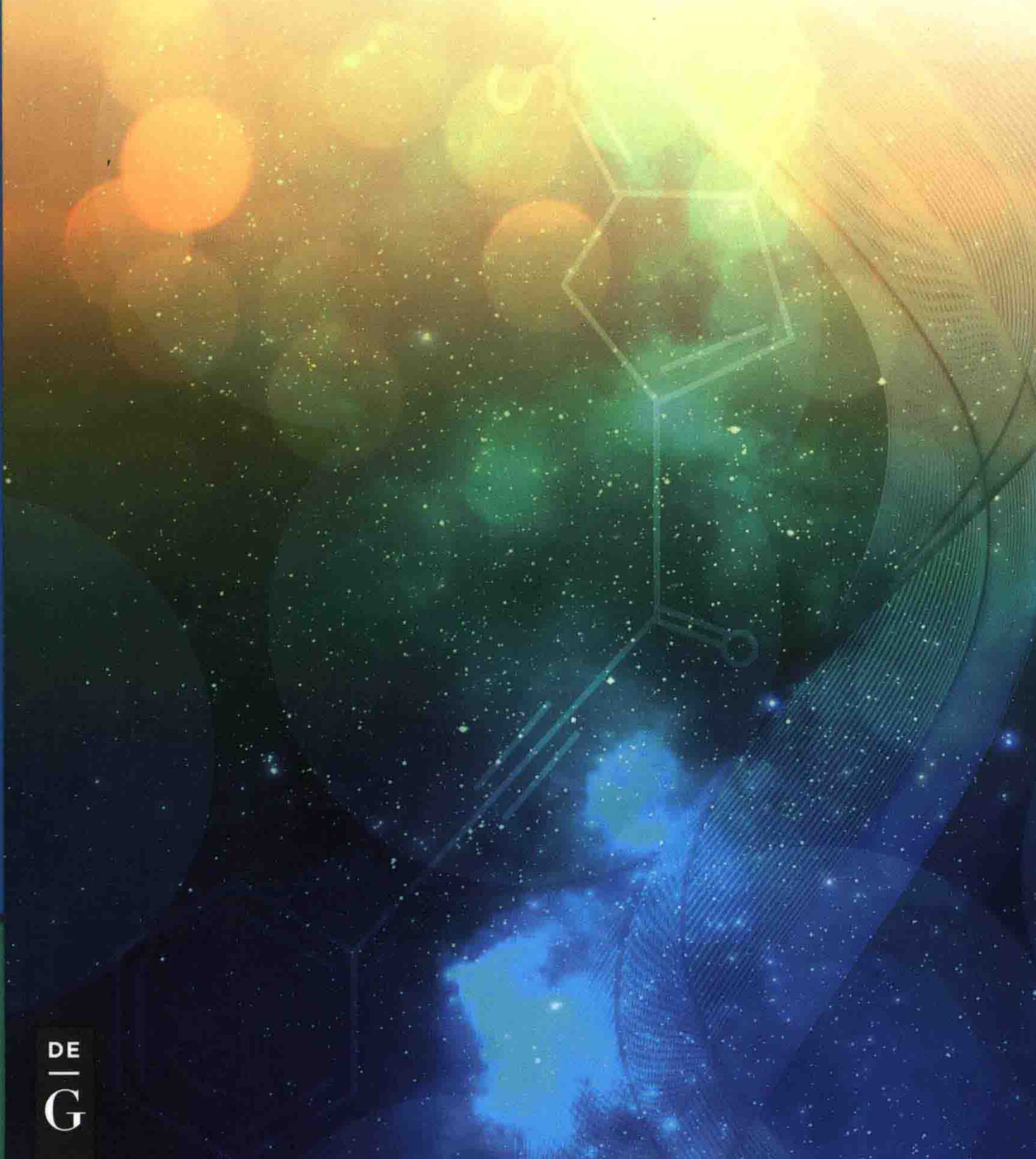
DE GRUYTER GRADUATE

Ferenc Darvas, György Dormán, Volker Hessel (Eds.)

FLOW CHEMISTRY

VOLUME 2: APPLICATIONS



DE G

Flow Chemistry

Volume 2: Applications

Edited by
Ferenc Darvas, György Dormán, Volker Hessel

DE GRUYTER

Editors

Ferenc Darvas
Florida International University
College of Medicine
University Park, 495
11 200 S.W. 8th St.
Miami 33 199
USA
e-mail: ferenc.darvas@darholding.com

György Dormán
ThalesNano Nanotechnology Inc
Graphisoft Park
Zahony u. 7
Budapest 1031
Hungary
e-mail: gyorgy.dorman@thalesnano.com

Volker Hessel
Eindhoven Univ. of Technology
Micro Flow Chem. & Proc. Techn. Group
Dept. of Chemistry & Chemical Eng.
Den Dolech 2
5600 MB Eindhoven
The Netherlands
e-mail: v.hessel@tue.nl

ISBN 978-3-11-036707-2
e-ISBN 978-3-11-036750-8

Library of Congress Cataloging-in-Publication Data
A CIP catalog record for this book has been applied for at the Library of Congress.

Bibliographic information published by the Deutsche Nationalbibliothek
The Deutsche Nationalbibliothek lists this publication in the Deutsche Nationalbibliografie; detailed bibliographic data are available on the Internet at http://dnb.dnb.de.

Typesetting: le-tex publishing services GmbH, Leipzig
Printing and binding: CPI books GmbH, Leck
Cover image: Book cover design by Reka Darvas (www.zenurdel.com)
♾ Printed on acid-free paper
Printed in Germany

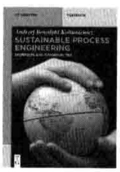
MIX
Papier aus verantwortungsvollen Quellen
FSC® C003147

www.degruyter.com

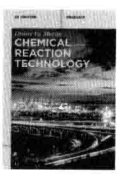
De Gruyter Graduate

Darvas, Dormán, Hessel • Flow Chemistry

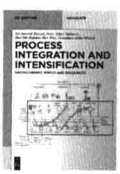
Also of Interest



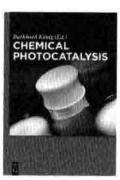
Sustainable Process Engineering – Prospects and Opportunities
Koltuniewicz, 2014
ISBN 978-3-11-030875-4, e-ISBN 978-3-11-030876-1



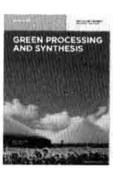
Chemical Reaction Technology
Murzin, 2015
ISBN 978-3-11-033643-6, e-ISBN 978-3-11-033644-3



Process Integration and Intensification – Saving Energy, Water and Resources
Klemeš, Varbanov, Wan Alwi, Manan, 2014
ISBN 978-3-11-030664-4, e-ISBN 978-3-11-030685-9



Chemical Photocatalysis
König, 2013
ISBN 978-3-11-026916-1, e-ISBN 978-3-11-026924-6,
Set-ISBN 978-3-11-026925-3



Green Processing and Synthesis
Hessel (Editor-in-Chief)
ISSN 2191-9550

Preface

Flow chemistry – the use of small flow reactors to perform chemical synthesis – has matured over the past two decades from early demonstrations of simple chemical transformations in microstructured reactors (microreactors) to complex, multistep synthesis relevant to fine chemistry and pharmaceuticals in commercial systems. This evolution in synthetic methods and equipment has been motivated by advantages inherent to continuous synthesis in small scale, specifically enhanced rates from improved heat and mass transfer along with an expanded space of reactions and process conditions. Continuous operation also eliminates headspace issues and avoids accumulation of reactive or toxic intermediates offering opportunities for telescoping of reactions. Synthesis applications are further enhanced by automated optimization as well as mechanistic and kinetic information gained from integrating reaction components with sensors, actuators, and automated fluid handling. Moreover, the steady state operation inherent in continuous operation provides robustness, stability, and scalability.

The expansion in flow chemistry applications and equipment has been detailed in numerous review papers and monographs, but there has been a longstanding need for a comprehensive coverage of the many concepts underlying flow chemistry for graduate students in chemistry and chemical engineering. The present *Graduate Textbook on Flow Chemistry* fills the gap in graduate education by covering chemistry and reaction principles along with current practice, including examples of relevant commercial reaction, separation, automation, and analytical equipment. It motivates the reasons for flow chemistry and importantly when flow chemistry will and will *not* be advantageous compared to batch processing. Basic theory and practical considerations are summarized to enable the reader to appreciate the difference between conventional batch chemistry and flow chemistry as well as to implement flow chemistry in the laboratory. A very useful feature is the inclusion of validate reactions that can serve as laboratory test experiments. The subsequent treatment of theoretical foundations for flow chemistry, also know as reaction engineering, provides useful in depth understanding of continuous reactions.

The second portion of the *Graduate Textbook on Flow Chemistry* covers specific reaction classes, concepts, and experimental methods. Homogeneous and heterogeneous catalysis, supercritical processes, photochemistry, green chemistry, and radiolabelled chemistry applications are described in individual chapters along with examples of flow chemistry for nanotechnology and materials science. Practical oriented chapters address (i) analytical techniques, specifically in-line monitoring methods, (ii) examples of automation, (iii) how to build your own flow chemistry set-up as well an overview of commercially available units, and (iv) importantly, safety aspects of flow chemistry systems and processes.

The Editors of this *Graduate Textbook on Flow Chemistry*, Drs. Ferenc Darvas, Volker Hessel and György Dormán are commended for having taken the initiative to bring together experts from the field to provide a comprehensive treatment of fundamental and practical considerations underlying flow chemistry. It promises to become a useful study text and as well as reference for the graduate students and practitioners of flow chemistry.

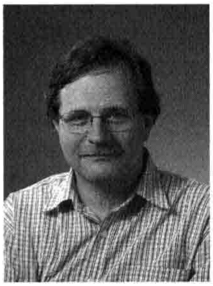
June 2014

Klavs Jensen
Department Head Chemical Engineering,
Massachusetts Institute of Technology, USA

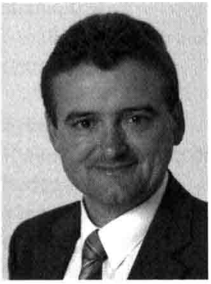
The Editors would like to express their gratitude to the many people who helped to complete this textbook. They are indebted to all the authors for their outstanding contribution and the valuable and constructive suggestions during the planning. They are very grateful to Prof. Dr. Jan van Hest (POAC Committee, Radboud University Nijmegen, The Netherlands); to Prof. Floris Rutjes (Radboud University Nijmegen); to Dr. Varsha Kapoerchan (Organisation for Scientific Research NWO, Advanced Chemical, Technologies for Sustainability (ACTS), The Netherlands) and to Darholding Inc. (Hungary) for their financial support. Prof. Volker Hessel kindly acknowledges the funding provided by the Advanced European Research Council Grant "Novel Process Windows – Boosted Micro Process Technology" (no 267 443). Special thanks should be given to all the instrument suppliers for their contributions to the Microreactor Chapter (Chemtrix, FutureChemistry, Invenios, Microinnova, Syrris, ThalesNano, Uniqsis). The Editors' thanks is extended to Ms. Szilvia Gilmore (Flow Chemistry Society) for the coordination and monitoring duties during the preparation of the textbook, to Ms. Karin Sora, Editorial Director Chemistry/Materials Science and Ms. Julia Lauterbach, Project Editor STM, DeGruyter Publishing House for their enthusiasm, continuing motivation and technical support as well as to Reka Darvas for the great cover design.

About the editors

Prof. Ferenc Darvas acquired his degrees in Budapest, Hungary (medical chemistry MS, computer sciences BS, degree in patent law, PhD in experimental biology). He has been teaching in Hungary, Spain, Austria, and in the United States of America at different universities, presently serves as associate professor at the Florida International University in Miami. He is author of 140 pre-reviewed papers and 5 books. Dr. Darvas has been involved in introducing microfluidics/flow chemistry methodologies for synthetizing drug candidates since the late 90's, which led him to found ThalesNano. One of his team's inventions, the desktop high pressure/high temperature flow hydrogenator H-Cube won several innovation awards in the United States of America and also in Europe, and has been used in more than 60 countries. Dr. Darvas is also the founder and active President of the Flow Chemistry Association located in Switzerland.



Prof. György Dormán obtained his Ph.D. in organic chemistry from the Technical University of Budapest in 1986. Between 1986–1988 and 1996–1999 he worked at Sanofi–Chinoin in Budapest. In 1988–1989 he spent a post-doctoral year in the UK (University of Salford). Between 1992 and 1996 he was a Visiting Scientist at the State University of New York, Stony Brook. Between 1999 and 2008 he served ComGenex/AMRI as Chief Scientific Officer. Since 2008 he is responsible for the scientific innovation of ThalesNano. Dr. Dormán is involved in many training courses in the area of (bio)organic and flow chemistry. In 2011 he became Professor at University of Szeged. He is an author of 85 scientific papers and book chapters. He is a member of the editorial board of Molecular Diversity and the advisory board of J. Flow Chemistry.



Prof. Volker Hessel studied chemistry at Mainz University (PhD in organic chemistry, 1993). In 1994 he entered the Institut für Mikrotechnik Mainz GmbH (1996: group leader microreaction technology). In 2002, Prof. Hessel was appointed Vice Director R&D at IMM and in 2007 as Director R&D. In 2005 and 2011, he was appointed as part-time and full professor at Eindhoven University of Technology, respectively, for the chair of "Micro Flow Chemistry and Process Technology". He is (co-)author of more than 270 peer-reviewed publications, with 18 book chapters and 5 books. He received the AIChE award "Excellence in Process Development Research" in 2007 and in 2010 the ERC Advanced Grant "Novel Process Windows". Prof. Hessel is in the scientific advisory board of the "International Conference on Microreaction Technology". He is Editor-in-Chief of the journal "Green Processing and Synthesis".

Contributing authors

Reka Angi
NanGenex
Budapest, Hungary
e-mail: reka.angi@nangenex.com
Chapter 6

Claude de Bellefon
CPE Lyon
University of Lyon
Lyon, France
e-mail: claude.debellefon@lgpc.cpe.fr
Chapter 2

Clemens Brechtelsbauer
Department of Chemical Engineering
Imperial College London
London, UK
e-mail: c.brechtelsbauer@imperial.ac.uk
Chapter 1

Ana Cukalovic
SynBioC
Department of Sustainable Organic Chemistry and Technology
Ghent University
Gent, Belgium
e-mail: ana.cukalovic@ugent.be
Chapter 9

Ferenc Darvas
College of Medicine
Florida International University
Miami, USA
e-mail: ferenc.darvas@darholding.com
Chapter 6, 8

György Dormán
ThalesNano Nanotechnology Inc
Budapest, Hungary
e-mail: gyorgy.dorman@thalesnano.com
Chapter 8

Melinda Fekete
ThalesNano
Budapest, Hungary
e-mail: fekete.mela@gmail.com
Chapter 8

Genoveva Filipcsei
NanGenex
Budapest, Hungary
e-mail: filipcsei.genoveva@nangenex.com
Chapter 6

Samar Haroun
Department of Chemistry
Simon Fraser University
Burnaby, Canada
e-mail: sharoun2@gmail.com
Chapter 7

Volker Hessel
Dept. of Chemistry & Chemical Eng.
Eindhoven Univ. of Technology
Eindhoven, The Netherlands
e-mail: v.hessel@tue.nl
Chapter 10

King Kuok (Mimi) Hii
Department of Chemistry
Department of Chemical Engineering
Imperial College London
London, UK
e-mail: mimi.hii@imperial.ac.uk
Chapter 1

Dana Kralisch
Institute for Technical Chemistry and Environmental Chemistry
Friedrich-Schiller-University
Jena, Germany
e-mail: dana.kralisch@uni-jena.de
Chapter 10

Paul C.H. Li
Department of Chemistry
Simon Fraser University
Burnaby, Canada
e-mail: paulli@sfu.ca
Chapter 7

Holger Loewe
Fraunhofer ICT-IMM
and
Institute for Organic Chemistry
Johannes Gutenberg-University
Mainz, Germany
e-mail: Loewe@imm-mainz.de
Chapter 4

David Tyler McQuade
Department of Chemistry and Biochemistry
Florida State University
Tallahassee, FL, USA
e-mail: mcquade@chem.fsu.edu
Chapter 5

L. Zane Miller
Department of Chemistry and Biochemistry
Florida State University
Tallahassee, FL, USA
e-mail: levimiller@chem.fsu.edu
Chapter 5

Jean-Christophe Monbaliu
Department of Chemistry
Center for Integrated Technology and
Organic Synthesis
University of Liège, Sart-Tilman
Liège, Belgium
e-mail: jc.monbaliu@ulg.ac.be
Chapter 9

Zsolt Otvos
NanGenex
Budapest, Hungary
e-mail: zsolt.otvos@nangenex.com
Chapter 6

Thomas H. Rehm
Fraunhofer ICT-IMM
Mainz, Germany
e-mail: Rehm@imm-mainz.de
Chapter 3

Julian Schuelein
Fraunhofer ICT-IMM
and
Institute for Organic Chemistry
Johannes Gutenberg-University
Mainz, Germany
e-mail: julschue@students.uni-mainz.de
Chapter 4

Jeremy L. Steinbacher
Department of Chemistry and Biochemistry
Canisius College
Buffalo, NY, USA
e-mail: steinbaj@canisius.edu
Chapter 5

Christian V. Stevens
SynBioC
Department of Sustainable Organic Chemistry
and Technology
Ghent University
Gent, Belgium
e-mail: Chris.Stevens@UGent.be
Chapter 9

Qi Wang
Micro Flow Chemistry & Process Technology
Department of Chemical Engineering
and Chemistry
Eindhoven University of Technology
Eindhoven, The Netherlands
e-mail: Q.Wang1@tue.nl
Chapter 10

Abbreviations

Ad	adamantyl
ADA	adipic acid
ADP	abiotic resource depletion
AE	atom economy
AO	anthraquinone oxidation
AP	acidification
API	active pharmaceutical ingredient
ATR	attenuated total reflectance
BEMP	2-tert-2-diethylamino-1,3-dimethyl-perhydro-1,2,3-diazophosphorine
C-11	carbon-11
Ca	capillary number
CEENE	extraction from the natural environment
CFD	computational fluid dynamics
cGMP	current good manufacturing practice
CQD	colloidal quantum dots
CRTR	continuous recycled tube reactor
CSB	chemical safety and hazard investigation board
CSTR	continuous stirred-tank reactor
CV	coefficients of variation
DBU	1,8-diazabicyclo-[5.4.0]undec-7-ene
DEDAM	diethyl(diallyl)malonate
DFT	density functional theory
DHA	dihydroacetone
DIBAL-H	diisobutyl-aluminum hydrid
DIPEA	*N*, *N*-diisopropylethylamine
DLS	dynamic light scattering
DLVO theory	Deryaguin and Landau and Verwey and Overbeek
DMF	*N*, *N*-dimethyl formamide
DMIT	dimethyl itaconate
DMR	desmethyl raclopride
DMSO	dimethyl sulfoxide
ee	enantiomeric excess
EGDMA	ethyleneglycol dimethacrylate
ELMI	electrochemical microreactor
EMIM	[CF_3SO_3] 1-ethyl-3-methilimidazolium trifluoromethanesulfonate
EP	eutrophication
ESI	electrospray ionisation

ETP	eco-toxicity
FDG	fluorodeoxyglucose
FEP	fluorinated ethylenepropylene
FT-IR	Fourier transform-infrared spectroscopy
GC	gas chromatography
GNRs	gold nanorods
GWP	global warming
HOMO	highest occupied molecular orbital
HPLC	high performance liquid chromatography
HSV	hourly space velocity
HTP	human toxicity
ILs	ionic liquids
IR	infrared
IS	internal standard
ISO	the International Standard Organisation
KFT	Karl–Fischer titration
LC	liquid chromatography
LC/MS	liquid chromatography/mass spectrometry
LCA	life cycle assessment
LCC	life cycle costing
LED	light emitting diode
LH	Langmuir Hinshelwood
LHSV	liquid hourly space velocity
LIGA	lithography galvanic molding
LOC	lab-on-a-chip
LU	land use
LUMO	lowest unoccupied molecular orbital
MCT	mercury cadmium telluride
MD	molecular dynamics
MEMS	microelectromechanical system module
MI	mass intensity
MMA	alpha-acetamidoacrylic acid methyl ester
MRT	micro reaction technology
NCA	lysine, alanine, leucine, or glutamic acid
NMO	*N*-methylmorpholine-*N*-oxide
NMR	nuclear magnetic resonance
NPV	net present value
NSAIDs	non-steroidal anti-inflammatory drugs
NTU	number of transfer units
ODP	ozone depletion
OLEDs	organic light emitting diodes
OSN	organic solvent nanofiltration

PBRs	packed-bed reactors
PDI	polydispersity index
PDMS	poly(dimethylsiloxane)
Pe	peclet number
PEEK	polyether ether ketone
PET	positron emission tomography
PF	plug flow
PFA	perfluoroalkoxy
PFR	plug-flow reactor
PLGA	poly(d,l-lactic acid-co-glycolic acid)
PMI	process mass intensity
POCP	photochemical ozone creation
PPi	pyrophosphate
PS-TBD	polystyrene-supported 1,5,7-triazabicyclo[4.4.0]dec-5-ene
PTFE	polytetrafluoroethylene
PVA	poly(vinylalcohol)
PVC	polyvinyl chloride
PVP	poly(vinyl)pyridine
RAD	radioactivity detector
RAFT	reversible addition-fragmentation chain transfer
RCM	ring closing metathesis
RCY	radiochemical yield
Re	Reynolds Number
REL	reaction engineering laboratory module
REO	robust, efficient and orthogonal
Rf	radiofrequency
RME	reaction mass efficiency
ROMP	ring-opening polymerization
RTD	resistive thermal device
RTILs	room temperature ionic liquids
RU	repeating units
S/C ratio	substrate/catalyst
SCFs	supercritical fluids
SET	single electron transfer
SFT	staggered fed tube
SILP	supported ionic-liquid phase
SLCA	simplified LCA
SM	Suzuki–Miyaura
SMB	simulated moving-bed
SNR	signal-to-noise ratio
SSRE	solid-state-reference electrodes
STBE	solketal t-butyl ether

TEM	transmission electron microscopy
TFSI	trifluoromethylsulfonyl)imide
TMAOH	tetramethylammonium hydroxide
TOF	turnover frequency
TON	turnover number
TPGDA	tripropyleneglycol diacrylate
UV	ultraviolet
We	Weber number
WHSV	weight hourly space velocity
µSSRE	miniaturized solid-state-reference electrodes

Contents