

FBBF UNIVERSITY OF ZAGREB
FACULTY OF
PHARMACY AND
BIOCHEMISTRY

Chlorinated nucleobases

An unexpected (eco)toxicological profile

Assoc. prof. Davor Šakić, PhD



EEA Technical report | No 1/2010

Pharmaceuticals in the environment

Results of an EEA workshop

“The situations looks worse than a decade ago”

ISSN 1725-2237

Klaus Kümmerer
Editor

Pharmaceuticals in the Environment

Sources,
Fate,
Effects
and Risks

Third, revised and enlarged edition

 Springer

PHARMA- ECOLOGY

*The Occurrence and Fate of
Pharmaceuticals and Personal Care
Products in the Environment*



PATRICK K. JJEMBA

 WILEY

Environmental Degradation and Transformation of Organic Chemicals

Alasdair H. Neilson
and Ann-Sofie Allard

Human Pharmaceuticals in the Aquatic Environment: A Challenge to Green Chemistry

Sushil K. Khetan* and Terrence J. Collins*

Department of Chemistry, Carnegie Mellon University, Pittsburgh, Pennsylvania 15213

Environ Chem Lett (2004) 1:237–241
DOI 10.1007/s10311-003-0045-4

ORIGINAL PAPER

M. DellaGreca · M. Brigante · M. Isidori · A. Nardelli ·
L. Previtara · M. Rubino · F. Temussi

Phototransformation and ecotoxicity of the drug Naproxen-Na



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Journal of Photochemistry and Photobiology A: Chemistry 158 (2003) 63–66

Journal of
Photochemistry
and
Photobiology
A: Chemistry

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Short communication

Photochemical conversion of triclosan to 2,8-dichlorodibenzo-*p*-dioxin in aqueous solution

Douglas E. Latch^a, Jennifer L. Packer^b, William A. Arnold^{b,1}, Kristopher McNeill^{a,*}

^a Department of Chemistry, University of Minnesota, 207 Pleasant St. SE, Minneapolis, MN 55455, USA

^b Department of Civil Engineering, University of Minnesota, 500 Pillsbury Dr. SE, Minneapolis, MN, USA

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Fate of Pharmaceuticals in the Environment and in Water Treatment Systems

Edited by

Diana S. Aga



+



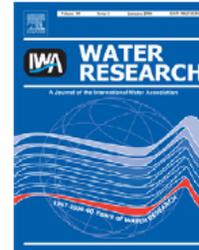


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Review

Reactions of chlorine with inorganic and organic compounds during water treatment—Kinetics and mechanisms: A critical review

Marie Deborde^a, Urs von Gunten^{a,b,*}

^aDepartment of Water Resources and Drinking Water, EAWAG, Swiss Federal Institute of Technology, CH-8600 Dübendorf, Switzerland

^bInstitute of Biogeochemistry and Pollutant Dynamics, ETH Zürich, CH-8092

Bull. Environ. Contam. Toxicol. (2005) 74:24–31

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DOI: 10.1007/s00128-004-0543-5

Bulletin of
**Environmental
Contamination
and Toxicology**

Effects of Chlorination on the Persistence of Pharmaceuticals in the Environment

S. T. Glassmeyer, J. A. Shoemaker

United States Environmental Protection Agency, Office of Research and Development, National Exposure Research Laboratory, MS 564, Cincinnati, OH 45268, USA

Transformation of Acetaminophen by Chlorination Produces the Toxicants 1,4-Benzoquinone and *N*-Acetyl-*p*-benzoquinone Imine

MARY BEDNER* AND
WILLIAM A. MACCREHAN

Analytical Chemistry Division, National Institute of
Standards and Technology, Mailstop 8392,
Gaithersburg, Maryland 20899-8392

CHART 1



liver microsomes oxidize acetaminophen to *N*-acetyl-*p*-benzoquinone imine (NAPQI; II), a toxic metabolite that results in hepatic necrosis (1). NAPQI, however, is known to be fairly unstable and readily hydrolyzes to the toxicant 1,4-

Environ. Sci. Technol. 2007, 41, 6228–6233

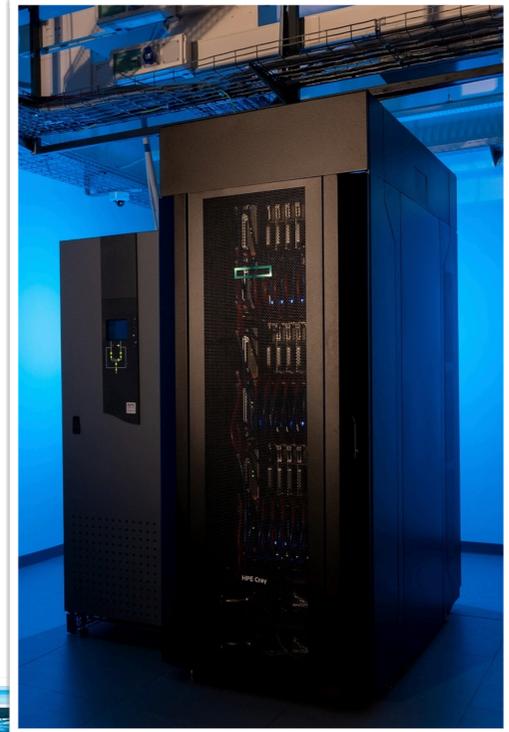
Unexpected Products and Reaction Mechanisms of the Aqueous Chlorination of Cimetidine

JEFFREY M. BUTH,[†]
WILLIAM A. ARNOLD,^{*,‡} AND
KRISTOPHER MCNEILL^{*,†}

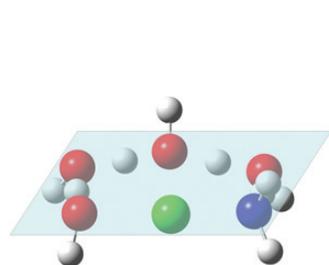
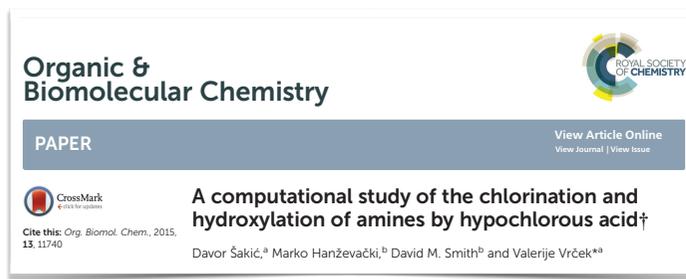
Department of Chemistry, University of Minnesota,
207 Pleasant Street SE, Minneapolis, Minnesota 55455, and
Department of Civil Engineering, University of Minnesota,
500 Pillsbury Dr. SE, Minneapolis, Minnesota 55455

ically designed to elicit a biological response, it has been suggested that some can inflict biological harm even at trace concentrations, with possible synergistic effects (1, 2). It has been demonstrated that many PPCPs are not effectively removed by conventional wastewater treatment processes (3–5), thus passing the compounds to surface waters that receive wastewater effluent. Consequently, a wide range of PPCPs have been detected in rivers throughout the world (6–8). Their increasing production and use present a continuous source of these compounds to surface waters.

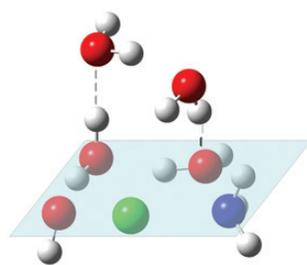
Because PPCPs often persist through the wastewater treatment processes, they may be available to react with free chlorine or other oxidants used for disinfection. Free chlorine (HOCl/OCl⁻) is a nonspecific oxidant used in wastewater disinfection that has been shown to degrade various PPCPs to chlorinated, oxidized, and fragmented byproducts (9–



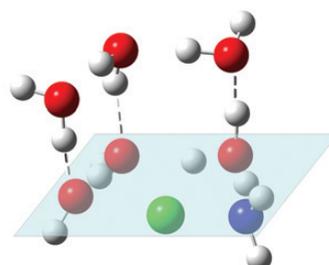
N-chlorination of amines



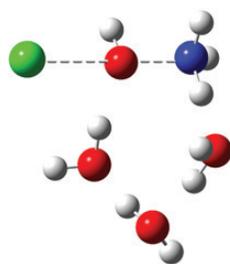
$TS_{Cl} \cdot 3H_2O$



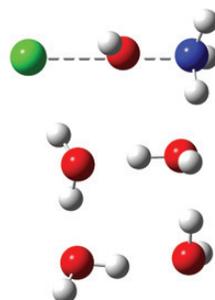
$TS_{Cl} \cdot 4H_2O$



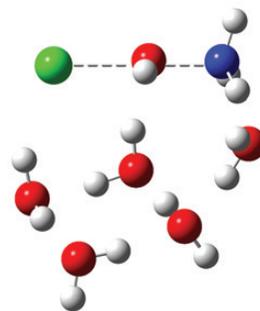
$TS_{Cl} \cdot 5H_2O$



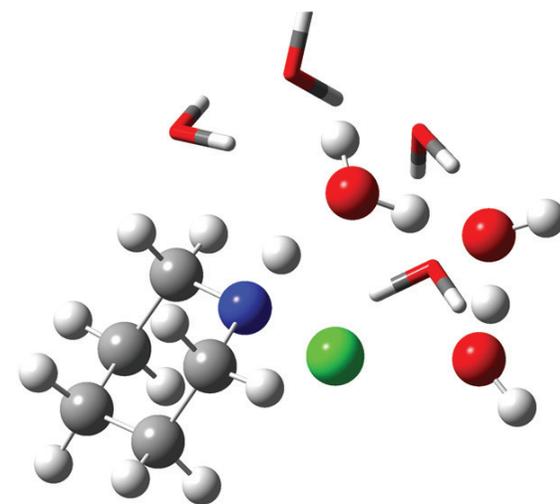
$TS_{OH} \cdot 3H_2O$



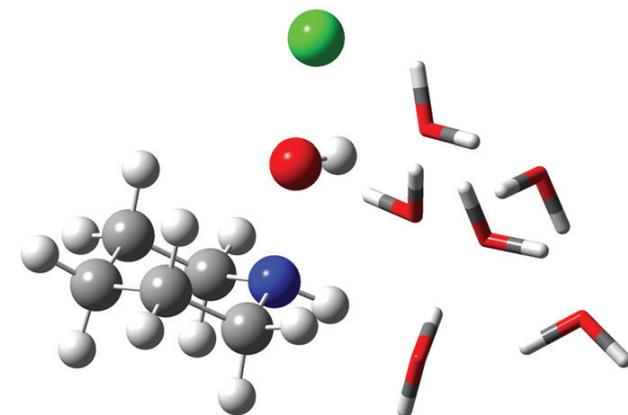
$TS_{OH} \cdot 4H_2O$



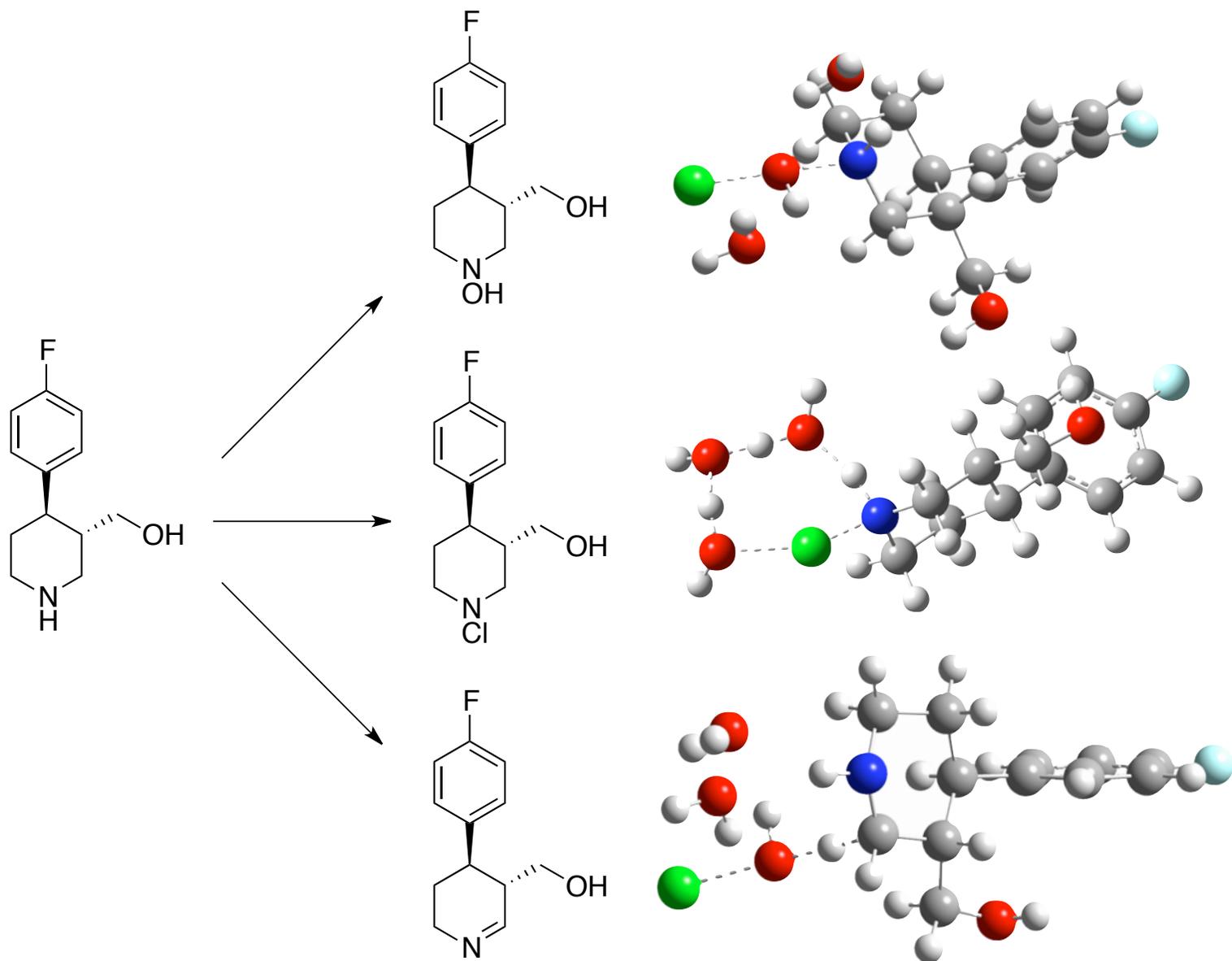
$TS_{OH} \cdot 5H_2O$



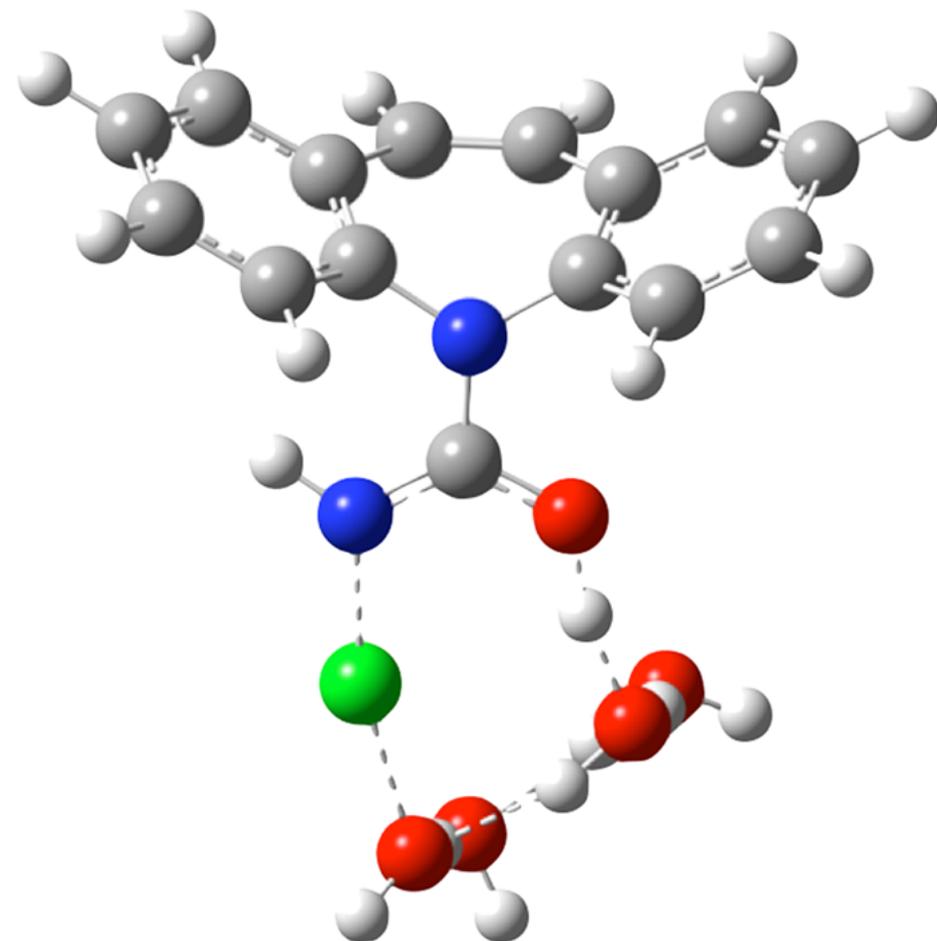
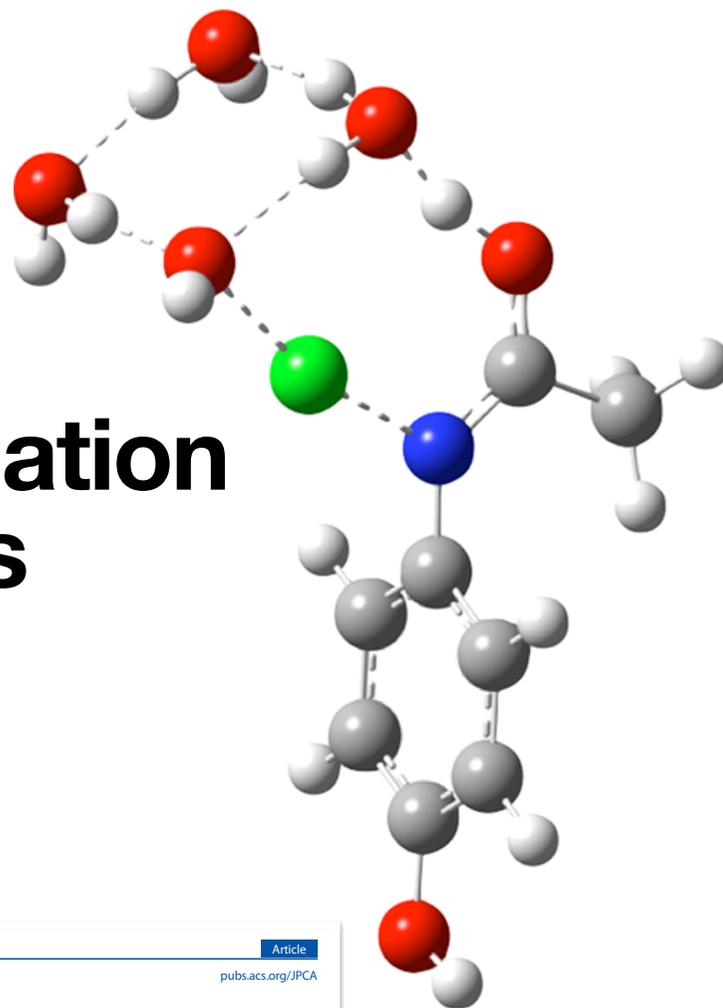
$TS_{N1-Cl} \cdot 6H_2O$



$TS_{N1-OH} \cdot 6H_2O$



N-chlorination of amides



THE JOURNAL OF
PHYSICAL CHEMISTRY A

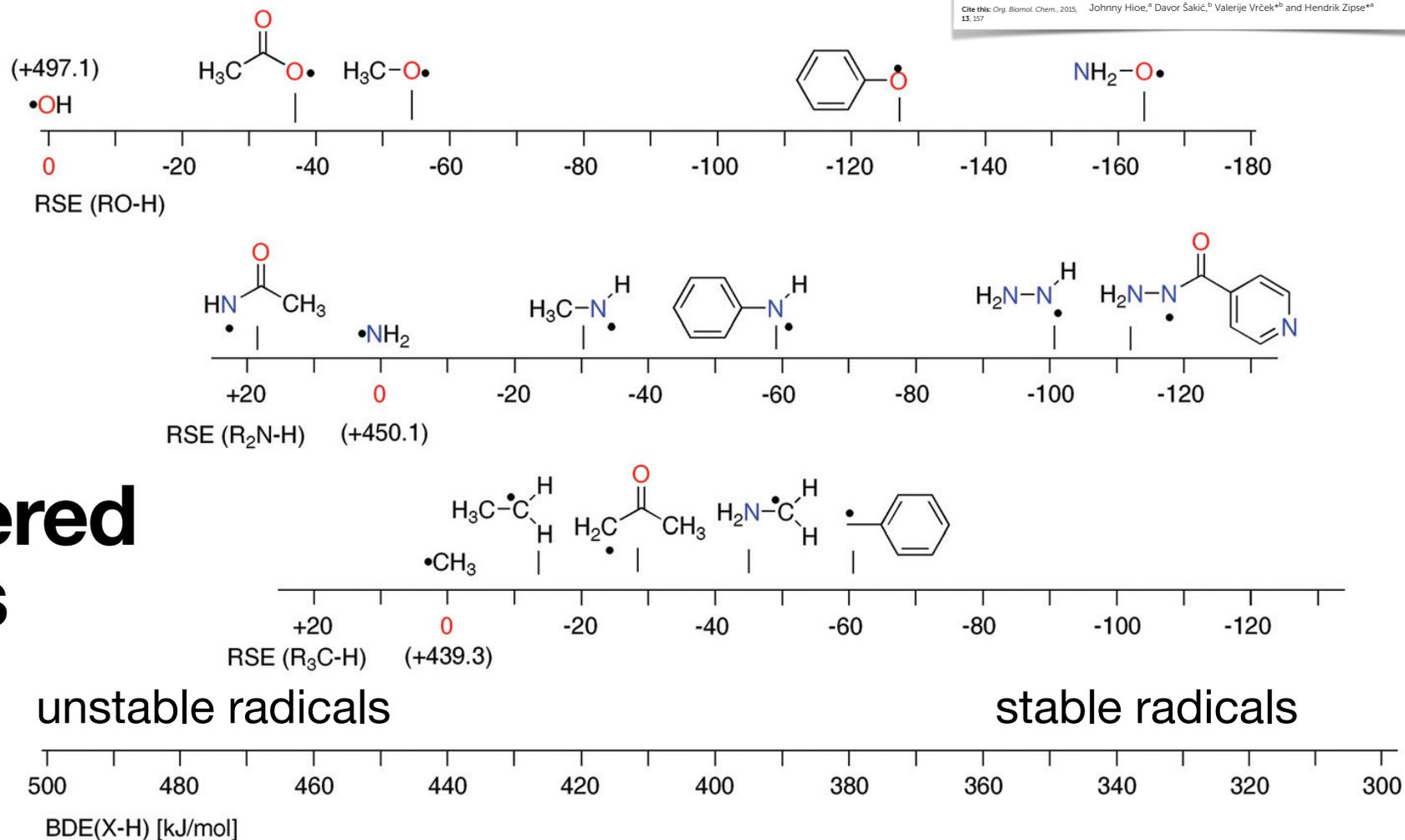
Article

pubs.acs.org/JPCA

Chlorination of *N*-Methylacetamide and Amide-Containing Pharmaceuticals. Quantum-Chemical Study of the Reaction Mechanism

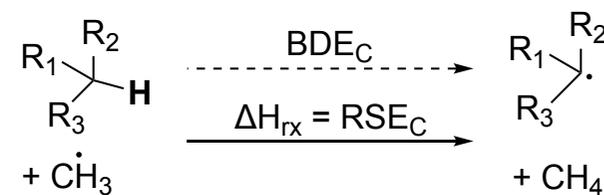
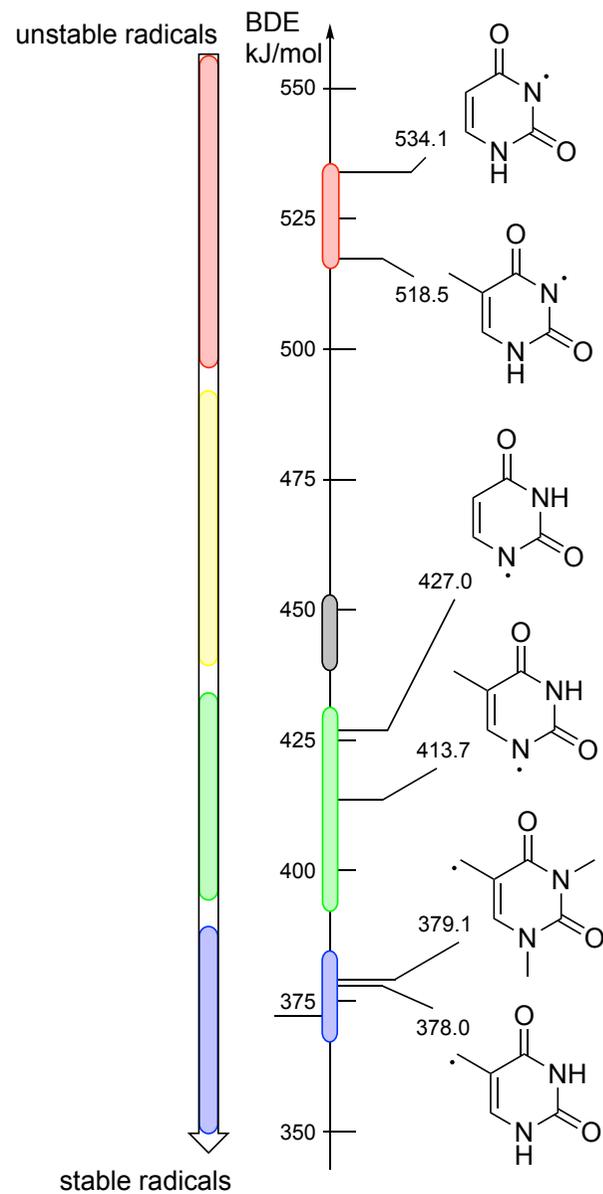
Davor Šakić, Pavica Šonjić, Tana Tandarić, and Valerije Vrčec*

Faculty of Pharmacy and Biochemistry, University of Zagreb, A. Kovačića 1, 10000 Zagreb, Croatia

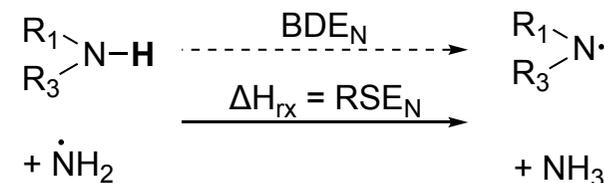


N-centered radicals

N-centered radicals in nucleobases

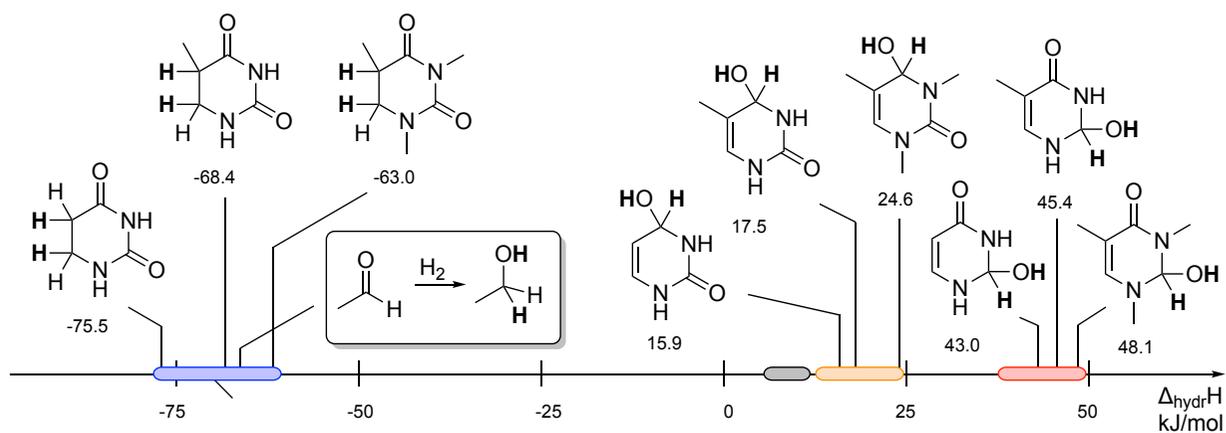


$$BDE_C = RSE_C + BDE_{REF}(CH_4/CH_3)$$

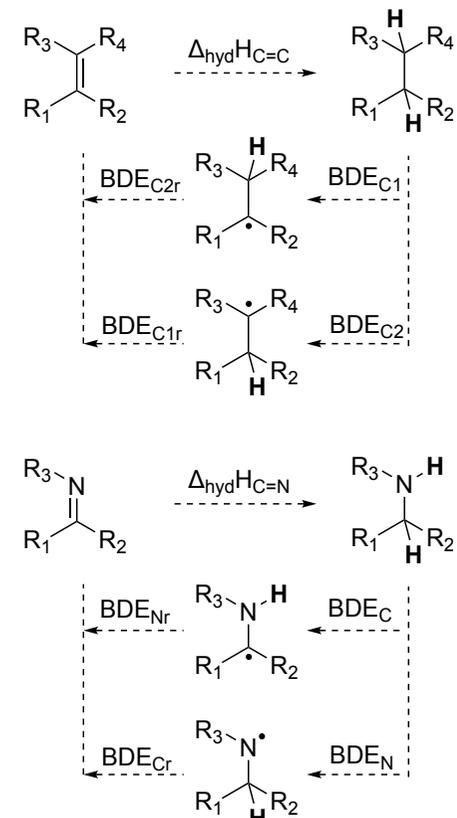
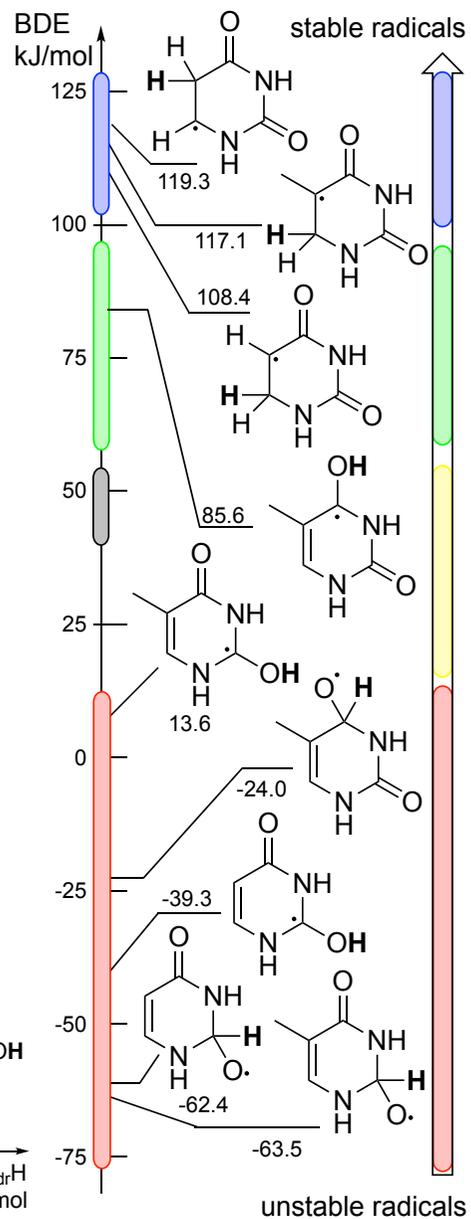


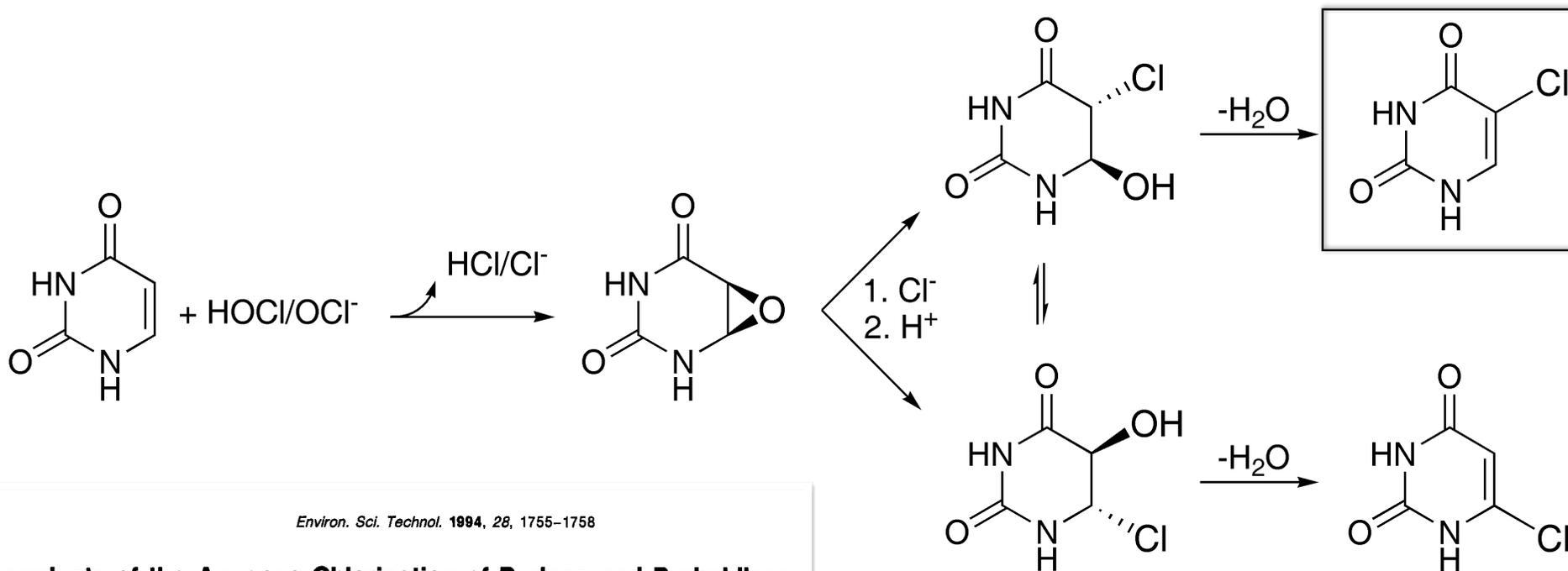
$$BDE_N = RSE_N + BDE_{REF}(NH_3/NH_2)$$

N-centered radicals in nucleobases



unpublished results





Environ. Sci. Technol. **1994**, *28*, 1755–1758

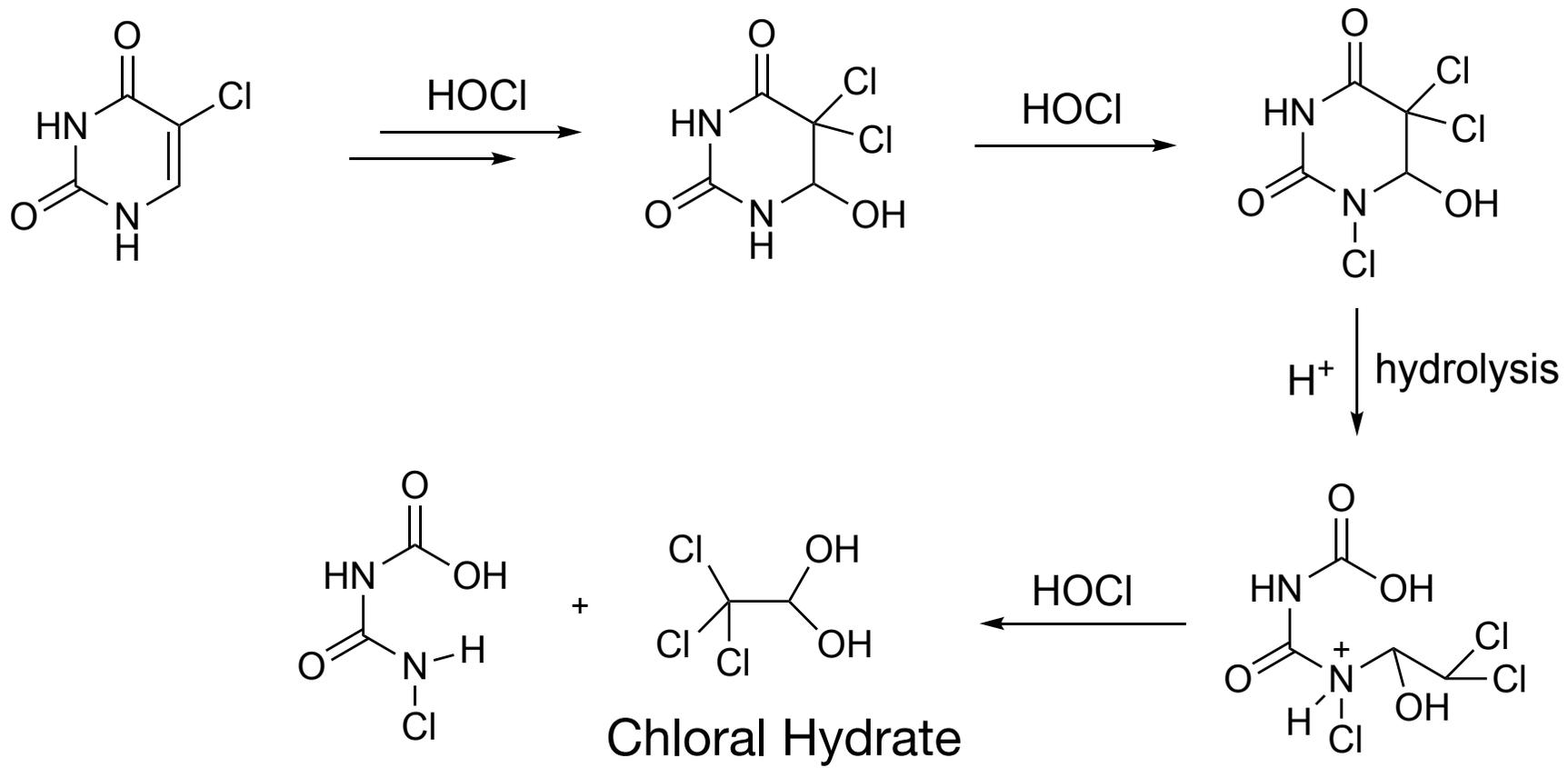
Byproducts of the Aqueous Chlorination of Purines and Pyrimidines

Michael S. Young*

META Environmental, Inc., 49 Clarendon Street, Watertown, Massachusetts 02172

Peter C. Uden

Department of Chemistry, University of Massachusetts, Amherst, Massachusetts 01003





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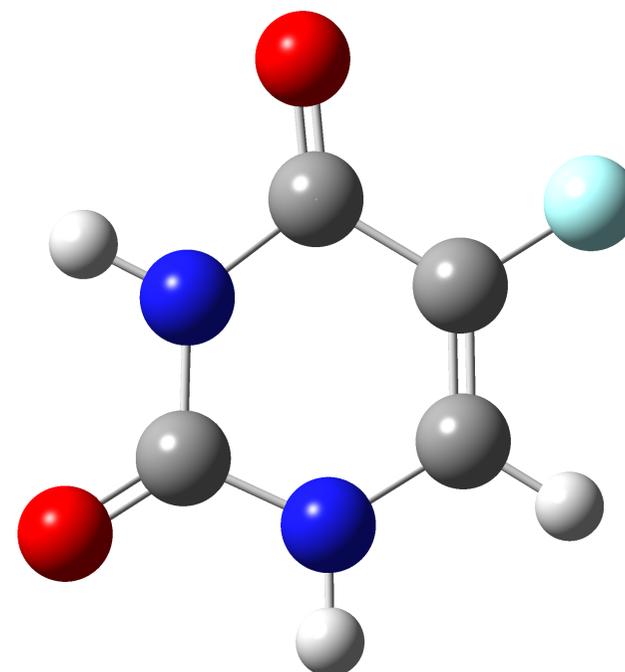


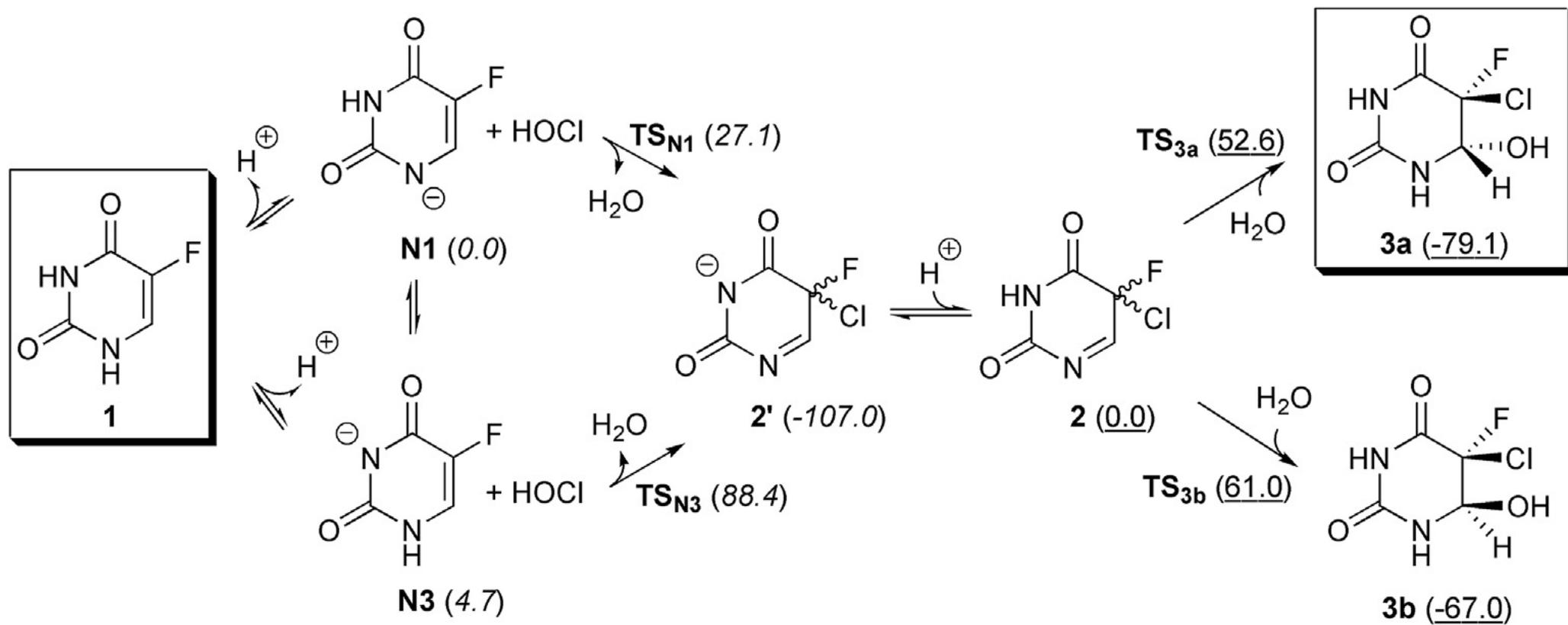
Fluorouracil in the environment: Analysis, occurrence, degradation and transformation

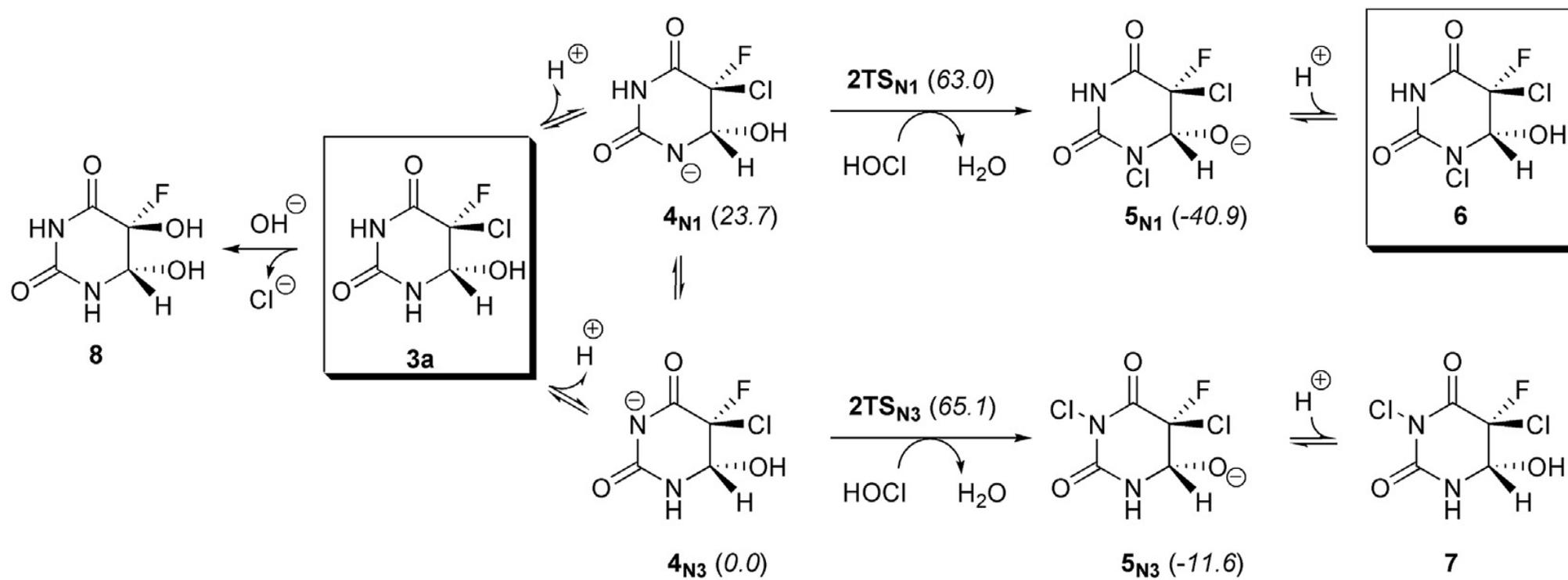
Tina Kosjek^{a,*}, Silva Perko^a, Dušan Žigon^a, Ester Heath^{a,b}

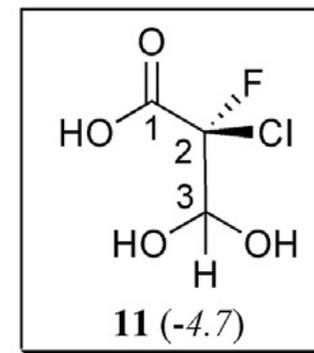
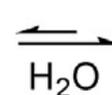
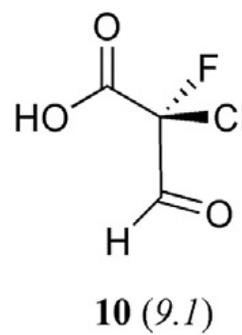
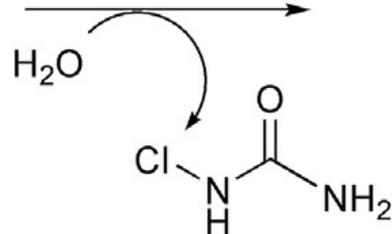
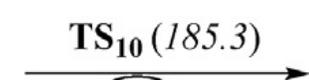
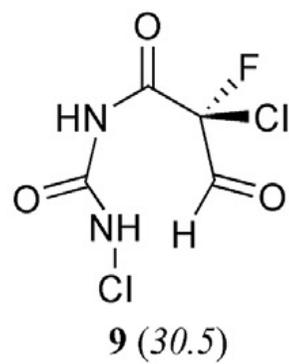
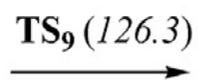
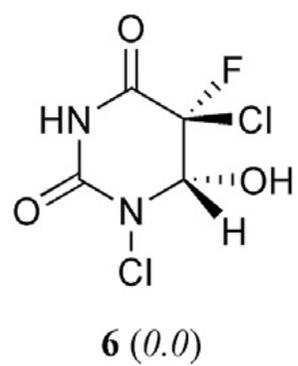
^a Jožef Stefan Institute, Jamova 39, Ljubljana, Slovenia

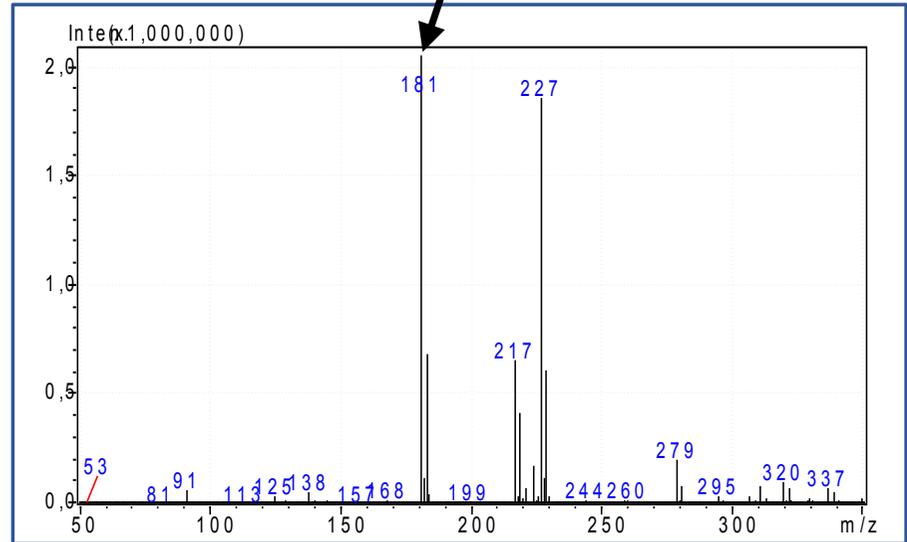
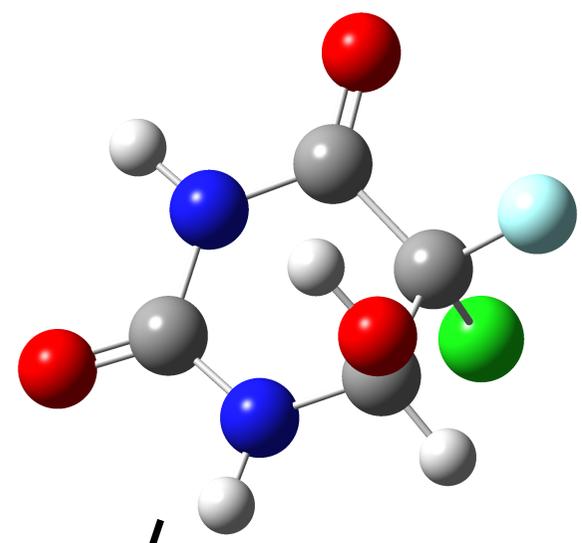
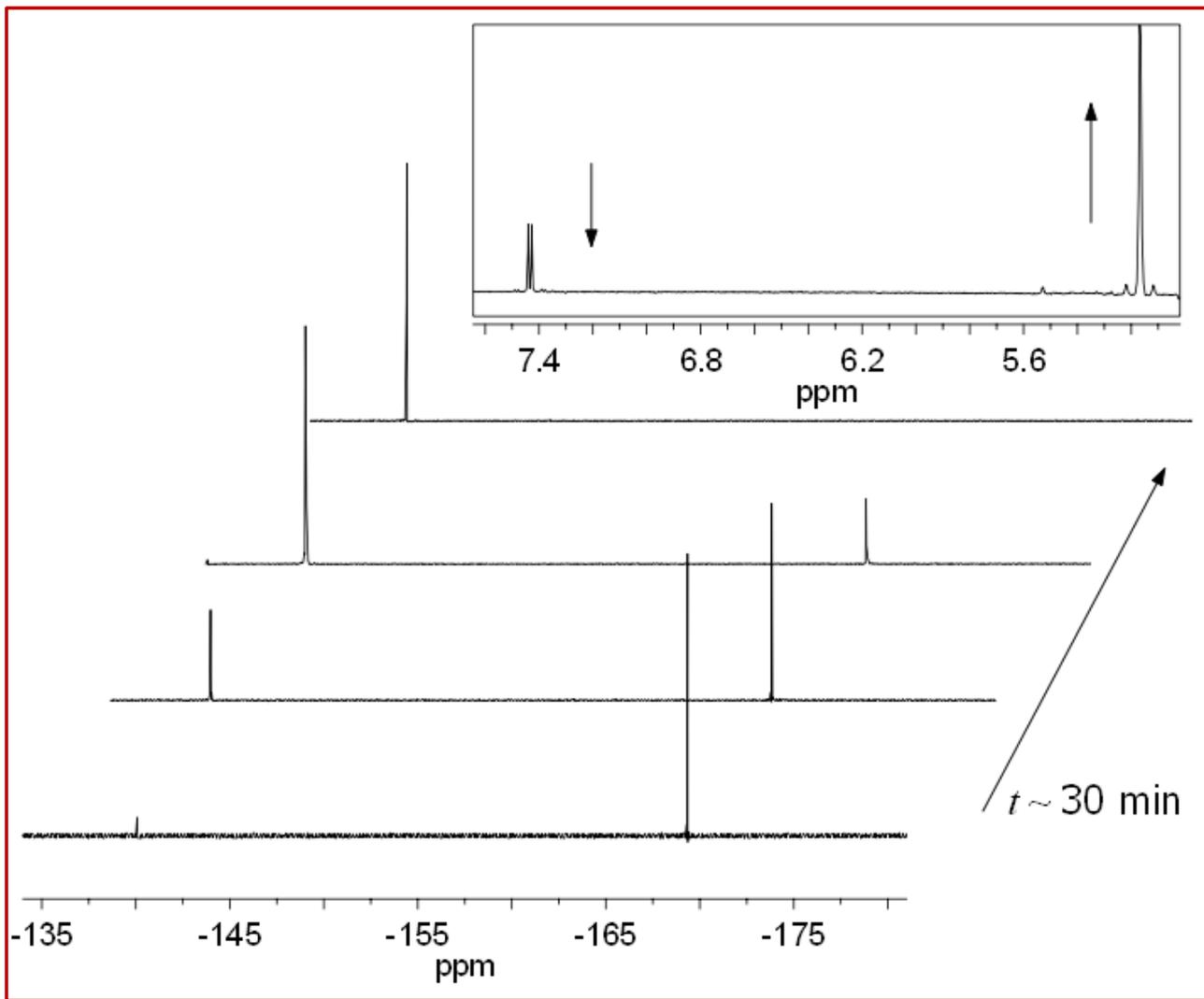
^b Jožef Stefan International Postgraduate School, Ljubljana, Slovenia

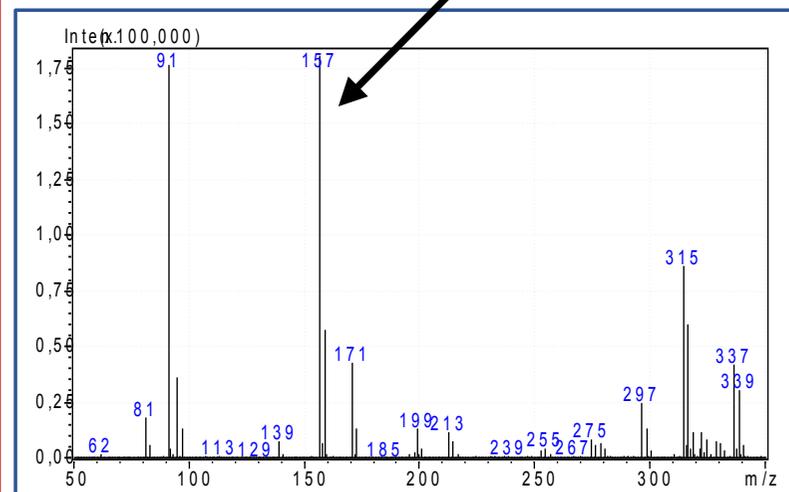
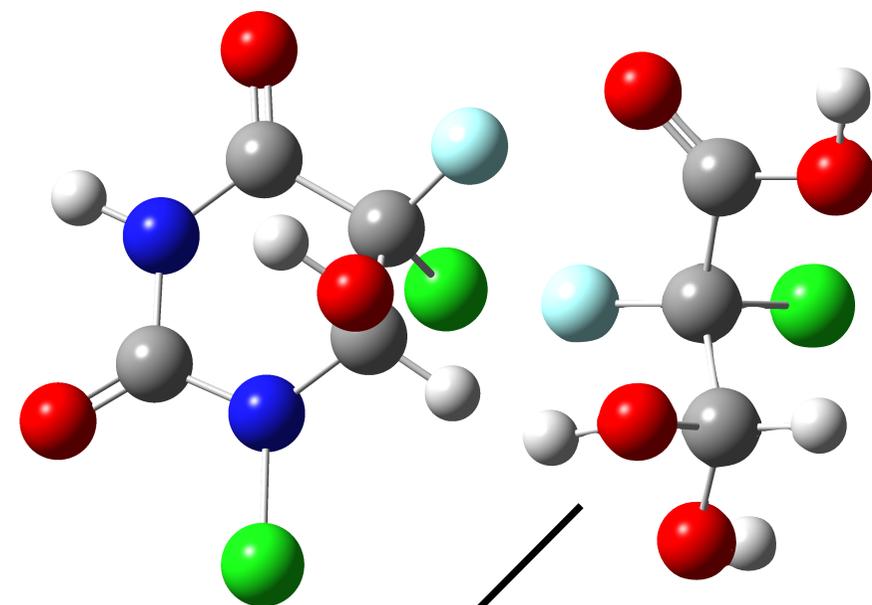
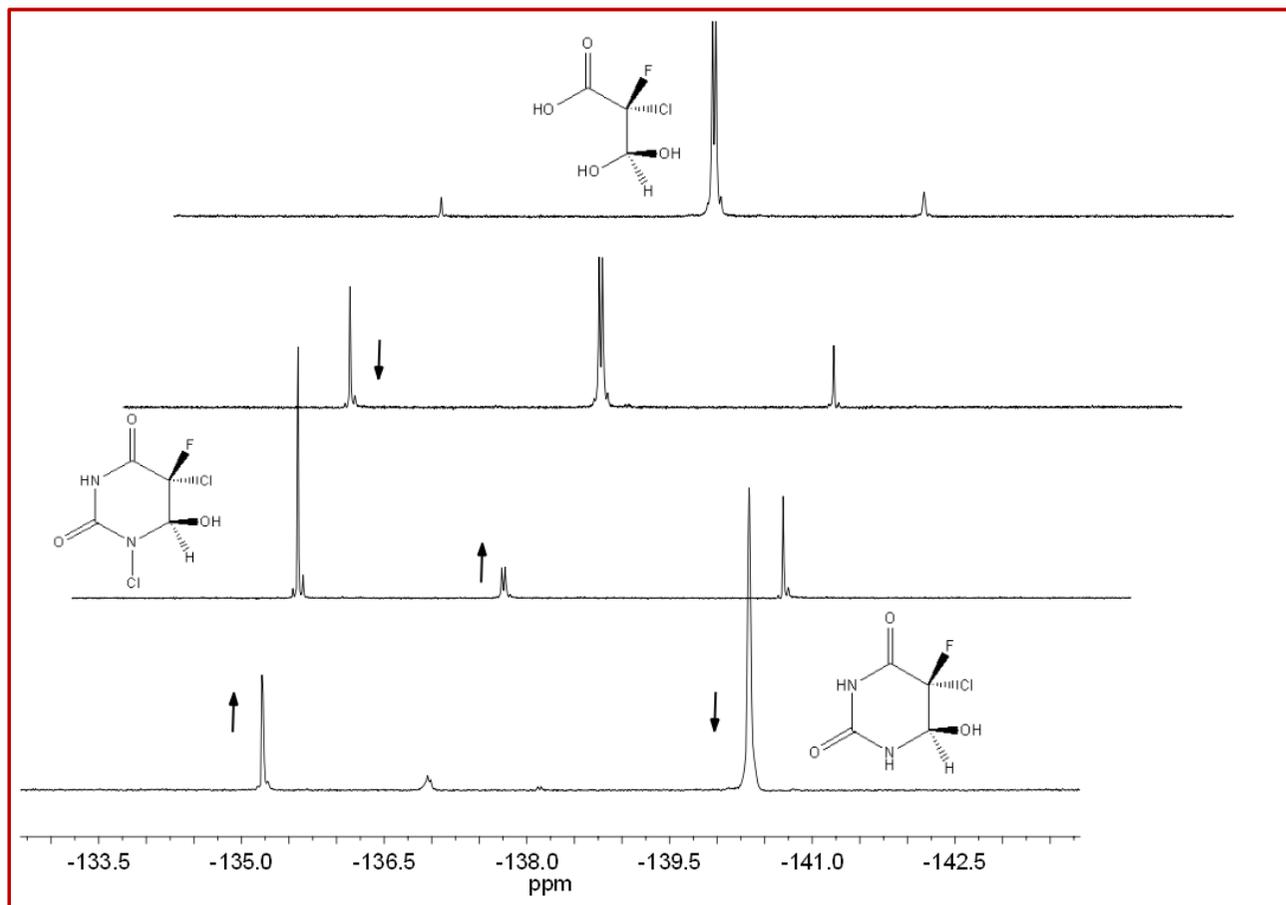




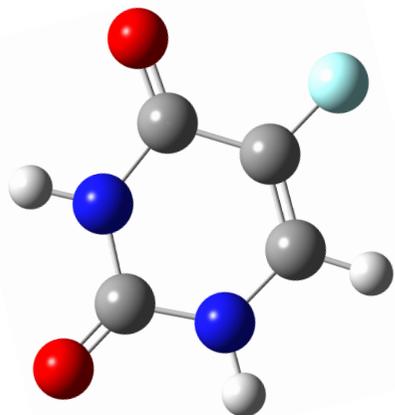




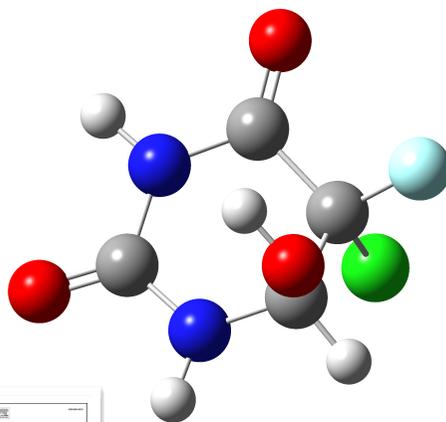




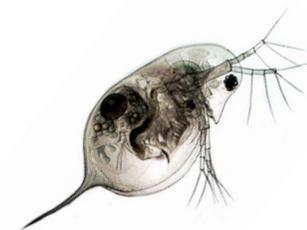
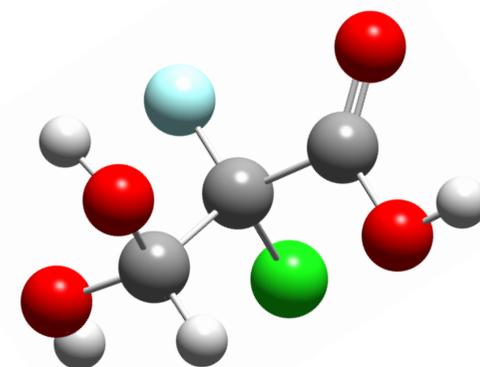
$EC_{50} = 285.8 \text{ mg/L}$



$EC_{50} = 425.5 \text{ mg/L}$



$EC_{50} = 212.6 \text{ mg/L}$



Daphnia magna
immobilization assay



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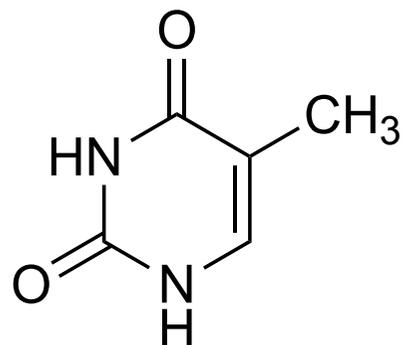


Chlorination of 5-fluorouracil: Reaction mechanism and ecotoxicity assessment of chlorinated products

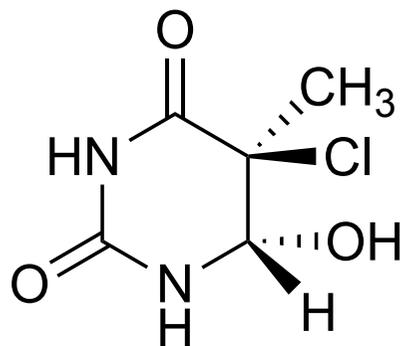


Lucija Hok^a, Lea Ulm^b, Tana Tandarić^c, Adela Krivohlavek^b, Davor Šakić^a, Valerije Vrčec^{a,*}

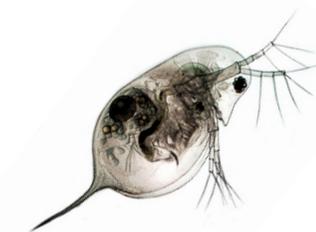
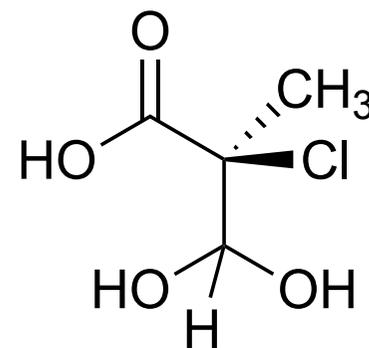
At 1000 mg/L
Survival 100%



EC₅₀ = 80.0 mg/L (24h)



At 100 mg/L
Survival 95%



Daphnia magna
immobilization assay

What to do?

Basic & Clinical Pharmacology & Toxicology, 108, 224–233

Doi: 10.1111/j.1742-7843.2011.00682.x

The 'Wise List' – A Comprehensive Concept to Select, Communicate and Achieve Adherence to Recommendations of Essential Drugs in Ambulatory Care in Stockholm

Lars L. Gustafsson^{1,2}, Björn Wettermark^{1,3}, Brian Godman¹, Eva Andersén-Karlsson^{3,4}, Ulf Bergman^{1,2}, Jan Hasselström⁵, Lars-Olof Hensjö⁶, Paul Hjendahl^{2,7}, Ingrid Jägre³, Margaretha Julander³, Bo Ringertz⁸, Daniel Schmidt⁹, Susan Sjöberg³, Folke Sjöqvist¹, Carl-Olav Stiller^{2,7}, Elisabeth Törnqvist¹, Rolf Tryselius³, Sigurd Vitols^{2,7} and Christer von Bahr¹⁰, for the Regional Drug Expert Consortium*

¹Division of Clinical Pharmacology, Department of Laboratory Medicine, Karolinska Institutet at Karolinska University Hospital Huddinge, Stockholm, Sweden, ²Clinical Pharmacology Services, Karolinska University Hospital, Stockholm, Sweden, ³Regional Drug and Therapeutics Committee, Medical Knowledge Centre, Stockholm County Council (Healthcare Region), Stockholm, Sweden, ⁴Department of Internal Medicine, Södersjukhuset, Stockholm, Sweden, ⁵Storvreten General Practice Centre, Tumba, Sweden, ⁶Inera Ltd, National Information Services for Swedish Healthcare, Stockholm, Sweden, ⁷Clinical Pharmacology Unit, Department of Medicine, Karolinska Institutet at Karolinska University Hospital Solna, Stockholm, Sweden, ⁸Division of Rheumatology, Department of Medicine, Karolinska Institutet at Karolinska University Hospital Solna, Stockholm, Sweden, ⁹Department of Internal Medicine, St Göran Hospital, Stockholm, Sweden, and ¹⁰Section of Clinical Pharmacology, Department of Internal Medicine, Södersjukhuset, Stockholm, Sweden

(Received 12 September 2010; Accepted 4 January 2011)

PBT index

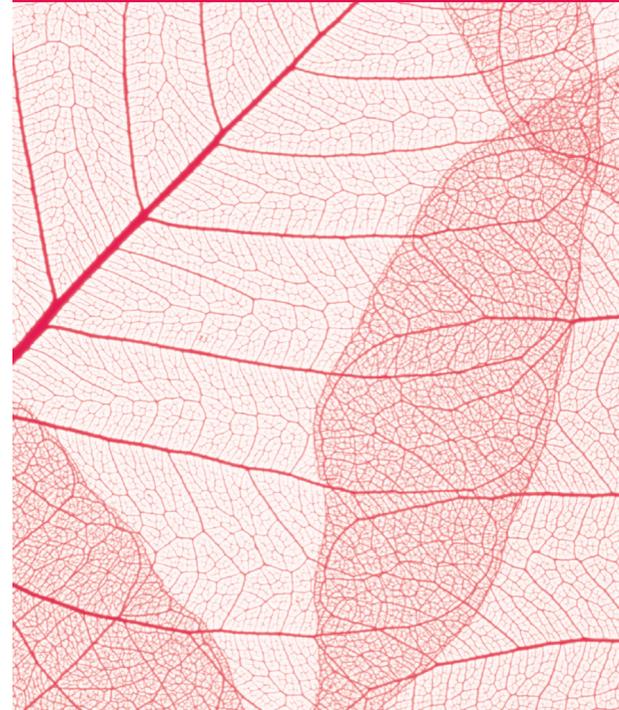
(0 😊 – 9 😞)

Persistence (0 – 3),

Bioaccumulation (0 – 3),

Toxicity (0 -3)

2012 ENVIRONMENTALLY CLASSIFIED PHARMACEUTICALS



 **Stockholms läns landsting**
Stockholm County Council

SUBSTANCE	RISK	P	B	T	VOLUME IN DDD
Other dermatological preparations					
finasteride	insignificant	7	3	3	1 3 548 544
salicylic acid	cannot be excl	4*	3*0	1*	E -
minoxidil	cannot be excl	-	-	-	E -
selenium sulfide	cannot be excl	-	-	-	E -
G Genito-Urinary System and Sex Hormones					
Gynecological anti-infectives and antiseptics					
metronidazole	insignificant	4	3	0	1 206 193
					E 21 409
clindamycin	cannot be excl	6*	3	0	3* 240 993
					E -
clotrimazole	cannot be excl	-	-	-	E -
econazole	cannot be excl	-	-	-	E 2 746 789
Other gynecologicals					
etonogestrel	insignificant	8*	3	3	2* 4 215 000
					E -
ethinylestradiol	high	9	3	3	3 C 21 618 898
					E -
methyleergometrine	cannot be excl	7*	3	3	1* 14 008
atosiban	cannot be excl	-	-	-	398
dinoprostone	cannot be excl	-	-	-	11 355
cabergoline	cannot be excl	-	-	-	19 744
carboprost	cannot be excl	-	-	-	78
bromocriptine		9	3	3	3 140 322
gemprost	cannot be excl	-	-	-	-
quinagolide	cannot be excl	-	-	-	58 116
Sex hormones and modulators of the genital system					
desogestrel	insignificant	8	3	3	2 9 391 844
					C 1 092 000
etonogestrel	insignificant	8*	3	3	2* 4 215 000
					E -
ethinylestradiol	high	9	3	3	3 C 21 618 898
					E -
estradiol	moderate	9	3	3	3 5 207 377
					C 3 193 994
estriol	cannot be excl	6*	3*0	3*	1 691 134
norethisterone	cannot be excl	9	3	3	3 1 114 669
					C 3 217 928
levonorgestrel	cannot be excl	9*	3	3	3* -
					C 10 762 556
ulipristal	cannot be excl	-	-	3	-



Safe by design

The safe-and-sustainable-by-design concept: innovating towards a more sustainable future

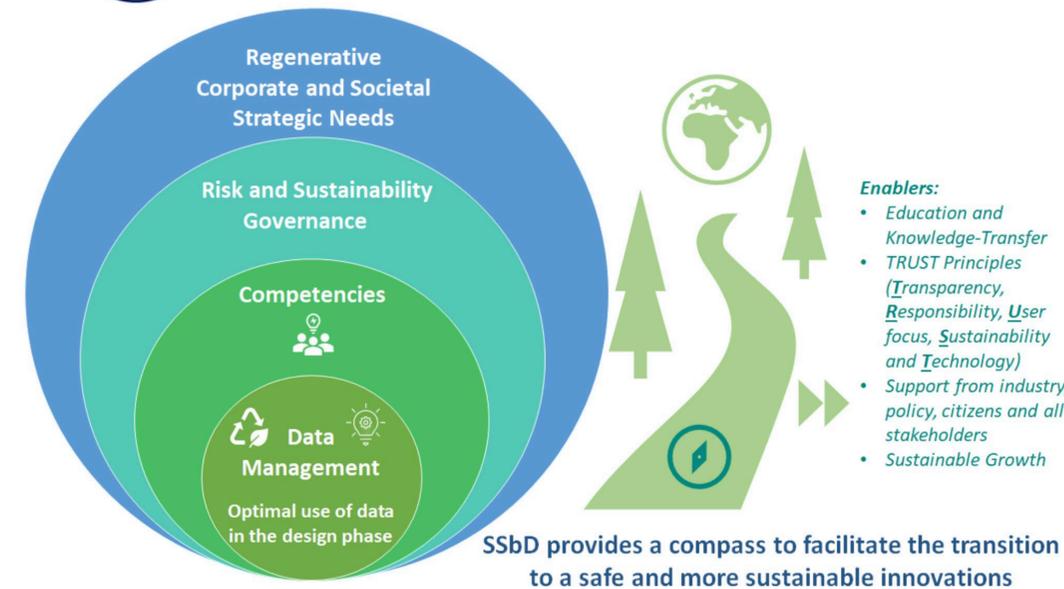
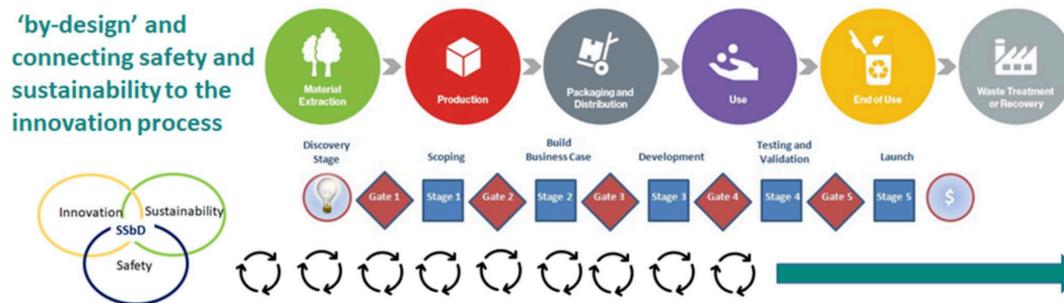
Environmental Sustainability (2024) 7:363–368

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'by-design' and connecting safety and sustainability to the innovation process



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