Supporting Information

Re-examining the Role of Dichloramine in High-Yield NDMA Formation from *N,N*-dimethyl-α-arylamines

*Meredith E. Huang, Shiyang Huang, Daniel L. McCurry**

Astani Department of Civil and Environmental Engineering, University of Southern California, Los Angeles, CA 90089

*Corresponding author phone: (213) 740-0762; e-mail: dmccurry@usc.edu

Contents

Text S1: Reagents. NDMA precursors (Figure 1) were obtained commercially as follows: Dimethylamine hydrochloride (DMA) (99%; Sigma), Ranitidine (99%; Alfa Aesar), *N,N*-dimethylbenzylamine (DMBzA) (≥ 99%; Sigma), 5-*(*dimethylaminomethyl)-furfuryl alcohol hydrochloride (DFUR) (98%; Sigma), 2-(dimethylaminomethyl)-aniline (DMAMA) (Sigma). NDMA was obtained as a 5 g/L analytical standard in methanol (MeOH) from Sigma and used to prepare 500 mg/L stocks in acetonitrile, which were stored at -20 ºC. Phosphate buffers were prepared from a mixture of monobasic and dibasic potassium phosphates (99%; Acros Organics), and adjusted to pH 7.0 with 1 M NaOH or HCl. Monochloramine stocks were prepared fresh daily as described previously.[1] Briefly: a 40 mM free chlorine solution was prepared from a sodium hypochlorite stock (reagent grade; Sigma), which was standardized daily (ε_{292} = 365 M^{-1} cm^{-1}) on a Cary 60 ultraviolet-visible spectrophotometer (Agilent Technologies, Santa Clara, CA). This solution was slowly titrated into an equal volume of 48 mM ammonium chloride (≥ 99.5%; Sigma) at pH 8.5. Dichloramine was prepared by titrating ~20 mM solutions of monochloramine to pH 3.7 with 1 M HCl and maintaining at pH 3.7 via periodic addition of HCl until reaction completion (~1 h). Dichloramine solutions were used within 1 h. Monochloramine and dichloramine were standardized spectrophotometrically as described previously.[2]

Text S2: HPLC-UV Analysis of NDMA. Aqueous samples were injected (100 μL) and separated on a Poroshell 120 column (C18, 4.6 × 100 mm × 2.7 μm; Agilent) maintained at 30 ºC with an integrated column heater. The mobile phase consisted of 10 mM phosphate in Milli-Q water (pH 9) and methanol (HPLC grade, Omnisolv) supplied at 1.0 mL/min according to the following program: 5% MeOH for 2 minutes, followed by a 2 min gradient to 50% MeOH, followed by 5 min isocratic at 50% MeOH, followed by a 0.1 min gradient to 5% MeOH, followed by 2.9 min isocratic at 5% MeOH, for 12 min total analysis time. NDMA was detected using a photodiode array detector at 228 nm[3], at a retention time of 2.1 min.

Text S3: NDMA formation from an expanded range of molar ratios. To confirm that elevated NDMA yields from dichloramine was not confined to the set of experimental conditions used above (100 μM; 1 – 20 M.E. chloramines), two additional experiments were performed with DFUR as a representative precursor. To evaluate lower doses of chloramines, 1000 μM DFUR was treated with 0.01 – 10 M.E. of chloramines (Figure S2A). Dichloramine consistently formed more NDMA than monochloramine chloramine doses <5 M.E. At the highest dose (5 M.E.), NDMA yield from dichloramine declined somewhat, possibly due to intermediate-oxidizing side reactions, as discussed in the manuscript, or rapid breakpoint reactions at the elevated dichloramine concentration (5 mM). Loss of combined chlorine to breakpoint has previously been shown to proceed faster at higher starting concentrations. Jafvert and Valentine (1992) showed that at pH 7 and with a Cl/N ratio of 2, combined chlorine was lost within 10 minutes at a starting concentration of ~0.1 mM versus ~5 minutes at a starting concentration of 0.2 mM. Similar results were observed at pH 6 and pH 8. To evaluate formation from a lower starting concentration, and higher oxidant doses, 10 μM DFUR was treated with 1 – 1000 M.E. of monochloramine and 1 – 300 M.E. of dichloramine (Figure S2B). Dichloramine treatment consistently produced higher NDMA yields than monochloramine. NDMA yields from monochloramine treatment began to approach yields from dichloramine at the highest doses (100 – 1000 M.E.), likely due to chlorine transfer reactions producing sufficient dichloramine for NDMA formation.

Table S1: Previously reported yields of NDMA from dimethylamine under indicated reaction conditions.

$[DMA]_0$	$[NH_2Cl]_0$	$[NH_2Cl]_0$/ $[DMA]_0$	pH	Rxn time (h)	NDMA yield (%)	Reference
73 µg/L	2 mM	1233	6.8	240	0.5%	(4)
0.1 mM	2 mM	20	6.9	240	2.6%	(5)
0.1 mM	2 mM	20	7	240	3.0%	(6)
500 nM	2.5 mM	5000	8	24	2.3%	(7)
200 nM	100 mg/L	7042	7.5	120	1.2%	(8)
160 nM	100 mg/L	8803	7.5	120	1.5%	(9)

Table S2: Previously reported yields of NDMA from ranitidine under indicated reaction conditions.

$[Ranitidine]_0$	$[NH_2Cl]_0$	$[NH_2Cl]_0$/ $[Ranitidine]_0$	pH	Rxn time (h)	NDMA yield (%)	Reference
25 nM	28.4 mg/L	16000	7	24	89.9	(10)
5 nM	2.5 mg/L @ 24 h*	n/a	7.5	24	85.2	(11)
25 nM	2.5 mg/L @ 24 h*	n/a	7.5	24	82.7	(11)
25 nM	2.5 mg/L	1408	7	24	~91	(12)
3 μM	2.5 mM	833	7	120	42.2	(13)
200 nM	100 mg/L	7042	7.5	120	80.5	(8)
160 nM	3 mg/L	264	7.5	120	78.4	(9)
2.5 μM	43 μM	17.2	8	30	97	(3)
15 μM	270 μM	18	8	11	89.9	(14)

*Chloramine residual after SDS testing

Table S2: Kinetic model equations for chloramine evolution and nitrosamine formation. Reprinted from McCurry, D.L.; Ishida, K.P.; Oelker, G.L.; Mitch, W.A. *Environ. Sci Technol.*, **2017**, *51*, 8589-8596. Copyright 2017 American Chemical Society.

Reaction	k	Rate Expression	Units	Reference
$HOCl + NH_3 \rightarrow NH_2Cl$	3.1E+06	$k[HOCl][NH_3]$	$M^{-1}\ s^{-1}$	(15)
$NH_2Cl \rightarrow HOCl + NH_3$	2.1E-05	$k[NH_2Cl]$	s^{-1}	(15)
$HOCl + NH_2Cl \rightarrow NHCl_2$	2.8E+02	$k[HOCl][NH_2Cl]$	$M^{-1}\ s^{-1}$	(15)
$NHCl_2 \rightarrow HOCl + NH_2Cl$	6.5E-07	$k[NHCl_2]$	s^{-1}	(15)
[a] $NH_2Cl + NH_2Cl \rightarrow NHCl_2 + NH_3$	6.9E+03	$k[[H^+][NH2Cl]^2$	$M^{-2}\ s^{-1}$	(15)
$NHCl_2 + NH_3 \rightarrow NH_2Cl + NH_2Cl$	6.0E+04	$k[[H^+][NHCl_2][NH_3]$	$M^{-2}\ s^{-1}$	(15)
[b] $NHCl_2 \rightarrow I$	1.1E+02	$k[NHCl_2][OH^-]$	$M^{-1}\ s^{-1}$	(15)
$I + NHCl_2 \rightarrow HOCl + prod$	2.8E+04	$k[I][NHCl_2]$	$M^{-1}\ s^{-1}$	(15)
$I + NH_2Cl \rightarrow prod1$	8.3E+03	$k[I][NH_2Cl]$	$M^{-1}\ s^{-1}$	(15)
$NHCl_2 + NH_2Cl \rightarrow prod2$	1.5E-02	$k[NHCl_2][NH_2Cl]$	$M^{-1}\ s^{-1}$	(15)
$HOCl + NHCl_2 \rightarrow NCl_3$	3.3E+09	$k[HOCl][NHCl_2][OH^-]$	$M^{-2}\ s^{-1}$	(15)
$NCl_3 \rightarrow HOCl + NHCl_2$	3.2E-05	$k[NCl_3]$	s^{-1}	(16)
$NHCl_2 + NCl_3 \rightarrow HOCl + HOCl + prod4$	5.6E+10	$k[NHCl_2][NCl_3][OH^-]$	$M^{-2}\ s^{-1}$	(15)
$NH_2Cl + NCl_3 \rightarrow HOCl + prod5$	1.4E+09	$k[NH_2Cl][NCl_3][OH^-]$	$M^{-2}\ s^{-1}$	(15)
$DMA + HOCl \rightarrow DMACl$	6.1E+07	$k[DMA][HOCl]$	$M^{-1}\ s^{-1}$	(17)
$DMAH^+ + NH_2Cl \rightarrow DMACl + NH_4^+$	2.1E-01	$k[DMAH^+][NH_2Cl]$	$M^{-1}\ s^{-1}$	(18)
$DMACl + NH4+ \rightarrow NH2Cl + DMAH+$	5.8E-03	$k[DMACl][NH_4^+]$	$M^{-1}\ s^{-1}$	(18)
$NH_2Cl + DMA \rightarrow UDMH$	8.1E-02	$k[NH_2Cl][DMA]$	$M^{-1}\ s^{-1}$	(18)
$NH_3 + DMACl \rightarrow UDMH$	4.9E-03	$k[NH_3][DMACl]$	$M^{-1}\ s^{-1}$	(18)
$NHCl_2 + DMA \rightarrow UDMHCl$	5.2E+01	$k[NHCl_2][DMA]$	$M^{-1}\ s^{-1}$	(19)
$NHCl_2 + UDMH \rightarrow DMA + prod6$	4.5E+00	$k[NHCl_2][UDMH]$	$M^{-1}\ s^{-1}$	(20)
$NHCl_2 + UDMHCl \rightarrow prod7$	7.5E-01	$k[NHCl_2][UDMHCl]$	$M^{-1}\ s^{-1}$	(19)
$UDMHCl + O_2 \rightarrow NDMA$	1.4E+00	$k[UDMHCl][O_2]$	$M^{-1}\ s^{-1}$	(20)
$DMACl \rightarrow CH_3NCH_2^+ + Cl^-$	4.2E-10	$k[DMACl]$	s^{-1}	(21)
Equilibrium	pKa			
$HOCl \rightleftharpoons OCl^-$	7.5		-	(22)
$NH_4^+ \rightleftharpoons NH_3 + H^+$	9.3		M	(22)
$DMAH^+ \rightleftharpoons DMA + H^+$	10.7		M	(23)
$UDMHH^+ \rightleftharpoons UDMH + H^+$	7.2		M	(24)

[a] General acid catalysis by H_2CO_3 ($k = 7.5 \times 10^{-1}\ M^{-2}\ s^{-1}$) and HCO_3^- ($k = 2.0 \times 10^{-3}\ M^{-2}\ s^{-1}$) was also included in the model. Carbonate acid catalysis rate constants retrieved from SI Reference 25.

[b] I is an unknown intermediate, and prod1, prod2, prod3, prod4, and prod5 refer to uncharacterized reaction products, potentially including N_2, NO_3^-, H^+, Cl^-

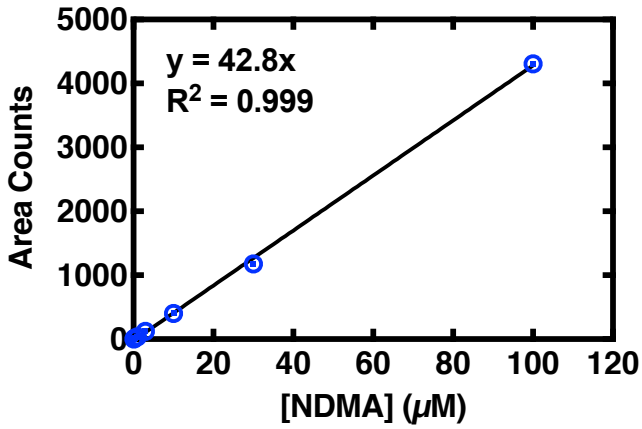

Figure S1: Example NDMA standard curve data generated from HPLC analysis. Standards (0.1, 0.3, 1, 3, 10, 30, 100 µM) were analyzed via HPLC as described in the manuscript. Calculated detection limit was 1 µM.

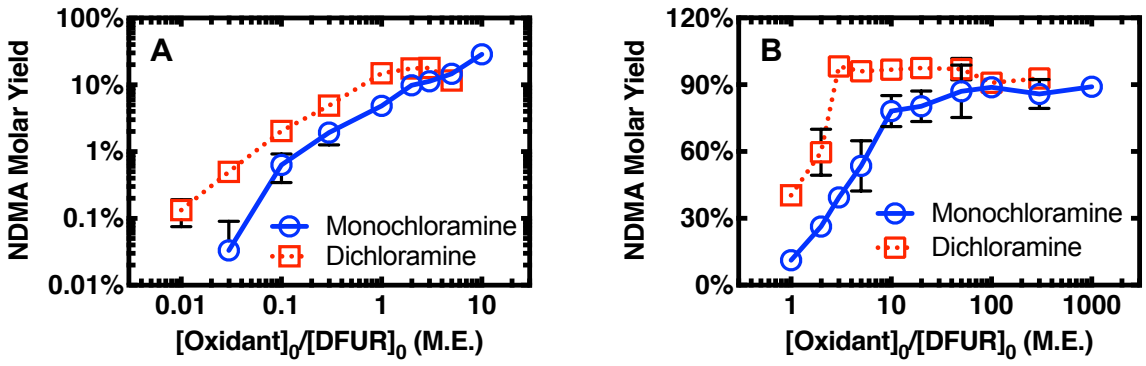

Figure S2: NDMA molar yield as a function of chloramine dose from DFUR. (A) $[DFUR]_0$ = 1000 µM; (B) $[DFUR]_0$ = 10 µM. [PO_4 buffer] = 10 mM, pH = 7.0, T = 22 ± 1 ºC, t_{rxn} = 24 h. All plotted points are the mean of three experimental replicates with 95% confidence interval error bars calculated based on Student's t-distribution (smaller than symbols when not shown).

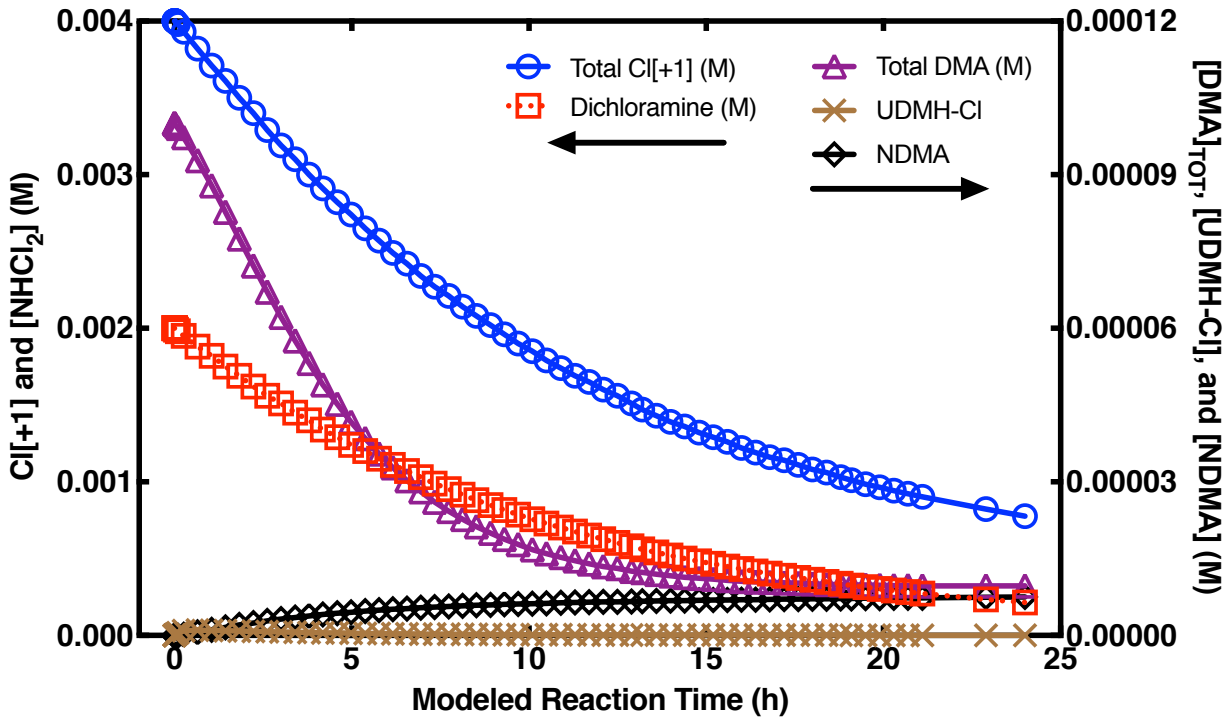

Figure S3: Modeled concentrations of total dimethylamine (including protonated dimethylamine), total chlorine residual, dichloramine, UDMH-Cl, and NDMA. Total chloraine and dichloramine concentrations are plotted on the left y-axis; total dimethylamine, UDMH-Cl, and NDMA concentrations are plotted on the right y-axis.$[DMA]_0$ = 100 µM, [PO_4 buffer] = 10 mM, pH = 7.0, T = 22 ºC, t_{rxn} = 24 h.

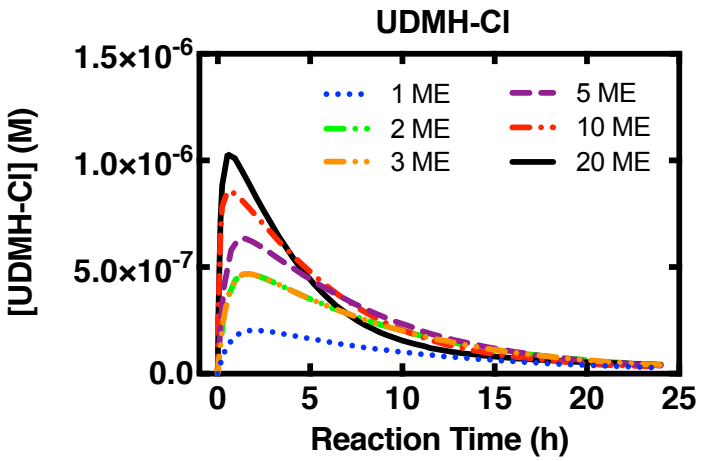

Figure S4: Modeled concentrations of UDMH-Cl. $[DMA]_0$ = 100 µM, $[NHCl_2]_0$ = 100 µM, 200 µM, 300 µM, 500 µM, 1 mM, or 2 mM, [PO_4 buffer] = 10 mM, pH = 7.0, T = 22 ºC.

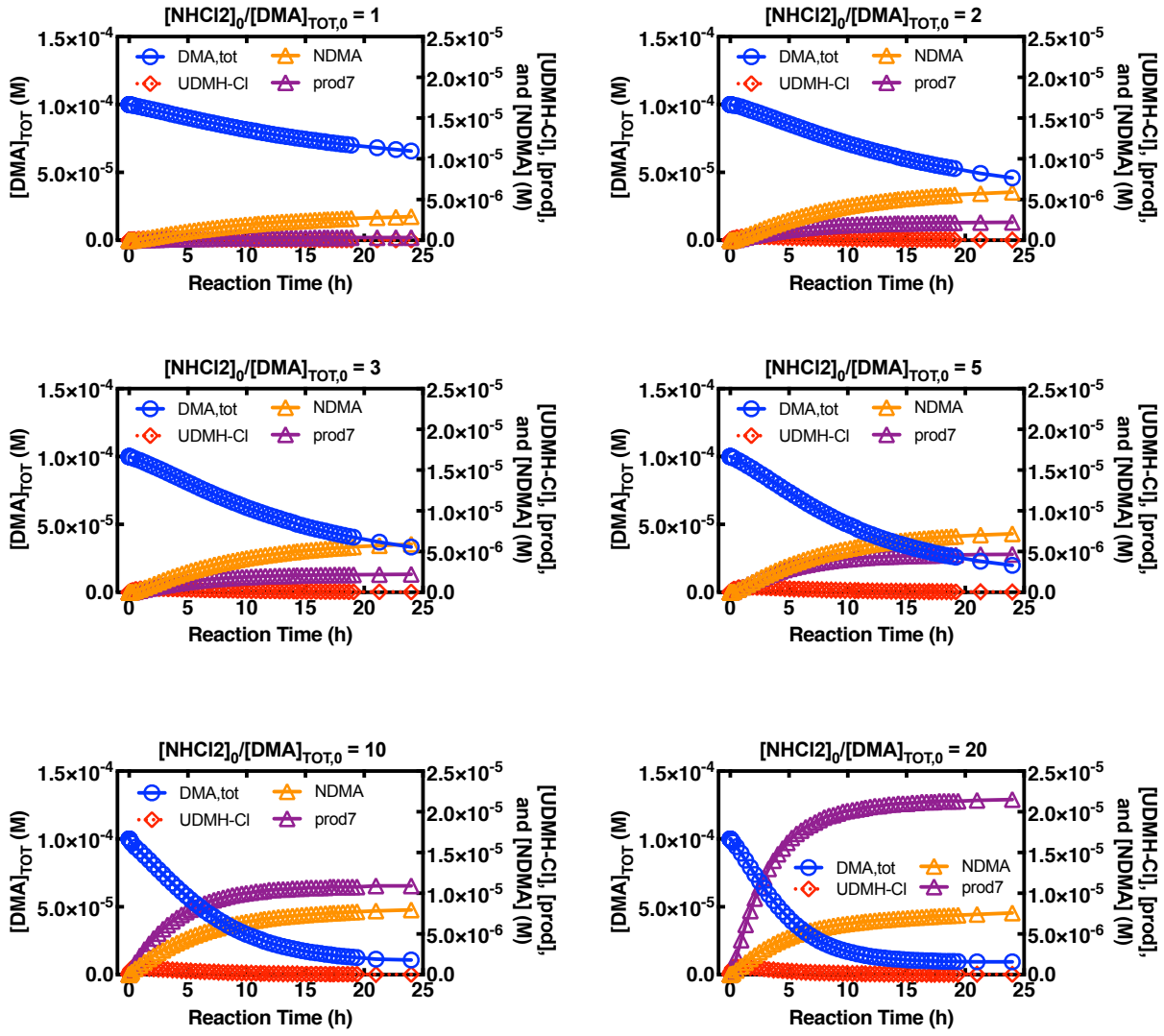

Figure S5: Computationally modeled concentrations of total dimethylamine (including protonated dimethylamine), dichloramine, UDMH-Cl, NDMA, and unidentified product 7 ('prod7'). DMA concentrations plotted on the left y-axis; all other concentrations plotted on the right y-axis. $[DMA]_0$ = 100 µM, $[NHCl_2]_0$ = 100 µM, 200 µM, 300 µM, 500 µM, 1 mM, or 2 mM, $[PO_4$ buffer] = 10 mM, pH = 7.0, T = 22 ºC.

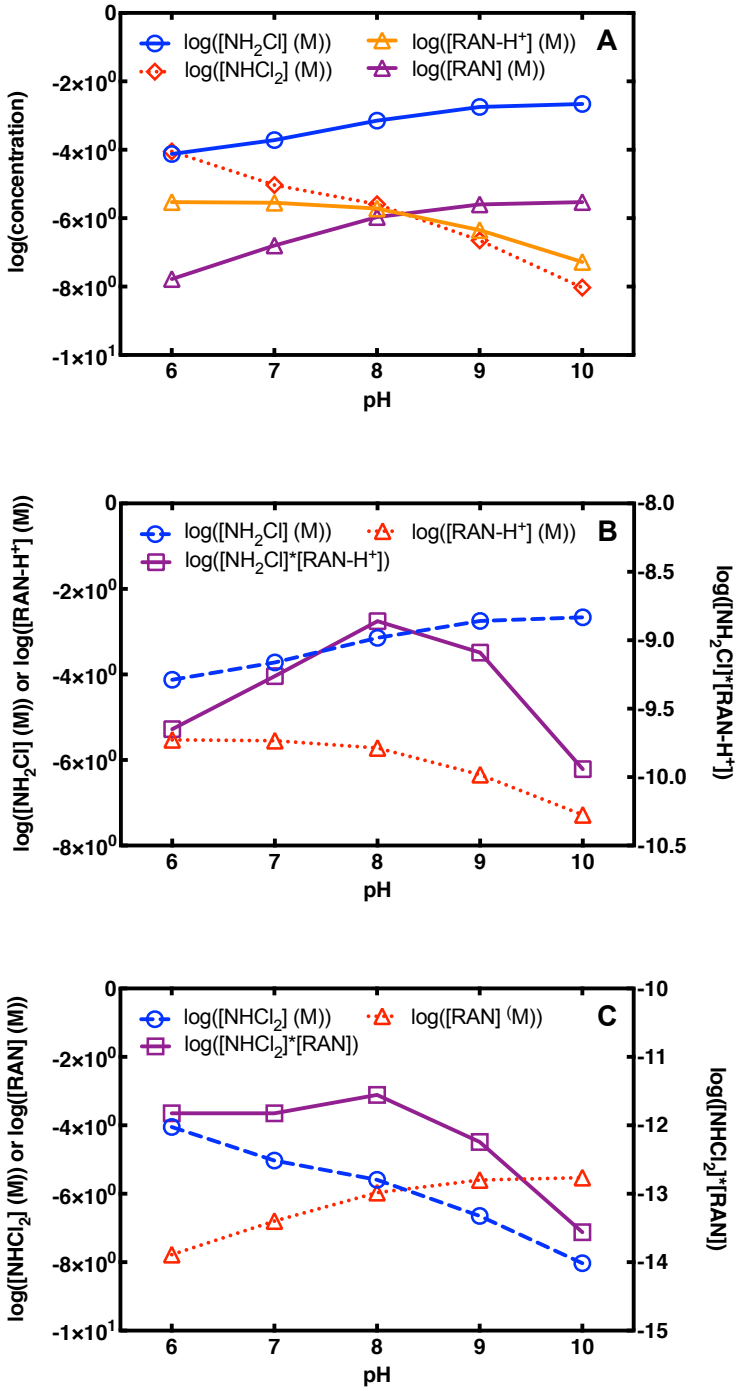

Figure S6: Modeled concentrations of monochloramine, dichloramine, ranitidine, and protonated ranitidine with respect to pH. (A) shows all concentrations; (B) shows monochloramine, protonated ranitidine, and their concentration product; (C) shows dichloramine, neutral ranitidine, and their concentration product; individual concentrations plotted on the left y-axis; concentration products plotted on the right y-axis. $[RAN]_0$ = 3 µM, $[NH_2Cl]_0$ = 2.5 mM [PO_4 buffer] = 10 mM, reaction time = 5 d.

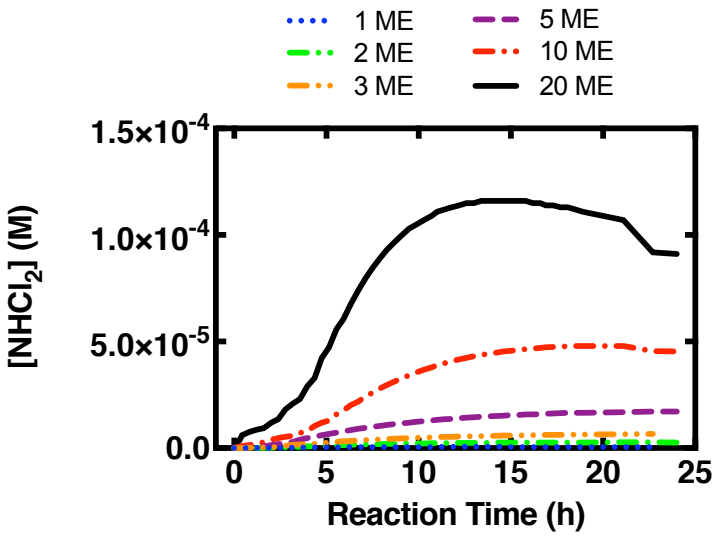

Figure S7: Modeled concentrations of dichloramine during simulated chloramination of dimethylamine. $[DMA]_0$ = 100 µM, $[NHCl_2]_0$ = 100 µM, 200 µM, 300 µM, 500 µM, 1 mM, or 2 mM, [PO_4 buffer] = 10 mM, pH = 7.0, T = 22 ºC.

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