Atom Economy, Biodegradation, Catalysis, and Green Toxicology: Tools for the Delivery of Sustainable Chemistry based on Ionic Liquids

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ERA Chair of Green Chemistry
Tallinn University of Technology, Estonia

Oslo, June 2017
12 Principles of Green Chemistry

1. Prevent waste
2. Atom Economy
3. Less Hazardous Chemical Syntheses
4. Designing Safer Chemicals
5. Safer Solvents and Auxiliaries
6. Design for Energy Efficiency
7. Use of Renewable Feedstock's
8. Reduce Derivatives
9. Catalysis (vs. Stoichiometric)
10. Design for Degradation
11. Real-time analysis for Pollution Prevention
12. Inherently Safer Chemistry for Accident Prevention

Three Tiers of Assessment

Toxicity

Biodegradation

Bioaccumulation

PERSISTENCE OF ‘TOXIC’ CHEMICALS
Ionic Liquids

Poorly coordinated ionic species

Most often low melting points
(<100 °C)

Properties:

- Highly solvating
- Non-flammable
- Low vapour pressure
- High thermal stability
- Large liquid range

$X = \text{Br, Cl, BF}_4, \text{PF}_6, \text{OctOSO}_3, \text{N(CN)}_2, \text{NTf}_2 \text{ etc}$
Ionic Liquids

Suitable for a range of organic reactions and provide:

- Control of product distribution
- Enhanced rate/or reactivity
- Ease of product recovery
- Catalyst immobilisation
- Recyclability

Green alternatives to VOCs?

Designing Biodegradable ILs

$X = \text{Br, NTF}_2, \text{BF}_4, \text{Octyl sulfate, PF}_6, \text{N(CN)}_2$

Effect of introduction of oxygen (i.e. ester/amide) on biodegradability and toxicity
Soft Antimicrobials

Effective at ppm concentrations

Amino acid based ILs

Low toxicity towards clinically relevant bacteria strains or fungi screened against

Readily Biodegradable CO₂ headspace test 61%, 28 days

Readily Biodegradable CO₂ headspace test 64%, 28 days

Amino acid based ILs

- Head Group
- Amide Bond
- Side Chain
**Unexpected Catalysis**

**Earlier study:** thiourea catalysis of ketone reduction

Earlier study: thiourea catalysis of ketone reduction

![Chemical structures and reactions]

**Unusual observation:**
acetal protection of benzaldehyde in the absence of an acid

Unusual observation:
acetal protection of benzaldehyde in the absence of an acid

![Chemical structures and reactions]

Connon *et al.* *Org. Lett.*, 2008, 10, 4935-4938
Acetalisation of benzaldehyde:

\[
\text{Ph} = \text{Ph} + \text{Br}^- \rightarrow \text{Ph} = \text{Ph} + \text{Br}^- + 90\% \text{ Yield}
\]

Pyridinium Catalysis

Effect of ester group

Change heterocycle from pyridinium to imidazolium
Introduce EWGs, esters (c.f. amides)
1\textsuperscript{st} Gen Imidazolium Catalysis

Gathergood, N. and Connon, S. J. et al. 
*Green Chemistry*, 2010, 12, 1157-1162.
Effect of ring substitution

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Green Metrics Lab Book Spreadsheet (Lapkin and BRITEST)
Green Metrics Lab Book Spreadsheet (Lapkin and BRITEST)
Green Chemistry Metrics

Atom Economy

Hydrogenation of cyclohexene

Alkylation of Pyridine

Ester Hydrolysis
Green Chemistry Metrics

Atom Economy

Hydrogenation of cyclohexene

Alkylation of Pyridine

Ester Hydrolysis

BRITEST Project
Green Chemistry Metrics

Atom Economy

Hydrogenation of cyclohexene

Alkylation of Pyridine

Ester Hydrolysis

BRITEST Project

*Green Chem.*, 2015, 17, 3111-3121
### Key for Traffic Signal Light Classification in Table

**Catalyst Activity (Cat. Act.)**
- **Green**: ≥90% yield with 0.1 mol% catalyst loading
- **Amber**: ≥90% yield with 1 mol% catalyst loading
- **Red**: <90% yield with 1 mol% catalyst loading

**Catalysts Synthesis**
**Catalysts Synthesis**
(“Cat. Syn., Number of steps, NS”)
- **Green**: <3
- **Amber**: 3
- **Red**: >3

**Catalyst Synthesis**
(Cat. Syn., Average Atom Economy, AAE)
- **Green**: 1–0.85
- **Amber**: 0.85–0.70
- **Red**: <0.70

**Antibacterial Toxicity (Tox. Bac.)**
- **Green**: >2 mM all strains, or up to solubility limit
- **Amber**: MIC 0.25–2.0 mM
- **Red**: MIC <0.25 mM

**Antifungal Toxicity (Tox. Fung.)**
- **Green**: >2 mM all strains, or up to solubility limit
- **Amber**: MIC 0.25–2.0 mM
- **Red**: MIC <0.25 mM

**Biodegradation (Biodeg.)**
- **Green**: 60+% Readily Biodegradable
- **Amber**: 20–59%
- **Red**: 0–19%

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**Table 14** Proposed ‘Traffic Light’ system to applied to salts 9–42

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(OctSO₄ salt). A = no reaction at 20 mol% loading. Entries in italics are estimated. NS = number of synthetic steps, AAE = Average Atom Economy.


The catalytic versatility of low toxicity dialkyl-triazolium salts: \textit{in situ} modification facilitates diametrically opposed catalysis modes in one pot

Lauren Myles, Nicholas Gathergood* and
Stephen J. Connan*

A triazolium salt can serve as a precatalyst for both a strong acid and a powerful base/nucleophile simultaneously (depending on the additive employed) which allows a unique \textit{in situ} modification strategy in which the role played by the catalyst is sequentially controlled in an ‘on-off’ fashion.

\textit{Chem. Commun.}, 2013, 49 (46), 5316
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Effect of ring substitution

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Two Bites at the Cherry

Have we failed?

Guidelines to assist design of safer chemicals

Transformation product directed library selection

Transient Transformation product identification

Tandem Approach
  Catalyst Performance/Atom Economy/Green Toxicology

Education
Acknowledgements

Stephen Connon, Klaus Kümmerer, Teresa M. Garcia, Marcel Spulak, Brid Quilty, Andrew Kellett, Milan Pour, Ian Beadham, Habio Xie, Bruce Pegot, Jaywant Phophase, Tru Throng, Deborah Coleman, Lauren Myles, Dan Canning, Saibh Morrisey, Ewa Kowalska, Brian Deegan, Thomas Hayes, Shelly Long, Monika Gurbisz, Rohitkumar Gore, Mukund Ghavre, Dong Yang, Alan Coughlan, Bo Lui, Adam Porter, Andrew Jordan, Hannah Prydderch, Jaco Jacobs, Natasha McStay, Andreea Prisecaru

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Henkel Ireland
MacFarlan Smith
PhD Omar Parve (senior research scientist);
PhD Victor Borovkov (senior research scientist)
PhD Yevgen Karpichev (senior research scientist)
PhD Dzmitry Kananovich (senior research scientist)
PhD Illia Kapitanov (senior research scientist)
PhD Vijai Kumar Gupta (senior research scientist)

PhD Yuri Ermolovich (postdoctoral researcher,)
PhD Mohammed Hassan (postdoctoral researcher)
Pille Pata (researcher), Jaan Parve (chemist)

Eva Doyle (PhD student), Estelle Silm (PhD student)
Grete Raba (PhD student), Gabor Zoltan Elek (PhD student)
Dewi Kurnianingsih Arum (PhD student)
Yulia Konik (Visiting PhD student, Sept 2016-Feb 2017)
Oleksandra Mariichak (Visiting PhD student, Jan 2016-Jun 2017)
Natasha McStay (PhD student, DCU)

Erni Metsal (MSc student), Bo Lui (MSc Student, DCU)
Aizhamal Subanbekova, (Erasmus student July, August, 2016)
Nele Konrad (BSc student), Anastassia Sikerina (BSc student)
Estonia is a country in the Baltic region of Northern Europe. Capital and largest city is Tallinn.
Tallinn – capital of Estonia
Main research area: environmentally friendly chemicals and procedures (biorenewable starting materials, sustainable chemistry, ‘benign by design’, environmentally friendly procedures and chemicals, catalysis, biodegradation, green toxicology, efficient synthesis, atom economy, green chemistry metrics, asymmetric synthesis, ionic liquids, surfactants, green analytical chemistry (including host-guest interactions), drug discovery (antimicrobials, analgesics, cancer therapeutics) and safer anaerobic adhesives).

This project has received funding from the European Union’s 7th Framework Programme for research, technological development and demonstration under grant agreement no 621364.
The concept of Green Chemistry was first introduced in 1998 with the publication of Anastas and Warner's "12 Principles of Green Chemistry". Today, these principles are becoming adopted as general practice in the chemical industries in order to reduce or eliminate the use and generation of hazardous materials, reduce waste, and make use of sustainable resources. New, safer materials and products are being released all the time. Alternative technologies are being developed to improve the efficiency of the chemical industry, while reducing its environmental impact. Sustainable resources are being investigated to replace our reliance on fossil fuels – not only as source of energy but also a source of chemicals — be they feedstock, bulk, or fine. Consideration is now given to the whole life cycle of a product or chemical — from design to disposal. And, as more of the Earth's resources become scarce so new alternatives must be found.

As the world works towards meeting the needs of the present generation without compromising the needs of the future, this series presents comprehensive books from leaders in the field of green and sustainable chemistry. The volumes will offer an excellent source of information for professional researchers in academia and industry, and postgraduate students across the multiple disciplines involved.
**Sonochemistry**

New Opportunities for Green Chemistry
by Gregory Chatel (Université Savoie Mont Blanc, France)

This book first introduces the basics of ultrasonic waves and the history of sonochemistry before moving on to look at acoustic cavitation and the estimation of ultrasonic parameters. After this comes a discussion of the equipment needed for experimentation with sonochemistry. Finally there is an in-depth look at green sonochemistry in different fields of research, covering concepts such as new combinations of ultrasound with ionic liquids, microwave irradiation, enzyme combination, and sono-assisted electrochemistry. In conclusion, distinguished sonochemists from around the world share their opinions on the green sonochemistry, and their predictions in the field.

**Contents:** Introduction; Acoustic Cavitation; Ultrasonic Parameters Estimation; Ultrasonic Equipment; Applications in Green Chemistry; Conclusion and Outlook.

**Readership:** Undergraduate and graduate students in chemistry, and practitioners of ultrasonic technology.

188pp  
978-1-78634-127-3  US$80 / £66  
978-1-78634-150-1(pbk)  US$45 / £37

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**Analytical Applications of Ionic Liquids**

edited by Mihkel Koel (Tallinn University of Technology, Estonia)

This book reviews the current research in analytic chemistry, covering subjects as diverse as separation science, chromatography, spectroscopy and analytical electrochemistry.

**Readership:** Analytical chemists, undergraduate and graduate students, university professors.

436pp  
978-1-78634-071-9  Dec 2016  US$195 / £162
The Division of Green and Sustainable Chemistry (DGSC) was approved by EuCheMS in 2015.

Prof. Pietro Tundo, Chair of the Working Group.

Members: 24, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Israel, Italy, Netherlands, Poland, Portugal, Spain, Slovakia, Turkey, United Kingdom

In 2016, the positions of Chair (Nicholas Gathergood, Estonia), Vice-Chair (Piotr Stepnowski, Poland), Secretary (Katalin Barta, Netherlands) and Treasurer (James Sullivan, Ireland) have been elected.

The Steering Committee of the DGSC was elected in winter 2016 and consists of Nicholas Gathergood, Piotr Stepnowski, Katalin Barta, James Sullivan, Michael North (Next DGSC Conference Chair), José Nuno C Lopes and Ana Aguiar-Ricardo (Past DGSC conference Chairs) and Joel Barault, according to the procedures and practices 3.5(i) of the DGSC.
DGSC Conference Presentation

- EuCheMS Division of Analytical Chemistry supported ECOBALT 2016 conference in Tartu, Estonia in October
- DGSC presentation in DCE conference in Oslo 2017
- DCE presentation in DGSC conference in York 2017
DGSC Activities

Provide expert opinion on green and sustainable chemistry issues

Contribution to a white paper, Biopharma for Europe
DGSC Conferences

• 1st EuCheMS Green and Sustainable Chemistry conference in Budapest in the Autumn of 2013

• 2nd EuCheMS Green and Sustainable Chemistry conference in Lisbon in the Autumn of 2015
3rd EuGSC
3rd EuCheMS Congress on Green and Sustainable Chemistry
3-6 September 2017
York, United Kingdom
www.york.ac.uk/3EUGSC
Plenary Speakers

Paul Anastas
James Clark
Ben Feringa
Nicholas Gathergood
Babette Pettersen
Michael Grätzel

Yale University
University of York
University of Groningen
Tallinn University of Technology
Capricorn Venture Partners
EPFL

Save the Date

Early bird registration deadline
28 February 2017

Oral abstract submission deadline
28 February 2017

Poster abstract submission deadline
30 June 2017