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# 1 NDMA Formation by Chloramination of Ranitidine:

## 2 Kinetics and Mechanism

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### 14 ABSTRACT

15 The kinetics of decomposition of the pharmaceutical ranitidine (a major precursor of NDMA) during  
16 chloramination was investigated and some decomposition by-products were identified by using high  
17 performance liquid chromatography coupled with mass spectrometry (HPLC-MS). The reaction between  
18 monochloramine and ranitidine followed second order kinetics and was acid-catalyzed. Decomposition  
19 of ranitidine formed different by-products depending on the applied monochloramine concentration.

20 Most identified products were chlorinated and hydroxylated analogues of ranitidine. In excess of  
21 monochloramine, nucleophilic substitution between ranitidine and monochloramine led to by-products  
22 that are critical intermediates involved in the formation of NDMA, e.g. a carbocation formed from the  
23 decomposition of the methylfuran moiety of ranitidine. A complete mechanism is proposed to explain  
24 the high formation yield of NDMA from chloramination of ranitidine. These results are of great  
25 importance to understand the formation of NDMA by chloramination of tertiary amines.

## 26 KEYWORDS

27 NDMA, Nitrosamine, Chloramination, Disinfection By-products, Ranitidine

## 28 **Introduction**

29 Nitrosamines, especially N-nitrosodimethylamine (NDMA), form during disinfection of drinking  
30 waters at near nanogram per liter levels<sup>1</sup> or wastewaters at concentrations up to several hundred ng/L.<sup>2</sup>  
31 They are considered as probable human carcinogens by the US Environmental Protection Agency,<sup>3</sup> and  
32 are listed in the USEPA's Contaminant Candidate List 3.<sup>4</sup> They can be formed in the presence of nitrites  
33 and free chlorine (HOCl-enhanced nitrosation) but are preferentially formed during chloramines  
34 disinfection.<sup>5</sup> Over the last decade, several formation mechanisms have been proposed to explain  
35 NDMA formation by chloramination of secondary and tertiary amines. Most of them involve a  
36 nucleophilic substitution between dimethylamine (DMA) and monochloramine (NH<sub>2</sub>Cl) to form an  
37 Unsymmetrical Dimethylhydrazine intermediate (UDMH).<sup>6,7</sup> Dichloramine (NHCl<sub>2</sub>) was proposed to  
38 favor the production of NDMA, through the formation of a chlorinated UDMH (UDMH-Cl)  
39 intermediate instead of UDMH.<sup>8</sup> In the presence of bromide ion, it has been suggested that a brominated  
40 UDMH (UDMH-Br) would probably be formed.<sup>9,10</sup> These intermediates were never detected during  
41 experiments because they are expected to be rapidly oxidized to NDMA.

42 The contribution of tertiary amines to the production of substantial amounts of NDMA during  
43 chloramination has been pointed out.<sup>2,11,12</sup> In particular, the pharmaceutical ranitidine has been  
44 demonstrated to produce high yields of NDMA (> 60%).<sup>11-13</sup> Ranitidine is a histamine H<sub>2</sub>-receptor

45 antagonist used in treatment of peptic ulcer diseases, and was one of the most prescribed drug in the 80s.  
46 It has been progressively superseded by proton pump inhibitors, but it still remains in the top 15 sold-list  
47 of prescribed drugs in different European countries.<sup>14</sup> Ranitidine has been detected in European and US  
48 wastewaters at concentrations ranging from 220 ng/L to 550 ng/L.<sup>15,16</sup> Such high concentrations in  
49 wastewaters could explain the important NDMA formation potentials of wastewaters as compared to  
50 model waters containing similar amounts of DMA,<sup>2</sup> because of the higher conversion rate of ranitidine  
51 in NDMA (> 60% as compared to < 3% for DMA).<sup>11,13</sup> The presence of a pool of tertiary and quaternary  
52 amines acting as NDMA precursors (e.g., pesticides, pharmaceuticals and personal care products) could  
53 also participate in the overall NDMA yields observed in wastewaters.<sup>13,17</sup> Ranitidine has been identified  
54 in surface waters of Italy at concentrations ranging from 1 to 10 ng/L,<sup>18,19</sup> and has been detected in 1.2%  
55 of US streams at 0.01 µg/L.<sup>20</sup> Several studies have addressed the photochemical degradation of  
56 ranitidine in the environment.<sup>21,22</sup> Several photodecomposition products of ranitidine have been  
57 identified, but the by-products formed during the reaction between ranitidine and common oxidants used  
58 in water treatment (e.g., chlorine, monochloramine or ozone) have not been investigated.

59 Many kinetic studies have addressed chlorine reactivity with model compounds but the reactivity of  
60 monochloramine with simple model compounds is not well documented.<sup>23</sup> NDMA formation kinetics of  
61 some tertiary amines (i.e., ranitidine, chlorphenamine and doxylamine) have been recently investigated  
62 in various matrices.<sup>24</sup> In this study, real water matrices had a significant impact on NDMA formation  
63 kinetics, especially leading to an initial lag period because of competitive reactions between natural  
64 organic matter (NOM) and tertiary amines. Studies about the decomposition kinetics of NDMA  
65 precursors such as anthropogenic tertiary amines are lacking. Moreover, potential intermediate species  
66 involved in the formation of NDMA remain unidentified.

67 The aim of this study was to investigate the kinetics of decomposition of ranitidine by chloramination  
68 and to identify its decomposition by-products by using high performance liquid chromatography coupled  
69 with mass spectrometry (HPLC-MS). Reactions were conducted in deionized water to determine the  
70 kinetic constants for the reaction between monochloramine and ranitidine in pure solutions; hence

71 potential competitive effects of NOM with ranitidine were not studied. The identification of the reaction  
72 by-products should be useful to determine nucleophilic or electrophilic substitution sites in order to  
73 better understand the reaction mechanisms leading to the formation of NDMA by chloramination of  
74 ranitidine.

75

## 76 **Materials and Methods**

77 **Materials.** All experiments were conducted using deionized water (Milli-Q, Millipore) buffered with  
78 sodium acetate (pH = 4.0-5.5), a mixture of sodium phosphate monobasic and sodium phosphate dibasic  
79 (pH = 7.0-8.5), or sodium carbonate (pH = 10). pH values were adjusted as needed using sodium  
80 hydroxide or sulfuric acid (0.1 N, Fisher Scientific). Ranitidine was supplied through Sigma-Aldrich and  
81 was used without further purification. All other reagents were reagent grade or described previously.<sup>13</sup>  
82 All glassware used was washed with deionized water and baked at 500 °C for at least 5 hours prior to  
83 use.

84 **Experimental Methods.** Preparation of monochloramine stock solutions was previously described,<sup>13</sup>  
85 and is summarized in the Supporting Information (SI) Text S1. The concentration of monochloramine  
86 stock solutions was chosen to get the desired concentration in the working solution. Ranitidine solutions  
87 were prepared by dissolving a pre-determined amount of ranitidine in 1 L of 10 mM acetate, phosphate  
88 or carbonate buffer. 100 mL of monochloramine stock solution was then added to the working solution  
89 and reactions were conducted in amber glass bottles at 20 °C, under dark conditions to avoid the  
90 photolysis of NDMA. At given contact times, residual oxidants were quenched using a slight excess of  
91 sodium thiosulfate (2 g/L) and samples were transferred to glass vials for HPLC-MS<sup>n</sup> analyses. Most of  
92 the experiments were performed using high initial concentrations of ranitidine in order to ensure full  
93 detection of the parent compound and its by-products. This level of concentrations was not  
94 representative of what can be detected in wastewater treatment plants or environmental samples.

95 **Total Chlorine and Chloramines Analyses.** Free chlorine and total chlorine concentrations in the  
96 sodium hypochlorite stock solutions were determined by iodometric titration with sodium thiosulfate 0.1

97 M (Prolabo, >99.9%).  $\text{NH}_2\text{Cl}$  and  $\text{NHCl}_2$  concentrations were determined by spectrophotometric  
98 measurement using their respective molar extinction coefficients at 245 nm and 295 nm and solving  
99 simultaneous equations.<sup>25</sup> Residual oxidant was analyzed by iodometric titration.

100 **Analyses of Ranitidine and its Chloramination By-products.** High performance liquid  
101 chromatography coupled with diode array detection and mass spectrometry (HPLC-DAD-MS<sup>n</sup>) analyses  
102 were performed with a Thermo Surveyor chromatographic system including two detectors: a Thermo  
103 Surveyor diode array detector and a Thermo DECA XP Plus ion trap mass spectrometer. Ranitidine and  
104 its chloramination by-products were separated using a Phenomenex Luna PFP2 column (250 × 4.6 mm,  
105 pore size: 100 Å, particle size: 5 μm). The mobile phase consisted in (A) formic acid/methanol (1:1000  
106 v/v) and (B) formic acid/milliQ water (1:1000 v/v) pumped at a flow rate of 0.6 mL/min. Elution started  
107 at 5% of A for 5 min, increased to 30% of A in 20 min and holding for 5 min, then increased to 90% of  
108 A in 10 min and holding for 2 min, and then returned to initial conditions. Total run time was 60 min  
109 (including the conditioning of the column to the initial conditions). Injection volume was 100 μL. All  
110 samples were analyzed in full scan mode and MS<sup>2</sup> simultaneously. Chemical ionization was performed  
111 in atmospheric pressure chemical ionization mode (APCI), in positive and negative mode. The  
112 parameters were: capillary temperature of 250 °C, vaporizer temperature 450 °C, gas flow 95 u.a.,  
113 auxiliary gas flow 56 u.a., corona discharge at 5 μA with a voltage 4.5 kV and capillary voltage 14 V.  
114 Mass range detection was 50-500 uma (to detect the formation of dimers). MS<sup>2</sup> experiments were  
115 performed on protonated molecular ions in order to identify by-products. MS<sup>2</sup> experiments were  
116 performed as follows: collision energy of 35%, Q activation of 0.25 and activation time of 30 ms.  
117 Analyses were performed in both APCI positive and APCI negative mode, but chloramination by-  
118 products of ranitidine were only detected in positive mode. For the determination of ranitidine  
119 decomposition kinetics, a series of ranitidine solutions at different concentrations (ranging from 0.05  
120 μM to 2 μM) was analyzed in APCI positive mode to obtain a calibration curve ( $R^2 = 1.000$ ).

121

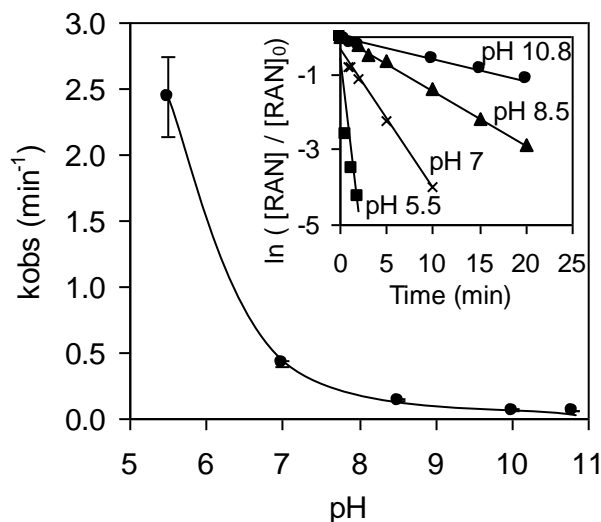
122 **Results and Discussion**

123 **Ranitidine Decomposition Kinetics at Several pH.** The reaction of  $\text{NH}_2\text{Cl}$  with ranitidine was  
124 assumed to follow second-order kinetics, first-order with respect to each reactant. The rate of ranitidine  
125 decomposition in the presence of a large excess of monochloramine ( $[\text{NH}_2\text{Cl}]_0/[\text{RAN}]_0 > 100 \text{ mol/mol}$ )  
126 can be considered as pseudo first-order with respect to ranitidine (equation 1):

$$127 \quad -\frac{d[\text{RAN}]}{dt} = k_{\text{obs}}[\text{RAN}] \quad (1)$$

128 where  $k_{\text{obs}} = k_{\text{app}} [\text{NH}_2\text{Cl}]_0$

129 Ranitidine decomposition rates were determined at different pH from the reaction of  $1.5 \mu\text{M}$  ranitidine  
130 with  $200 \mu\text{M}$   $\text{NH}_2\text{Cl}$ , using HPLC-MS analyses. The linear plots obtained between  $\ln([\text{RAN}]/[\text{RAN}]_0)$   
131 and reaction time confirmed the pseudo first-order rate with respect to the concentration of ranitidine  
132 (Figure 1). At  $\text{pH} < 5.5$ , ranitidine was instantaneously decomposed and kinetics could not be studied.  
133 Ranitidine chloramination rate decreased when increasing pH, indicating an acid-catalyzed  
134 decomposition (Figure 1). Ranitidine was found to exhibit a maximum NDMA formation yield around  
135  $\text{pH} 8$  after 5 days of reaction.<sup>13</sup> However, ranitidine decomposition did not show a maximum at  $\text{pH} 8$ .  
136 This finding indicates that the higher formation of NDMA at this pH and long contact times is not  
137 directly related to the decomposition rate of molecular ranitidine. Moreover, previous work  
138 demonstrated that the formation of NDMA was very slow (maximum NDMA formation occurring after  
139 24h of contact time<sup>13</sup>) as compared to the fast decomposition rate of ranitidine observed in this study.  
140 The value of  $k_{\text{app}}$  at  $\text{pH} 7$  was  $34.9 \text{ M}^{-1} \cdot \text{s}^{-1}$ , which is much lower than the kinetic constants obtained for  
141 the chloramination of DMA ( $7.98 \cdot 10^8 \text{ M}^{-1} \cdot \text{s}^{-1}$ )<sup>26</sup> and resorcinol ( $7.5 \cdot 10^5 \text{ M}^{-1} \cdot \text{s}^{-1}$ )<sup>23</sup>. Steric hindrance  
142 could be responsible for the slower reaction of  $\text{NH}_2\text{Cl}$  with the DMA group of ranitidine as compared to  
143 DMA. Furthermore, chlorine transfer between  $\text{NH}_2\text{Cl}$  and DMA is subjected to general acid  
144 catalysis.<sup>26,27</sup> In a similar manner, chlorine transfer to the DMA group of ranitidine (i.e., electrophilic  
145 substitution) could be favored at acidic pH, which would explain the higher decomposition rate  
146 observed (Figure 1). Moreover,  $\text{NH}_2\text{Cl}$  decomposes at acidic pH by disproportionation and hydrolysis  
147 and thus may create species (e.g.,  $\text{NHCl}_2$  or  $\text{HOCl}$ ) that enhance the decomposition of ranitidine.<sup>28</sup>



149

150 **Figure 1.** Ranitidine decomposition rates during chloramination at different pH.  $[RAN]_0 = 1.5 \mu\text{M}$ ,  
 151  $[\text{NH}_2\text{Cl}]_0 = 200 \mu\text{M}$ .

152 **Identification of Ranitidine By-products around Equimolar Conditions.** Chromatographic and  
 153 mass spectral data for ranitidine and its decomposition products analyzed by HPLC-MS are summarized  
 154 in Table 1. Structures of decomposition products are proposed based on their MS and MS<sup>2</sup> spectral data.  
 155 Attempts were made to identify the reaction by-products of 5-(dimethyl-aminomethyl)furfuryl alcohol  
 156 (or DFUR, a molecular structure found in ranitidine and a major precursor of NDMA<sup>10,11</sup>) but they were  
 157 probably too polar to be detected in our analytical conditions.

158 **Table 1.** Ranitidine reaction products detected by HPLC-MS in APCI positive mode. \*By-products non-  
 159 detected when reactions were stopped using sodium thiosulfate.

Compound	Fragmentation	Nominal mass	Structure	RT (min)
Ranitidine (RAN)	315, 270 (4 %), 176 (1.6%), 111 (2%)	314		24.1
NDMA	75	74		16.0
Dimethyl-aminomethyl furfuryl alcohol (DFUR)	156, 111 (38%)	155		8.0



thioethyl-N-methyl-2-nitroethene-1,1-diamine (P175)	<b>176</b> , 145 (10%), 130 (6%), 116 (4%)	175		16.6
RAN + NH <sub>2</sub> (P330)	<b>330</b> , 270 (5%), 113 (8%)	330		22.7
RAN + NH <sub>2</sub> + Cl (P364)	<b>364</b> (366), 304 (6%, 306), 223 (4%), 95 (4%)	364		22.1
RAN + Cl (P348)	<b>349</b> (351), 304 (3%), 223 (7%), 170 (3%)	348		24.8
RAN + 2 Cl (P382) *	<b>383</b> (385, 387), 349 (6%, 351), 170 (19%), 111 (10%)	382		38.8
RAN + OH	<b>331</b> , 286 (7%), 193 (29%), 154 (22%), 111 (34%)	330		12.7
RAN + OH + Cl	<b>365</b> (367), 227 (19%, 229), 181 (49%), 154 (32%), 111 (52%)	364		11.4
RAN + OH + 2 Cl *	<b>399</b> (401,403), 270, 215 (217), 167 (169), 154, 139, 111	398		40.0
P175 + OH (P191)	<b>192</b>	191		17.2
P175 + 2 OH + Cl (P241)	<b>242</b> (244), 192 (9%)	241		39.6
P175 + 2 OH + 3 Cl	<b>310</b> (312, 314), 192 (9%), 181 (13%), 145 (8%)	309		24.4
RAN - DMA + 2 OH + Cl (P337)	<b>338</b> (340), 320 (12%), 259 (37%), 227 (31%), 192 (41%), 181 (86%), 111 (154%)	337		23.9
RAN - DMA + 3 OH + Cl (P353)	<b>354</b> (356), 259 (10%), 249 (53%), 185 (22%), 152 (14%), 111 (17%)	353		26.5

160

161

162 Ranitidine and monochloramine were introduced in the reaction buffer at 167  $\mu\text{M}$  and 400  $\mu\text{M}$ ,  
163 respectively (similar concentration range), to identify the first compounds produced by ranitidine  
164 decomposition in the presence of low concentrations of  $\text{NH}_2\text{Cl}$ . Major ions produced were chlorinated  
165 and/or hydroxylated derivatives, i.e., m/z 331 (hydroxylated ranitidine), m/z 349 (chlorinated ranitidine),  
166 m/z 365 (chlorinated and hydroxylated ranitidine), m/z 383 (ranitidine with two chlorine atoms) and m/z  
167 399 (hydroxylated ranitidine with two chlorine atoms) (see SI, Figure S1). These products can result

168 from chlorination and further oxidation of the N-methyl-2-nitroethene-1,1-diamine group. As proposed  
169 by Joo and Mitch for the chloramination of monomethylamine, chlorine attack on nitrogen atom and  
170 oxidation leads to the formation of organic chloramines and hydroxylamines.<sup>29</sup> The presence of m/z 399  
171 can be attributed to the subsequent chlorine substitution on N-methyl or ethene double bond or on the  
172 sulfur atom. Some other by-products were detected in smaller amounts. Experiments were carried out  
173 without quenching residual oxidant at the desired reaction time in order to investigate the potential  
174 influence of sodium thiosulfate on the by-products stability, because sodium thiosulfate can break N-Cl  
175 bonds formed after chlorination.<sup>30</sup> Only products containing two chlorine atoms (i.e., molecular ions m/z  
176 383 and m/z 399) were not detected when sodium thiosulfate was added. All the other by-products were  
177 detected with and without sodium thiosulfate addition. MS<sup>2</sup> experiments were conducted on ranitidine  
178 and the above-mentioned by-products to determine the position of chlorine substitution and  
179 hydroxylation. Figure S2a in SI gives the MS<sup>2</sup> spectrum obtained for ranitidine. A loss of dimethylamine  
180 (DMA) group (45 Da) gave the fragment ion m/z 270, and the following loss of NO<sub>2</sub> radical ion (46 Da)  
181 generated the radical fragment ion m/z 224. Different ruptures of C-S bonds led to the formation of  
182 fragments m/z 176, 144 and 124. These results are in accordance with MS<sup>2</sup> fragments observed in a  
183 previous study by Radjenović et al.,<sup>31</sup> using a quadrupole-time of flight (Q-Tof) detection. In the same  
184 study, the compound with molecular ion m/z 331 has been identified as a photocatalytic by-product of  
185 ranitidine.<sup>31</sup> The difference of 16 Da was attributed to the hydroxylation of ranitidine. MS<sup>2</sup> experiments  
186 on this molecular ion revealed similar fragments than those observed by Radjenović et al.<sup>31</sup> (See SI,  
187 Figure S3b). The typical loss of DMA group led to the fragment m/z 286 and further loss of water led to  
188 the fragment m/z 268, which confirms the hydroxylation of ranitidine. Different ruptures of C-S bonds  
189 in the molecular ion m/z 331 generated pairs of fragments m/z 156 and 176, and fragments m/z 188 and  
190 143. Fragment ion m/z 156 can be attributed to the previously mentioned DFUR, i.e. the hydroxylated  
191 dimethylaminomethylfuran group. Dehydroxylation of DFUR led to the fragment m/z 138 (Figure S3).

192 By comparing the MS<sup>2</sup> fragments of chlorinated ranitidine (m/z 349) with that of ranitidine (m/z 315),  
193 several similarities could be observed (see SI, Figure S2). Losses of DMA and NO<sub>2</sub> groups from

194 chlorinated ranitidine generated chlorinated fragments  $m/z$  304 and 258. This indicates that chlorine  
195 transfer did not occur on the dimethylamino group as it was previously suggested during chloramination  
196 of tertiary amines.<sup>32</sup> This implies that chlorine transfer leading to the release of DMA is not a pathway  
197 of NDMA formation by chloramination of ranitidine. Moreover, the major fragment ion of chlorinated  
198 ranitidine was  $m/z$  210. This fragment is the chlorinated analogue of the fragment ion  $m/z$  176 of  
199 ranitidine, which indicates that chlorine substitution does not occur on the furan group but probably on  
200 nitrogen or sulfur atoms. This is confirmed by the fact that a chlorinated analogue of  $m/z$  124 (i.e. the  
201 dimethylaminomethylfuran fragment) was not detected.

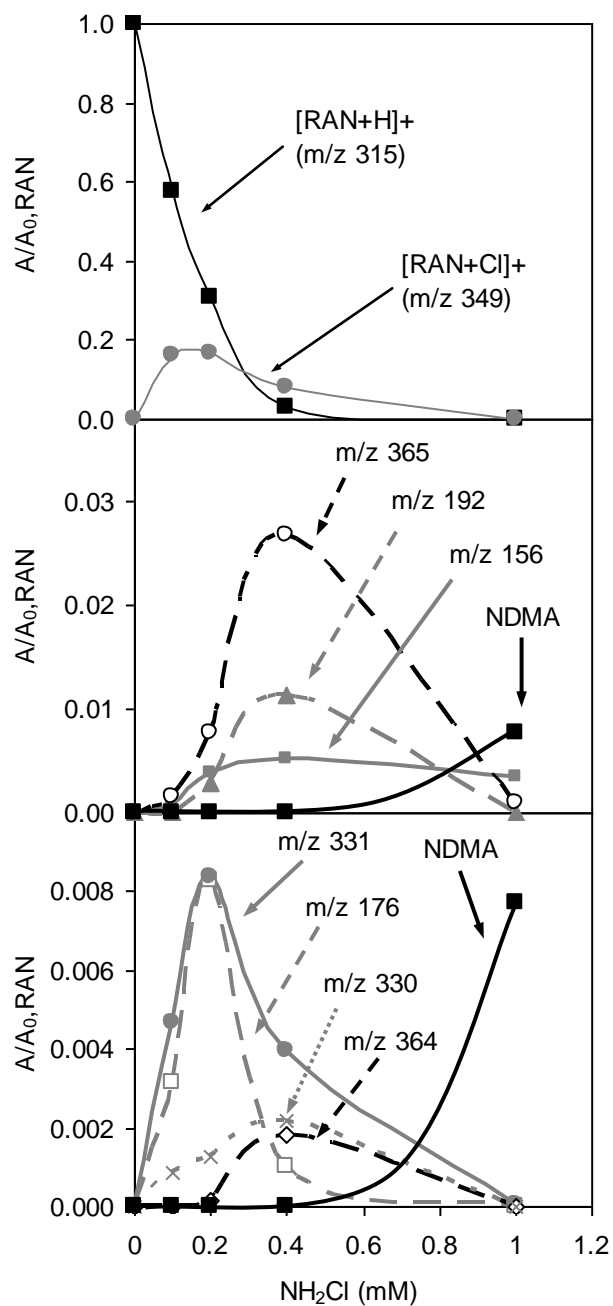
202 Some minor by-products exhibited a gain of 15 Da as compared to molecular ranitidine and  
203 chlorinated ranitidine. Chromatograms exhibited small peaks with a molecular ion  $m/z$  330  
204 (intermediate product P330) and a molecular ion  $m/z$  364 (P364) at retention times of 22.7 min and 22.1  
205 min, respectively. P364 was identified as the chlorinated analogue of P330. The observation of such  
206 products is consistent with the occurrence of a nucleophilic substitution between  $\text{NH}_2$  group of  
207 monochloramine and the DMA group of ranitidine, leading to a gain of 15 Da as compared to ranitidine  
208 (i.e. P330) (Scheme 1). Moreover, the odd nominal mass of this product indicates an odd number of  
209 nitrogen atoms, confirming the gain of a nitrogen atom as compared to ranitidine. The relatively low  
210 abundance of this peak suggests that it is rapidly decomposed to other degradation by-products.  $\text{MS}^2$   
211 experiment conducted on P330 generated the same fragments as ranitidine (i.e.,  $m/z$  270, 258, 224, 176  
212 and 124, Figure S3). This indicates that the fragmentation of P330 leads to the loss of the  $\text{NH}_2$  group,  
213 probably because of a weak bond.  $\text{MS}^2$  fragmentation of the chlorinated analogue of P330 did not  
214 provide any additional information.

215

216 **Influence of  $\text{NH}_2\text{Cl}$  Concentration.** The reaction between ranitidine (167  $\mu\text{M}$ ) and various  
217 concentrations of  $\text{NH}_2\text{Cl}$  (ranging from 0 to 1 mM) after 2h of reaction time at pH 8 (with 10 mM  
218 phosphate buffer) was monitored using HPLC-MS (Figure 2). Decomposition rate of ranitidine  
219 increased with increasing  $\text{NH}_2\text{Cl}$  concentration until full degradation for concentrations greater than 0.5

220 mM. The formation of chlorinated ranitidine (i.e., m/z 349) decreased with increasing NH<sub>2</sub>Cl  
221 concentration. Maximum chlorinated ranitidine formation occurred when ranitidine and NH<sub>2</sub>Cl were  
222 introduced in equimolar concentrations.

223 Most of the major by-products were preferentially formed for a NH<sub>2</sub>Cl/ranitidine ratio of  
224 approximately 2 mol/mol (e.g., m/z 176, 192, 330, 331, 364, 365) (Figure 2). By-products with  
225 molecular ions m/z 176 (P175) and m/z 192 (P191) were detected at retention times of 16.6 min and  
226 17.2 min respectively. P191 was identified as the hydroxylated analogue of P175 (i.e. the thioethyl-N-  
227 methyl-2-nitroethene-1,1-diamine moiety). NDMA formation occurred only for a NH<sub>2</sub>Cl concentration  
228 of 1 mM, i.e. in a large excess of NH<sub>2</sub>Cl, and after disappearance of the other by-products. Products  
229 P330 and P364 (postulated as resulting from nucleophilic substitution on the DMA group of ranitidine)  
230 were totally degraded at NH<sub>2</sub>Cl concentrations where NDMA formed (i.e., 1 mM), observation  
231 consistent with their potential implication as intermediate compounds involved in the formation of  
232 NDMA.

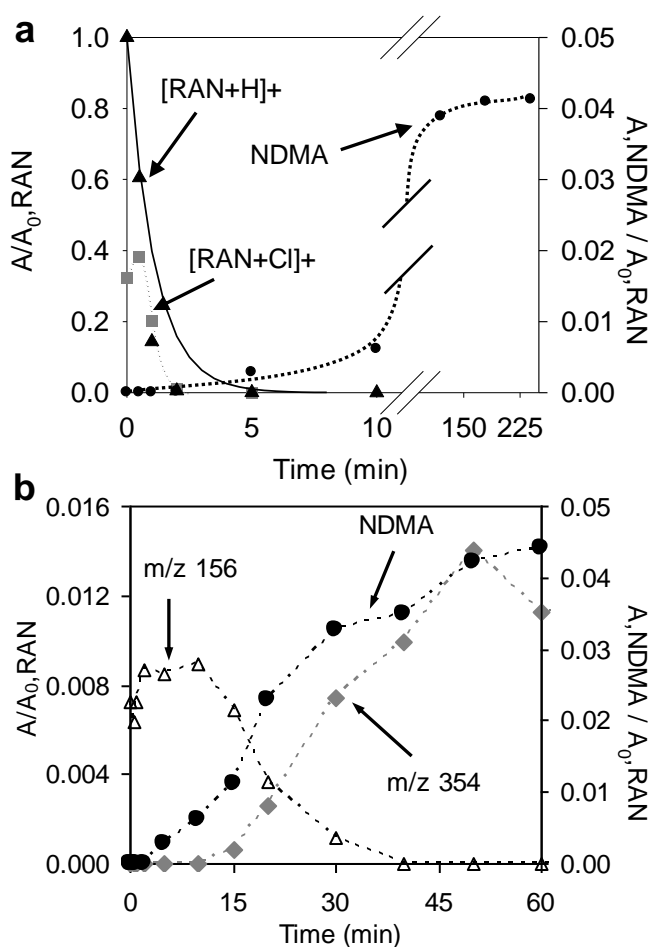


233

234 **Figure 2.** Influence of  $\text{NH}_2\text{Cl}$  concentration on the decomposition of ranitidine and the formation of  
 235 ranitidine by-products.  $[\text{RAN}]_0 = 167 \mu\text{M}$ ,  $t = 2 \text{ h}$ ,  $\text{pH} = 8$ . Relative scale based on initial ranitidine  
 236 concentration.

237 **Ranitidine By-products Formed in Excess of Monochloramine.** In order to determine the by-  
 238 products formed in the presence of an excess of monochloramine, i.e. in the conditions where NDMA  
 239 formation is favored, the decomposition of ranitidine ( $12 \mu\text{M}$ ) was investigated in the presence of 2.5  
 240 mM  $\text{NH}_2\text{Cl}$  over 48 h at pH 8 (with 10 mM phosphate buffer). These conditions have been

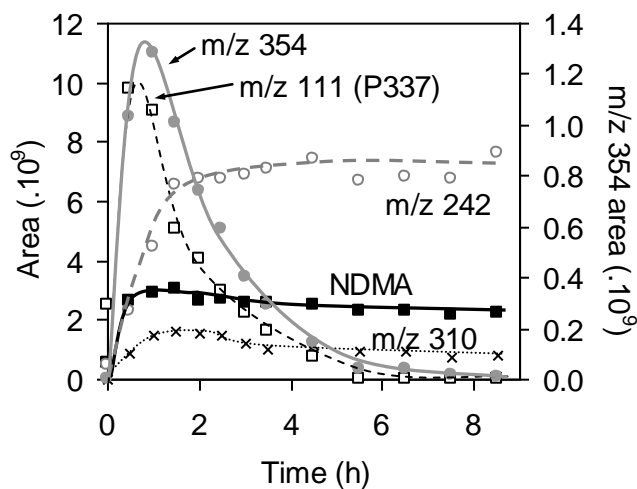
241 demonstrated to maximize the formation of NDMA.<sup>13</sup> Decomposition of ranitidine was complete in less  
 242 than 2 min, while the formation of NDMA was much slower (Figure 3a). Chlorine transfer (i.e., the  
 243 formation of chlorinated ranitidine) was very fast and chlorinated ranitidine was entirely decomposed in  
 244 less than 2 min as well as ranitidine. NDMA formation reached a plateau after 75 min. This is in  
 245 agreement with our previous observations of NDMA formation in similar conditions and monitored by  
 246 GC/MS.<sup>13</sup> Products that were previously detected when NH<sub>2</sub>Cl was introduced at equimolar  
 247 concentrations or with a slight excess as compared to ranitidine (e.g., fragments m/z 156, 330, 331, 364,  
 248 365, Figure 2) were not detected, probably because they were rapidly decomposed in the presence of a  
 249 large excess of NH<sub>2</sub>Cl (Figure 3b).



250

251 **Figure 3.** Decomposition of ranitidine (a) and formation of NDMA and other by-products (a and b) by  
 252 chloramination monitored by HPLC-MS in APCI positive mode.  $[\text{RAN}]_0 = 12 \mu\text{M}$ ;  $[\text{NH}_2\text{Cl}]_0 = 2.5 \text{ mM}$ ;

253 pH = 8 with 10 mM phosphate buffer. Relative area is based on initial ranitidine concentration. Solid  
254 line (a) represents model values of ranitidine decomposition based on the rate constant obtained at pH 8.  
255



256  
257 **Figure 4.** Formation of NDMA and other by-products by chloramination of ranitidine monitored by  
258 HPLC-MS in APCI positive mode.  $[\text{RAN}]_0 = 120 \mu\text{M}$ ;  $[\text{NH}_2\text{Cl}]_0 = 10 \text{ mM}$ ; pH = 8. Lines represent best  
259 fits of data.

260 Figure 4 depicts the formation of ranitidine by-products for higher initial concentrations (i.e.,  $120 \mu\text{M}$   
261 of ranitidine and  $10 \text{ mM}$  of  $\text{NH}_2\text{Cl}$ ) and longer contact times. Different products were slowly formed  
262 along with NDMA (m/z 111, 242, 310, and 354). NDMA (m/z = 75) and products with molecular ions  
263 m/z 242 and m/z 310 reached a plateau after 30 min of contact time. The product with a molecular ion  
264 m/z 242 (P241) was generated by hydroxylation and chlorination of P175, probably on nitrogen atoms  
265 of the N-methyl-2-nitroethene-1,1-diamine moiety as previously mentioned for molecular ranitidine.  
266 Subsequent chlorination of P241 led to the product with a molecular ion m/z 310 (the presence of 3  
267 chlorine atoms was confirmed by its isotopic distribution).

268 The ion m/z 111 was identified as the major fragment of the molecular ion m/z 338 (P337) (see Table  
269 1). The odd nominal mass of this product indicates an odd number of nitrogen atoms, reflecting the loss  
270 of the DMA group. MS spectra of this product revealed the presence of a chlorine atom and a gain of 32  
271 Da. This molecule can be attributed to the dihydroxylation and chlorination of ranitidine after the loss of

272 the DMA group (corresponding to fragment m/z 270). The product with molecular ion m/z 354 (P353)  
273 was identified as a hydroxylated analogue of P337, thus explaining the short delay between the  
274 formations of these products (Figure 4). P337 and P353 reached a maximum after around 1 h of reaction  
275 and then slowly decreased. Their formation was strongly correlated to NDMA formation during the first  
276 45 min of reaction. Hence, these compounds may be products resulting from carbocation intermediates  
277 formed during the last step of NDMA formation, as discussed below.

278

279 **Influence of Free Chlorine.** The influence of free chlorine (180  $\mu\text{M}$  HOCl) on ranitidine (180  $\mu\text{M}$ ) was  
280 investigated to compare chlorination and chloramination by-products produced at pH 8 and after 2 h of  
281 contact time. Similar chlorinated and hydroxylated by-products (i.e., molecular ions m/z 156, 176, 192,  
282 331, 349, 365) were formed after chlorination and chloramination and exhibited similar responses.  
283 However, P330 and P364 (chlorinated analogue of P330) were not detected in the presence of HOCl.  
284 This confirms the hypothesis of a nucleophilic substitution between  $\text{NH}_2\text{Cl}$  and the DMA group of  
285 ranitidine, leading to the P330 intermediate. Subsequent electrophilic substitution of P330 gives the  
286 chlorinated analogue P364.

287

### 288 **Proposed NDMA Formation Pathway**

289 During chloramination of amines, either chlorine transfer or nucleophilic substitution can occur.  
290 Chlorine transfer from  $\text{NH}_2\text{Cl}$  to the nitrogen atom of the DMA group of ranitidine is unlikely to occur  
291 as a predominant pathway because it would only lead to the formation of DMA or dimethylchloramine  
292 (DMCA) that are minor precursors of NDMA (i.e., < 3% molar yields).<sup>2,6,7</sup> Several tertiary amines have  
293 been demonstrated to produce important yields of NDMA, especially ranitidine (> 60% molar yield),<sup>11-13</sup>  
294 and more recently dimethylbenzylamine (64% molar yield).<sup>17</sup> Hence, a chlorine transfer (i.e.,  
295 electrophilic substitution) cannot explain the high yields of NDMA obtained for those tertiary amines.

296 The formation of NDMA by chloramination of DMA was previously proposed to occur via the  
297 formation of an UDMH, UDMH-Cl or UDMH-Br intermediate, followed by an oxidation in the



298 presence of dissolved oxygen.<sup>6,7,9,10</sup> This last step of the mechanism remains quite unclear because the  
299 kinetics of UDMH oxidation have not been clearly investigated in the presence of both dissolved oxygen  
300 and NH<sub>2</sub>Cl. UDMH (m/z 61) or equivalent intermediates UDMH-Cl (m/z 95) and UDMH-Br (m/z 139)  
301 were not detected in our analysis conditions. They were probably not separated correctly by liquid  
302 chromatography because of their low molecular weight. Moreover, they are expected to be rapidly  
303 oxidized to NDMA in the presence of dissolved oxygen and monochloramine or free chlorine, which  
304 explains why they have never been observed when NDMA was formed during chlorination or  
305 chloramination of water solutions containing amines.<sup>7,8</sup> Experiments were conducted to investigate the  
306 formation of NDMA by oxidation of UDMH (500 nM) by NH<sub>2</sub>Cl (2.5 mM) in the presence of dissolved  
307 oxygen. Molar yields after 24h of contact time were very low (i.e., < 0.01 %) as compared to NDMA  
308 formation from ranitidine (i.e., > 60%). Our results are in accordance with several studies that  
309 investigated UDMH oxidation by dissolved oxygen or NH<sub>2</sub>Cl.<sup>33-35</sup> Hence, these results suggest that  
310 UDMH is not likely to be a major intermediate involved in the formation of NDMA during  
311 chloramination, especially from tertiary amines such as ranitidine.

312 Based on these observations, we propose that DMA groups must be attached at the benzylic position  
313 of aromatic or heterocyclic rings in order to produce high yields of NDMA. Indeed, as shown in **Scheme**  
314 **1**, the release of NDMA from ranitidine leads to the formation of a stable carbocation at benzylic  
315 position of the furan ring that is favored thermodynamically. These carbocation intermediates are prone  
316 to react with nucleophiles such as water and thus may lead to the observed products P337 and P353 after  
317 hydroxylation on the methylene group. This mechanism is in accordance with the simultaneous  
318 production of P337, P353 and NDMA observed during chloramination of ranitidine (Figure 4).

319 In a previous study, we demonstrated that almost no NDMA was formed in the absence of dissolved  
320 oxygen during chloramination of ranitidine.<sup>13</sup> Because the formation of UDMH and its oxidation by  
321 dissolved oxygen is not likely to occur, dissolved oxygen incorporation has to occur directly on the  
322 intermediate formed after the reaction between NH<sub>2</sub>Cl and the DMA group of ranitidine (i.e. products  
323 P330 or P364). Hence, we propose that the positive charge on the nitrogen atom of the DMA moiety

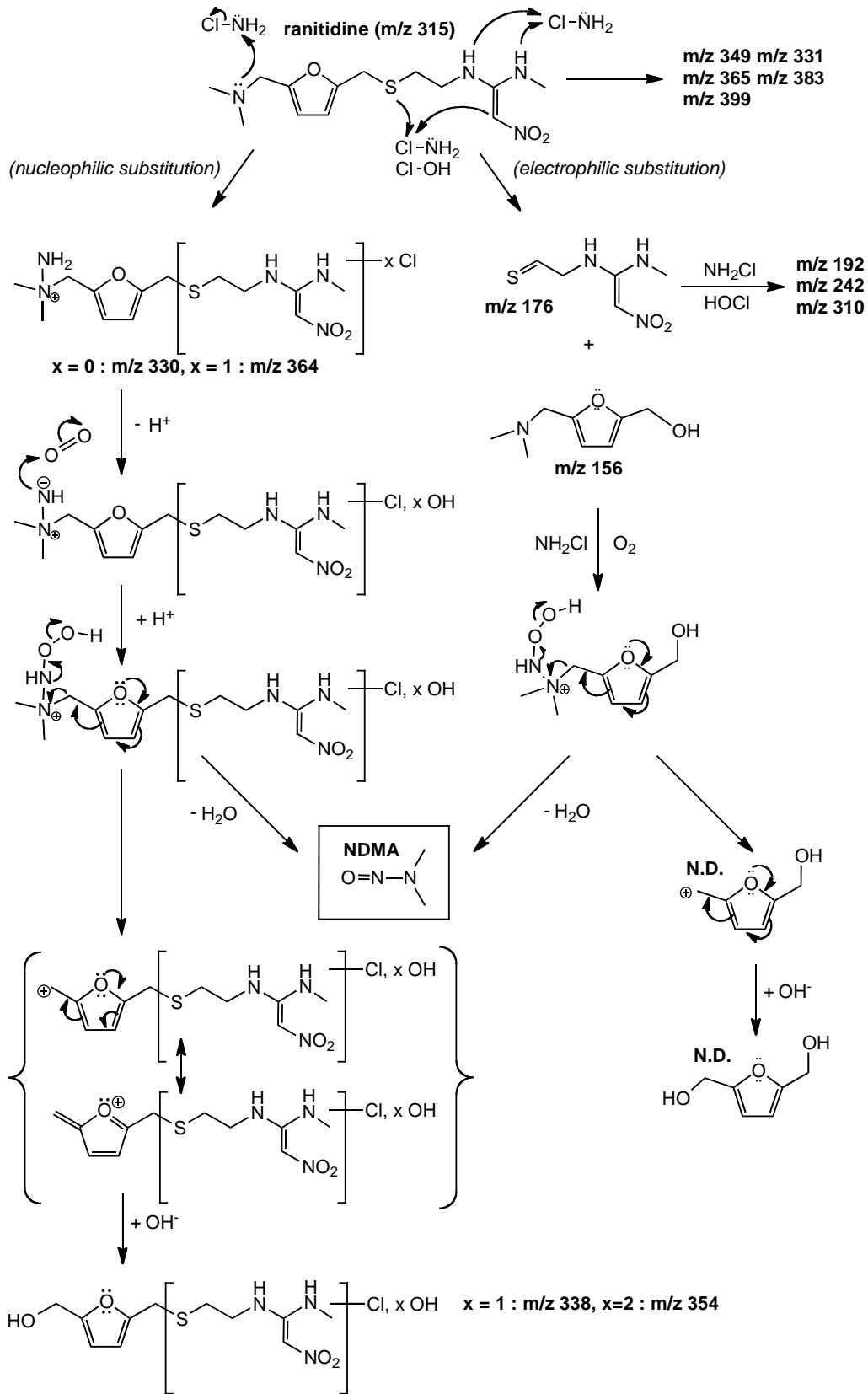
324 reduces the pKa of hydrogen on the NH<sub>2</sub> group, therefore favoring the formation of a highly reactive  
325 NH<sup>-</sup> intermediate which reacts with dissolved oxygen to yield a NDMA precursor group.

326 We hypothesize that nucleophilic substitution rather than chlorine transfer is the main reaction  
327 occurring on the DMA moiety of ranitidine. In this case the steric hindrance brought by the two methyl  
328 groups probably disfavors the transfer of the bulky chlorine atom of NH<sub>2</sub>Cl to the amine. However,  
329 chlorine transfer is likely to take place on less hindered moieties of ranitidine, especially on nitrogen  
330 atoms of the thioethyl-N-methyl-2-nitroethene-1,1-diamine moiety, producing the chlorinated analogues  
331 of ranitidine (i.e., m/z 349 and m/z 383) and then hydroxylated analogues after further oxidation.  
332 Chlorine transfer can also take place on the sulfur atom and cause sulfoxide compounds formation,<sup>36</sup> or  
333 the cleavage of the C-S bond leading to the release of the observed product P175 and  
334 5-(dimethylaminomethyl)furfuryl alcohol (DFUR, m/z 156) (see SI, Scheme S1). Our results are  
335 consistent with three initial reactions: i) fast chlorine transfer leading to chlorinated analogues of  
336 ranitidine, ii) the cleavage of the C-S bond leading to DFUR and iii) nucleophilic substitution leading to  
337 P330. The proposed pathways are also probably interconnected because chlorinated ranitidine (P348)  
338 can also react with NH<sub>2</sub>Cl through nucleophilic substitution and lead to P364, and both hydroxylated  
339 and chlorinated ranitidine analogues can liberate DFUR through the cleavage of C-S bond. DFUR is  
340 known to be a decomposition product of ranitidine,<sup>37</sup> and to produce important amounts of NDMA as  
341 well as ranitidine (i.e., > 50% molar yields).<sup>10,11</sup> Hence, DFUR produced via chlorine addition on  
342 ranitidine and C-S bond cleavage could react with NH<sub>2</sub>Cl to contribute to the overall formation of  
343 NDMA. The stable carbocation (i.e. methylfurfuryl alcohol) that would form along with NDMA via this  
344 pathway and its hydroxylated analogue were not detected, probably because they were not properly  
345 separated in our chromatographic conditions.

346

347

348 **Scheme 1.** NDMA formation mechanism proposed for the chloramination of ranitidine (N.D. = Not  
349 Detected).



350

351

352 **Implications for Water Treatment**

353 The kinetics study revealed that ranitidine decomposition was favored at acidic pH, while NDMA  
354 formation reaches a maximum around pH 8.<sup>13</sup> Hence, NDMA formation cannot be directly related to the  
355 decomposition of molecular ranitidine. The influence of pH on NDMA formation depends on complex  
356 reactions involving monochloramine stability, the potential formation of chloramines decomposition  
357 products (e.g., peroxydinitrite ions or hydrazine intermediates), or acid dissociation constants of ranitidine  
358 and its by-products. Even if the disproportionation of  $\text{NH}_2\text{Cl}$  to  $\text{NHCl}_2$  has been proposed to favor the  
359 formation of NDMA from the reaction with DMA,<sup>8</sup> the decomposition of  $\text{NH}_2\text{Cl}$  at acidic pH is  
360 expected to limit the production of NDMA in the case of ranitidine oxidation.<sup>13</sup> Moreover, no analogue  
361 to P330 with a chlorine atom on the amine group (i.e.,  $\text{RAN} + \text{NHCl}$ ) was detected, as it could be  
362 expected to form from the reaction of ranitidine with dichloramine. In our experimental conditions (i.e.,  
363 pH 8), the production of  $\text{NHCl}_2$  was limited. Hence,  $\text{NHCl}_2$  does not seem to play a major role in the  
364 formation of NDMA during chloramination of ranitidine, as we already proposed in a previous study.<sup>13</sup>  
365 Chlorine transfer between  $\text{NH}_2\text{Cl}$  and DMA is also subjected to general acid catalysis.<sup>25,27</sup> In a similar  
366 manner, chlorine transfer to the DMA group of ranitidine (i.e., electrophilic substitution) could be  
367 favored at acidic pH, which would explain the higher decomposition rate observed (Figure 1), and thus  
368 would limit the occurrence of a nucleophilic substitution and subsequent NDMA formation. Hence, the  
369 formation of NDMA from ranitidine during water treatment processes could be reduced by favoring  
370 electrophilic substitution (i.e., chlorine attack) at  $\text{pH} < 7$ .

371 Many by-products were identified during the chloramination of ranitidine. Different compounds are  
372 produced depending on  $\text{NH}_2\text{Cl}$ :ranitidine ratio and reaction time. Nucleophilic substitution of DMA  
373 group is not affected by C-S bond cleavage and formation of chlorinated and hydroxylated analogues of  
374 ranitidine. Thus NDMA formation occurs through multiple pathways, which explains the high yields  
375 observed. In real water disinfection conditions, ranitidine (or another major precursor of NDMA) is  
376 expected to be at very low concentrations (i.e. at ng/L levels) as compared to  $\text{NH}_2\text{Cl}$  concentrations.  
377 Hence, NDMA formation from ranitidine is likely to be maximized in these conditions and could only

378 be limited by lowering the pH or by reducing the initial concentration of ranitidine (or other NDMA  
379 precursors).

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383 **Supporting Information.** Additional details of the materials and methods, additional figures  
384 (chromatogram and MS spectra of ranitidine and several by-products) and scheme of P155 (DFUR) and  
385 P175 formation.

386

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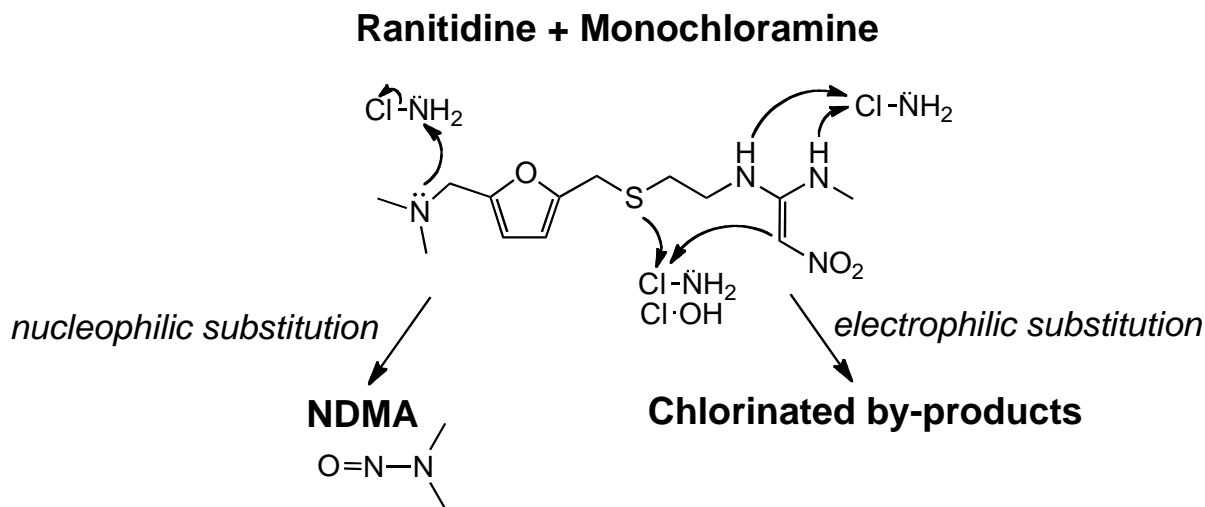
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478

479 **SYNOPSIS TOC art.**



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