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Article

Production of Dichloroacetonitrile from Derivatives of Isoxaflutole Herbicide during Water Treatment

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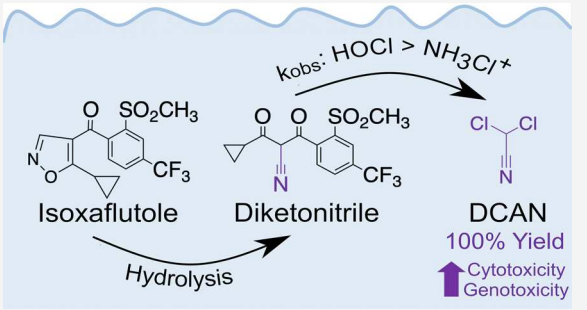
ABSTRACT: The herbicide isoxaflutole has the potential to contaminate drinking water directly, as well as upon hydrolyzing to its active form diketonitrile. Diketonitrile also may impact water quality by acting as a precursor for dichloroacetonitrile (DCAN), which is an unregulated but highly toxic disinfection byproduct (DBP). In this study, we investigated the reaction of diketonitrile with free chlorine and chloramine to form DCAN. We found that diketonitrile reacts with free chlorine within seconds but reacts with chloramine on the time scale of hours to days. In the presence of both oxidants, DCAN was generated at yields up to 100%. Diketonitrile reacted fastest with chlorine at circumneutral pH, which was consistent with base-catalyzed halogenation involving the enolate form of diketonitrile present at alkaline pH and electrophilic hypochlorous acid, which decreases in abundance above its pK_a (7.5). In contrast, we found that diketonitrile reacts faster with chloramine as pH values decreased, consistent with an attack on the enolate by electrophilic protonated monochloramine that increases in abundance at acidic pH approaching its pK_a (1.6). Our results indicate that increasing isoxaflutole use, particularly in light of the recent release of genetically modified isoxaflutole-tolerant crops, could result in greater occurrences of a high-yield DCAN precursor during disinfection.



KEYWORDS: *disinfection byproduct (DBP), haloacetonitrile (HAN), diketonitrile, base-catalyzed halogenation, chlorination, chloramination, oxidation*

INTRODUCTION

The herbicide isoxaflutole is a known contaminant of drinking water sources.[1] Its increasing use[2] has recently garnered concern due to its potential for expanded application associated with the release of isoxaflutole-tolerant genetically modified (GM) crops in the U.S. in 2020.[1,3] After application, isoxaflutole is readily hydrolyzed to its active form,[1] diketonitrile (Figure 1), by both abiotic and biotic processes on the time scale of hours to days in surface waters,[4] soils,[5−7] and plants.[8] Due to this conversion, both isoxaflutole and diketonitrile are present in drinking water sources, where diketonitrile and, to a lesser extent, isoxaflutole are highly mobile and likely to remain in the water column.[6,9−11] A prior study detected both isoxaflutole and diketonitrile in 10 tributaries to the Missouri and Mississippi Rivers; however, diketonitrile was typically found to be the dominant species.[12] For example, during the postplanting season (i.e., May to June), diketonitrile was detected in all samples, while isoxaflutole was only detected in 15% of the samples.[12] The mobility of isoxaflutole and diketonitrile also may contribute to persistence during drinking water treatment,[6,9−11] as chemicals with comparable properties are not removed during flocculation or filtration.[13,14]

Together, isoxaflutole and diketonitrile in water sources pose a threat to drinking water quality due to their toxicity. Because of its rapid metabolism to diketonitrile in mammals,[15] the apparent carcinogenicity and developmental toxicity of administered isoxaflutole represents the aggregate of isoxaflutole and its products, predominantly diketonitrile.[1,15,16] The overall drinking water level of comparison (DWLOC), determined by the U.S. Environmental Protection Agency based on administered isoxaflutole, is 100 nM,[16] which is within 100-fold of previously reported maximum diketonitrile surface water concentrations (i.e., 1.5 nM) in 2004.[12] This margin is smaller—in some cases by orders of magnitude—than many other agrochemicals (SI section 1).[17] More recent measurements of surface water concentrations are unavailable; however, isoxaflutole use has increased by 40% from 2004 to 2019,[2] which may contribute to higher current concentrations. Although use data after the commercial release of GM

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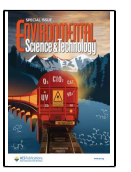

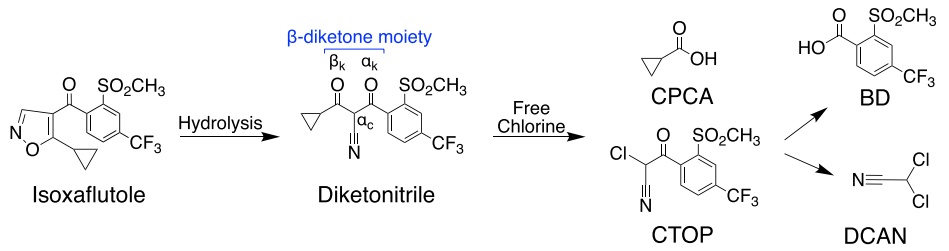

Figure 1. Structure of isoxaflutole, its hydrolysis product diketonitrile, and the products of the reaction of diketonitrile with free chlorine (i.e., cyclopropane carboxylic acid, CPCA; 2-chloro-3-[2-(methylsulfonyl)-4(trifluoromethyl)phenyl]-3-oxopropanenitrile, CTOP; benzoic acid derivative, BD; dichloroacetonitrile, DCAN). On the diketonitrile structure, the β-diketone moiety is indicated by the blue bracket. Within the β-diketone moiety, the two ketones, labeled relative to the aromatic ring (i.e., β_k, α_k), are connected by a carbon, labeled relative to the ketones (i.e., α_c).

isoxaflutole-tolerant crops are unavailable, other herbicides (i.e., dicamba) have exhibited increased use after the release of their corresponding tolerant crops.[18] Additionally, isoxaflutole in particular may exhibit increasing use with its GM crop because it is considered a key alternative to the widely used herbicide glyphosate, which has declining efficacy due to the emergence of glyphosate-resistant weeds.[1,19]

During water treatment, isoxaflutole and diketonitrile also may serve as precursors for disinfection byproducts (DBPs). Diketonitrile formed from isoxaflutole in the presence of free chlorine was previously found to produce the nitrogenous DBP, dichloroacetonitrile (DCAN), along with two additional products: a benzoic acid derivative (BD) and cyclopropane carboxylic acid (CPCA) (Figure 1).[20,21] Among the three products, DCAN poses the greatest threat to drinking water as a highly toxic DBP,[22] while BD and CPCA have been determined to be nontoxic or toxic only at high concentrations, respectively.[15,23] Although unregulated,[24] haloacetonitriles like DCAN are orders of magnitude more cytotoxic and genotoxic than regulated DBPs (i.e., trihalomethanes, haloacetic acids).[22,24−27] Because of this high toxicity, DCAN and other haloacetonitriles have been suggested to represent the greatest contribution to overall DBP toxicity in treated drinking water despite their occurrence at relatively low concentrations (i.e., median [DCAN] = 9.1 nM in U.S. drinking water treatment plant effluent during 2000−2002).[22,24−29] Consequently, the potential for diketonitrile to generate DCAN may contribute to increased drinking water toxicity, particularly if isoxaflutole is used at increasing rates in coming years.

To enable more accurate characterization of the risk posed by increased isoxaflutole use to drinking water quality, we evaluated the rates at which diketonitrile reacts with common water disinfectants, as well as the yield of reaction products including DCAN. We hypothesized that diketonitrile reacts quickly with free chlorine due to the inclusion of a β-diketone moiety (Figure 1), which readily enolizes to a strong nucleophile that reacts rapidly with electrophilic hypochlorous acid. We further hypothesized that this reaction would generate DCAN at high yields due to the presence of a nitrile moiety on the α-carbon (Figure 1). We also evaluated the potential for chloramine to undergo a related reaction with diketonitrile, as well as for the preoxidant permanganate to remove diketonitrile. Finally, we applied our findings to understand how increased isoxaflutole use might contribute to greater drinking water toxicity due to diketonitrile acting as either a drinking water contaminant itself or as a DBP precursor.

MATERIALS AND METHODS

Chemical Sources and Preparation. Chemicals used in this study were sourced as detailed in SI section 2.1. To generate stocks, isoxaflutole and diketonitrile were dissolved in 100% acetonitrile and 40:60 (v/v) methanol:water, respectively, resulting in experimental samples with <5.8% co-solvent by volume. All other solutions were prepared in Milli-Q water (18.2 MΩ·cm). Glassware was rinsed four times with reverse osmosis-treated water and twice with Milli-Q water, followed by baking at 450 °C for 4 h. Plastic caps were rinsed with water as above, followed by rinsing twice with methanol instead of baking.

Diketonitrile was prepared by hydrolyzing isoxaflutole for all experiments excluding controls to demonstrate equivalent reactivity to a diketonitrile standard, which was available only in limited quantities. Isoxaflutole was hydrolyzed for 48 h in 10 mM carbonate buffer with pH greater than 9.5 ($t_{1/2}$ = 1.1 ± 0.1 h, diketonitrile yield at 32 ± 0.15 h: 100 ± 8%, SI section 2.2). Consequently, all samples including diketonitrile hydrolyzed from isoxaflutole contained ≤0.6 mM carbonate buffer. Diketonitrile hydrolyzed from isoxaflutole was verified to react at similar rates with free chlorine and chloramine as diketonitrile standard purchased from Toronto Research Chemicals Inc. (SI section 2.2).

Detailed oxidant preparation and quantification methods are provided in SI section 3.1. Sodium hypochlorite, monochloramine, and potassium permanganate were prepared following standard methods and photo-standardized before use. We measured the residual free chlorine and monochloramine to determine the oxidant demand of diketonitrile across pH conditions using Hach DPD (*N*,*N*-diethyl-*p*-phenylenediamine) methods.[30] Consistent with the higher nitrogen to chlorine ratio,[31] monochloramine was confirmed to account for >90% of chloramine species (i.e., monochloramine, dichloramine) in solutions across pH (SI section 3.1). Permanganate residual concentrations were measured at the same absorbance used for photo-standardization.

Experimental and Analytical Procedure. Experimental solutions were prepared at room temperature (21.9−23.0 °C) with an initial diketonitrile concentration of 10 μM. Buffers (10 mM) were selected so their pK_a values were within 1 pH unit of the measured experimental pH: sodium acetate (pK_a 4.76) for solutions with pH value of 4.8 ± 0.15; sodium phosphate (pK_a 7.2) for solutions with pH values of 6.4 ± 0.1, 7.1 ± 0.1, and 8.0 ± 0.15; and sodium carbonate (pK_a 10.33) for solutions with a pH value of 9.5 ± 0.1. Buffers were adjusted with concentrated sulfuric acid or sodium hydroxide. The pH did not change during the reaction (SI section 3.2).

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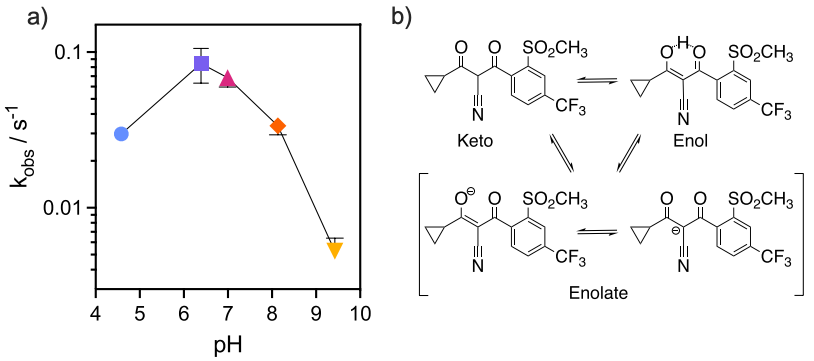

Figure 2. Loss of diketonitrile (initial concentration = 10 μM) in the presence of free chlorine (30 μM) at varying solution pH values. Observed pseudo-first-order rate constants, determined from data with corresponding symbols (SI section 4.2), are plotted across pH (a). The error bars represent the standard error of the observed rate constant (SI section 4.2) and are not shown if smaller than the symbol. Diketonitrile converts among its keto, enol, and enolate forms (b). The negative charge on the enolate is distributed over the β-diketone moiety.

Oxidants were subsequently added to the samples at concentrations indicated alongside corresponding data sets. Diketonitrile did not degrade to a measurable extent in the absence of oxidants (SI section 3.3). Sodium thiosulfate or ascorbic acid was added at >3-fold molar excess relative to initial oxidant concentration to quench permanganate, while ascorbic acid was added at 3-fold molar excess relative to initial oxidant concentration to quench free chlorine and chloramine. Due to the fast rate of the reaction, kinetic experiments involving free chlorine were performed by adding free chlorine into a stirred solution followed by addition of ascorbic acid at 90-fold molar excess to rapidly quench the reaction. The degradation of diketonitrile and formation of nonvolatile products, BD and CPCA, were measured in solutions prepared in amber vials with headspace using high-performance liquid chromatography with UV detection (SI section 3.4). The formation of DCAN, a volatile compound, was measured in solutions prepared in amber vials without headspace using gas chromatography−mass spectrometry (SI section 3.5). We used liquid chromatography−mass spectrometry to confirm the reaction intermediate that we observed was the same reaction intermediate identified in a previous study[20] (SI section 3.6), 2-chloro-3-[2-(methylsulfonyl)-4-(trifluoromethyl)phenyl]-3-oxopropanenitrile (CTOP, Figure 1). Detailed analytical methods along with limits of quantification (LOQ) and detection (LOD) are provided in SI sections 3.4−3.6.

Statistical Analysis. Concentrations are reported as the mean determined from duplicate samples. Error bars on concentrations represent the range of the duplicate sample measurements. Errors on yield calculations represent the propagated error of the range of duplicate sample measurements. Errors on rate constants represent the standard error of the slope determined from linear regression. All analyses were done using Microsoft Excel or GraphPad Prism9.

RESULTS AND DISCUSSION

Reaction of Diketonitrile with Free Chlorine. The rate of diketonitrile degradation, which followed observed pseudo-first-order kinetics, was measured in the presence of free chlorine at a 3:1 molar excess relative to diketonitrile, selected to slightly exceed the measured 2.2 ± 0.4 mol of free chlorine demand per mole of diketonitrile (SI section 4.1). At circumneutral pH, the diketonitrile degradation rate was extremely fast, removing diketonitrile on the time scale of seconds (Figure 2a, SI section 4.2). The rapid degradation of diketonitrile by free chlorine is consistent with a prior study that was unable to detect diketonitrile when isoxaflutole was in solution with free chlorine over hours, likely due to rapid consumption of diketonitrile by free chlorine upon its formation.[21]

Similar to degradation at circumneutral pH, diketonitrile degradation with free chlorine also followed observed pseudo-first-order kinetics in solutions with pH values ranging from 4.8 to 9.5 (SI section 4.2). However, in some samples, we observed initial rapid degradation of diketonitrile within the first time point (5−10 s), followed by subsequent degradation at a slower rate following observed pseudo-first-order kinetics (SI section 4.2). We found that the extent of diketonitrile degradation before the initial time point decreased when diketonitrile was equilibrated at pH 4.8 for 1 h prior to free chlorine addition (SI section 4.2, Figure S9). We hypothesize that the initial fast degradation of the diketonitrile at pH 4.8 reflects degradation of a highly reactive diketonitrile species (i.e., enolate, Figure 2b) favored in the alkaline solution that was used to generate diketonitrile via hydrolysis from isoxaflutole (SI section 2.2). When allowed greater time to equilibrate at lower pH, the speciation shifts to less reactive species (i.e., the keto and/or enol, Figure 2b).[32−34] Equilibration for 1 h reduced the amount of diketonitrile removed during the initial rapid phase at pH 4.8 (SI section 4.2, Figure S9) and was therefore applied in kinetic experiments across all pH conditions (Figure 2a, SI section 4.2, Figure S7). Despite equilibration, fast initial degradation of diketonitrile persisted in experiments at pH 7.1 and 8.0, which may be attributed to factors including diketonitrile speciation at equilibrium (SI section 4.2). Consequently, the observed pseudo-first-order rate constants, which do not account for this initial fast phase, represent a conservative measurement of diketonitrile degradation at these conditions.

We determined that diketonitrile degradation in the presence of free chlorine was fastest at pH 6.4 and 7.1 (Figure 2a). One factor contributing to the pH dependence of the observed rate constant is likely the distribution of diketonitrile among the keto, enol, and enolate forms (Figure 2b). The acceleration of the reaction rate when solution pH is increased from acidic to neutral values may result from increased abundance of the more reactive species (e.g., enolate) at more alkaline conditions. However, above neutral pH, the reaction slows at progressively more alkaline conditions (Figure 2a), which is not predicted by diketonitrile speciation alone. Slower

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rates above the pK_a of hypochlorous acid (pK_a 7.5)[35] may result from decreasing abundance of hypochlorous acid relative to the less reactive conjugate base.[35] Consequently, the reaction of diketonitrile with free chlorine may be enabled at circumneutral pH due to the abundance of the reactive forms of both the oxidant (i.e., hypochlorous acid) and the substrate (i.e., the enolate).

To gain further insight into the reaction mechanism, we next investigated the formation of products (i.e., CPCA, BD, DCAN, Figure 1) from the reaction of diketonitrile with free chlorine across pH conditions (Figure 3a). We aimed to

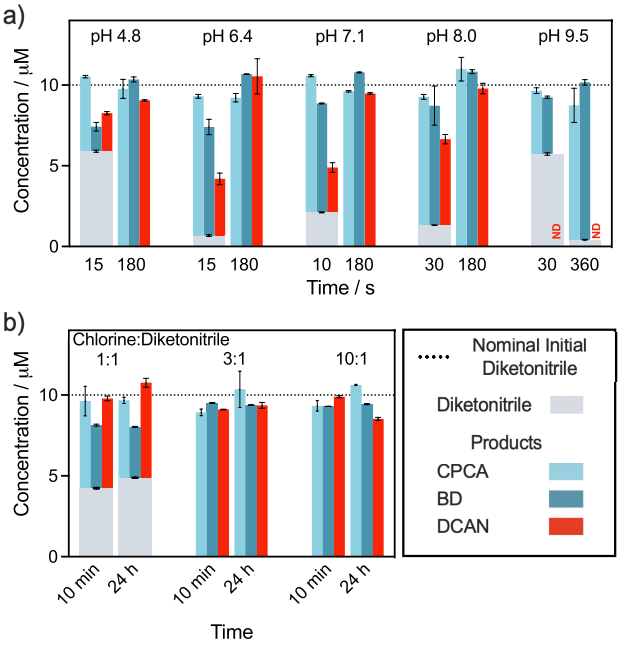

Figure 3. Product formation from diketonitrile (initial concentration = 10 μM) with free chlorine. Product formation with free chlorine (30 μM) from pH 4.8 to 9.5 (a). Product formation with free chlorine (10, 30, 100 μM) at 10 min and 24 h at neutral pH with varying oxidant to diketonitrile molar ratio (b). All data at pH 4.8 were collected after a 1 h equilibration period (SI section 4.2). Diketonitrile concentrations below the limit of detection (LOD = 0.12 μM) are not shown. Product concentrations below the LOD (i.e., CPCA = 0.62 μM, BD = 0.087 μM, DCAN = 0.52 μM) are shown as not detected (ND). Error bars show the range of duplicate samples.

characterize both the order of product formation as well as final yields after reaction completion. Therefore, for each pH condition, products were measured at an earlier time point (i.e., 10−30 s)—selected to ensure both measurable diketonitrile remained in solution and the products were formed at quantifiable concentrations—and a later time point (i.e., 180−360 s)—selected to investigate product formation after reaction completion across all pH conditions. Because the time points varied across pH conditions, we limited our analysis of product yields to comparisons within each pH condition rather than across pH conditions.

At each pH condition, CPCA was formed at approximately 100% yields at both the early and late time points (Figure 3a). At neutral and basic pH, BD was also formed at near 100% yields. However, in acidic conditions, BD was formed at lower yields relative to CPCA at early time points, though it was present at near-100% yields after reaction completion (Figure 3a). CTOP, a known precursor for BD formed during diketonitrile degradation (Figure 1),[20] was verified to be present at pH 4.8 early in the reaction, potentially accounting for slow formation of BD at acidic pH (SI section 4.3).

Unlike CPCA and BD, DCAN yields were lower than 100% at the early time points across all pH conditions (Figure 3a). At acidic pH, low initial DCAN yields along with low BD yields may result from the slower reaction of the CTOP intermediate. However, at neutral and alkaline pH, high yields of both BD and CPCA suggested that both ketone moieties were rapidly cleaved, indicating that the formation of DCAN involves additional steps requiring longer timeframes. With the exception of the pH 9.5 condition, DCAN, along with CPCA and BD, formed at >90% yields after 180 s regardless of pH, indicating that this slower reaction is completed within minutes. DCAN was not detected at pH 9.5 after 360 s, which is consistent with a recent study that did not detect DCAN produced from a known precursor (i.e., acetaminophen) at pH 9[29] attributable to the instability of DCAN at alkaline pH.[36−38]

To investigate reaction stoichiometry and product stability at neutral pH, we compared product yields under various free chlorine concentrations (i.e., 1:1, 3:1, and 10:1 chlorine:diketonitrile molar ratios) at longer time points up to 24 h (Figure 3b). In the presence of both moderate and large excess free chlorine concentrations, all three products were present at high yields (ranging from 85 ± 1% to 106.2 ± 0.3%) after 24 h, indicating both their formation and stability in the presence of excess free chlorine at neutral pH over this time frame. At a 1:1 chlorine:diketonitrile molar ratio (below the 2.2 ± 0.4 mol of free chlorine demand per mole of diketonitrile, SI section 4.1), only 51 ± 2% of the diketonitrile was degraded (Figure 3b). While the yields of both CPCA and DCAN were ∼100%, the yield of BD was only ∼60% of the degraded diketonitrile (Figure 3b). Because BD is stable in the presence of free chlorine (SI section 4.4), its lower yield relative to the other two products suggests its intermediate precursor (e.g., CTOP) may undergo a side reaction in chlorine-limited conditions that does not generate BD.

Reaction of Diketonitrile with Chloramine. Diketonitrile reacted with chloramine according to observed pseudo-first-order kinetics (SI section 4.2), consuming a similar amount of monochloramine as free chlorine (i.e., 2.3 ± 0.4 mol of monochloramine per mole of diketonitrile, SI section 4.1). In comparison to the reaction of diketonitrile with free chlorine that occurred on the time scale of seconds, the reaction with chloramine at a 3:1 chloramine:diketonitrile molar ratio occurred over slower time scales of hours to days (Figure 4). Like free chlorine, we considered the most acidic condition to examine whether the pH shift and subsequent potential changes in diketonitrile speciation would impact the observed reaction rate. At pH 4.8 in the presence of chloramine, diketonitrile was rapidly lost initially, followed by slower degradation following observed pseudo-first-order kinetics, like free chlorine. However, the extent of diketonitrile degradation during the fast phase was small relative to the overall amount of diketonitrile degraded over the duration of the experiment (SI section 4.2). Therefore, across pH conditions, solutions were not equilibrated before addition of monochloramine.

When plotted on a log scale, the observed rate constants decreased linearly with increasing pH values (Figure 4). We propose this decrease may result from declining concentrations of a reactive species (e.g., protonated monochloramine,

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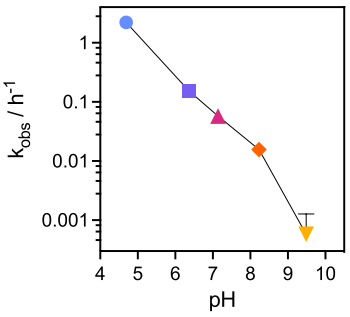

Figure 4. Loss of diketonitrile (DKN) (initial concentration = 10 μM) in the presence of chloramine (30 μM) at varying solution pH values. Observed pseudo-first-order rate constants were determined from data with corresponding symbols (SI section 4.2). The error bars represent the standard error of the observed rate constant (SI section 4.2) and are not shown if smaller than the symbol. At pH 9.5, the lower error bar was not plotted because the rate constant was not significantly different from zero.

NH_3Cl^+) at higher pH, as detailed in the mechanistic discussion below. However, the log of the observed rate constants declined across pH with a slope of 0.71 ± 0.06 rather than with a near-unity slope, which may indicate the involvement of another species with an opposing pH dependence (e.g., the diketonitrile enolate favored at alkaline conditions, SI section 4.5).

We determined that diketonitrile reacted with monochloramine to form the same three products generated from its reaction with free chlorine; namely CPCA, BD, and DCAN (Figure 5a). We again analyzed their concentrations at an early and late time point (i.e., 5 and 24 h). Both CPCA and BD were produced at approximately 100% yields at both time points across pH conditions if the amount of diketonitrile degraded exceeded the respective LOQ of each product. The high yields of these two products suggest that a reaction intermediate (e.g., CTOP) preceding their formation reacts quickly in the presence of chloramine. When quantifiable, DCAN yields ranged from 43 ± 5% to 82 ± 4%. At pH 4.8, no change in DCAN concentrations occurred from 5 to 24 h, suggesting DCAN yields below 100% may result from side reactions rather than slow reaction steps leading to DCAN formation. In contrast, at neutral and alkaline pH, both factors in principle may have contributed to partial DCAN yield from reacted diketonitrile because the reaction of diketonitrile with chloramine was incomplete.

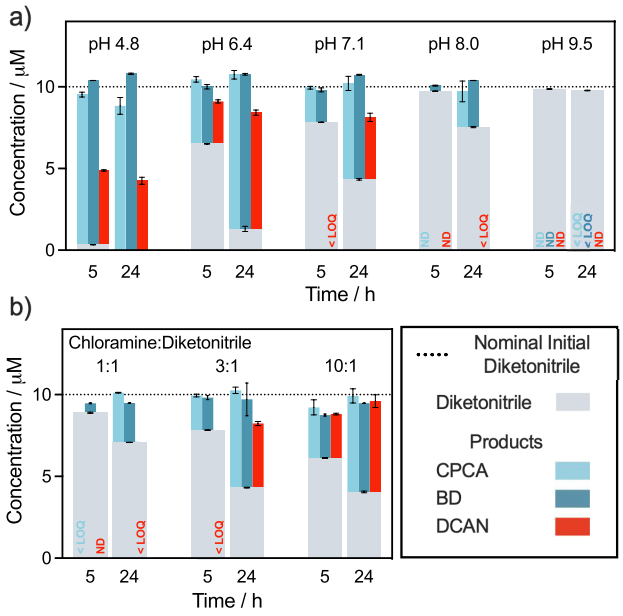

Figure 5. Product formation from diketonitrile (initial concentration = 10 μM) with chloramine at 5 and 24 h. Product formation with chloramine (30 μM) from pH 4.8 to pH 9.5 (a). Product formation with chloramine (10 μM, 30 μM, 100 μM) at neutral pH with varying oxidant to diketonitrile molar ratio (b). Diketonitrile concentrations below the LOD (i.e., 0.12 μM) are not shown. Product concentrations below the LOQ (i.e., CPCA = 1.9 μM, BD = 0.26 μM, DCAN = 1.6 μM) and LOD (i.e., CPCA = 0.62 μM, BD = 0.087 μM, DCAN = 0.52 μM) are shown as <LOQ and ND, respectively. Error bars show the range of duplicate samples.

To further evaluate the factors that contribute to DCAN formation, we measured product formation at varying chloramine:diketonitrile molar ratios at neutral pH (Figure 5b). Higher chloramine concentrations increased both diketonitrile degradation extents and, when quantifiable, DCAN yields. At a 10:1 chloramine:diketonitrile molar ratio after 24 h, DCAN yield was 93 ± 8%, whereas the yield was only 69 ± 4% at a 3:1 chloramine:diketonitrile molar ratio. Higher chloramine concentrations may increase the importance of DCAN formation relative to side reactions upon diketonitrile degradation, suggesting that chloramine concentrations may be a more important factor than free chlorine concentrations when determining the contribution of diketonitrile to DCAN formation.

Diketonitrile Reactivity with Permanganate. Due to the high yield of DCAN from the reaction of diketonitrile with both free chlorine and chloramine, we investigated the reaction of diketonitrile with permanganate, which is used as a preoxidant in water treatment to prevent DBP formation.[39,40] Diketonitrile minimally reacted with permanganate (e.g., diketonitrile concentrations decreased by <3% in the presence of excess permanganate over 92 h, SI section 4.6), consistent with permanganate only reacting with certain drinking water contaminants.[39−46] Diketonitrile does not contain moieties susceptible to reaction with permanganate such as olefins,[39−42] aliphatic amines, tertiary aromatic amines, and thioethers.[43] The lack of reaction between diketonitrile and permanganate indicates that preoxidation by permanganate is unlikely to remove diketonitrile as a DCAN precursor in drinking water.

Mechanism for the Reaction of Diketonitrile with Free Chlorine. The rapid reaction of diketonitrile with free chlorine to form DCAN at high yields is attributable to base-catalyzed halogenation involving the β-diketone moiety containing a nitrile group on the α-carbon (Figure 1). Relative to single ketone moieties, the β-diketone moiety converts readily to its enolate form, which is stabilized by the delocalization of electrons across the conjugated system (Figure 2b).[34,47,48] The enolate form of a β-diketone structure is a stronger nucleophile than the keto or enol form.[49,50] Therefore, the formation of the resonance-stabilized carbanion of the enolate (Figure 6a, Step 1) creates an ideal site for diketonitrile to undergo an electrophilic attack by hypochlorous acid (Figure 6a, Step 2). The reaction rate is likely slowed at acidic pH due to decreasing abundance of the enolate[34,51−53] and at alkaline pH due to decreasing abundance of hypochlorous acid above its pK_a (7.5)[35] (SI section 4.5). Consequently, the reaction is fastest at circumneutral pH due to the co-occurrence of the enolate and hypochlorous acid.

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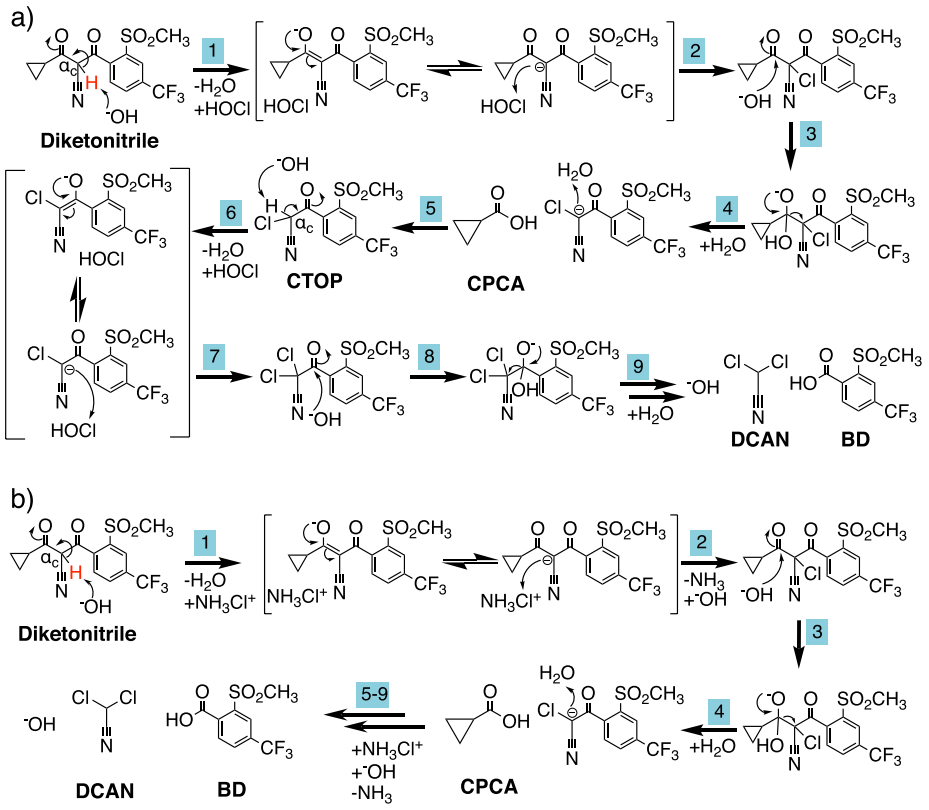

Figure 6. Proposed halogenation pathway by hypochlorous acid (a) and by protonated monochloramine (b) catalyzed by base species (shown here as hydroxide, $^{-}$OH). The acidic proton on α-carbon (α_c) of the β-diketone moiety is indicated in red.

After halogenation of the enolate (Figure 6a, Step 2), the next steps lead to cleavage of the two ketones, which in principle could occur first at either the α- or the β-ketone (Figure 1). The addition of the electron-withdrawing chlorine increases the electrophilicity of the ketone. The ketone then becomes a favorable site for a nucleophilic attack by a base (e.g., hydroxide, Figure 6a, Step 3), resulting in its cleavage (Figure 6a, Step 4).[35,52,53] The order of ketone cleavage is indicated in acidic conditions by the initial formation of CPCA and the intermediate, CTOP, which suggests the nucleophilic attack first occurs at the β-ketone rather than at the α-ketone (Figure 6a, Step 5). However, the fast formation of both CPCA and BD at neutral and basic pH, likely due to increased enolate abundance in more alkaline conditions,[34,51−53] prevents the reaction order from being determined. Due to the steric hindrance at the α-ketone, the β-ketone is more accessible for a nucleophilic attack.

The remaining ketone in CTOP is cleaved following a similar set of reactions as the first ketone to generate the final two products, BD and DCAN. Like diketonitrile, the enolate of CTOP acts as a stronger nucleophile compared to the keto or enol forms of CTOP. Therefore, the formation of the CTOP enolate (Figure 6a, Step 6) leads to halogenation of CTOP by hypochlorous acid (Figure 6a, Step 7). This second halogenation step accounts for the consumption of the second mole of chlorine per mole of diketonitrile and the formation of a single dichlorinated product. The α-ketone within CTOP is then cleaved by a nucleophilic attack by hydroxide (Figure 6a, Step 8), forming BD directly (Figure 6a, Step 9) and DCAN after an additional reaction step (Figure 6a, Step 9), accounting for slower formation of DCAN relative to BD.

Our proposed mechanism to generate DCAN via base-catalyzed halogenation of the enolate by hypochlorous acid is consistent with evidence presented herein; these data may also exclude some alternative mechanisms. A prior study reporting the identity of products from diketonitrile degradation in the presence of free chlorine—but neither kinetic nor yield data—proposed that hypochlorite nucleophilically attacks diketonitrile.[20] However, in contrast to our observations, reactions involving hypochlorite as a nucleophile accelerate above the pK_a of hypochlorous acid due to increased hypochlorite concentrations and may not generate chlorinated products.[54] Nucleophilic attack by hypochlorite is also inconsistent with high electron density at the β-diketone moeity.[55] The involvement of other chlorine species (e.g., chlorine monoxide, molecular chlorine), which have been reported to accelerate chlorination reactions at lower pH conditions, is also not supported by the slower reaction rate at acidic pH.[56,57] Another possible pathway involves the acid-catalyzed halogenation of the enol rather than the enolate, which has been proposed to describe trihalomethane formation from ketone-containing structures alongside base-catalyzed halogenation.[35,51,53] However, the acid-catalyzed pathway is reported to only dominate below a pH of 5.[35] Therefore, the acid-catalyzed pathway is unlikely to contribute at environmentally relevant pH.

Mechanism for the Reaction of Diketonitrile with Chloramine. Although the reaction of diketonitrile with monochloramine forms the same products as the reaction with free chlorine, the reaction rate is substantially slower and has a notably different dependence on solution pH. The decreasing reaction rate constants from acidic to alkaline pH indicate the dominant reactive chloramine species is protonated mono-

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chloramine rather than monochloramine. Although monochloramine has been determined to act as an electrophile, producing a chlorinated product,[58−61] previous studies have identified protonated monochloramine as a much stronger electrophile.[62−64] Monochloramine and protonated monochloramine have computationally determined positive charges of +0.08 and +0.26 on their respective chlorines,[64] indicating protonated monochloramine has increased electrophilicity. Despite its low pK_a of 1.6,[65] protonated monochloramine as an active chlorinating agent has been observed to drive halogenation reactions even at trace concentrations.[62−64] While other trace chlorinating species (e.g., dichloramine, hypochlorous acid) also occur, there is less evidence for their contribution to halogenation under our reaction conditions than protonated monochloramine (SI section 5). Therefore, we propose diketonitrile degradation in the presence of chloramine occurs along a comparable pathway to free chlorine; however, protonated monochloramine halogenates diketonitrile (Figure 6b). Like free chlorine, we propose the reaction pathway is not only dependent on the speciation of the chlorinating agent, but also on the speciation of diketonitrile among its keto, enol, and enolate forms.

From acidic to alkaline pH, the log of the observed pseudo-first-order rate constants decreased by 0.7 per pH unit. In contrast, a near-unity decrease would be expected for a reaction only dependent on the concentration of protonated monochloramine, suggesting increasing enolate abundance at alkaline conditions offsets the effects of declining protonated monochloramine on the observed rate constant (SI section 4.5). Therefore, we propose protonated monochloramine halogenates the enolate of diketonitrile in a reaction pathway similar to free chlorine (Figure 6b). However, other reaction pathways cannot be excluded. For example, an acid-catalyzed pathway involving halogenation of the enol, comparable to that described for free chlorine, could contribute to diketonitrile degradation in the presence of chloramine.

Environmental Implications. Our study demonstrates that transformation of diketonitrile during drinking water treatment will depend on parameters including oxidant type and pH conditions. Diketonitrile reacts with free chlorine orders of magnitude faster compared to chloramine, while preoxidation by permanganate is unlikely to decrease diketonitrile concentrations due to minimal reactivity. Despite the relatively rapid reaction of diketonitrile with chlorine, isoxaflutole itself may be more persistent in drinking water due to its reported long half-life in chlorinated tap water.[21] Therefore, if isoxaflutole is incompletely hydrolyzed to diketonitrile prior to entering water treatment plants, removal by oxidants will be much less effective. Upon consumption, isoxaflutole is expected to be rapidly metabolized to diketonitrile,[1,15] which will contribute to toxicity alongside any diketonitrile remaining in the treated drinking water.[1,15,16] While one study reported that diketonitrile occurred at higher concentrations than isoxaflutole in surface water,[12] the specific concentrations of each species in drinking water sources should be assessed further due to their different potentials to react during water treatment.

Due to the high yield of DCAN from diketonitrile upon reaction with both free chlorine and chloramine, the parameters that increase diketonitrile transformation are also likely to increase DCAN formation. Yields of DCAN up to 100% from diketonitrile are unique among known DCAN precursors, which produce DCAN at <1% molar yields in the presence of free chlorine and chloramine (with the exception of a few higher yield precursors that produce DCAN at about 10% molar yields with free chlorine; i.e., tryptophan).[29,66−68] Lower DCAN yields produced in the presence of free chlorine and chloramine along previously proposed pathways (e.g., the "decarboxylation pathway") can be attributed to the formation of other end products besides DCAN.[59] However, DCAN formed from diketonitrile occurs along a more direct pathway due to the preexisting nitrile group on the α-carbon of the β-diketone moiety.

Due to the high-yield production of DCAN, diketonitrile may be a significant precursor for DCAN in U.S. drinking water. The last observed maximum concentration of diketonitrile reported in 2004 (e.g., 1.5 nM)[12] would account for approximately 17% of median DCAN concentration (e.g., 9.1 nM) observed in drinking water treatment plant effluents across the U.S. from 2000 to 2002,[28] assuming 100% yield. From 2004 to 2019, isoxaflutole had already increased by 40%.[2] Additionally, the recent commercial release of GM soybeans that tolerate herbicides in 2020[1,3] may result in increased isoxaflutole use; notably, other herbicides like dicamba were used to greater extents following the release of GM crops with corresponding herbicide-tolerant traits.[18] Updated measurements of isoxaflutole and diketonitrile concentrations in drinking water sources are needed to determine the impact of isoxaflutole on drinking water quality under these changing use scenarios.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.est.2c06376.

Comparison of isoxaflutole concentration and toxicity to other agrochemicals, chemical sources, experimental and analytical methods, supporting results, and examination of reactive species (PDF)

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Notes

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