Environmental Science & Technology LETTERS

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Letter

Overlooked Chlorination of Aqueous Alcohols: Aldehyde Formation and Artifactual Chlorine Consumption

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Cite This: *Environ. Sci. Technol. Lett.* 2024, 11, 1002−1007

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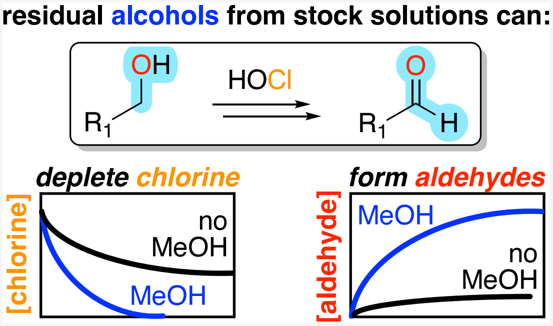


ABSTRACT: In environmental chemistry research, stock solutions of organic compounds are commonly prepared in alcohols (e.g., methanol), including during experiments to quantify oxidation kinetics and disinfection byproduct formation. Lacking an obviously oxidizable functional group, alcohols are tacitly assumed to be inert with respect to common water treatment oxidants and favored for their low cost, low toxicity, and miscibility with water. While attempting to duplicate a previous result reporting formaldehyde as a product of dimethylamine chlorination, we found that a substantial amount of formaldehyde was generated when the dimethylamine dosing solution was prepared in methanol but not when it was prepared in water. We further found that under conditions typical of chlorination kinetics experiments, aqueous methanol concentrations as low as 0.4% (v/v) could significantly deplete chlorine compared to methanol-free controls. In the presence of increasing methanol concentrations, chlorine depletion half-lives decreased to ∼4 h at 2% methanol. Finally, we examined the chlorination of five primary alcohols and one secondary alcohol, which all formed the corresponding carbonyls at comparable rates. These findings raise doubts about the routine use of alcohols as carrier solvents for the preparation of stock solutions in research on aqueous chlorination reactions and highlight alcohols as a potential source of aldehyde formation during chlorination.

KEYWORDS: *chlorination reaction kinetics, alcohols, carbonyl compounds*

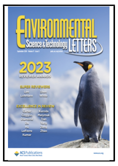
INTRODUCTION

Chlorination reactions have been among the most widely studied oxidative processes in water treatment for decades.[1−6] Research on chlorination reactions has spanned inactivation of pathogens,[7−10] transformation of trace chemical contaminants such as pharmaceuticals and endocrine-disrupting compounds,[11,12] formation and degradation of taste and odor compounds,[13−15] oxidation of reduced metals,[16−18] and production of disinfection byproducts.[19−21] Aqueous chlorination reactions have long been assumed to be driven by hypochlorous acid (HOCl), with its conjugate base, hypochlorite (OCl^-), acting as an inert reservoir of chlorine.[1] More recently, other chlorine species (e.g., Cl_2 and Cl_2O) present at trace concentrations have been found to contribute to the halogenation of nucleophiles, particularly those reacting slowly with hypochlorous acid, and especially in acidic or salty solutions.[22−26] Hypochlorite, rather than hypochlorous acid, was recently found to be responsible for the reactions of free chlorine with unsaturated aldehydes, through a presumed nucleophilic attack at one of the electrophilic carbons of the aldehyde.[27] While recent efforts have focused on understanding the chemistry of chlorine and its reactive species, the organic substrate scope for chlorination reactions has been little revised and includes reduced nitrogen and sulfur, C═C and C═N π bonds, and certain inorganic ions (e.g., nitrite, sulfite, bromide, and Fe^{2+}), with rate constants spanning several orders of magnitude.[1]

Collection of chlorination rate constants typically involves the addition of chlorine and a concentrated nucleophile from stock solutions to buffered deionized water in batch reactors. Stock solutions of nucleophiles, if organic, are often prepared as in an organic solvent (e.g., methanol, methyl-*tert*-butyl ether, or acetonitrile).[28−31] The use of organic solvents for stock solution preparation conveys several advantages. The solutions typically remain sterile, avoiding microbial degradation of the nucleophile; they can be stored in freezers without freezing, further postponing decay, and they permit high concentrations of even highly hydrophobic nucleophiles (e.g., PAHs and PCBs), which could not be achieved in water.

Implicit in the use of organic solvents as stock solution carriers is an assumption that they are inert with respect to the reactants of interest. Saturated alcohols, lacking functional groups broadly recognized as being able to be oxidized by

Received: July 5, 2024
Revised: July 31, 2024
Accepted: August 1, 2024
Published: August 6, 2024



https://doi.org/10.1021/acs.estlett.4c00540

chlorine, are often favored because they are miscible with water. In the synthetic organic chemistry literature, alcohol chlorination reactions have been reported, although under conditions unlike the environment (e.g., employing the use of an exotic single-electron-transfer catalyst or conducting experiments in acetic acid[32] or polar organic solvents[33−35]). Likely due to the absence of reliable reports of aqueous alcohol chlorination under mild conditions in the literature, the assumption of alcohol inertness is so widespread that aliphatic alcohols (most commonly methanol) are among the most frequently used as solvents for preparing stock solutions in chlorination kinetics experiments. Stock solutions have been prepared in methanol and spiked into experimental samples to assess the reactivity of free chlorine with numerous environmental organic compounds, including the antibacterial agent triclosan,[36] tetracycline antibiotics,[37] benzodiazepine pharmaceuticals,[38] estrogenic compounds bisphenol A and 17*β*-estradiol,[39] benzophenone-type ultraviolet filters,[40] haloacetonitrile disinfection byproducts,[41] and precursors of disinfection byproducts (e.g., cyclic alkenes,[42] olefins,[28] and resorcinols[13]). While these represent a small subset of studies explicitly stating that compound solutions were prepared in methanol, many others fail to disclose the solvent chosen for stock preparation.

This work describes experiments that began with a failed attempt to duplicate a published result. Aldehydes have been observed as disinfection byproducts at wastewater reuse facilities,[43,44] which is easily explained for plants using ozone for primary disinfection[45,46] but not for those using chlorine. One study reported formaldehyde as a chlorination byproduct of dimethylamine,[47] which is present in wastewater.[48,49] The formation of formaldehyde from chlorination of dimethylamine was not repeatable in an interlab comparison, which led us to hypothesize, after ruling out other potential causes, that the discrepancy arose from differing dimethylamine stock solvents (water vs methanol). The objectives of this study were (1) to quantify artifactual aldehyde formation during chlorination of a nucleophile prepared in a methanolic stock solution, (2) to determine the extent to which residual alcohols from stock solution preparation might consume free chlorine, jeopardizing the steady-state assumption intrinsic to most chlorination kinetics experiments, and (3) to quantify the rates of formation of carbonyl compounds from chlorination of a range of aqueous alcohols.

■ METHODS AND MATERIALS

Materials and Reagents. Reagents, buffers, and analytical standards were obtained at the highest purity available (Table S1). Solutions were prepared using 18.2 MΩ Milli-Q water from a Millipore system or LC-MS grade water (Millipore-Sigma). Free chlorine stock solutions were standardized weekly by ultraviolet spectroscopy (details in Text S1).

Chlorination Experiments. The formation of formaldehyde from the reaction between dimethylamine (DMA) and chlorine was studied under pseudo-first-order conditions ($[\mathrm{DMA}]_0 = 100\ \mu\mathrm{M}$, and $[\mathrm{NaOCl}]_0 = 4$ mM). Stock solutions of 50 mM DMA prepared in methanol or water were added, together with standardized aqueous free chlorine, to pH 7 phosphate buffer (50 mM) prepared in ultrapure water, and the mixture was immediately distributed into 2 mL sacrificial headspace-free vials and stored in the dark at 22 °C until sampling was performed.

Alcohol chlorination kinetics were determined by measuring the rates of formation of carbonyl products under pseudo-zeroth-order conditions (i.e., initial rate conditions during the first ≤10% of the reaction). Alcohols and free chlorine were added to pH 6 phosphate buffer (50 mM) prepared in ultrapure water, distributed into sacrificial vials in the same fashion as the mixture for the reaction between DMA and chlorine. Residual chlorine was quantified using *N*,*N*-diethyl-*p*-phenylenediamine (DPD) colorimetry to verify that ≤10% of the initial chlorine dose was depleted over the duration of the experiment (Text S2).

Following quenching with sodium thiosulfate, samples were immediately derivatized with 2,4-dinitrophenylhydrazine (DNPH) for carbonyl compound quantification using previously established methods (Text S3).[50] Thiosulfate consumes superstoichiometric chlorine, and the stoichiometry of this reaction is a complex function of pH.[51,52] Quenching was performed at an initial 0.5:1 $[\mathrm{Na_2S_2O_3}]_0{:}[\mathrm{NaOCl}]_{\mathrm{TOT},0}$ molar ratio, consistent with its previously reported quenching ratio at neutral pH,[51] and we verified minimal interference with subsequent derivatization (Text S4 and Figures S1−S4). Sodium thiosulfate and chlorine were added to all calibration standards at the same ratio of 0.5:1 to account for any effects on the DNPH derivatization efficiency.

Analytical Methods. DNPH-derivatized carbonyl compounds were detected using high-performance liquid chromatography coupled with triple-quadrupole mass spectrometry (LC-MS/MS, Agilent 1290/6470). A Phenomenex Kinetex biphenyl column (2.6 μm, 100 mm × 4.6 mm) was used with a 30:30:40 methanol/ethanol/water mobile phase, a flow rate of 1.5 mL/min, and a column heater set to 40 °C. Detailed MS parameters and compound-specific method information can be found in Text S3 and Table S2.

Kinetics Modeling. The potential for chlorine depletion by methanol to interfere with the collection of accurate nucleophile chlorination kinetics data was assessed by reaction kinetics modeling in Kintecus.[53] Reactions were modeled with fixed initial concentrations of chlorine (10 mM) and a hypothetical nucleophile (1 μM). The rate of the reaction between chlorine and methanol was the average of our experimental values determined as described below [$k_{\mathrm{app}} = (1.08 \pm 0.17) \times 10^{-4}\ \mathrm{M^{-1}\ s^{-1}}$], and the rate of the reaction between chlorine and the hypothetical nucleophile was varied between 0.001 and 0.1 $\mathrm{M^{-1}\ s^{-1}}$. These hypothetical rate constants, while slow, are near values reported for the chlorination of a number of nucleophiles, including gemfibrozil (0.9 $\mathrm{M^{-1}\ s^{-1}}$),[11] alkoxybenzenes (0.01−0.35 $\mathrm{M^{-1}\ s^{-1}}$),[11] salicylic acid (∼0.1 $\mathrm{M^{-1}\ s^{-1}}$),[54] pyrene (0.23 $\mathrm{M^{-1}\ s^{-1}}$),[55] 4-chlorophenol (0.02 $\mathrm{M^{-1}\ s^{-1}}$),[4] anatoxin A (0.71 $\mathrm{M^{-1}\ s^{-1}}$),[56] and anisole (∼0.2 $\mathrm{M^{-1}\ s^{-1}}$).[23] Further details related to modeling are provided in Text S6.

■ RESULTS AND DISCUSSION

Artifactual Formation of Formaldehyde from the Chlorination of DMA Prepared in Methanol. Previous research reported that DMA and free chlorine reacted quickly to produce chlorinated DMA, before degrading slowly to formaldehyde in 20−35% yield at pH 7.[47,57] However, an attempt to replicate this result resulted in a yield of formaldehyde of <10% from DMA when the stock solution was prepared in water (Figure 1). When the experiment was repeated using DMA dosed from a stock solution prepared in methanol [resulting in [MeOH] = 0.4% (v/v)], the apparent formaldehyde yields (relative to $[\mathrm{DMA}]_0$) approached 50% (Figure 1), which is more consistent with past results. Despite

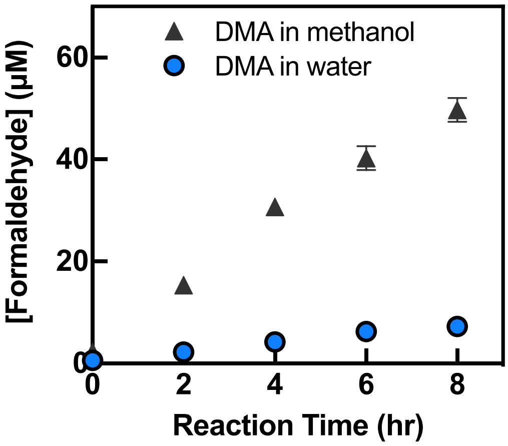


Figure 1. Formation of formaldehyde from the reaction of free chlorine (4 mM) with dimethylamine (DMA, 100 μM) added from a DMA stock (50 mM) prepared in methanol [0.4% (v/v)] compared to DMA added from a stock (50 mM) prepared in ultrapure water. All values were measured in triplicate. Error bars represent the standard deviation; those not shown are eclipsed by markers. Other reaction conditions: pH 7.0 ± 0.1, [phosphate buffer] = 50 mM, and $T = 22 \pm 1$ °C.

the relatively low molar yield of formaldehyde from chlorination of methanol (~0.1%), methanol was the dominant source of formaldehyde formation because its initial concentration was orders of magnitude higher than that of DMA, as is typical when dosing nucleophiles into water from stock solutions prepared in organic solvents. Previous studies investigating aldehyde formation from reactions with chlorine might have overestimated the formaldehyde yield if precursor stock solutions were prepared in methanol,[47,58−60] but stock solution solvents are often not disclosed.

Unintended Chlorine Depletion in the Presence of Methanol. In addition to the artifactual formation of formaldehyde, the introduction of methanol into reaction mixtures during chlorination was suspected to deplete residual chlorine, potentially invalidating pseudo-first-order assumptions if chlorine was presumed to react with only target nucleophiles. Addition of ≥100 mM methanol (≥0.4% by volume) to 10 mM chlorine in buffered ultrapure water led to a statistically significant degradation of chlorine [Figure 2 and Figure S5D ($p < 0.001$)]. The observed first-order chlorine depletion rate constant (k') increased from $(1.2 \pm 0.1) \times 10^{-5}$ s^{-1} at 0.4% methanol (Figure S5D) to $(4.4 \pm 0.6) \times 10^{-5}$ s^{-1} at 2% MeOH (Figure S5F). Corresponding chlorine half-lives decreased from 16.7 h at 0.4% MeOH to 4.3 h at 2% MeOH. Augmenting aqueous chlorine with ≤0.2% methanol did not result in significant chlorine depletion (Figure S5A−C).

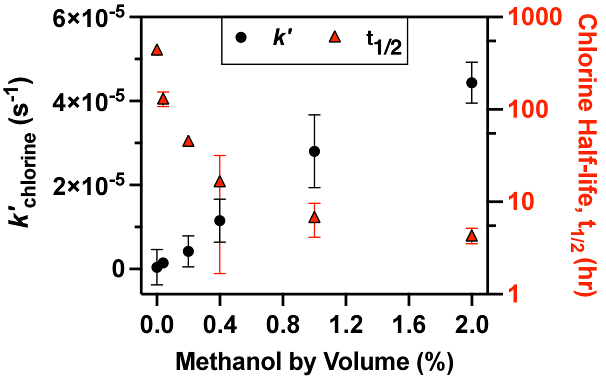


Figure 2. Observed first-order chlorine decay rate constants (k') and corresponding half-lives ($t_{1/2}$) as a function of aqueous methanol concentration. Conditions: $[\mathrm{NaOCl}]_0$ = 10 mM, pH 6.0 ± 0.1, [phosphate buffer] = 50 mM, and $T = 22 \pm 1$ °C. Error bars represent 95% confidence intervals; those not shown are eclipsed by markers.

Depletion of chlorine by methanol introduced during dosing of nucleophile stock solutions may unintentionally interfere with the collection of accurate chlorination kinetics data, particularly for slowly reacting nucleophiles. In past work, if chlorine concentrations were assumed to be constant rather than monitored, unobserved decreases in chlorine concentration throughout experiments could have led to underestimates of chlorination rate constants. Additionally, assumptions of pseudo-first-order conditions might have been unjustified if initial chlorine concentrations were only slightly in excess of a 10:1 molar ratio relative to target nucleophiles.

To simulate such scenarios, reaction kinetics were modeled for the chlorination of hypothetical nucleophiles with a range of chlorine k_{app} values in the presence of excess free chlorine under presumed pseudo-first-order conditions. Reactions were modeled in the presence of 0−2% methanol, using our experimentally determined second-order apparent rate constant between free chlorine and methanol [$k_{app} = (1.08 \pm 0.17) \times 10^{-4}$ M^{-1} s^{-1}; the average of values calculated from experiments at 0.4%, 1%, and 2% MeOH in Figure S5 (Text S6)]. Nucleophile concentrations decreased more slowly at higher methanol concentrations and increasingly deviated from first-order behavior (Figure 3A). The resulting pseudo-first-order rate constant estimate was 80% lower in the presence of 1% methanol than in the methanol-free case for a hypothetical nucleophile with a k_{app} of 0.001 M^{-1} s^{-1} (Figure 3B and Figure S6). For faster reacting nucleophiles, the error was less pronounced but remained greater than a 5% deviation from methanol-free conditions for k_{app} values of ≤0.1 M^{-1} s^{-1} in 1% methanol, with errors increasing as a function of methanol concentration (Figure 3B and Figures S7 and S8). Decreased reaction rates could be attributed to decreasing free chlorine concentrations over time, as free chlorine was consumed by methanol (Figures S1 and S6−S8).

Formation of Carbonyl Compounds from the Reaction of Chlorine with a Range of Alcohols. In addition to methanol, a range of saturated alcohols were chlorinated to measure the potential formation of the corresponding carbonyl compound. Our rationale in assessing chlorination of other alcohols was to determine whether (1) this reaction was unique to methanol or applied to other primary or secondary alcohols, as well, (2) the detection of ≥2 carbon aldehydes in recycled water might be attributable to oxidation of longer chain alcohols, and (3) experimental artifacts induced by methanol could be avoided by switching to other alcohols, which have similarly convenient properties (e.g., miscibility with water, excellent solvation of hydrophobic compounds, and lower toxicity relative to other solvents). The chlorination of ethanol, 1-propanol, 1-butanol, 1-pentanol, and 2-propanol resulted in the formation of the respective aldehyde or ketone (i.e., acetaldehyde, propionaldehyde, butyraldehyde, pentanal, and acetone, respectively) at rates comparable to that of the formation of formaldehyde from the chlorination of methanol (Figure 4).

The rates of formation of carbonyl compounds obtained under pseudo-zeroth-order (i.e., initial rate) conditions were

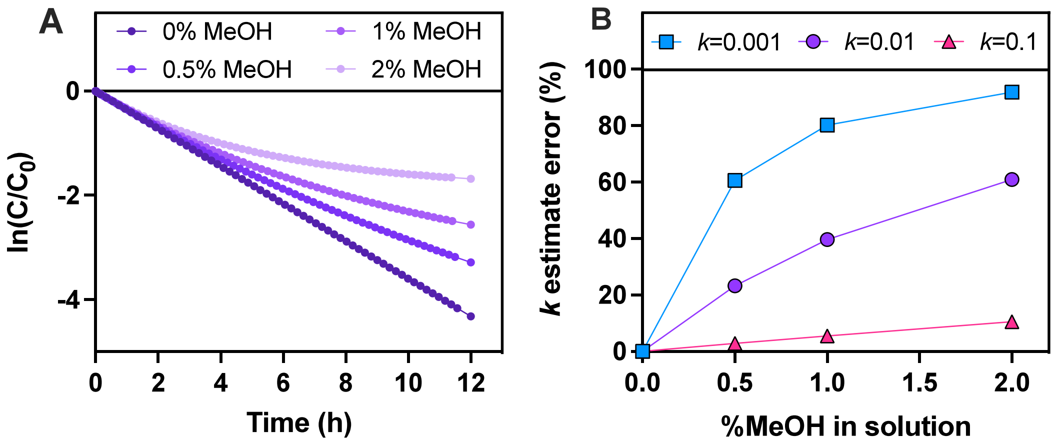


Figure 3. (A) Modeled depletion of a hypothetical nucleophile with an apparent chlorine rate constant (k_{app}) of 0.01 M^{-1} s^{-1} in the presence of 0−2% MeOH. (B) Rate constant estimation error induced by 0−2% MeOH for three hypothetical nucleophiles with a k_{app} of 0.001−0.1 M^{-1} s^{-1}. Data used to construct panel B are shown in Figures S6 and S8, and the modeling approach is described in Text S8.

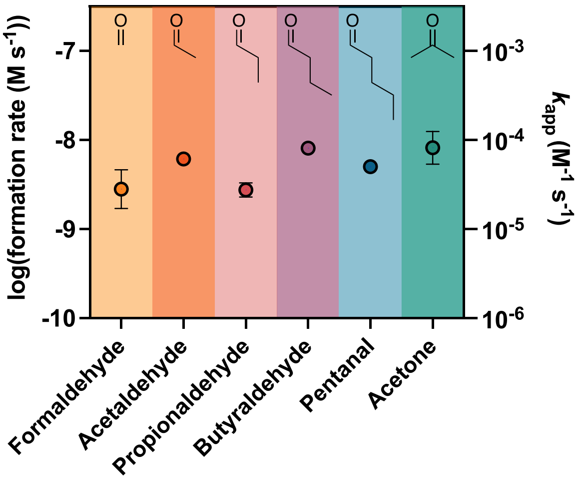


Figure 4. Carbonyl compound formation rates and second-order rate constants from the reaction between alcohols and free chlorine. Respective aldehydes and ketone from the chlorination of alcohols: methanol, ethanol, 1-propanol, 1-butanol, 1-pentanol, and 2-propanol from left to right, respectively. Other reaction conditions: $[\text{alcohol}]_0$ = 10 mM, $[\text{NaOCl}]_0$ = 10 mM, pH 6.0 ± 0.1, [phosphate buffer] = 50 mM, and T = 22 ± 1 °C. Filled circles represent mean rate values, and error bars represent the standard deviation (n = 3 or 6). Error bars that are not shown are eclipsed by the markers. Results from individual replicate experiments are provided in Figures S9−S13. The results of control experiments indicating that the phosphate buffer did not catalyze the reaction are shown in Figure S14.

converted to second-order apparent rate constants [k_{app} (M^{-1} s^{-1}) (Figure 4, secondary y-axis)] by dividing formation rates by the initial alcohol and chlorine concentrations (Text S7). Second-order apparent rate constants for carbonyl formation (Figure 4, secondary y-axis) were comparable to the rate constant of chlorine decay by reaction with methanol under similar conditions [k_{app} = (1.08 ± 0.17) × 10^{-4} M^{-1} s^{-1}]. The similarity between rate constants obtained by product formation and reactant consumption suggests a reasonable mass balance, although we were unable to directly quantify the carbon mass balance, because a sufficiently sensitive method for measuring trace aqueous methanol was unavailable. Alignment of aldehyde formation and chlorine consumption rate constants also suggests that the rate-limiting step of the reaction involves both chlorine and the alcohol or an intermediate as opposed to, for example, a unimolecular decomposition of an intermediate.

■ ENVIRONMENTAL IMPLICATIONS

The use of methanol in stock solution preparation for experiments with chlorine can bias experimental findings by producing artifactually low estimates for rate constants and by causing deviations from pseudo-first-order conditions, potentially leading to confusion about the reaction rate order. Errors in experimental findings generated by this oversight could lead to the misrepresentation of predicted degradation and/or (trans)formation rates of important environmental contaminants in model treatment systems.

Our results suggest that methanol should be avoided when preparing stock solutions to study chlorination reactions. Stock solution preparation in water, if permitted by the nucleophile solubility, is likely the safest option. If an organic solvent is required for nucleophile dissolution, we recommend selecting a non-alcohol solvent (e.g., acetonitrile or methyl-*tert*-butyl ether), preparing stock solutions at high concentrations to minimize the solvent contribution to the aqueous solution [e.g., <0.05% (v/v)], and performing blank control experiments with the same volume of added solvent as in nucleophile chlorination reactions.

In addition to biasing reaction kinetics results, alcohols in solution can react with chlorine to form analogous carbonyl compounds. Chlorination of alcohols to carbonyl compounds might explain aldehyde formation detected during the chlorination of wastewater effluent in potable water reuse.[43] No known formation pathway of aliphatic aldehydes from aqueous chlorination has been published; however, methanol and ethanol are frequently used as supplemental carbon sources during wastewater treatment,[61−63] and formaldehyde and acetaldehyde comprise the majority of the carbon-based mass of carbonyl compounds formed during disinfection of wastewater with chlorine. Further investigation, including the detection and quantification of alcohols in reuse waters and the elucidation of the mechanism by which they react with chlorine over a range of experimental conditions (e.g., varying pH and temperature), is necessary to better understand the role of alcohols in carbonyl compound formation during water treatment.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.estlett.4c00540.

Analytical method details, kinetics modeling approach and results, chlorine depletion and carbonyl compound formation data (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors acknowledge funding from the National Science Foundation (CHE-2304860 to E.L.M. and CHE-2304861 and CBET-1944810 to D.L.M.).

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