Environmental Science & Technology Letters

pubs.acs.org/journal/estlcu

Letter

Methanol as a Carrier Solvent Can Influence Chlorination Rates of Phenolic Compounds in Chlorinated Waters

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Cite This: https://doi.org/10.1021/acs.estlett.4c00656

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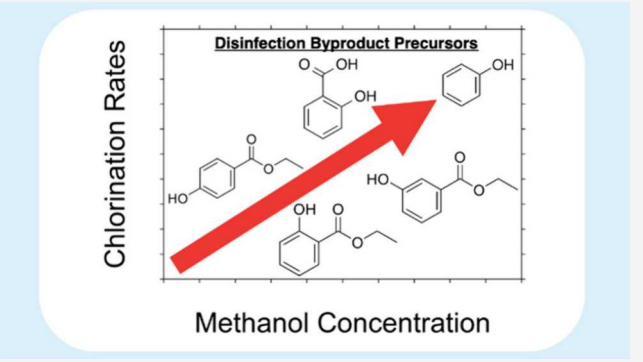
ABSTRACT: Methanol is commonly used as a carrier solvent in environmental chemistry experiments; however, the possible influence of methanol on the kinetics of chemical transformations is often overlooked. The effects of methanol and other frequently used carrier solvents on the chlorination rates of aromatic precursors of disinfection byproducts during water chlorination were investigated. At concentrations as low as 0.50 vol %, methanol increased chlorination rates of ethylparaben, phenol, 4-hydroxybenzoic acid, ethyl 3-hydroxybenzoate, and ethyl 2-hydroxybenzoate. Methanol did not increase the chlorination rates of salicylic acid, dimethenamid, or 1,2-dimethoxybenzene. Ethylparaben and phenol chlorination were especially sensitive to methanol, with pseudo-first-order rate constants (k_{obs}) increasing by a factor of >2 in water containing 2.0 vol % methanol compared to those in methanol-free controls. Rate enhancements persisted across differing reaction conditions (pH 6−10 and in buffers containing borate or phosphate). The rate enhancements of unsubstituted and *para*-substituted phenols were larger than those of *meta*- and *ortho*-substituted phenols. The carrier solvents acetone, acetonitrile, and *tert*-butanol had no appreciable impact on the chlorination rates of ethylparaben. Overall, our findings suggest that methanol as a carrier solvent can cause systematic errors in lab-scale chlorination experiments. To avoid experimental artifacts, researchers should prepare stock solutions in water (when feasible) or minimize carrier solvent concentrations present in reaction solutions.



KEYWORDS: *solvent effects, disinfection byproducts, reaction kinetics, structure−reactivity relationships, parabens, phenols*

1. INTRODUCTION

Studies of the environmental fate of organic compounds in aqueous systems routinely employ carrier solvents (i.e., organic solvents used to prepare spiking solutions of analytes possessing modest to low water solubility). Carrier solvents, including methanol, acetonitrile, acetone, and *tert*-butanol, are miscible with water. Despite the widespread use of carrier solvents,[1−10] the propensity of carrier solvents to cause experimental artifacts is often discounted and is seldom investigated. In reaction solutions, maximum concentrations of carrier solvent commonly range from 0.050 to 2.5 vol %.[1−10] Such concentrations are below the threshold (∼5 vol %) typically associated with cosolvent effects resulting from changes in bulk solvation properties.[11] Even at minimal concentrations, however, carrier solvents could influence reaction kinetics via mechanisms involving direct participation of the carrier solvent (e.g., in stabilizing activated complexes).[12]

Laboratory studies of electrophilic chlorination provide important insights into the formation of disinfection byproducts (DBPs)[13] and often employ a carrier solvent (Table S1). Nevertheless, such studies rarely include control experiments to test the influence of carrier solvents. As notable exceptions, Lau et al. determined that ≤0.1 vol % methanol did not affect the chlorination kinetics of phenol,[2] but 0.25 vol % methanol decreased chlorination rate constants of β-ionone by ≤14%.[6] The consumption of free chlorine by methanol is unlikely to explain the attenuation of the rate of β-ionone chlorination because methanol reacts sluggishly with free chlorine compared to most DBP precursors.[13] Indeed, a study investigating the formation of chloroform from chlorination of triclosan reported that methanol (at 0.2 vol %) had no effect on free chlorine concentrations over 60 min.[14] Notably, the ability of carrier solvents to increase the rates of chlorination of organic compounds has not been previously reported. Additionally, the possible influence of carrier solvents at >0.25 vol % has not been investigated, despite the presence of

Received: August 6, 2024
Revised: September 10, 2024
Accepted: September 11, 2024

carrier solvents at concentrations of ≤2.5 vol % in previous studies of organic compound chlorination (Table S1).

This study explores the influence of carrier solvents on the chlorination kinetics of eight aromatic compounds known or anticipated to react with free available chlorine (FAC) on environmentally relevant time scales. Organic precursors selected for study include ethylparaben (ethyl 4-hydroxybenzoate), two regioisomers of ethylparaben (ethyl 2-hydroxybenzoate and ethyl 3-hydroxybenzoate), and six additional aromatic compounds (phenol, 4-hydroxybenzoic acid, 2,4,6-trichlorophenol, dimethenamid, 1,2-dimethoxybenzene, and salicylic acid). Tested carrier solvents include methanol, acetonitrile, acetone, and *tert*-butanol, with particular attention paid to methanol, being the preferred carrier solvent for many previous studies of aromatic compound chlorination.[1,2,4,5,7,8,10] The influence of methanol on chlorination kinetics was also tested across different pH values, buffer compositions, temperatures, and purity grades of methanol.

2. METHODS AND MATERIALS

A list of reagents, solvents, and standards is provided in Table S2. All aqueous solutions and standards were prepared in ultrahigh-purity water (18 MΩ cm resistivity). Nitric acid and sodium hydroxide were used for pH adjustments, and the pH values of reaction solutions were measured after each time course experiment (Fisher Accumet pH electrode, AB 150 meter with automatic temperature compensation).

2.1. Time Course Experiments. Time course reactions were conducted in 40 mL amber glass vials containing 25.0 mL of a phosphate or borate buffer (10 mM, pH 6.00−10.00) amended with $NaNO_3$ (70−100 mM) and NaCl (0−30 mM) to fix the ionic strength and chloride concentration, respectively. An aqueous spike of a NaOCl stock solution (∼1 M) was added to buffer solutions to achieve a FAC initial concentration of 0.300−5.00 mM. The NaOCl stock solution was standardized weekly via ultraviolet−visible spectrophotometry.[15] FAC-amended solutions were allowed to equilibrate for 5 min in a circulating water bath at 20.00 ± 0.02 °C. A parent compound (ethylparaben, phenol, 4-hydroxybenzoic acid, 2,4,6-trichlorophenol, dimethenamid, 1,2-dimethoxybenzene, salicylic acid, ethyl 2-hydroxybenzoate, or ethyl 3-hydroxybenzoate) was added to achieve an initial concentration of 12−20 μM. Stock solutions of parent compounds were prepared in methanol, acetonitrile, acetone, or *tert*-butanol. Reaction solutions contained 0−2.0 vol % methanol, acetonitrile, acetone, or *tert*-butanol. For control reactors containing no carrier solvent, stock solutions of parent compounds prepared in acetone were spiked into empty, uncapped 40 mL amber glass vials and allowed adequate time for acetone to evaporate in a fume hood; the parent compound was reconstituted in 25.0 mL of aqueous buffer preamended with the NaOCl stock solution. After a parent compound was combined with NaOCl, reactors were shaken manually for 10 s and returned to the water bath. Aliquots (1.00 mL) of reaction solutions were obtained periodically, and reactions were quenched with sodium thiosulfate such that the transformation of parent compounds could typically be observed over at least two half-lives. A quenching solution was added at a 40% molar excess relative to the initial concentration of FAC ([sodium thiosulfate] ≥ 1.4$[FAC]_o$). To determine activation parameters, selected experiments with ethylparaben were conducted over a range of temperatures (5−30 °C) (see Text S1 of the Supporting Information). Three methanol grades (ACS reagent grade, HPLC grade, and LC-MS grade) were tested to examine whether solvent purity influenced the rates of chlorination of ethylparaben. Analytes and selected reaction products were monitored using high-performance liquid chromatography with diode-array detection (Text S2). Specific solution conditions for all time course experiments are summarized in Tables S8−S13.

2.2. Quality Assurance. Reactions were performed in triplicate for each independent variable tested and for the control reactions. Unless indicated otherwise, uncertainties herein denote 95% confidence intervals. Concentrations of analytes and selected chlorination products were quantified using external calibration standards. Example time courses are shown in Figures S1−S11. Carbon mass balances were closed for all phenolic compounds examined herein, suggesting that analytes and monitored chlorination products were stable in quenched solutions. Control experiments examining the effects of carrier solvents on FAC consumption (quantified via derivatization with 1,3,5-trimethoxybenzene)[16] are described in Text S3.

2.3. Calculation of Rate Constants. Pseudo-first-order chlorination rate constants were calculated by quantifying the concentrations of parent organic compounds over time. Pseudo-first-order rate constants (k_{obs}, s^{-1}) were calculated via eq 1

$$\ln[\text{parent compound}] = -k_{obs}t + \ln[\text{parent compound}]_o \quad (1)$$

where $[\text{parent compound}]_o$ denotes the concentration of parent compounds at time zero.

3. RESULTS AND DISCUSSION

To examine the effects that carrier solvent identity and concentration have on chlorination rates, we used ethylparaben as the principal model compound. Ethyl 3-chloro-4-hydroxybenzoate and ethyl 3,5-dichloro-4-hydroxybenzoate were the chlorination products that were quantified, and they were also quantified previously.[7] Carbon mass balances did not decrease over the reaction time (e.g., Figure S1), suggesting no appreciable formation of unmonitored products. FAC recoveries did not vary appreciably for solutions containing 0 versus 2.0 vol % methanol (Figure S12). Oxidation of methanol[17] and hydrolysis of ethylparaben[18] are unlikely to influence rates of chlorination of ethylparaben under the examined reaction conditions and time scales (i.e., <2 min).

3.1. Carrier Solvent Identity. Methanol increased k_{obs} values for ethylparaben chlorination by a factor of >2 in going from 0 to 2 vol % methanol (Figure S13A). All methanol grades tested (reagent, HPLC, and LC-MS grade) enhanced chlorination rates to similar degrees (Table S9), suggesting that methanol, rather than an impurity in the methanol, is causing the observed rate enhancement. Other solvents tested (acetone, acetonitrile, and *tert*-butanol) did not exhibit a discernible dose−response relationship with k_{obs} (Figure S13). Acetone and acetonitrile cannot serve as hydrogen-bond donors, which may limit their effect on chlorination rates. For *tert*-butanol, steric effects and hydrophobic clustering[19] could conceivably influence interactions with reactants during aqueous chlorination.

In a previous study of toluene chlorination by Cl_2, a positive correlation was observed between dielectric constants of solvents and toluene chlorination rates.[20] No such trend in dielectric constants (or other solvent physical properties) was

https://doi.org/10.1021/acs.estlett.4c00656
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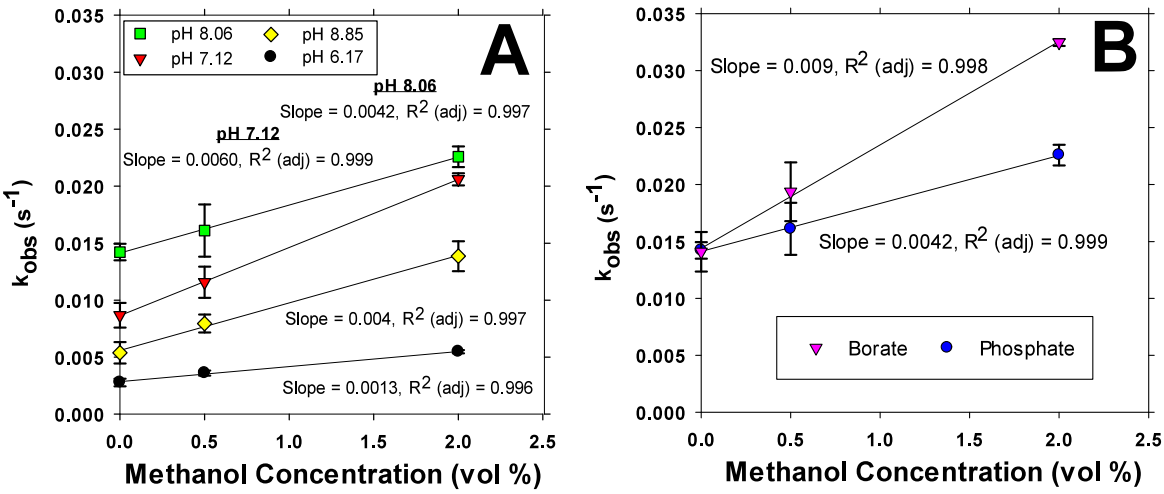

Figure 1. Pseudo-first-order rate constants (k_{obs}) as a function of methanol concentration for ethylparaben chlorination at 20 °C (A) as a function of pH and (B) in phosphate or borate buffers. Error bars represent the 95% confidence intervals. Unit conversion note: 1.0 vol % methanol = 0.247 M. Solution conditions: (A) [Na_2HPO_4] = 10 mM, [FAC]$_o$ = 300 μM, [ethylparaben]$_o$ = 12 μM, [NaCl] = 10 mM, and [$NaNO_3$] = 90 mM and (**B**) [buffer salt] = 10 mM, [FAC]$_o$ = 300 μM, [ethylparaben]$_o$ = 12 μM, [NaCl] = 10 mM, [$NaNO_3$] = 90 mM, and pH 8.06 ± 0.01.

observed for the carrier solvents tested here (Table S14). Specific structure−activity effects, rather than changes in the bulk properties of the solvent mixture, likely account for the effects of carrier solvents on chlorination rates of ethylparaben observed herein.

3.2. Effects of pH and Buffer Salt Identity. To further evaluate the effects of methanol on the kinetics of ethylparaben chlorination, k_{obs} values were measured as a function of methanol concentration at varying pHs (6.17−8.85) and buffer salt identities (phosphate and borate). At all examined pH values, as the methanol concentration increased, k_{obs} increased (Figure 1A). Methanol had the strongest influence on k_{obs} at pH 7.12, indicated by the largest slope in Figure 1A. At pH 8.06 and 8.85, k_{obs} values had similar sensitivities to methanol, and the lowest sensitivity was observed at pH 6.17.

Speciation of both ethylparaben and FAC could influence the sensitivity to methanol. The deprotonated (anionic) form of ethylparaben (pK_a = 8.34) is ostensibly a more inherently reactive nucleophile than is the protonated (neutral) form. Conversely, HOCl (pK_a = 7.58)[21] is a more reactive chlorinating agent than is OCl^-.[2,8,22] A speciation diagram of ethylparaben and FAC is provided in Figure S14. The pH with the highest k_{obs} values (pH 8.06) does not correspond to the pH of greatest sensitivity to methanol (pH 7.12). The discrepancy between these pH levels suggests that methanol may increase the reactivity of more than one combination of ethylparaben and FAC reactants over the tested pH range, with HOCl and (anionic) ethylparaben likely serving as the predominant reactants that are susceptible to methanol-derived rate enhancement. Conceivably, methanol could also accelerate reactions involving other chlorinating agents (e.g., Cl_2O) that exist in equilibrium with HOCl.[22]

Reactions conducted in borate and phosphate buffers both yielded positive correlations between k_{obs} and the methanol concentration (Figure 1B). With borate buffers at pH 8.06, k_{obs} values more than doubled upon going from 0 to 2 vol % methanol. With phosphate buffers at pH 8.06, k_{obs} values increased by 59% over the same methanol concentration range. The difference in sensitivities to methanol in the two buffers could be related to differences in formal charges and/or hydrogen-bonding ability of the principal buffer species (i.e., HPO_4^{2-} and H_3BO_3) at pH 8.06.

3.3. Effects of Methanol on the Chlorination of Other Organic Compounds. The chlorination of additional organic compounds was studied to determine whether the effects of methanol extend to compounds beyond ethylparaben. Sensitivity to methanol-associated rate enhancement, indicated by slopes in plots of k_{obs} versus methanol concentration (Figure 2A), increases in the following order: ethyl 2-hydroxybenzoate < ethyl 3-hydroxybenozoate < ethyl 4-hydroxybenzoate (i.e., ethylparaben). For all three isomers of ethyl hydroxybenzoate, chlorination rates approximately doubled upon going from 0 to 2 vol % methanol (Figure 2A). These findings suggest that regiochemistry can affect the magnitude of the methanol effect. Interestingly, as inherent reactivity toward FAC (*y*-intercepts in Figure 2A) increases, sensitivity to methanol-associated rate enhancement (slopes in Figure 2A) also increases.

To further explore how organic compound structure influences methanol-derived impacts on chlorination rates, additional aromatic compounds were examined, including phenol,[23] 4-hydroxybenzoic acid,[24] salicylic acid,[8] 1,2-dimethoxybenzene,[5] and dimethenamid.[25] These compounds were selected for study because they contain a diversity of functional groups known to react with FAC on environmentally relevant time scales (i.e., minutes). Hydroxy- and methoxy-substituted benzenes represent functional groups in natural organic matter that are reactive toward FAC.[26] Dimethenamid is a commonly used herbicide that has been detected in surface waters and drinking water.[27−29] The chlorination kinetics of dimethenamid have been characterized previously in experiments that included methanol (<0.1 vol %); however, the possible influence of methanol was not assessed.[25]

As with ethylparaben, phenol (pK_a = 9.99)[23] and 4-hydroxybenzoic acid (pK_{a1} = 4.47, pK_{a2} = 9.17)[30] undergo accelerated chlorination in the presence of methanol (Figure 2B). Linear regressions of k_{obs} versus methanol concentration yielded similar slopes for ethylparaben, phenol, and 4-hydroxybenzoic acid, suggesting substituents *para* to the hydroxyl group do not substantially alter the methanol effect. The pK_a values of phenolic compounds increase slightly as the

https://doi.org/10.1021/acs.estlett.4c00656
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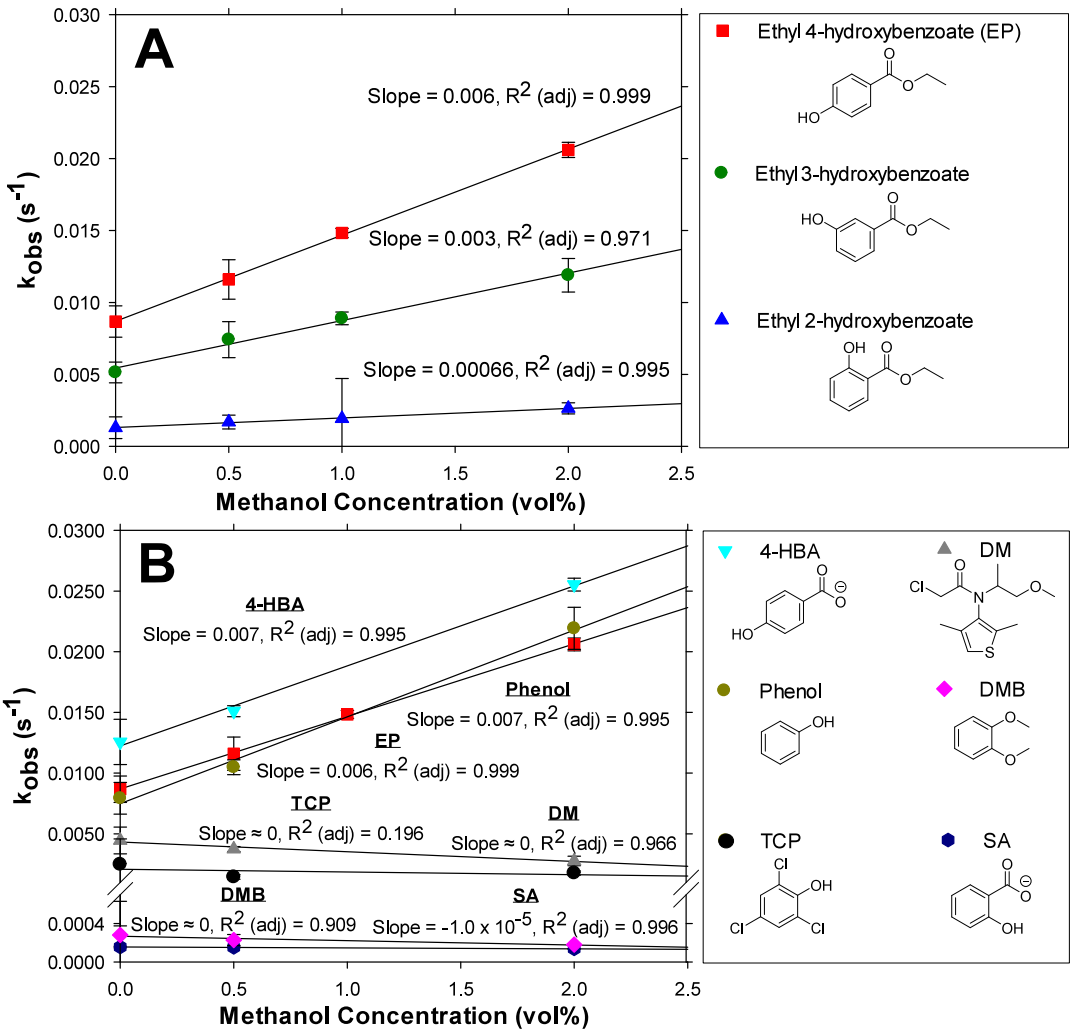

Figure 2. Pseudo-first-order rate constants (k_{obs}) as a function of added methanol concentration for chlorination at 20 °C of (A) hydroxybenzoate isomers and (B) ethylparaben, phenol, 4-hydroxybenzoic acid (4-HBA), dimethenamid (DM), 1,2-dimethoxybenzene (DMB), and salicylic acid (SA). Slopes have units of $(s\ vol\ \%)^{-1}$; slopes associated with DM and DMB were not significantly different than zero at the 95% confidence level. For additional statistical information, see Table S13. Error bars represent 95% confidence intervals. Unit conversion note: 1.0 vol % methanol = 0.247 M. Solution conditions: (A) $[Na_2HPO_4]$ = 10 mM, $[FAC]_o$ = 300 μM, [NaCl] = 10 mM, $[NaNO_3]$ = 90 mM, and pH 7.07 ± 0.02 and (B) $[Na_2HPO_4]$ = 10 mM, $[FAC]_o$ = 300−600 μM, [NaCl] = 10 mM, $[NaNO_3]$ = 90 mM, and pH 7.12 ± 0.06. Initial concentrations of organic precursors were as follows: $[hydroxybenzoates]_o$ = $[DM]_o$ = $[phenol]_o$ = $[TCP]_o$ = 12 μM and $[SA]_o$ = $[DMB]_o$ = $[4\text{-HBA}]_o$ = 20 μM.

concentration of methanol increases (e.g., the pK_a of phenol increases from 9.99 in water to ~10.02 in 2 vol % methanol).[31] Phenol experienced methanol-associated rate enhancements across the pH range of 6−10, with the highest sensitivity to methanol occurring at pH 8 and 9 (Figure S15), close to the average of the pK_a values of HOCl and phenol (8.8). These findings suggest that reactions of phenolate with HOCl are principally affected by methanol. Unlike methanol, acetone and acetonitrile had no appreciable influence on the rates of chlorination of phenol (Figure S16).

In contrast to ethylparaben, phenol, and 4-hydroxybenzoic acid, chlorination rate constants of 2,4,6-trichlorophenol, dimethenamid, 1,2-dimethoxybenzene, and salicylic acid (pK_{a1} = 2.97, pK_{a2} = 13.4)[32] do not increase as a function of methanol concentration (Figure 2B). For 2,4,6-trichlorophenol, dimethenamid, and 1,2-dimethoxybenzene, linear regression of k_{obs} as a function of methanol concentration yielded slopes not significantly different than zero. For salicylic acid, a negative slope was observed, indicating that salicylic acid is the only compound tested with a significant, albeit modest, rate-attenuating methanol effect, corresponding to a 13% decrease in k_{obs} upon going from 0 to 2.0 vol % methanol. This rate attenuation could be associated with the formation of salicyloyl hypochlorite (i.e., salicylic acid with H^+ of the carboxylic acid replaced with Cl^+) as a reactive intermediate.[8] Notably, the concentration of methanol influenced the product ratios of phenol but not those of salicylic acid (Table S15). Consequently, methanol can influence the rates of chlorination and products of some but not all analytes possessing a phenolic moiety.

For chlorination of ethylparaben in the absence of methanol, the activation enthalpy ($\Delta H^{\ddagger}$) and entropy ($\Delta S^{\ddagger}$) were determined from variable-temperature experiments to be 21 ± 3 kJ/mol and −206 ± 9 J mol^{-1} L^{-1}, respectively (Figure S17). In the presence of 2.0 vol % methanol, $\Delta H^{\ddagger}$ = 17 ± 4 kJ/mol and $\Delta S^{\ddagger}$ = −218 ± 14 J mol^{-1} K^{-1}. The decrease in $\Delta H^{\ddagger}$ (but not $\Delta S^{\ddagger}$) is significant at the 90% confidence level (p = 0.07), suggesting that the rate-enhancing influence of methanol corresponds to preferential stabilization of the activated

https://doi.org/10.1021/acs.estlett.4c00656
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complex without an appreciable change to the amount of (dis)order associated with formation of the activated complex.

Overall, the largest methanol-induced rate enhancements were observed for phenolic compounds with unsubstituted *ortho* and *meta* positions relative to the hydroxyl group. We postulate that methanol preferentially stabilizes the activated complexes of these phenolic compounds during reactions with chlorinating agents. Such stabilization could stem from methanol being both a superior H-bond donor and H-bond acceptor relative to water (Scheme S1).[33,34] The presence of substituents *ortho* to the hydroxyl group could inhibit stabilizing interactions with methanol and could explain the lower (ethyl 2-hydrozybenzoate), negative (salicylic acid), or apparent lack of (2,4,6-trichlorophenol) sensitivity to methanol compared to phenol. Additional mechanistic discussion is provided in Text S4.

4. ENVIRONMENTAL SIGNIFICANCE

Our findings highlight the effects that carrier solvents, particularly methanol, can have on rates and products of chlorination reactions. Contrary to common assumptions in the environmental literature, carrier solvents can increase the rates of chlorination of some (but not all) phenolic compounds, including those commonly used as surrogates of DBP formation in chlorinated waters (e.g., ethylparaben, phenol, and 4-hydroxybenzoic acid). The chlorination of ethylparaben is of particular interest because parabens are emerging contaminants in surface water and wastewater.[35] Additionally, the toxicological and ecological risks of halogenated byproducts of parabens are greater than those of their parent compounds.[36] Our results also indicate that salicylic acid, another micropollutant in surface water and wastewater,[37,38] experiences a modest decrease in its rate of chlorination that is proportional to methanol concentration. This observation suggests that chlorination rate constants of salicylic acid published previously[8] for reaction solutions containing $\leq$1.0 vol % methanol likely underestimate chlorination rate constants in methanol-free solutions by $\lesssim$10%.

To minimize experimental artifacts, our findings indicate that chlorination experiments should be designed to minimize or exclude carrier solvents, particularly methanol. When feasible, stock solutions of organic solutes should be prepared in water.[23,39] For ionizable organic solutes, stock solutions could be prepared in water using the salt form of the organic solutes, which have greater water solubility than do un-ionized analytes. Alternatively, carrier solvents could be allowed to evaporate prior to reconstitution of the organic solute in an aqueous solution; however, this approach is not recommended for (semi)volatile analytes. If carrier solvents cannot be avoided, consider solvents other than methanol (e.g., acetonitrile), minimize carrier solvent concentrations (e.g., <0.5 vol %), and maintain uniform carrier solvent concentrations throughout all experiments. Methanol should also be avoided in ozonation experiments because ozonation products of methanol can consume ozone and because methanol scavenges hydroxyl radicals produced during ozone decomposition.[40] Whether carrier solvents can influence other environmentally relevant transformations merits future study.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.estlett.4c00656.

List of chemicals, additional methodological details, and supplementary experimental results and discussion (PDF)

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

The authors acknowledge valuable feedback from the anonymous peer reviewers, whose comments strengthened the manuscript. The authors also acknowledge funding from Towson University's Fisher College of Science and Mathematics (to R.N.K.), the Ronald and Linda Raspet Summer Research Endowed Fellowship (to S.G.B.), the U.S. National Science Foundation (Grant CHE-2003578 to J.D.S. and K.P.R., Grant CHE-2003472 to D.L.M., and Grant CBET-1651536 to J.D.S.), the U.S. Environmental Protection Agency (Grant R840605 to J.D.S.), and The Camille & Henry Dreyfus Foundation (Grant TH-20-021 to J.D.S.).

REFERENCES

(1) Cai, M.; Feng, L.; Jiang, J.; Qi, F.; Zhang, L. Reaction kinetics and transformation of antipyrine chlorination with free chlorine. *Water Res.* **2013**, *47*, 2830−2842.

(2) Lau, S. S.; Abraham, S. M.; Roberts, A. L. Chlorination Revisited: Does Cl^- serve as a catalyst in the chlorination of phenols? *Environ. Sci. Technol.* **2016**, *50*, 13291−13298.

(3) Ma, L.; Li, J.; Xu, L. Aqueous chlorination of fenamic acids: Kinetic study, transformation products identification and toxicity prediction. *Chemosphere* **2017**, *175*, 114−122.

(4) Dodd, M. C.; Shah, A. D.; von Gunten, U.; Huang, C.-H. Interactions of fluoroquinolone antibacterial agents with aqueous chlorine: Reaction kinetics, mechanisms, and transformation pathways. *Environ. Sci. Technol.* **2005**, *39*, 7065−7076.
(5) Sivey, J. D.; Roberts, A. L. Assessing the reactivity of free chlorine constituents Cl_2, Cl_2O, and HOCl toward aromatic ethers. *Environ. Sci. Technol.* **2012**, *46*, 2141−2147.
(6) Lau, S. S.; Reber, K. P.; Roberts, A. L. Aqueous chlorination kinetics of cyclic alkenes—Is HOCl the only chlorinating agent that matters? *Environ. Sci. Technol.* **2019**, *53*, 11133−11141.
(7) Psoras, A. W.; McCoy, S. W.; Reber, K. P.; McCurry, D. L.; Sivey, J. D. Ipso substitution of aromatic bromine in chlorinated waters: Impacts on trihalomethane formation. *Environ. Sci. Technol.* **2023**, *57*, 18801.
(8) Broadwater, M. A.; Swanson, T. L.; Sivey, J. D. Emerging investigators series: comparing the inherent reactivity of often-overlooked aqueous chlorinating and brominating agents toward salicylic acid. *Environ. Sci.: Water Res. Technol.* **2018**, *4*, 369−384.
(9) Li, J.; Jiang, J.; Manasfi, T.; von Gunten, U. Chlorination and bromination of olefins: Kinetic and mechanistic aspects. *Water Res.* **2020**, *187*, No. 116424.
(10) Rebenne, L. M.; Gonzalez, A. C.; Olson, T. M. Aqueous chlorination kinetics and mechanism of substituted dihydroxybenzenes. *Environ. Sci. Technol.* **1996**, *30*, 2235−2242.
(11) Schwarzenbach, R. P.; Gschwend, P. M.; Imboden, D. M. *Environmental Organic Chemistry*, 3rd ed.; John Wiley & Sons: Hoboken, NJ, 2016.
(12) Hunter, C. A. Quantifying intermolecular interactions: Guidelines for the molecular recognition toolbox. *Angew. Chem., Int. Ed.* **2004**, *43*, 5310−5324.
(13) Deborde, M.; von Gunten, U. Reactions of chlorine with inorganic and organic compounds during water treatment—Kinetics and mechanisms: A critical review. *Water Res.* **2008**, *42*, 13−51.
(14) Rule, K. L.; Ebbett, V. R.; Vikesland, P. J. Formation of chloroform and chlorinated organics by free-chlorine-mediated oxidation of triclosan. *Environ. Sci. Technol.* **2005**, *39*, 3176−3185.
(15) Wang, T. X.; Kelley, M. D.; Cooper, J. N.; Beckwith, R. C.; Margerum, D. W. Equilibrium, kinetic, and UV-spectral characteristics of aqueous bromine chloride, bromine, and chlorine species. *Inorg. Chem.* **1994**, *33*, 5872−5878.
(16) Dias, R. P.; Schammel, M. H.; Reber, K. P.; Sivey, J. D. Applications of 1,3,5-trimethoxybenzene as a derivatizing agent for quantifying free chlorine, free bromine, bromamines, and bromide in aqueous systems. *Anal. Methods* **2019**, *11*, 5521−5532.
(17) Lieberman, M.; McCurry, D. L.; Marron, E. L. Overlooked chlorination of aqueous alcohols: Aldehyde formation and artifactual chlorine consumption. *Environ. Sci. Technol. Lett.* **2024**, *11*, 1002.
(18) C. I. R. Cosmetic Ingredient Review Expert Panel. Final amended report on the safety assessment of methylparaben, ethylparaben, propylparaben, isopropylparaben, butylparaben, isobutylparaben, and benzylparaben as used in cosmetic products. *Int. J. Toxicol.* **2008**, *27*, 1−82.
(19) Freda, M.; Onori, G.; Santucci, A. Hydrophobic hydration and hydrophobic interaction in aqueous solutions of tert-butyl alcohol and trimethylamine-N-oxide: a correlation with the effect of these two solutes on the micellization process. *Phys. Chem. Chem. Phys.* **2002**, *4*, 4979−4984.
(20) Zhang, M.; Lund, C. R. F. An experimental and computational study of solvent effects in toluene chlorination. *J. Phys. Chem. A* **2002**, *106*, 10294−10301.
(21) Morris, J. C. The acid ionization constant of HOCl from 5 to 35°. *J. Phys. Chem.* **1966**, *70*, 3798−3805.
(22) Rose, M. R.; Lau, S. S.; Prasse, C.; Sivey, J. D. Exotic electrophiles in chlorinated and chloraminated water: When conventional kinetic models and reaction pathways fall short. *Environ. Sci. Technol. Lett.* **2020**, *7*, 360−370.
(23) Gallard, H.; von Gunten, U. Chlorination of phenols: kinetics and formation of chloroform. *Environ. Sci. Technol.* **2002**, *36*, 884−890.
(24) Chang, E. E.; Chiang, P. C.; Chao, S. H.; Lin, Y. L. Relationship between chlorine consumption and chlorination by-products formation for model compounds. *Chemosphere.* **2006**, *64*, 1196−1203.
(25) Sivey, J. D.; McCullough, C. E.; Roberts, A. L. Chlorine monoxide (Cl_2O) and molecular chlorine (Cl_2) as active chlorinating agents in reaction of dimethenamid with aqueous free chlorine. *Environ. Sci. Technol.* **2010**, *44*, 3357−3362.
(26) Hanna, J. V.; Johnson, W. D.; Quezada, R. A.; Wilson, M. A.; Lu, X. Q. Characterization of aqueous humic substances before and after chlorination. *Environ. Sci. Technol.* **1991**, *25*, 1160−1164.
(27) Hladik, M. L.; Roberts, A. L.; Bouwer, E. J. Removal of neutral chloroacetamide herbicide degradates during simulated unit processes for drinking water treatment. *Water Res.* **2005**, *39*, 5033−5044.
(28) Hladik, M. L.; Bouwer, E. J.; Roberts, A. L. Neutral chloroacetamide herbicide degradates and related compounds in Midwestern United States drinking water sources. *Sci. Total Environ.* **2008**, *390*, 155−165.
(29) Hladik, M. L.; Bouwer, E. J.; Roberts, A. L. Neutral degradates of chloroacetamide herbicides: Occurrence in drinking water and removal during conventional water treatment. *Water Res.* **2008**, *42*, 4905−4914.
(30) Miklautz, H.; Keller, D.; Lopez Holguin, F.; Woloszczak, R. Automated determination of the pKa values of 4-hydroxybenzoic acid in cosolvent−water mixtures and related solvent effects using a modified HPLC system. *Anal. Bioanal. Chem.* **2006**, *384*, 1191−1195.
(31) Rosés, M.; Rived, F.; Bosch, E. Dissociation constants of phenols in methanol-water mixtures. *J. Chrom. A* **2000**, *867*, 45−56.
(32) Lide, D., Ed. *Handbook of Chemistry and Physics*; CRC Press: Boca Raton, FL, 1996.
(33) Nedic, M.; Wassermann, T. N.; Larsen, R. W.; Suhm, M. A. A combined Raman- and infrared jet study of mixed methanol-water and ethanol-water clusters. *Phys. Chem. Chem. Phys.* **2011**, *13*, 14050−14063.
(34) Kenny, P. W. Hydrogen-bond donors in drug design. *J. Med. Chem.* **2022**, *65*, 14261−14275.
(35) Vale, F.; Sousa, C. A.; Sousa, H.; Santos, L.; Simões, M. Parabens as emerging contaminants: Environmental persistence, current practices and treatment processes. *J. Clean. Prod.,* **2022**, *347*, No. 131244.
(36) Terasaki, M.; Takemura, Y.; Makino, M. Paraben-chlorinated derivatives in river waters. *Environ. Chem. Lett.* **2012**, *10*, 401−406.
(37) Ternes, T. A. Occurrence of drugs in German sewage treatment plants and rivers. *Water Res.* **1998**, *32*, 3245−3260.
(38) Bulloch, D. N.; Nelson, E. D.; Carr, S. A.; Wissman, C. R.; Armstrong, J. L.; Schlenk, D.; Larive, C. K. Occurrence of halogenated transformation products of selected pharmaceuticals and personal care products in secondary and tertiary treated wastewaters from southern California. *Environ. Sci. Technol.* **2015**, *49*, 2044−51.
(39) Mao, Q.; Ji, F.; Wang, W.; Wang, Q.; Hu, Z.; Yuan, S. Chlorination of parabens: reaction kinetics and transformation product identification. *Environ. Sci. Pollut. Res.* **2016**, *23*, 23081−23091.
(40) von Sonntag, C.; von Gunten, U. *Chemistry of Ozone in Water and Wastewater Treatment*; IWA Publishing: London, 2012.

https://doi.org/10.1021/acs.estlett.4c00656
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