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OZONATION OF RANITIDINE UNDER VARIOUS PHYSICOCHEMICAL CONDITIONS.
DEGRADATION KINETICS AND INTERMEDIATE BY-PRODUCTS

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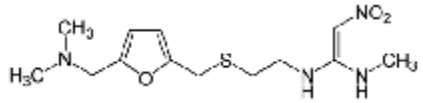
Presentation overview

- Pharmaceuticals – Ranitidine
- Ozonation
- Experimental part
- Effect of various parameters on the degradation of Ranitidine
- By-product determination workflow
- Main intermediate byproducts
- Conclusions

Pharmaceuticals - Ranitidine

- Numerous pharmaceuticals, personal care products and endocrine disrupting compounds have entered the environment.
- Levels of ng to several µg/L
- according to water solubility, physicochemical characteristics, local consumption rates and biodegradability

Ranitidine (Zantac)

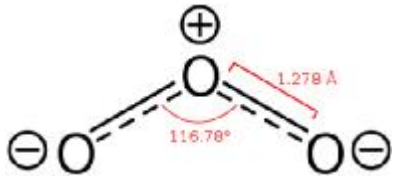


- common pharmaceutical (treatment of ulcer, gastrointestinal hypersecretory conditions and gastroesophageal refluxes)
- histamine H2-receptor antagonist with a furan ring structure
- mainly excreted in urine as an untransformed compound and its main metabolites formed in the liver (30-70%) are ranitidine N-oxide, N-desmethyl ranitidine and ranitidine S-oxide
- The presence of ranitidine in surface waters and wastewaters in the US has been determined and identified in several studies in the past
- contains multiple reactive sites that may be labile to ozone oxidation (e.g. conjugated diene, sulphide and electron-rich alkene group)

Ozonation

- effective, robust and widely accepted oxidation technique
- degradation occurs mainly through direct reaction with aqueous ozone and ozone decay products (mainly hydroxyl radicals).
- total mineralization is not entirely achieved for many pollutants, often leading to the production of more by-products with higher or increased toxicity levels.

- O_3 selectively attacks organic compounds with high electron density functional groups
  - double bonds C=C
  - activated aromatic rings with Electron donating groups like
    -NH_2
    -NHR
    -NR_2
    -OH
    -O^-
  - deprotonated amines



Objectives of this study

- to assess the effects of various operational parameters (pH, ozone concentration, presence of hydroxyl radical scavengers, matrix effects and natural organic matter) on the kinetics of the ozonation process

- to identify the intermediate oxidation by-products of ranitidine

Experimental

Ozonation experiments

- saturated ozone solution at 4^0C using ozone AZCOZON apparatus
- Aqueous solutions of ranitidine under various pH adjusted (ammonium acetate buffer)
- sealed bottles aqueous solution of ranitidine in the selected buffer was injected with various amounts of saturated ozone solution
- Samples withdrawn in predefined time frames

Effects studied

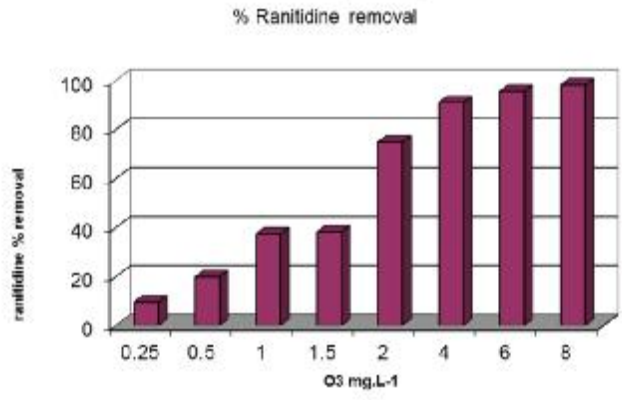
- Solution pH
- matrix
- Hydroxyl radical scavenger t-BuOH

Analysis

- Kinetics using HPLC – UV
- TPs using Bruker qTOFMS

Effect of ozone concentration

- 5 mg L^{-1} is enough to degrade more than 85% of the compound
- Fast reaction in first minutes
- Total removal with O3 > 4 mg L^{-1}
- Pseudo first order rates vary 0.19-6.06 min^{-1} (R^2 >0.956)



Effect of pH

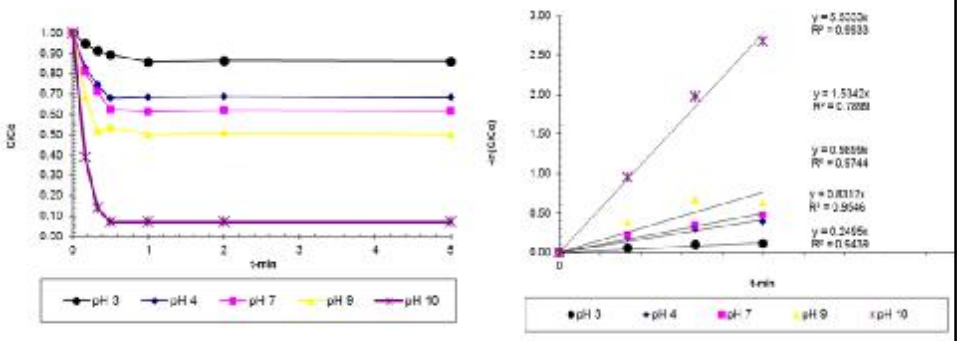
- Ranitidine removal is enhanced at higher pH
- Amine – ozone reactivity at non-protonated forms
- pH>7 ozone decomposed to hydroxyl radicals

$O_3^{\bullet-}$ D $O^{\bullet-} + O_2$

$O^{\bullet-} + H_2O \rightarrow {\bullet}OH + OH^-$

${\bullet}OH + O_3 \rightarrow HO_2^{\bullet} + O_2$

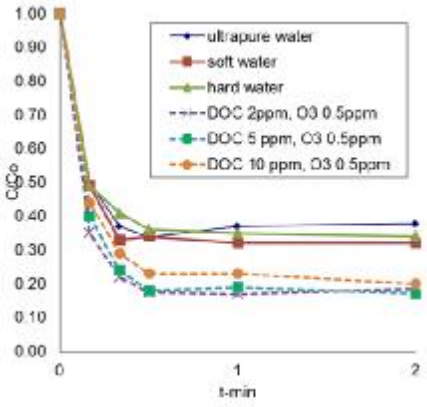
Pseudo first order reaction rates 0.250-5.533min^{-1}



C_o ranitidine 5 mg L^{-1}, ozone initial concentration 1 mg L^{-1}

Effect of matrix content

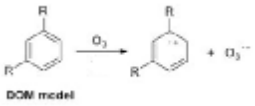
- Soft and Hard simulated drinking water indicated similar degradation rate
- Alkalinity and bicarbonates usually tend to stabilize aqueous ozone minimizing OH radical formation
- $HCO_3^- + {\bullet}OH \rightarrow CO_3^{\bullet-} + H_2O$ (5)
- $2\ CO_3^{\bullet-} \rightarrow CO_3^{2-}$



Effect of matrix content

DOM presence

- Direct ozone reaction OH radical creation
- Consuming ozon faster



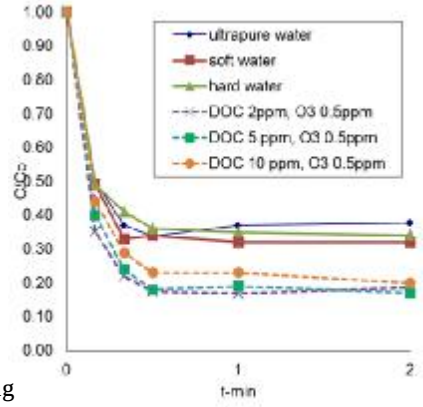
DOM model

$O_3^{\bullet-}$ D O_2 + $O^{\bullet-}$

$O^{\bullet-}$ +H_2O D $^{\bullet}OH$ + OH^-

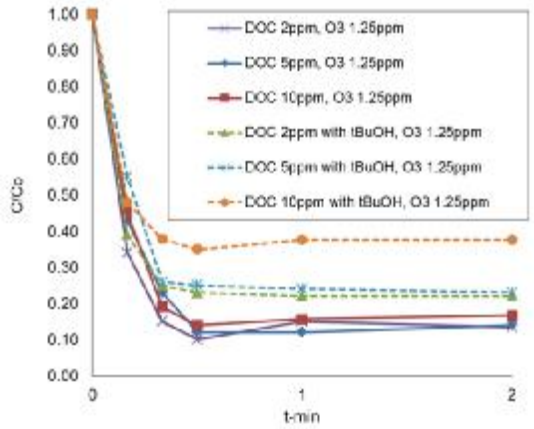
Nevertheless

Increased kinetic rates were determined regardless of DOC concentration indicating a role of hydroxyl radicals in the degradation of ranitidine



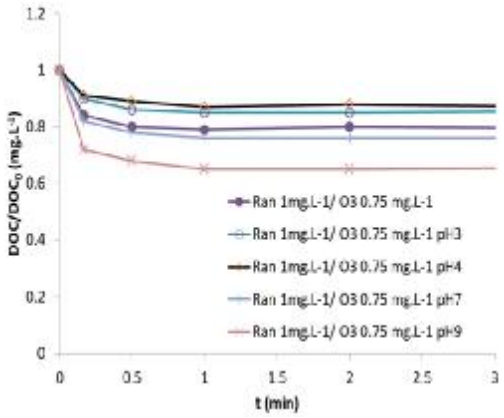
$OH^{\bullet}$ scavenger addition addition

- Presence of scavenger t-BuOH reduces the reaction rate and overall removal
- Apparent role of OH radicals produced with DOM and Ozone
- Antagonism of oxidative species between DOM and ranitidine
- Pseudo-first order rate constants are similar to higher pH values



ozone concentration 1.25 mg L^{-1}, initial ranitidine concentration 1 mg L^{-1}

Mineralization of Ranitidine



- Reduced mineralization at low ozone concentrations
- Although at the same concentration Ran is completely removed
- Transformed to various refractory ozonation by products
- Higher ozone doses need for complete mineralization
- Mineralization higher at increased pH

Overall kinetics

$C O_3$ (mg.L^{-1})	C_o Ran (mg L^{-1})	pH	t-BuOH (mM)	matrix	k_{obs} (min^{-1})	R^2
0.5	5	5.8	-	Ultrapure water	0.52	0.797
1	5	5.8	-	Ultrapure water	0.92	0.846
2	5	5.8	-	Ultrapure water	1.70	0.969
4	5	5.8	-	Ultrapure water	4.13	0.980
6	5	5.8	-	Ultrapure water	5.15	0.981
8	5	5.8	-	Ultrapure water	6.06	0.973
1	5	3	-	Acetate buffer	0.25	0.993
1	5	4	-	Acetate buffer	0.83	0.800
1	5	7	-	Acetate buffer	0.99	0.974
1	5	9	-	Acetate buffer	1.53	0.955
1	5	10	-	Acetate buffer	5.53	0.944
1	1.5	5.8	-	Ultrapure water	2.01	0.901
1	2	5.8	-	Ultrapure water	1.44	0.912
1	5	5.8	-	Ultrapure water	0.92	0.846

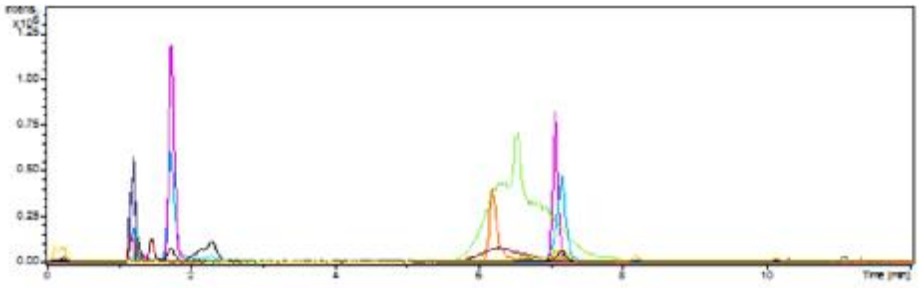
$C O_3$ (mg.L^{-1})	C_o Ran (mg.L^{-1})	pH	t-BuOH (mM)	matrix	k_{obs} (min^{-1})	R^2
0.5	1	7.6	-	Drinking Water (medium hardness)	1.27	0.734
0.5	1	7.6	-	Drinking Water (increased hardness)	1.72	0.669
1.25	1	5.8	-	DOC 2mg.L^{-1}	5.05	0.951
1.25	1	5.8	-	DOC 5mg.L^{-1}	4.35	0.993
1.25	1	5.8	-	DOC 10 mg.L^{-1}	4.29	0.961
1.25	1	5.8	20µM	DOC 2mg.L^{-1}	3.69	0.964
1.25	1	5.8	20µM	DOC 5mg.L^{-1}	3.19	0.903
1.25	1	5.8	20µM	DOC 10 mg.L^{-1}	2.50	0.767

By product determination workflow

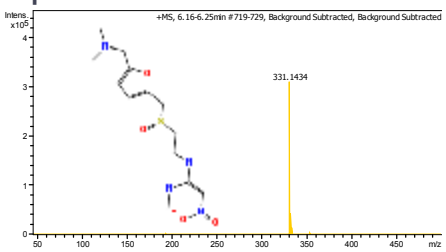
Full MS Chromatogram preparation	MS peak recognition	Structure elucidation MS/MS
Internal Calibration	***For each t_R, m/z accurate***	***(MS/MS)***
Background subtract	***Check presence in blank***	***minimum – maximum elemental formula, m/z tolerances***
Mass exclusions (known m/z)	***(plus m/z predicted, bibliographical references)***	***possible chemical formulas***
	EIC of possible by products	***Match with structure (best score based on error and isotope patterns)***
		insert possible by products in table using the theoretical and experimental m/z and the calculated error

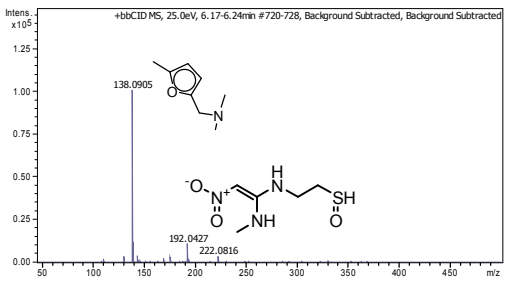
Main intermediate byproduct formation

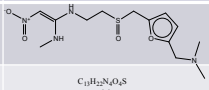
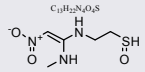
Non target screening gave 23 possible TPs
Blank subtraction and mass accuracy reduced this number to the following suspected TPs
EIC Chromatogram of possible TPs not present in blank



TP-300 formation of sulfoxide product



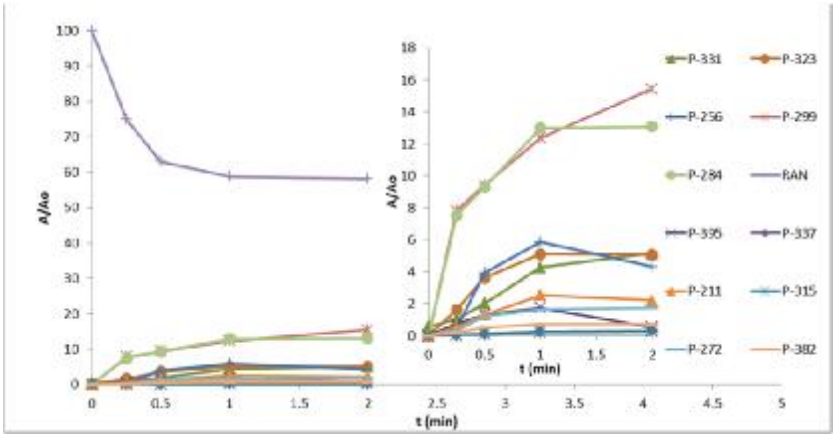


t_R	Compound	Precursor and production	Fragment losses	Proposed structure	Elemental formula	Exp mass $[M+H]^+$	Theor mass $[M+H]^+$	Error ppm	Error mDa	Error mSigma
6.6	P-330	$[M+H]^+$			$C_{13}H_{22}N_4O_4S$	331.1437	331.1435	0.1	0.2	19.1
		$[M+H-C_7H_{13}O_4S]^{+\cdot}$	193.0529		$C_6H_{10}N_4$	138.0905	138.0900		0.5	23.8
		$[M+H-C_6H_{12}NO]$	139.1000		$C_5H_{10}N_3O_3S$	192.0437	192.0427	5.5		50.7

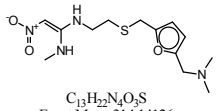
t_R	Compound	Precursor and production	Fragment losses	Elemental formula	Exp mass $[M+H]^+$	Theor mass $[M+H]^+$	Error ppm	Error mDa	Error mSigma
1.6	P-131	$[M+H]^+$		$C_4H_{10}N3O_2$	132.0763	132.0768	-3.79	0.2	9.1
1.8	P-299	$[M+H]^+$		$C_{13}H_{22}N_3O_3S$	300.1380	300.1376	-1.2	-0.4	18.4
		$[M+H-C_5H_{10}N_2O_3S]^+$	162.0472	$C_8H_{12}NO$	138.0908	138.0913		-0.5	4.1
1.8	P-381	$[M+H]^+$		$C_{13}H_{24}N_3O_6S_2$					
		$[M+H-H_2O_3S]^+$	81.9727	$C_{13}H_{22}N_3O_3S$	300.1376	300.1376		-0.2	11.6
		$[M+H-C_5H_{12}N_2O_5S_2]^+$	244.0197	$C_8H_{12}NO$	138.0908	138.0913		-0.5	4.1
2.3	P-315	$[M+H]^+$		$C_{13}H_{22}N_3O_4S$	316.1322	316.1326	1.2	0.4	11.5
		$[M+H-C_9H_{12}NO_3]^{+\cdot}$	182.0823	$C_4H_{10}N_2OS$	134.0498	134.0508		-1.0	5.2
6.6	P-330	$[M+H]^+$		$C_{13}H_{22}N_4O_4S$	331.1437	331.1435	0.1	0.2	19.1
		$[M+H-C_7H_{13}O_4S]^{+\cdot}$	193.0529	$C_6H_{10}N_4$	138.0905	138.0900		0.5	23.8
		$[M+H-C_8H_{12}NO]$		$C_5H_{10}N_3O_3S$	192.0437	192.0427	5.5		50.7
6.6	P-283	[M+H]-NHO		$C_{13}H_{21}N_3O_2S$	284.1427	284.1427	0.00	0.6	21.2
6.6	P-365	$[M+H]^+$		$C_{13}H_{24}N_3O_5S_2$	366.1158	366.1152	0.2	0.7	20.6
		$[M+H-CH_2NS]^{+\cdot}$	59.9910	$C_{12}H_{22}N_2O_5S$	306.1239	306.1244		-0.5	9.0
		$[M+H-SO_3H_2]^+$	81.9728	$C_{13}H_{22}N_3O_2S$	284.1422	284.1427		-0.6	8.6
		$[M+H-C_2H_9NO_2S]^+$	127.0306	$C_{11}H_{15}NO_3S$	239.0843	239.0849		-0.6	8.2
		$[M+H-C_8H_{15}NO_4S]^+$	221.0724	$C_5H_9N_2OS$	145.0425	145.0430		-0.5	24.6

t_R	Compound	Precursor and production	Fragment losses	Elemental formula	Exp mass $[M+H]^+$	Theor mass $[M+H]^+$	Error ppm	Error mDa	Error mSigma
7.1	P-394 P-330	$[M+H]^+$		$C_{13}H_{23}N_4O_6S_2$	395.1051	395.1054	-0.6	-0.2	25.4
		$[M+H-SO_3]^+$	79.9570	$C_{13}H_{23}N_4O_3S$	315.1481	315.1485		-0.4	10.3
		$[M+H-C_2H_7NO_3S]^+$	125.0149	$C_{11}H_{16}N_3O_3S$	270.0902	270.0907		-0.5	7.9
		$[M+H-C_4H_4N_3O_2S]^{+\cdot}$	158.0027	$C_9H_{19}NO_4S$	237.1024	237.1029		0.5	9.8
		$[M+H-C_6H_6O_3S]^+$	158.0027	$C_7H_{17}N_4O_3S$	237.1024	237.1016		0.8	11
		$[M+H-C_4H_{11}N_5O_5S]^+$	185.0363	$C_9H_{12}N_3OS$	210.0689	210.0696		-0.7	6.9
		$[M+H-C_8H_{13}NO_4S]^+$	219.0572	$C_5H_{10}N_3O_2S$	176.0479	176.0488	-5.5		14.2
7.4	P-299 P-255	$[M+H]^+$		$C_{13}H_{22}N_3O_3S$	300.1375	300.1376	0.4	0.1	19.5
		$[M+H-C_6H_{12}N_2O_2S]^+$	176.0621	$C_7H_{10}NO$	124.0754	124.0757		-0.2	10.6
		$[M+H-C_7H_{15}O_3]^{+\cdot}$	147.1016	$C_6H_7N_2S$	153.0359	153.0355		-0.4	12.4
		[M+H – C3H14N3S]	124.0899	$C_{10}H_8O_3$	176.0476	176.0468		0.8	n.a.
7.9	Ranitidine	$[M+H]^+$		$C_{13}H_{22}N_4O_3S$	315.1501	315.1495	2.2	0.6	4.5

Profile of TP production

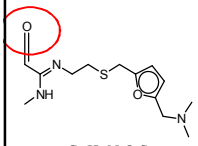


- Relative abundance >1%

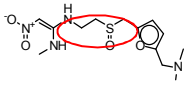


$C_{13}H_{22}N_4O_3S$
Exact Mass: 314.14126

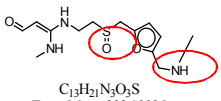
Some products with:
+SO_2
+OSO_2H



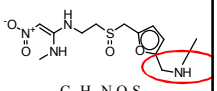
$C_{13}H_{21}N_3O_2S$
Exact Mass: 283.13545



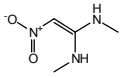
$C_{13}H_{22}N_4O_4S$
Exact Mass: 330.13618



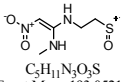
$C_{13}H_{21}N_3O_3S$
Exact Mass: 299.13036



$C_{12}H_{20}N_4O_4S$
Exact Mass: 316.12053



$C_4H_9N_3O_2$
Exact Mass: 131.06948



$C_5H_{11}N_3O_3S$
Exact Mass: 193.05211

Conclusions

- Ranitidine readily reacts with ozone producing various intermediate by products
- Reaction is enhances under increased pH and initial ozone concentration
- Pseudo first order K_{obs} reaches 6.06 min^{-1}
- DOM role as producer of OH radicals and ozone depleting agent
- 4 possible different TPs from the beginning of oxidation reaction
- Mass balance not closed
- Other ozone concentrations and differences in pH are needed

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- Thank you for your attention!