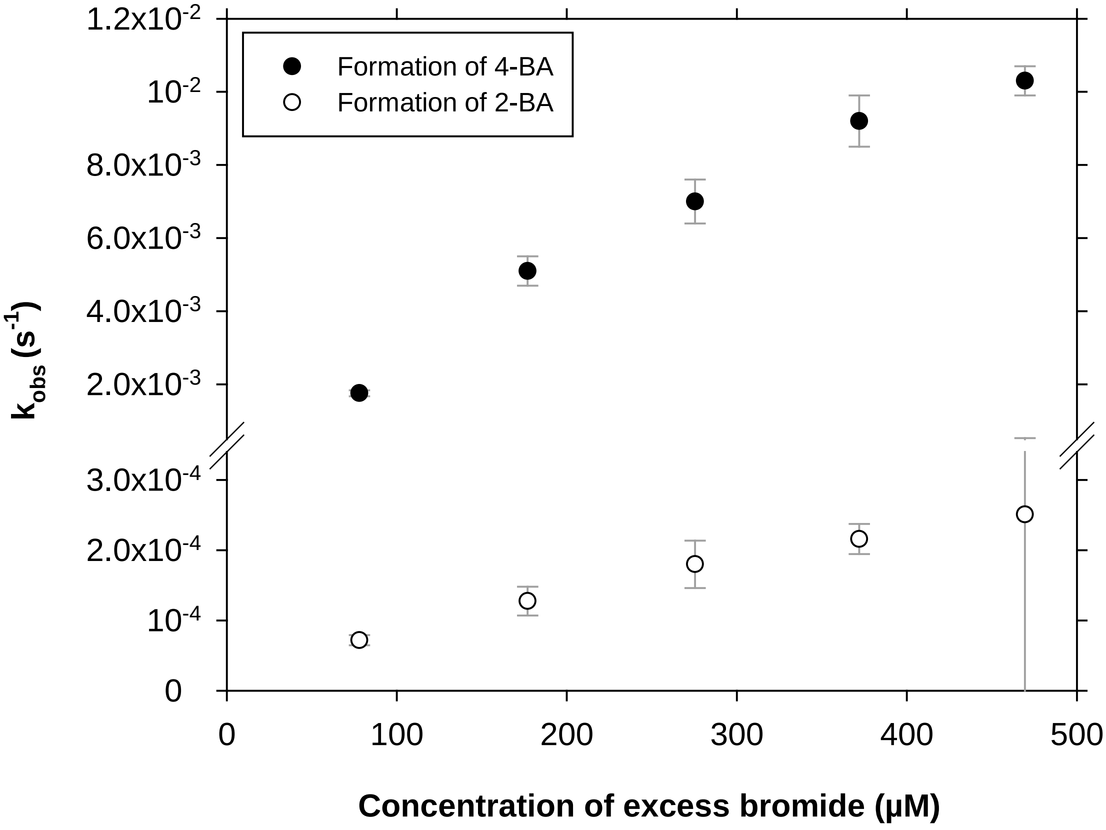


Figure S10. Pseudo-first-order rate constants corresponding to the formation of 4-bromoanisole (4-BA, filled circles) and 2-bromoanisole (2-BA, open circles) as a function of excess bromide concentration (calculated as $[NaBr]_o$ – $[HOCl]_{tot,o}$). Conditions: pH 7.31, bicarbonate buffer (20 mM), $[NaBr]_o$ = 197 – 588 μM, $[HOCl]_{tot,o}$ = 119 μM, $[anisole]_o$ = 10 μM, $[NaNO_3]$ = 98 mM, T = 20.0 °C.

Ortho Bromination of Anisole

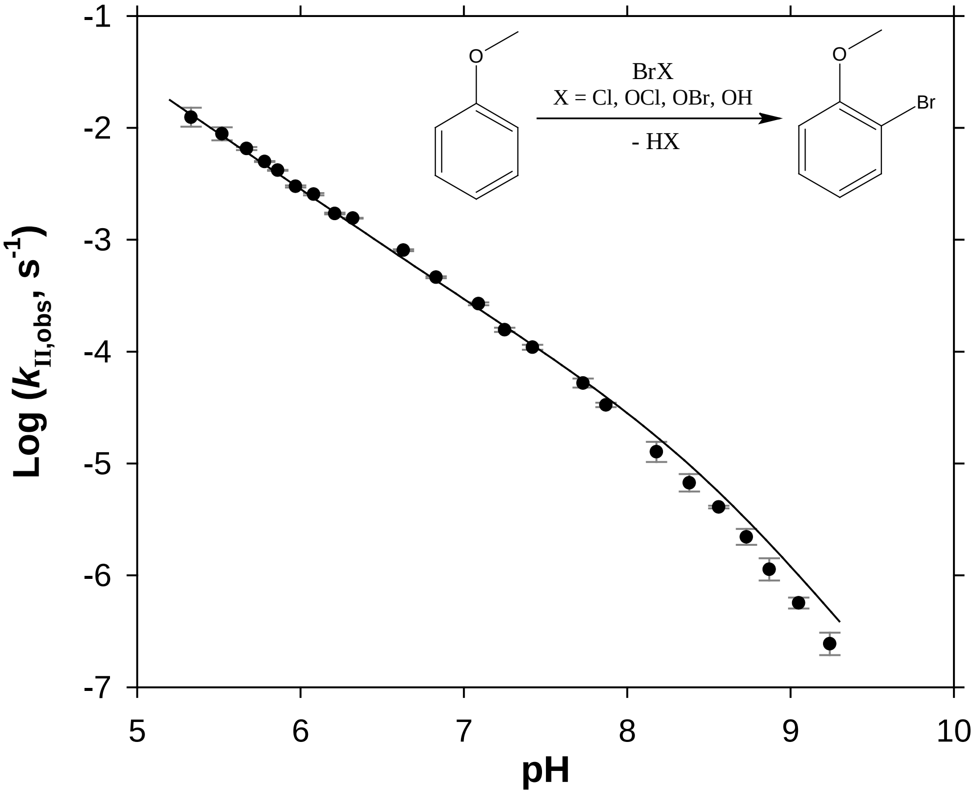


Figure S11. Pseudo-first-order rate constants (as log $k_{II,obs}$) for anisole bromination to give 2-bromoanisole as a function of pH. Error estimates denote 95% confidence intervals. Solid line denotes model fit of the form $k_{obs} = k_{BrCl}[BrCl] + k_{BrOCl}[BrOCl] + k_{Br2O}[Br_2O] + k_{HOBr}[HOBr]$ (noting that formation of Br_2 is negligible when free chlorine is added in excess relative to bromide). Conditions: $[anisole]_o = 10$ µM, $[NaBr]_o = 120$ µM, $[HOCl]_o = 570$ µM, $[NaNO_3] = 90$ mM, [NaCl] = 10 mM, [bicarbonate or borate buffer] = 20 mM, T = 20.0 ^oC.

Bromination of 4-Bromoanisole

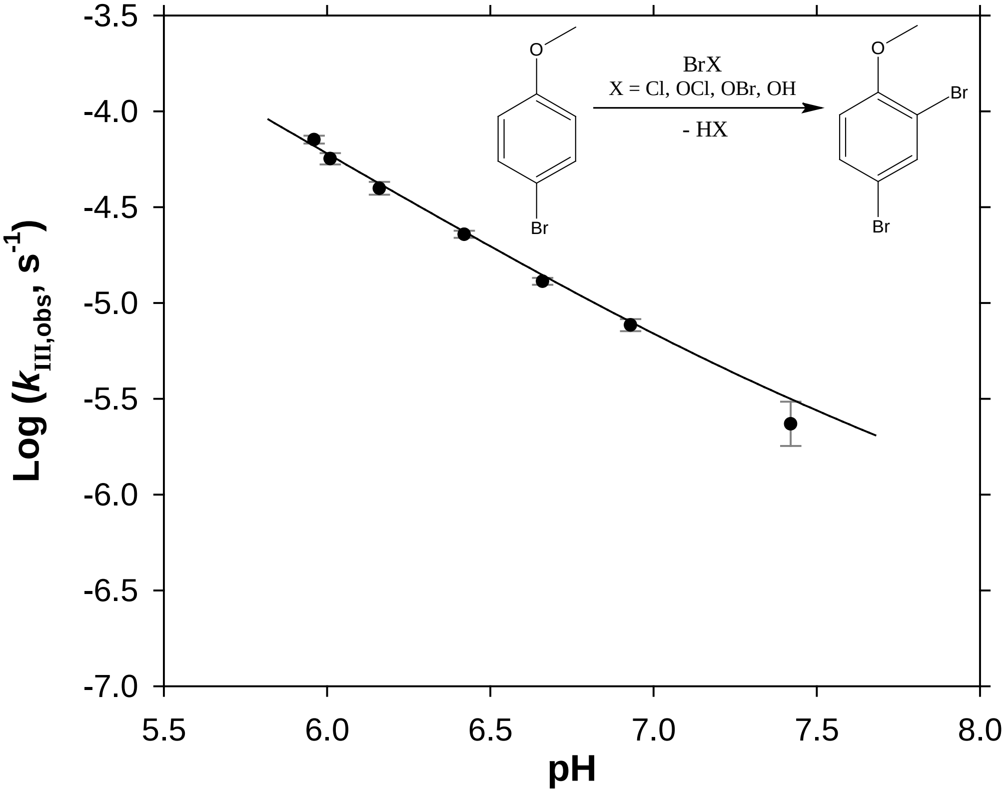


Figure S12. Pseudo-first-order rate constants (as log $k_{III,obs}$) for 4-bromoanisole bromination to give 2,4-dibromoanisole as a function of pH. Error estimates denote 95% confidence intervals. Solid line denotes model fit of the form $k_{obs} = k_{BrCl}[BrCl] + k_{BrOCl}[BrOCl] + k_{Br2O}[Br_2O] + k_{HOBr}[HOBr]$ (noting that formation of Br_2 is negligible when free chlorine is added in excess relative to bromide). Conditions: [4-bromoanisole]$_o$ = 30 µM, [NaBr]$_o$ = 550 µM, [HOCl]$_o$ = 570 µM, [$NaNO_3$] = 92 mM, [NaCl] = 2.8 mM, [bicarbonate buffer] = 20 mM, T = 20.0 °C.

Bromination of 2-Bromoansiole

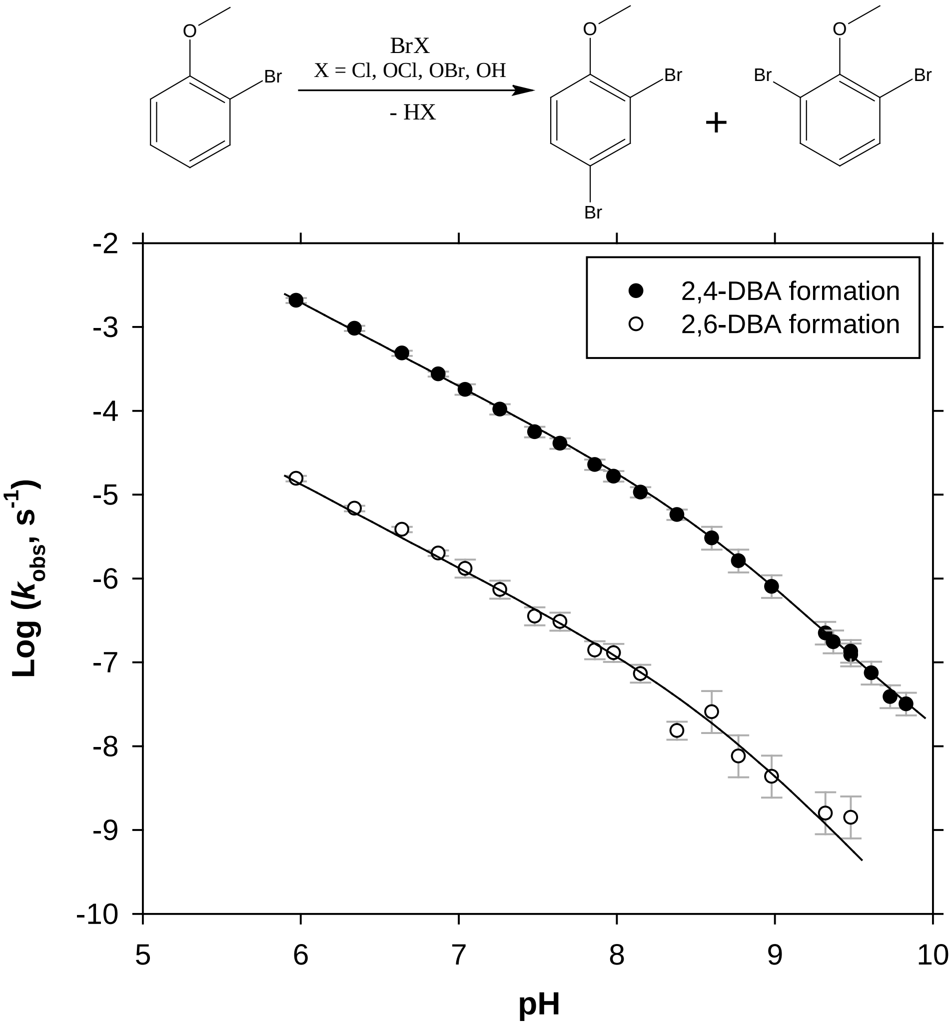


Figure S13. Pseudo-first-order rate constants corresponding to the formation of 2,4-dibromoanisole (2,4-DBA, closed circles, log $k_{obs,IV}$) and 2,6-dibromoanisole (2,6-DBA, open circles, log $k_{obs,V}$) upon bromination of 2-bromoanisole as a function of pH. Solid lines denote model fit of the form $k_{obs} = k_{BrCl}[BrCl] + k_{BrOCl}[BrOCl] + k_{Br2O}[Br_2O] + k_{HOBr}[HOBr]$ (noting that formation of Br_2 is negligible when free chlorine is added in excess relative to bromide). Conditions: $[NaBr]_o$ = 400 µM, $[HOCl]_{tot,o}$ = 500 µM, [NaCl] = 9.7 mM, $[NaNO_3]$ = 87 mM, 20 mM bicarbonate or borate buffer, $[\text{2-bromoanisole}]_o$ = 25 µM, T = 20.0 °C.

Regioselectivity of 2-Bromoanisole Bromination

The reaction of 2-bromoanisole with free bromine predominantly forms 2,4-dibromoanisole over 2,6-dibromoanisole, with selectivity ratios ranging from approximately 100 to 400 for experiments performed between pH 6.0 and 9.5 (**Figure S14**).

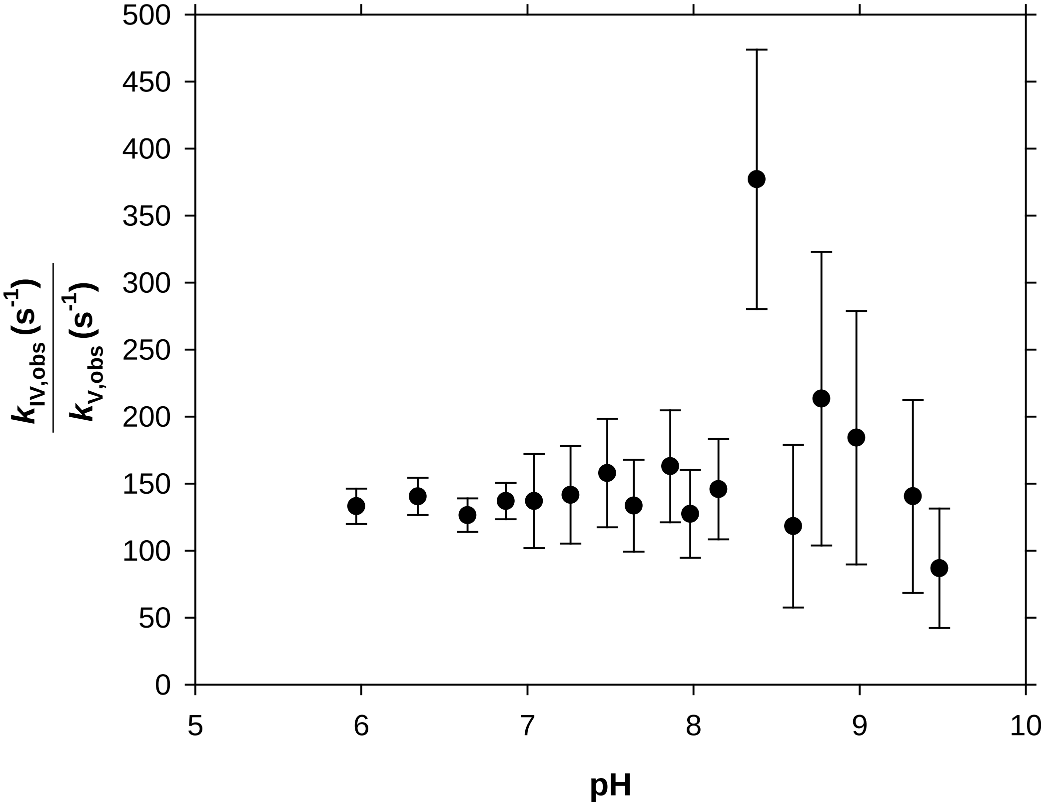


Figure S14. Ratios of rate constants for bromination of 2-bromoanisole to give the major (2,4-dibromoanisole, $k_{IV,obs}$) and minor (2,6-dibromoanisole, $k_{V,obs}$) products as a function of pH. Conditions: $[NaBr]_o$ = 400 µM, $[HOCl]_{tot,o}$ = 500 µM, [NaCl] = 9.7 mM, 20 mM bicarbonate or borate buffer, $[2\text{-bromoanisole}]_o$ = 25 µM, T = 20.0 °C.

Reactivity Trends Among Organic Compounds

Second-order rate constants for *para* versus *ortho* bromination of anisole yield a log-linear correlation (**Figure S15**). A similar correlation exists when plotting second-order rate constants for *para* bromination of anisole versus bromination of dimethenamid[8] (**Figure S15**). Such linear relationships suggest that each reaction shares the same rate-determination step[14] (presumably σ-complex formation).

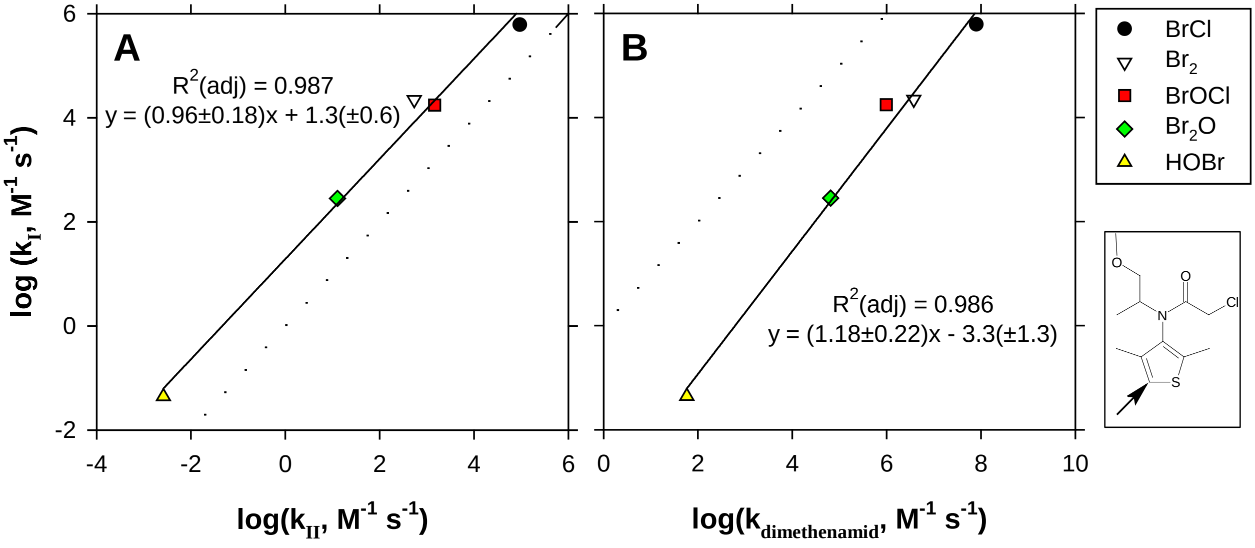


Figure S15. Log-log relationships between rate constants for *para* bromination of anisole and (**A**) *ortho* bromination of anisole and (**B**) bromination of dimethenamid (structure shown; arrow denotes site of bromination; data from ref 8). Dashed line denotes y = x. Error estimates denote 95% confidence intervals.

Reactivity Comparison Between BrOCl and Br_2

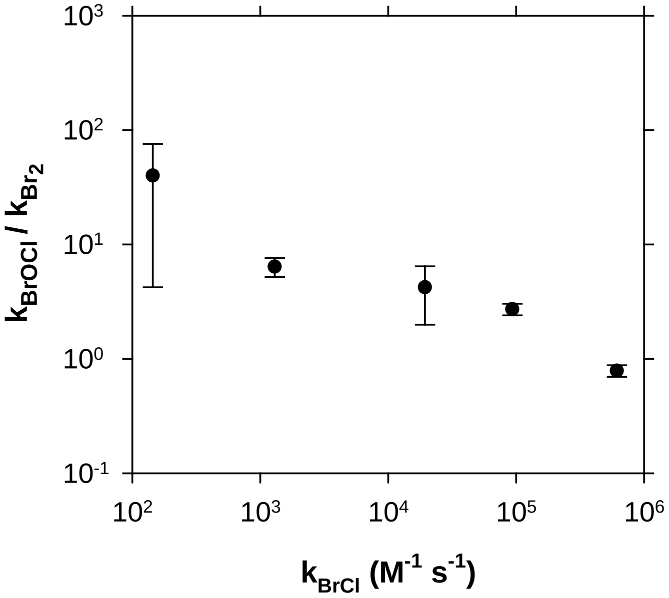


Figure S16. Ratio of second-order rate constants for BrOCl and Br_2 as a function of the nucleophilicity of the site of reaction on the parental anisole (quantified as k_{BrCl}). Note log scale on both axes. Inherent reactivity toward BrCl (i.e., k_{BrCl}) was selected as a means of quantifying nucleophilicity because second-order rate constants for this brominating agent yielded the greatest precision (as indicated by the uncertainties shown in Table 1) relative to those for the other brominating agents. Error estimates denote 95% confidence intervals.

Reactivity-Selectivity Analysis

For reactions in which the inherent nucleophilicity of the anisole exerts a significant influence on overall bromination rates, selectivity ratios (k_{BrCl}/k_{BrX} in **Figure S17**) are anticipated to decrease as the nucleophilicity of the aromatic compound (quantified as k_{BrCl}) increases (vis-à-vis, the reactivity-selectivity principle[10]). That most of the brominating agents do not follow this trend (excepting perhaps BrOCl) suggests that factors other than inherent nucleophilicity of the anisole (e.g., steric effects and polarizability[15]) are influencing bromination rates.

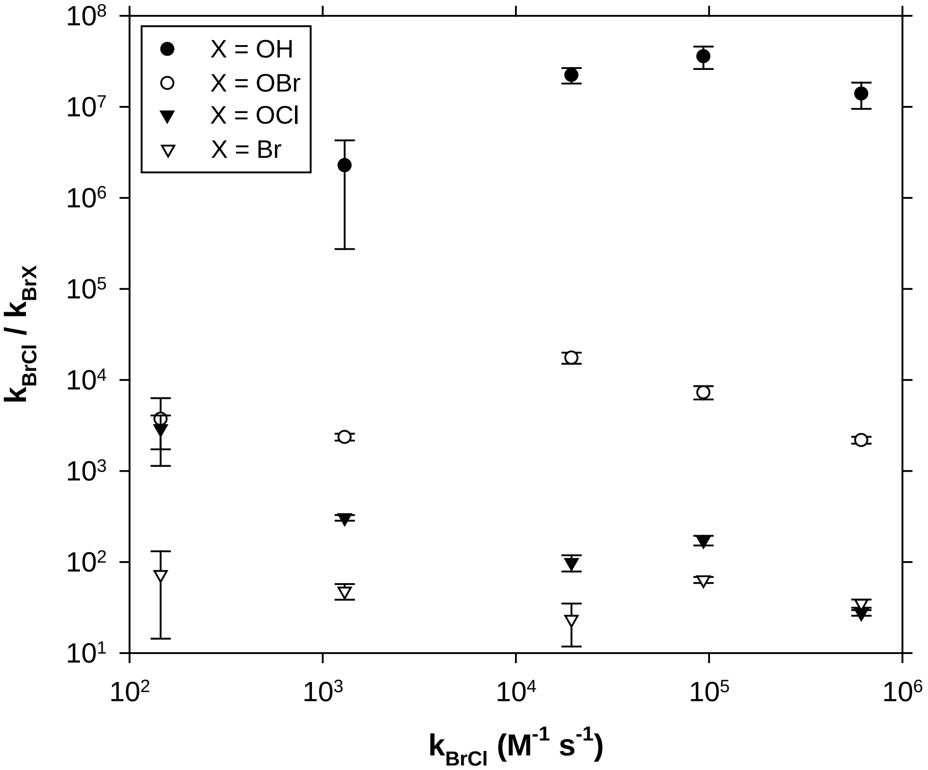


Figure S17. Selectivity ratio (as k_{BrCl}/k_{BrX}, where X = OH, OBr, OCl, or Br) as a function of regiospecific reactivity toward BrCl (k_{BrCl}) of anisole, 4-bromoanisole, and 2-bromoanisole. Rate constants are compiled in Table 1 (main text).

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