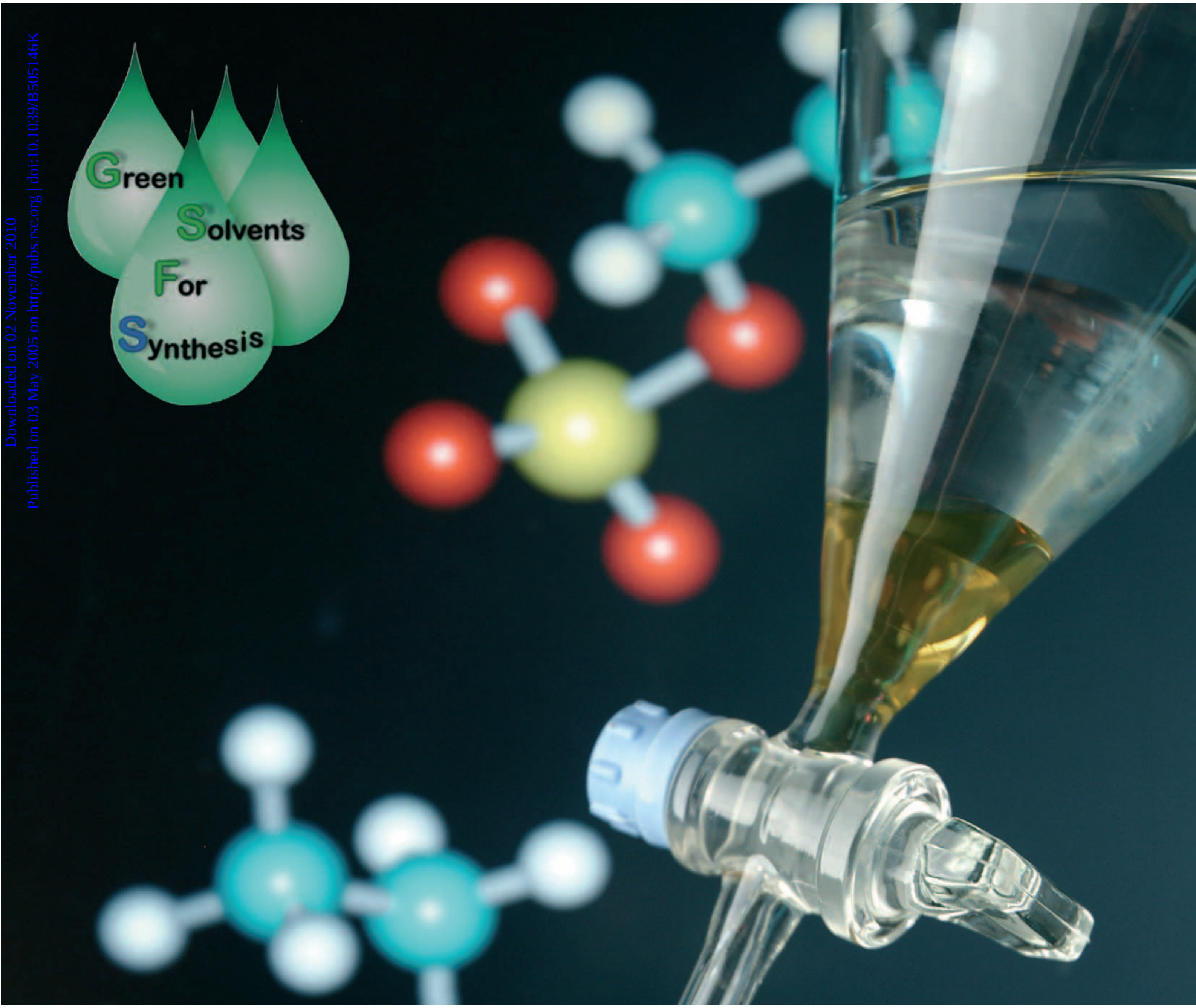
Green Chemistry

Cutting-edge research for a greener sustainable future

www.rsc.org/greenchem

Volume 7 | Number 5 | May 2005 | Pages 241–392



ISSN 1463-9262

WEYERSHAUSEN *et al.*
Ionic liquids as industrial processing aids

GARCIA-VERDUGO *et al.*
Partial oxidation in supercritical water

GIERNOTH *et al.*
High performance NMR in ionic liquids

SHELDON
Green synthesis: state of the art

RSC | Advancing the Chemical Sciences

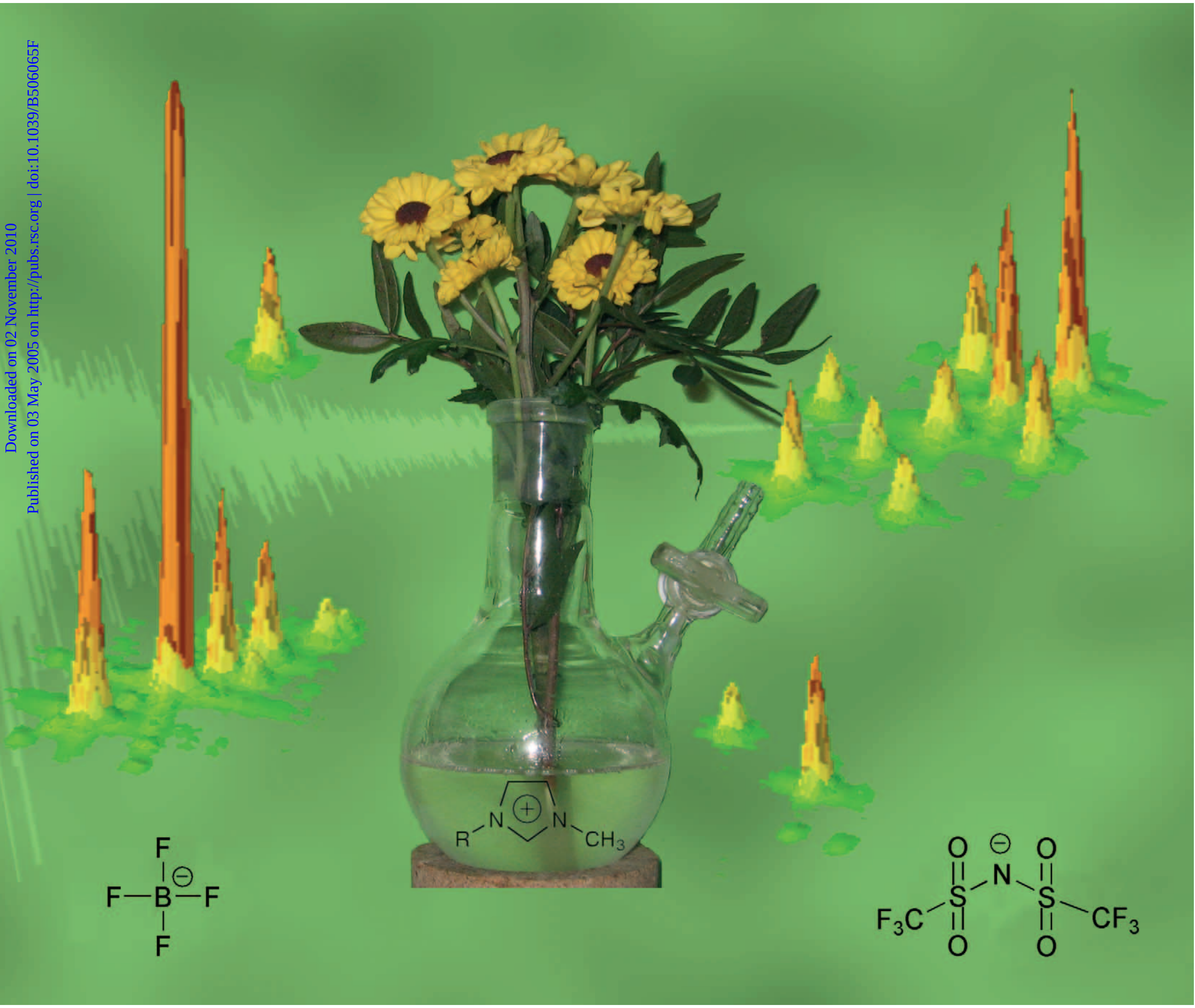
1463-9262(2005)7:5;1-B

Green Chemistry

Cutting-edge research for a greener sustainable future

www.rsc.org/greenchem

Volume 7 | Number 5 | May 2005 | Pages 241–392



ISSN 1463-9262

RSC | Advancing the Chemical Sciences

WEYERSHAUSEN *et al.*
Ionic liquids as industrial processing aids

GARCIA-VERDUGO *et al.*
Partial oxidation in supercritical water

GIERNOTH *et al.*
High performance NMR in ionic liquids

SHELDON
Green synthesis: state of the art

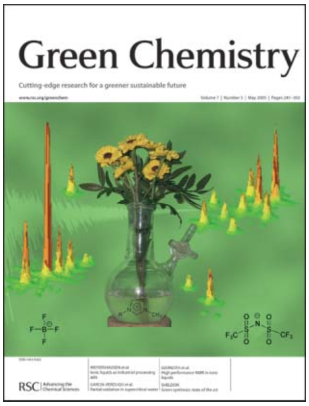
IN THIS ISSUE

ISSN 1463-9262 CODEN GRCHFJ 7(5) 241–392 (2005)

Cover

The use of an ionic liquid in industrial hydrosilylation processes allows for the easy recovery of the expensive precious metal catalyst and its direct reuse in a subsequent hydrosilylation reaction. From an economic and ecological point of view this process perfectly fits into the concept of Sustainable Chemistry. In the background of the photo the molecular structure of TEGO® IL IMES is shown. Recently, a new chemical substance notification for TEGO® IL IMES has been finalized in EEC.

Image reproduced by permission of Stefan Wildhirt, on behalf of Degussa AG, from *Green Chem.*, **7**(5), 283.



Inside Cover

The artwork symbolizes the three main topics of our work: ionic liquids, NMR spectroscopy, and green chemistry. The spectrum in the background is a real COSY NMR of a pure IL solvent as described in our article. We demonstrate that ionic liquids can be used as "normal" solvents for high-performance NMR spectroscopy.

Image reproduced by permission of Dennis Bankmann and Ralf Giernoth from *Green Chem.*, **7**(5), 279.

CHEMICAL TECHNOLOGY

T17

Chemical Technology highlights the latest applications and technological aspects of research across the chemical sciences.

Chemical Technology

May 2005/Volume 2/Issue 5

www.rsc.org/chemicaltechnology

EDITORIAL

253

Green Solvents for Synthesis Meeting Bruchsal, Germany, October 2004

This special issue brings together work presented at the Green Solvents for Synthesis meeting, which aimed to highlight innovative concepts for the substitution of volatile organic solvents in solution phase synthesis.

HIGHLIGHT

254

Highlights

View Online

Downloaded on 02 November 2010
Published on 03 May 2005 on http://pubs.rsc.org | doi:10.1039/B505147A

EDITORIAL STAFF

Editor
Harpal Minhas

Assistant editors
Nina Athey-Pollard, Merlin Fox, Katie Gibb

News writer
Markus Hölscher

Publishing assistant
Jackie Cockrill

Team leader, serials production
Stephen Wilkes

Technical editors
Katherine Davies, Christopher Ingle, Kathryn Lees

Editorial secretaries
Sonya Spring, Julie Thompson, Rebecca Gotobed

Publisher
Adrian Kybett

Green Chemistry (print: ISSN 1463-9262; electronic: ISSN 1463-9270) is published 12 times a year by the Royal Society of Chemistry, Thomas Graham House, Science Park, Milton Road, Cambridge, UK CB4 0WF.

All orders, with cheques made payable to the Royal Society of Chemistry, should be sent to RSC Distribution Services, c/o Portland Customer Services, Commerce Way, Colchester, Essex, UK CO2 8HP. Tel +44 (0) 1206 226050; E-mail sales@rscdistribution.org

2005 Annual (print + electronic) subscription price: £795; US$1310. 2005 Annual (electronic) subscription price: £715; US$1180. Customers in Canada will be subject to a surcharge to cover GST. Customers in the EU subscribing to the electronic version only will be charged VAT.

If you take an institutional subscription to any RSC journal you are entitled to free, site-wide web access to that journal. You can arrange access via Internet Protocol (IP) address at www.rsc.org/ip. Customers should make payments by cheque in sterling payable on a UK clearing bank or in US dollars payable on a US clearing bank. Periodicals postage paid at Rahway, NJ, USA and at additional mailing offices. Airfreight and mailing in the USA by Mercury Airfreight International Ltd., 365 Blair Road, Avenel, NJ 07001, USA.

US Postmaster: send address changes to Green Chemistry, c/o Mercury Airfreight International Ltd., 365 Blair Road, Avenel, NJ 07001. All despatches outside the UK by Consolidated Airfreight.

PRINTED IN THE UK

Advertisement sales: Tel +44 (0) 1223 432243; Fax +44 (0) 1223 426017; E-mail advertising@rsc.org

Green Chemistry

Cutting-edge research for a greener sustainable future

www.rsc.org/greenchem

Green Chemistry focuses on cutting-edge research that attempts to reduce the environmental impact of the chemical enterprise by developing a technology base that is inherently non-toxic to living things and the environment.

EDITORIAL BOARD

Chair
Professor Colin Raston, Department of Chemistry University of Western Australia Perth, Australia E-mail clraston@chem.uwa.edu.au

Scientific editor
Professor Walter Leitner, RWTH-Aachen, Germany E-mail leitner@itmc.rwth-aachen.de
Professor Joan Brennecke, University of Notre Dame, USA
Professor Steve Howdle, University of Nottingham, UK
Dr Janet Scott, Centre for Green Chemistry, Monash University, Australia
Dr A Michael Warhurst, WWF, Brussels, Belgium
Professor Tom Welton, Imperial College, UK E-mail t.welton@ic.ac.uk
Professor Roshan Jachuck, Clarkson University, USA E-mail rjachuck@clarkson.edu
Dr Paul Anastas, Green Chemistry Institute, USA Email p_anastas@acs.org

Associate editor for the Americas
Professor C. J. Li, McGill University, Canada E-mail cj.li@mcgill.ca

INTERNATIONAL ADVISORY EDITORIAL BOARD

James Clark, York, UK
Avelino Corma, Universidad Politécnica de Valencia, Spain
Mark Harmer, DuPont Central R&D, USA
Makato Misono, Kogakuin University, Japan
Robin D. Rogers, Centre for Green Manufacturing, USA
Kenneth Seddon, Queen's University, Belfast, UK
Roger Sheldon, Delft University of Technology, The Netherlands
Gary Sheldrake, Queen's University, Belfast, UK
Pietro Tundo, Università ca Foscari di Venezia, Italy
Tracy Williamson, Environmental Protection Agency, USA

INFORMATION FOR AUTHORS

Full details of how to submit material for publication in Green Chemistry are given in the Instructions for Authors (available from http://www.rsc.org/authors). Submissions should be sent *via* ReSourCe: http://www.rsc.org/resource.

Authors may reproduce/republish portions of their published contribution without seeking permission from the RSC, provided that any such republication is accompanied by an acknowledgement in the form: (Original citation) – Reproduced by permission of the Royal Society of Chemistry.

© The Royal Society of Chemistry 2005. Apart from fair dealing for the purposes of research or private study for non-commercial purposes, or criticism or review, as permitted under the Copyright, Designs and Patents Act 1988 and the Copyright and Related Rights Regulations 2003, this publication may only be reproduced, stored or transmitted, in any form or by any means, with the prior permission in writing of the Publishers or in the case of reprographic reproduction in accordance with the terms of licences issued by the Copyright Licensing Agency in the UK. US copyright law is applicable to users in the USA.

The Royal Society of Chemistry takes reasonable care in the preparation of this publication but does not accept liability for the consequences of any errors or omissions.

♾The paper used in this publication meets the requirements of ANSI/NISO Z39.48-1992 (Permanence of Paper).

Royal Society of Chemistry: Registered Charity No. 207890

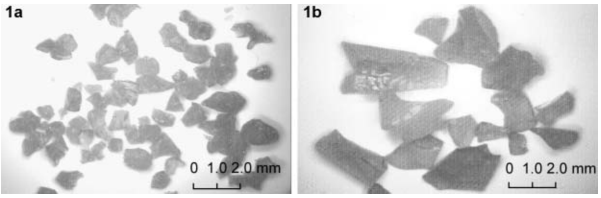
COMMUNICATIONS

256

Comparison of two preparative methods: a polymer-supported catalyst by metal-complexation with a polymeric ligand or by polymerization of a metal complex

Shinsuke Kinoshita, Fumitoshi Shibahara and Kyoko Nozaki*

The difference of two methods for the synthesis of polystyrene-supported (*R*,*S*)-BINAPHOS-Rh(I) complex **1a** and **1b** is investigated by comparison of their catalytic performance, by surface analysis and by particle-size measurement.

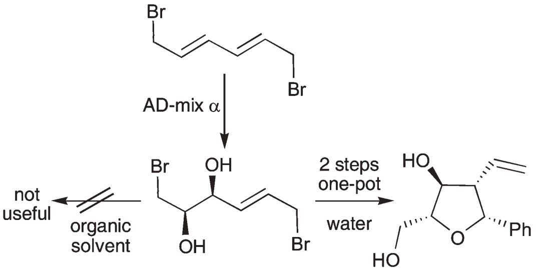


259

A chiral biselectrophile for efficient asymmetric synthesis in water

Olle Hidestål, Rui Ding, Ann Almesåker and Ulf M. Lindström*

The unique properties of water as solvent allow exploration of the synthetic potential of functionalized 1,6-biselectrophiles, the use of which has been hampered by their propensity to polymerize in organic media.

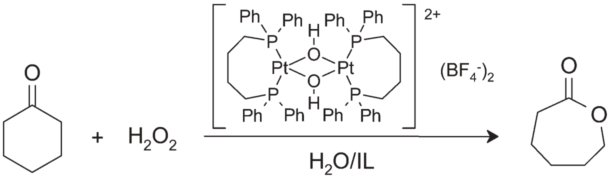


262

The Pt(II)-catalyzed Baeyer–Villiger oxidation of cyclohexanone with H_2O_2 in ionic liquids

Valeria Conte,* Barbara Floris, Pierluca Galloni, Valentina Mirruzzo, Alessandro Scarso, Daniela Sordi and Giorgio Strukul

Performing the title reaction in H_2O–IL mixtures produces improvements with regard to both yield of product and replacement of chlorinated solvents. Recycling of Pt(II)-containing IL appears a viable procedure.



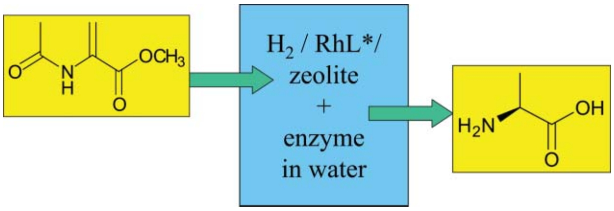
CRITICAL REVIEW

267

Green solvents for sustainable organic synthesis: state of the art

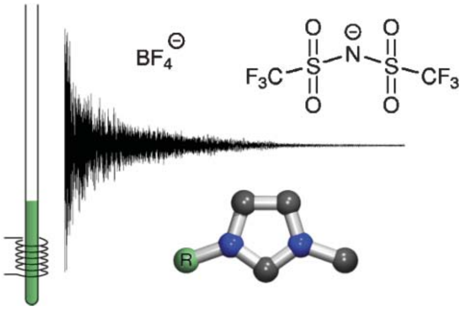
Roger A. Sheldon

The use of alternative reaction media—water, fluorous solvents, supercritical carbon dioxide and ionic liquids—which circumvent problems associated with conventional organic solvents, and facilitate the recovery of catalysts, is critically reviewed.



PAPERS

279

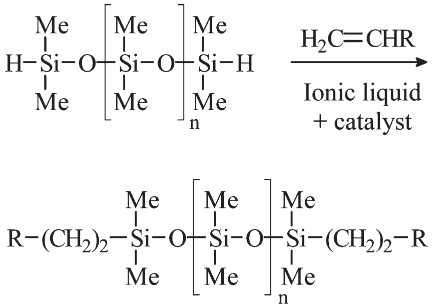


High performance NMR in ionic liquids

Ralf Giernoth,* Dennis Bankmann and Nils Schlörer

We present the first systematic approach towards routine NMR spectroscopy in neat ionic liquids, opening a new route for elucidation of the ILs bulk structure and *in situ* reaction monitoring.

283

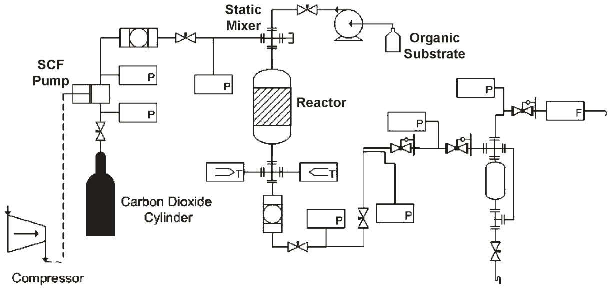


Industrial application of ionic liquids as process aid

Bernd Weyershausen,* Kerstin Hell and Ute Hesse

The use of an ionic liquid in a hydrosilylation reaction enables conventional hydrosilylation catalysts to be easily recycled, to be immediately reused after separation from the product at the end of the reaction without any further treatment.

288

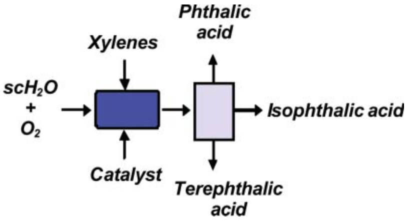


Continuous reactions in supercritical fluids; a cleaner, more selective synthesis of thymol in supercritical CO_2

Rodrigo Amandi, Jason R. Hyde, Stephen K. Ross, Tobias J. Lotz and Martyn Poliakoff*

Continuous Friedal–Crafts alkylations in supercritical carbon dioxide using solid acid catalysts are described. Reaction conditions were varied to optimise yield and selectivity for the fine chemical thymol.

294



Simultaneous continuous partial oxidation of mixed xylenes in supercritical water

Eduardo Garcia-Verdugo,* Joan Fraga-Dubreuil, Paul A. Hamley, W. Barry Thomas, Keith Whiston and Martyn Poliakoff*

We show that a mixture of isomeric xylenes can be simultaneously oxidised in supercritical water (scH_2O) in a continuous mode to a mixture of the corresponding carboxylic acids in high combined yield, despite the differences in reactivity of the xylene isomers in conventional oxidation.

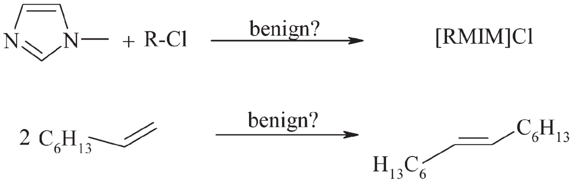
PAPERS

301

Energetic, environmental and economic balances: Spice up your ionic liquid research efficiency

Dana Kralisch,* Annegret Stark,* Swen Körsten, Günter Kreisel and Bernd Ondruschka

A strategic tool, based on energetic, environmental and economic assessment, combined with experimental evidence, for the development of benign processes is presented. The manufacture of ionic liquids as well as their use as solvents in metathesis is exemplary investigated.

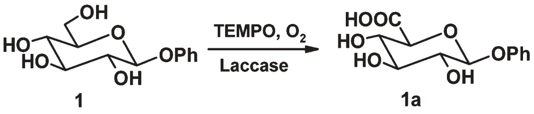


310

Selective laccase-mediated oxidation of sugars derivatives

Mattia Marzorati, Bruno Danieli, Dietmar Haltrich and Sergio Riva*

In the presence of a catalytic amount of TEMPO, the laccase from *Trametes pubescens* catalyzes the regioselective oxidation of the primary OHs of mono-, di- and polysaccharides by reducing molecular oxygen.

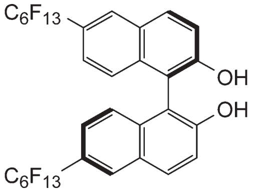


316

Recycling of a perfluoroalkylated BINOL ligand using fluorous solid-phase extraction

John Fawcett, Eric. G. Hope, Alison M. Stuart* and Andrew J. West

Highly efficient separation and recycling of a perfluoroalkylated BINOL ligand is reported using fluorous solid-phase extraction after the asymmetric allylation of benzaldehyde.



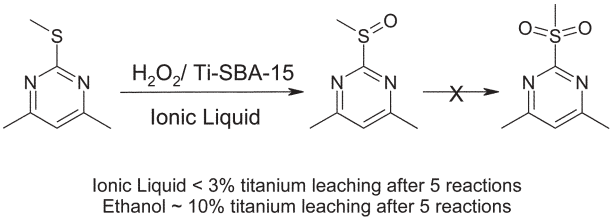
321

Corrosion behaviour of ionic liquids

Marc Uerdingen,* Claudia Treber, Martina Balser, Günter Schmitt and Christoph Werner

The first investigations of corrosion behaviour of different metals in seven commercially available ionic liquids under well defined conditions are presented and a corrosion inhibition concept proven.

326

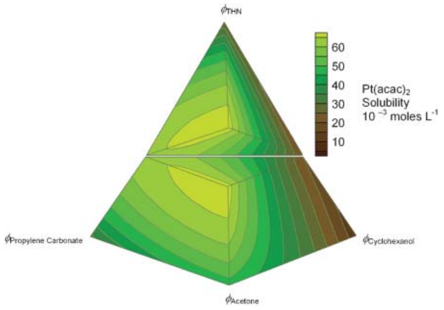


Stabilization of Ti-molecular sieve catalysts used in selective sulfoxidation reactions by ionic liquids

Valentin Cimpeanu, Christopher Hardacre,*
Vasile I. Pârvulescu* and Jillian M. Thompson

Ionic liquid mediated sulfoxidation reactions using titanosilicates catalysts show much higher selectivities and rates than found in conventional solvents. Furthermore the catalyst is stabilised in the ionic media and the leaching is reduced improving the catalyst recyclability.

333

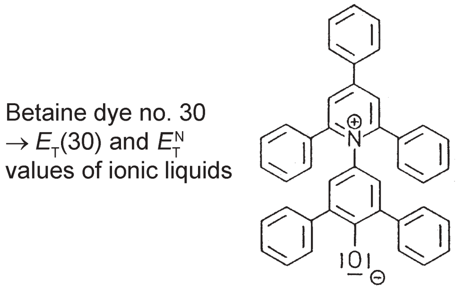


A design-of-experiments approach to modeling activity coefficients in solvent mixtures: a case study using platinum(II) acetylacetonate in mixtures of acetone, cyclohexanol, 1,2,3,4-tetrahydronaphthalene and propylene carbonate

Scott Flanagan,* Eric Hall, Wade Bowie, James W. Fuhs, Robbie Logan, Farzaneh Maniei and Andrew Hunt

The composition of mixtures of environmentally benign solvents can be optimized using a DOE-based activity coefficient model to enable the replacement of environmentally harmful solvents.

339



Polarity of ionic liquids determined empirically by means of solvatochromic pyridinium *N*-phenolate betaine dyes

Christian Reichardt

The available $E_T(30)$ and E_T^N polarity parameters of room temperature ionic liquids are summarized and discussed, because ionic liquids have gained importance as environmentally benign new reaction media.

352

Green Chemistry in Ethiopia: the cleaner extraction of essential oils from *Artemisia afra*: a comparison of clean technology with conventional methodology

Nigist Asfaw,* Peter Licence,* Alexander A. Novitskii and Martyn Poliakoff

We present early results from a comparative study of greener extraction methods (microwaves, ultrasound, supercritical fluids) on *Artemisia afra*, a plant traditionally employed as a fragrance, insect repellent and medicine.

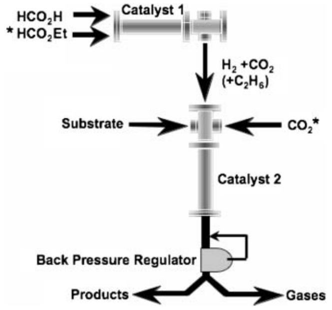
PAPERS

357

Continuous hydrogenation reactions in supercritical CO_2 "without gases"

Jason R. Hyde,* Ben Walsh, Jasbir Singh and Martyn Poliakoff*

A reactor and supporting equipment has been developed for continuous fixed-bed hydrogenation reactions under supercritical conditions. The high pressure hydrogen required is supplied by the *in situ* decomposition of formic acid.

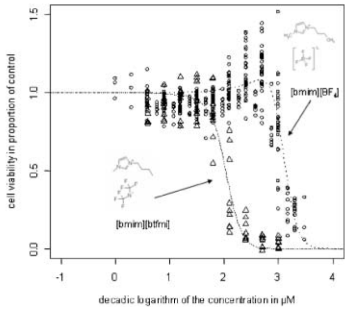


362

Progress in evaluation of risk potential of ionic liquids—basis for an eco-design of sustainable products

Bernd Jastorff, Kerstin Mölter, Peter Behrend, Ulrike Bottin-Weber, Juliane Filser, Anna Heimers, Bernd Ondruschka, Johannes Ranke,* Maike Schaefer, Heike Schröder, Annegret Stark, Piotr Stepnowski, Frauke Stock, Reinhold Störmann, Stefan Stolte, Urs Welz-Biermann, Susanne Ziegert and Jorg Thöming

Focusing on environmental risks, new and updated findings regarding a sustainable product design for ionic liquids are presented.

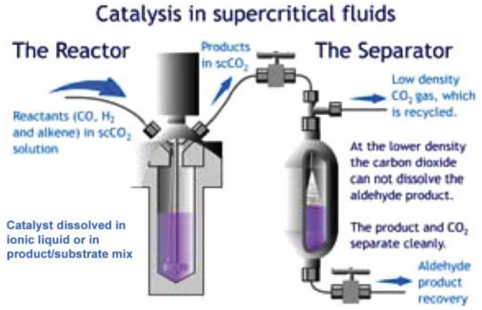


373

Continuous flow homogeneous hydroformylation of alkenes using supercritical fluids

Paul B. Webb, Thulani E. Kunene and David J. Cole-Hamilton*

Continuous flow homogeneous catalysis is demonstrated. The products are transported from the reactor in $scCO_2$. The ionic catalyst is dissolved in an ionic liquid or in the reaction product.



380

Chemical recycling of polycarbonate in a semi-continuous lab-plant. A green route with methanol and methanol–water mixtures

Raúl Piñero, Juan García* and María José Cocero

Green recycling of polycarbonate from compact disks and plastic wastes can be performed with a catalytic solution of methanol–H_2O and NaOH, providing bisphenol A and dimethyl carbonate.

AUTHOR INDEX

FREE E-MAIL ALERTS

Contents lists in advance of publication are available on the web *via* www.rsc.org/greenchem - or take advantage of our free e-mail alerting service (www.rsc.org/ej_alert) to receive notification each time a new list becomes available.

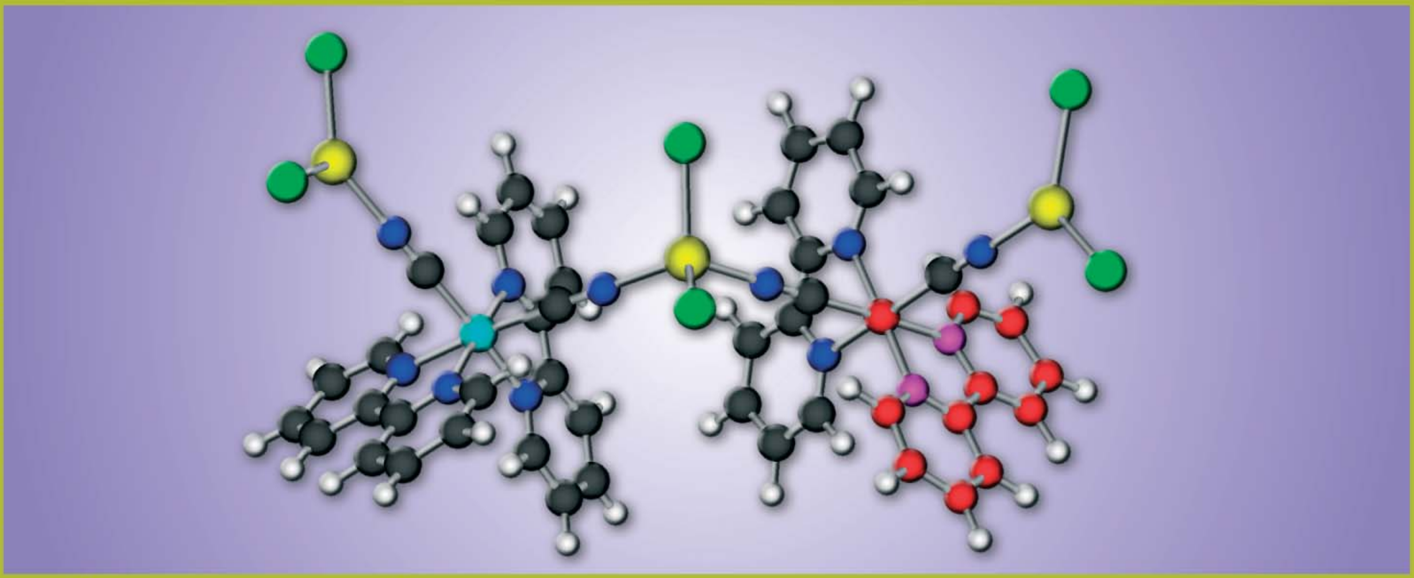
* Indicates the author for correspondence: see article for details.

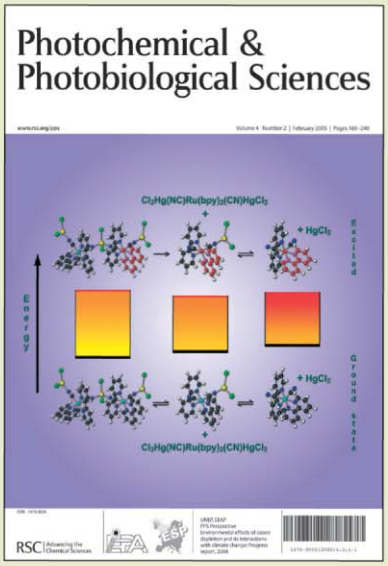
Electronic supplementary information (ESI) is available *via* the online article (see http://www.rsc.org/esi for general information about ESI).

ADVANCE ARTICLES AND ELECTRONIC JOURNAL

Free site-wide access to Advance Articles and the electronic form of this journal is provided with a full-rate institutional subscription. See www.rsc.org/ejs for more information.

Image reproduced by permission of Jean-Francois Niergarten, *New J. Chem.* 2004, 10




Photochemical & Photobiological Sciences
Cl2Hg(NC)Ru(bpy)2(CN)HgCl2
+ HgCl2
Energy
Excited
Ground state
Cl2Hg(NC)Ru(bpy)2(CN)HgCl2
RSC

Green Solvents for Synthesis Meeting Bruchsal, Germany, October 2004

DOI: 10.1039/b505452b

From October 3–6, 2004 the German Society of Chemical Engineering and Biotechnology (DECHEMA) presented the "Green Solvents for Synthesis" meeting in Bruchsal, Germany. The aim of the conference was to highlight innovative concepts for the substitution of volatile organic solvents in solution phase synthesis in academia and industry. The meeting followed the highly successful symposium "Green Solvents for Catalysis" held at the same venue in fall 2002 (see ref. 1). Again, the Green Solvents meeting brought together over 200 scientists from all over the world for fruitful scientific discussions in a stimulating environment. Although it is impossible to reflect the personal contacts and the dynamic atmosphere of such an event on printed paper adequately, the papers summarized in this issue provide a representative overview of the scope and depth of the excellent science presented in the various sessions.

Among the many exciting results presented at this meeting, one common theme seemed particularly intriguing: the utilization of novel solution phase concepts offers promising approaches to chemical synthesis that go way beyond simple solvent replacement. Increased reactivities and selectivities can be achieved when the physico-chemical properties of the medium and the molecular nature of the chemical transformation are matched properly. Integration of reaction and separation steps can lead to new reaction engineering concepts that are both environmentally benign and economically attractive. However, it also became clear that our current knowledge is far from sufficient to fully exploit these potential benefits. Consequently, an increasing demand for multidisciplinary efforts, in particular at the interface between molecular science and reaction engineering, has been identified in the discussions at poster sessions, during coffee breaks and while enjoying the conference dinner within the spectacular setting of the Baroque Castle of Bruchsal.

As a result, the organising committee together with DECHEMA has decided to continue the "Green Solvents Series" with an international symposium on "Green Solvents for Processes" on October 7–11, 2006. This meeting will be focused exactly on this interface and if you are interested in Green Solvents, you should mark these dates in your calendar immediately. However, don't book a ticket to Bruchsal yet, because the location will be shifted to Friedrichshafen at the Bodensee, one of the most scenic lakes in Germany.

We hope that you will enjoy reading the papers in this issue as much as we enjoyed organising and participating in this meeting.

For the organising committee
Walter Leitner (Chairman)
K. R. Seddon
P. Wasserscheid

References

1 *Green Chem.*, 2003, **5**, 2, 99—239, http://www.rsc.org/is/journals/current/green/GC005002.htm.

This special issue of *Green Chemistry* resulting from the Bruchsal conference is dedicated to the memory of Prof. Dr Birgit Drießen-Hölscher

Prof. Dr Birgit Drießen-Hölscher was born on August 1, 1964. She received an education in chemistry at the RWTH Aachen and finished her PhD under the supervision of Prof. Willi Keim in 1992. In June 2000, she obtained her Habilitation at the Institute for Technical and Macromolecular Chemistry (ITMC) and was appointed Privatdozent (lecturer) at the RWTH Aachen. In 2002, she was appointed Professor for Technical Chemistry and Polymer Reaction Engineering at the University of Paderborn. On November 16, 2004, at the age of only 40 years, Brigit Drießen-Hölscher collapsed during a lecture at a conference in South Africa and passed away a few hours later without regaining consciousness.

Birgit Drießen-Hölscher's contributions to the field of homogeneous catalysis and multiphase catalysis were widely recognized, in particular for chemo- and stereoselective hydrogenation of dienes, for the synthesis of chiral ligands, and for telomerisation reactions. The scientific community has lost a creative researcher, a gifted teacher and a wonderful person. We will remember Birgit as a warmhearted colleague and a true friend.

For the organising committee of Green Solvents for Synthesis and in the name of many friends and colleagues
Walter Leitner, K. R. Seddon and P. Wasserscheid

Highlights

DOI: 10.1039/b504206m

Markus Hölscher reviews some of the recent literature in green chemistry

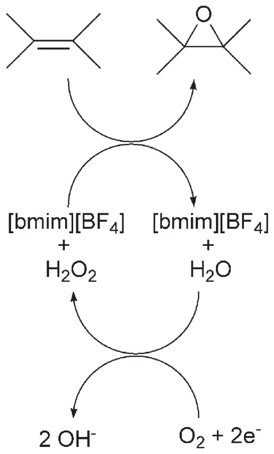
Hollow, mesoporous silica spheres by hydrothermal synthesis in $scCO_2/H_2O$ mixtures

For applications such as drug delivery, catalysis and adsorption, hollow spherical materials with ordered pore structures are potentially interesting, which explains the growing interest for synthetic methods to obtain such particles. The classic emulsion templating synthesis technique suffers from certain drawbacks one of them being the usage of large amounts of water-immiscible organic solvents or oil, which have to be disposed of. Compressed or supercritical carbon dioxide has been shown to act as an environmentally friendly replacement for classic organic solvents, which makes it an interesting candidate for use in CO_2/H_2O mixtures for the synthesis of hollow silica particles together with an appropriate templating agent. Poliakoff *et al.* from the University of Nottingham showed that by carefully adjusting the synthesis procedure CO_2 indeed is a suitable solvent for this purpose (*Chem. Commun.*, 2005, 210–212). Intact or spherical silica particles were obtained using the following procedure: a PEO–PPO–PEO triblock copolymer template was dissolved in HCl and water and tetraethyl orthosilicate (TEOS) was added. The vessel was pressurized with CO_2 to 200 bar for 45 h at 40 °C, and after pressure release and washing of the white powder obtained, the product was calcined at 500 °C in air. SEM and TEM analyses showed the presence of spherical and hollow silica particles, which have a type IV adsorption isotherm, suggesting the existence of a mesoporous material with a fairly narrow pore size distribution (average pore diameter according to BJH analyses: *ca.* 10 nm) and large surface area (700–800 $m^2\ g^{-1}$). A postulate for the reaction mechanism was made based on the CO_2-philic and CO_2-phobic properties of the PPO and the PEO block of the copolymer, respectively. As a result the novel technique adds to the tool box of applications for supercritical fluids in materials processing.

Epoxidation of alkenes *via* electrosynthetical *in situ* generation of H_2O_2 in ionic liquids

As the anthraquinone process which is commonly used for the production of H_2O_2 has severe drawbacks in terms of sustainability (*e.g.* large amounts of organic solvents) environmentally benign alternatives are welcome. Ionic liquids (ILs) are known for their fairly large electrochemical window, which makes them appropriate candidates for electrochemical reduction of oxygen in the presence of water. Chan *et al.* from the Hong Kong Polytechnic University showed that H_2O_2 can be produced electrochemically and furthermore it can be used for chemical reactions directly (*Chem. Commun.*, 2005, 1345–1347). They chose 3-butyl-1-methylimidazolium tetrafluoroborate $[bmim][BF_4]$ as IL and optimized the amount of water needed for beneficial oxygen reduction (IL : H_2O = 8 : 2 v/v). At an applied potential of −650 mV (*vs.* SCE) the yield of hydrogen peroxide reached a value of 102 mM after 4 h. Introduction of 0.04 M NaOH increased the H_2O_2 yield to 124 mM. The H_2O_2 generated in this way could be used directly without isolation or purification for the epoxidation of a variety of α,β-unsaturated ketones, yielding the corresponding epoxides in fair to good yields.

The products were extracted and the IL/H_2O mixture could be recycled and reused directly just by readjusting the water content (which is reduced during extraction). In four consecutive runs the yield of H_2O_2 generated was steady between 78 and 80 mM with the epoxide yields ranging between 86 and 80%.



Natural amino acids as anions in 20 novel ionic liquids

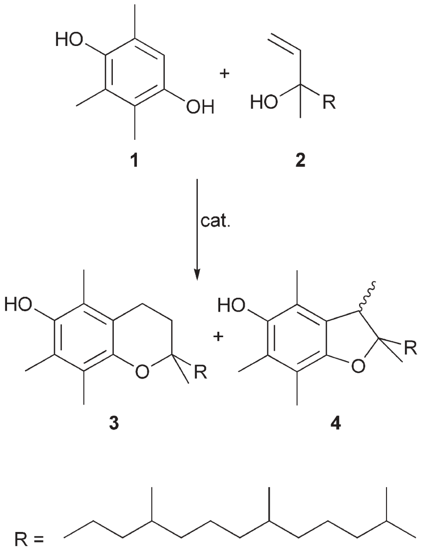
An expanding area in the field of research associated with ionic liquids (ILs) is the development of novel cation and anion structures which aim at the design of novel solvent properties as well as physical and chemical characteristics. Ohno *et al.* from the University of Tokyo combined the well known 1-ethyl-3-methylimidazolium (emim) cation with the anions of different natural amino acids by a simple acid base reaction to generate 20 novel ILs (*J. Am. Chem. Soc.*, 2005, **127**, 2398–2399). As a result the change in physical properties should rely predominantly on the anion. Among many other interesting features these novel ILs dissolve amino acids, which make the new solvents interesting for use in pharmaceutical chemistry. The ILs have no melting point but glass temperatures T_g in the range between −65 °C and 6 °C, and thermal stability of at least 200 °C (one exception is [emim][Cys], which decomposes at 173 °C). The alkyl chain length exerts a dominant influence on the T_g which increases with increasing chain length. The ionic conductivity seems to be correlated with the mobility of the ions, and measured values were between 10^{-9} and 10^{-4} S cm^{-1}. ILs containing anions with two carboxyl groups such as

[emim][Glu] and [emim][Asp] were insoluble in chloroform unlike all the others.

Highly selective synthesis of (all-*rac*)-α-tocopherol in supercritical carbon dioxide

The application of supercritical CO_2 ($scCO_2$) to the catalytic synthesis of natural products is an interesting alternative to conventional routes allowing for example simple product extraction and/or catalyst recovery. As an example an economically and ecologically compatible synthesis of α-tocopherol is currently under investigation, however different catalytic systems have not yet resulted in satisfying results. Ikariya *et al.* from the Tokyo Institute of Technology have recently contributed a synthesis which exploits the unique solvent characteristics of $scCO_2$ (*Adv. Synth. Catal.*, 2005, **347**, 220–224). The challenge lies in developing a highly active and selective catalyst system for the condensation of 2,3,6-trimethylhydroquinone **1** and isophytol **2** to yield α-tocopherol **3** without forming benzofuran derivatives like **4**, which are difficult to separate from the reaction mixture.

Interestingly they found a strong pressure dependence, when $scCO_2$ was used as solvent, which is in marked contrast to the usage of scN_2O. The reason is that the different solubilities of the reactants are dependent on the CO_2 pressure. At CO_2 pressures below 20 MPa the yield of desired product **3** is fairly high (up to 67%), but the selectivity remains under 40%. However, the selectivity rises sharply to values of up to 97% for (all-*rac*)-α-tocopherol when the CO_2 pressure is increased to 35 MPa.



Undesired compound **4** is formed in *ca.* 1% yield. The authors attribute this reaction behaviour to the poor solubility of **2** at CO_2 pressures below 20 MPa. In other words: a homogeneous phase is needed for a successful reaction. It was shown that the batch reaction can also be carried out in a continuous flow reactor with beneficial effect for both yield and selectivity.

Novel mechanism for the decay of organic aerosols in the atmosphere

Key environmental issues such as climate and human health are influenced heavily by the particles suspended in the atmosphere. Such aerosols mainly consist of sulfates over the oceans, however, over the continents the composition is mostly solid organic matter, which stems *e.g.* from smoke particles. The commonly accepted mechanism for the decay of gaseous organic substances is the reaction with oxidants such as hydroxyl and nitrate radicals, whereas solid organic aerosols are believed to be removed from the atmosphere mainly by precipitation. Molina *et al.* from the Massachusetts Institute of Technology describe an alternative mechanism (*Geophys. Res. Lett.*, 2004, **31**, L22104). Oxidative degradation of the organic surface on atmospheric particles could well take place by interaction with hydroxy radicals. To prove this hypothesis the oxidation reactions of model surfaces were examined. As a model for organic particle surfaces organic films were deposited on glass (paraffin films, representing surfaces of aliphatic aerosols and pyrene films representing carbon-ring structures). The surfaces were then exposed to model atmospheres consisting of NO_x, O_2, H_2O and various concentrations of hydroxy radicals. The degradation of the surfaces and the consumption of hydroxy radicals was monitored by state-of-the-art analytical methods. Interestingly both surface models clearly lost organic carbon and the degradation is linearly dependent on the concentration of hydroxy radicals. The aromatic compounds degraded slower than the aliphatic ones, suggesting different degradation reactions to be operative, with breaking of C–C bonds dominating the reaction behaviour. Given an average concentration of hydroxy radicals (10^6 molecules per cm^3) an aliphatic aerosol particle of 0.02–0.2 μm size could be converted into gaseous products within six days. This study made it very clear that more investigations—both laboratory and field studies—are necessary to fully understand the complex processes occurring during heterogeneous reactions of organic particles in the atmosphere.

Comparison of two preparative methods: a polymer-supported catalyst by metal-complexation with a polymeric ligand or by polymerization of a metal complex†

Shinsuke Kinoshita,[a] Fumitoshi Shibahara‡[b] and Kyoko Nozaki*[ab]

Received 8th December 2004, Accepted 1st March 2005
First published as an Advance Article on the web 21st March 2005
DOI: 10.1039/b418264b

The difference between two methods for the synthesis of polystyrene-supported (*R*,*S*)-BINAPHOS-Rh(I) complex, namely (1) copolymerization of the monomeric ligand with divinylbenzene–ethylstyrene and then Rh-complex formation with the polymer-supported ligand, and (2) Rh-complex formation with the monomeric ligand and then immobilization of the Rh complex to polystyrene by copolymerization with divinylbenzene–ethylstyrene, is investigated by comparison of their catalytic performance, by surface analysis and particle-size measurement.

Catalyst separation is often one of the major problems in homogeneous catalysis. Extensive research has been devoted to developing new methods which combine the ease of catalyst recovery associated with heterogeneous systems with the more desirable activity and selectivity obtained with homogeneous catalysts.[1–4] Attachment of metal-catalyst complexes to cross-linked polystyrene is one of the common approaches for this purpose. There are two methodologies most commonly employed for the attachment: grafting a metal complex to functionalized polystyrenes, such as Merrifield resin, and copolymerization of metal-containing monomers with styrene and divinylbenzene. As an example of the latter approach, we previously reported the synthesis of rhodium complexes of (*R*,*S*)-BINAPHOS [(*R*)-2-diphenylphosphino-1,1′-binaphthyl (*S*)-1,1′-binaphthalene-2,2′-diyl phosphite] covalently bound to highly-crosslinked polystyrene at the 6′-position of the phosphine unit.[5,6] Two methods were examined for the synthesis of this species, those are, Method A: copolymerization of the monomeric ligand with divinylbenzene–ethylstyrene and then Rh-complex formation of the polymer-supported ligand (**1a**), and Method B: Rh-complex formation with the monomeric ligand and then immobilization of the complex to polystyrene by copolymerization with divinylbenzene–ethylstyrene (**1b**). In this study, we further characterize the two catalysts by microscopic observations.

Both **1a** and **1b** were prepared as described in Scheme 1 according to the literature.[6] Vapour phase asymmetric hydroformylation of styrene was examined with **1a** and **1b** to obtain the corresponding iso- and normal-aldehydes and the results are summarized in Table 1 (see Experimental for details).[7] As was reported before, similar selectivities for the iso-aldehyde with similar enantiomeric excesses were detected (entries 1 and 3). Because the reaction was stopped at 6 h, before the complete consumption of styrene, a slight difference in TOF (turnover frequency) was observed, 450 h^{-1} with **1a** and 222 h^{-1} with **1b**.

The particle-size difference between **1a** and **1b** nicely explains the different catalytic activity. The mean diameters of **1a** and **1b** were 400 μm and 1500 μm (Fig. 1 and Table 1).§ As the smaller the particle, the larger the surface area accessible for the substrates, a higher catalytic activity should be detected. However, particle-size is not the only factor that controls the reaction rate because the difference in TOF is much smaller than the value that would be derived from the diameter difference. In other words, either the rhodium complexes attached to the internal pore surfaces of the crosslinked polystyrene significantly contribute to the reaction

---

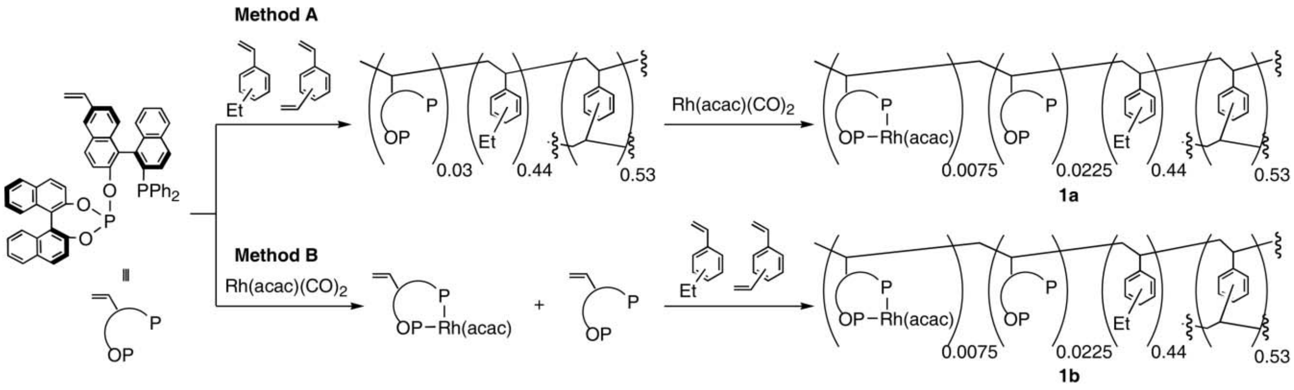
† This work was presented at the Green Solvents for Synthesis Meeting, held in Bruchsal, Germany, 3–6 October, 2004.

‡ Present address: Department of Chemistry, Gifu University, Yamagido, Gifu 501-1193 Japan.

*nozaki@chembio.t.u-tokyo.ac.jp

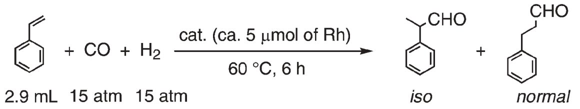
From the left: S. Kinoshita, K. Nozaki, and F. Shibahara

Kyoko Nozaki, born in Osaka, received her PhD from Kyoto University in 1991 and started her career as Instructor at the same University where she became Associate Professor in 1999. She moved to The University of Tokyo as Associate Professor in 2002, and was promoted to Full Professor in 2003. Her research interest concerns the development of homogeneous catalysis for organic synthesis, especially focused on the utilization of C1 resources. The target organic molecules are of various molecular sizes, from small molecules for intermediates to polymeric materials. Her accomplishments include the Chemical Society of Japan Award for Young Chemists (1998), OMCOS prize in organometallic chemistry (2003), and The Society of Polymer Science, Japan, Wiley Award (2004).



Scheme 1 Synthetic routes to polymer-supported catalysts **1a** and **1b**.

Table 1 Data obtained from microscopic observation of **1a** and **1b** before and after hydroformylation of styrene

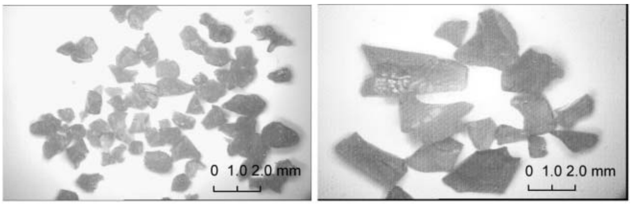


Entry	Catalyst	TOF/h^{-1}	iso : normal	%ee of iso	D3/μm^{a}	State	Rhodium/wt%^{b}	Phosphorus/wt%^{b}
1	**1a**	450	79 : 21	75 (*R*)	400	Before reaction	0.53	0.98
2						After reaction	0.45	0.93
3	**1b**	222	81 : 19	79 (*R*)	1500	Before reaction	0.71	1.90
4						After reaction	0.34	1.08

^{a} The mean particle diameter calculated based on the surface area. ^{b} Standard quantitative by scanning electron microscope equipped with energy-dispersive X-ray spectroscopy (SEM-EDS).

rate, or, one of the catalytic reaction steps competes with the diffusion rate.

Surface analyses of **1a** and **1b** were carried out using a scanning electron microscope[8,9] equipped with energy-dispersive X-ray spectroscopy.[10] The surfaces of a few particles of **1a** and **1b** were observed both before and after the hydroformylation reaction and the typical mappings of phosphorus and rhodium atom distributions are shown in Fig. 2. Both phosphorus and rhodium atoms are dispersed on the surface mostly uniformly. However, spots did exist where both phosphorus and rhodium atoms are localized as highlighted in Fig. 2 (c) and (d). There were no areas in which only phosphorus atoms or rhodium atoms predominantly existed. Most importantly, both **1a** and **1b** showed similar surface structures to each other, regardless of the difference in synthetic methodology. Quantitative analysis was carried out for the phosphorus- and rhodium-atom concentrations on the surface of **1a** and **1b** by standardless quantitative SEM-EDS and the results are summarized in Table 1. Although it seems that the rhodium concentration is lowered in **1b** after the reaction, the leaching of rhodium atoms may be less significant because the phosphorus : rhodium ratio is largely unchanged.¶



(a) (b)

Fig. 1 Yellow particles of (a) **1a** and (b) **1b**.

In conclusion, no obvious difference was observed between the two catalysts **1a** and **1b** except for the particle-size. Thus, the choice of **1a** or **1b** would mostly depend on their accessibilities. The polymer requires washing and drying twice in Method A and once in Method B. Meanwhile, thermal polymerization of the monomeric rhodium complex, the process included in Method B, was significantly retarded by a trace amount of residual oxygen, and thus, strict deoxygenation is required.

Experimental

Vapour phase asymmetric hydroformylation of styrene: polymer-supported catalyst (59 mg, *ca.* 2.5 μmol) was placed on glass wool on a wire-bed fixed at the center of a 50 mL autoclave.[10] The whole system was dried *in vacuo*. Styrene (2.9 mL, 25 mmol) was degassed in a 20 mL-Schenck tube by freeze–thaw cycles, and was transferred to the autoclave *via* a cannula. The autoclave was charged with syngas (H_2 : CO = 1 : 1, total 30 atm) and then heated at 60 °C for 6 h. All the volatiles were vented and dichloroethane (50 μL, 0.064 mmol) was added to the crude product. The yield of aldehyde and i/n ratio were determined by ^{1}H NMR using dichloroethane as an internal standard. Three drops of the crude products and $NaBH_4$ (50 mg, 1.3 mmol) were dissolved in 5 mL of ethanol and then heated at 50 °C for 12 h. The resulting mixture was diluted with water and extracted with dichloromethane. The organic layers were dried over $MgSO_4$.

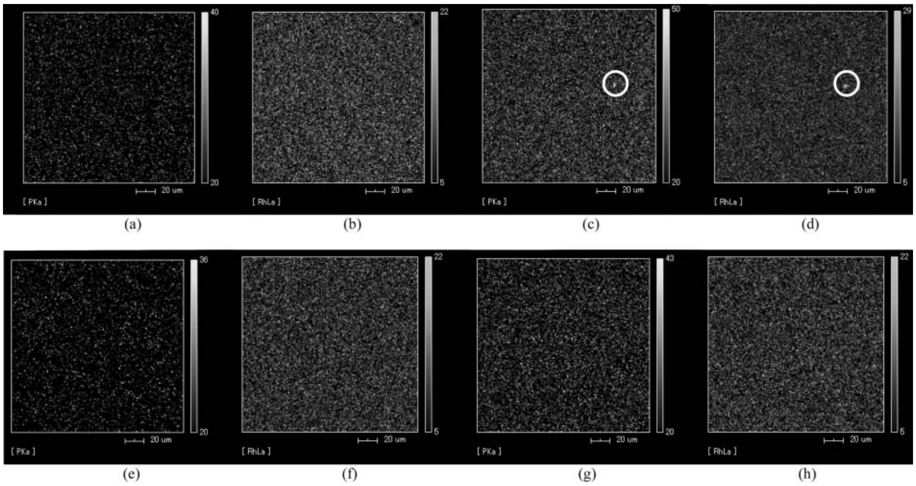


Fig. 2 Distribution of rhodium and phosphorus atoms on the surface of **1a** and **1b** (SEM-EDS). Before the reaction: distribution of (a) phosphorus atoms (P) in **1a**, (b) rhodium atoms (Rh) in **1a**, (c) P in **1b**, (d) Rh in **1b**. Both P and Rh distribute uniformly, but a spot does exist where both P and Rh are localized as highlighted by white circles in (c) and (d). After the reaction: distribution of (e) P in **1a**, (f) Rh in **1a**, (g) P in **1b**, (h) Rh in **1b**.

Evaporation of the solvents and purification by preparative HPLC (Mightysil Si 60 column from Kanto Chemical Co., Inc., 20 mm × 250 mm, Hex : AcOEt = 5 : 1) gave 2-phenyl-1-propanol as a colourless liquid. Enantiomeric excess of 2-phenyl-1-propanol was measured by HPLC equipped with a chiral column (CHIRALCEL OJ-H column from Daicel Chemical Industries, Ltd., 4.6 mm × 250 mm, Hex : ^{i}PrOH = 99.8 : 0.2, 2.0 mL min^{-1}, t_R 26.6 min (*R*), 36.2 min (*S*)).

Acknowledgements

The authors are grateful to Mr. Satoshi Yoshimi (Shimadzu Analytical&Measuring Center, Inc) for SEM-EDS measurement by Shimadzu SSX-550 and to Prof. A. Tsutsumi and Mr. S. Ona (The University of Tokyo) for their help in particle-size measurement.

Shinsuke Kinoshita,[a] **Fumitoshi Shibahara**‡[b] **and Kyoko Nozaki***[ab]
[a]*Department of Chemistry and Biotechnology, Graduate School of Engineering, University of Tokyo, Hongo, Bunkyo-ku,*
Tokyo 113-8656 Japan. E-mail: nozaki@chembio.t.u-tokyo.ac.jp;
Fax: (+81)-3-5841-7261; Tel: (+81)-3-5841-7261
[b]*Conversion and Control by Advanced Chemistry, PRESTO, Japan Science and Technology, 1-8, Honcho 4-Chome,*
Kawaguchi 332-0012 Japan

Notes and references

§ The particle-size difference originated from the different preparative methods. The particles are fragile and were broken in the freeze-drying processes, twice in Method A (after the polymerization and after the complex formation) and once in Method B (after the polymerization).

¶ We previously reported that leaching was not detected although the measurement limitation was in the ppm range by ICP analysis.[7,11]

1 Y. R. de Miguel, *J. Chem. Soc., Perkin Trans. 1*, 2000, 4213.
2 B. Clapham, T. S. Reger and K. D. Janda, *Tetrahedron*, 2001, **57**, 4637.
3 P. L. Osburn and D. E. Bergbreiter, *Prog. Polym. Sci.*, 2001, **26**, 2015.
4 P. Mastrorilli and C. F. Nobile, *Coord. Chem. Rev.*, 2004, **248**, 377.
5 K. Nozaki, Y. Itoi, F. Shibahara, E. Shirakawa, T. Ohta, H. Takaya and T. Hiyama, *J. Am. Chem. Soc.*, 1998, **120**, 4051.
6 F. Shibahara, K. Nozaki and T. Hiyama, *J. Am. Chem. Soc.*, 2003, **125**, 8555.
7 K. Nozaki, F. Shibahara and T. Hiyama, *Chem. Lett.*, 2000, 694–695.
8 R. Saladino, V. Neri, A. R. Pelliccia, R. Caminiti and C. Sadun, *J. Org. Chem.*, 2002, **67**, 1323.
9 S. A. Patel, S. Sinha, A. N. Mishra, B. V. Kamath and R. N. Ram, *J. Mol. Catal. A: Chem.*, 2003, **192**, 53.
10 L. Hong and E. Ruckenstein, *J. Mol. Catal.*, 1994, **90**, 303.
11 K. Nozaki, F. Shibahara, Y. Itoi, T. Ohta, H. Takaya and T. Hiyama, *Bull. Chem. Soc. Jpn.*, 1999, **72**, 1911–1918.

A chiral biselectrophile for efficient asymmetric synthesis in water†

Olle Hidestål, Rui Ding, Ann Almesåker and Ulf M. Lindström*

Received 5th October 2004, Accepted 22nd December 2004
First published as an Advance Article on the web 12th January 2005
DOI: 10.1039/b415300f

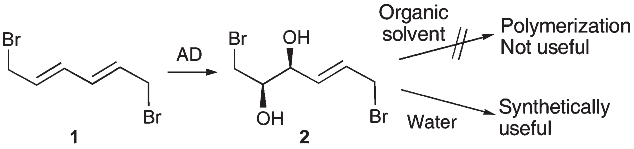
The development of an efficient asymmetric dihydroxylation of 1,6-dibromodiene afforded a chiral biselectrophilic diol that displayed highly useful reactivity in water, as demonstrated by a three-step, two-pot asymmetric synthesis of a highly functionalized tetrahydrofuran.

Water is generally considered a cheap, safe and environmentally benign alternative to unnatural solvents. Still, water has not yet become a widely accepted solvent for synthetic chemists. This may be due to concerns about aqueous solubility of organic compounds, but also about the weakly acidic, weakly basic, as well as nucleophilic character of water, which make it incompatible with many of the catalysts and reagents developed for use in inert media. In biological systems, however, essential compounds are synthesized efficiently and cleanly in water. An obvious goal for the synthetic chemist should therefore be to approximate the efficiency of biosynthetic pathways, and in the process eliminate the need for hazardous solvents, protecting group manipulations and tedious chromatographic separations. In recent years, many reagents and catalysts that effectively mediate organic reactions in aqueous media have been developed.[1]

Our research is focused on discovering unique reactivity in water, which may lead to new opportunities in the synthesis of attractive and useful target molecules. Towards this end, we would now like to report the use of dibromodiene **1** as a precursor for the chiral, biselectrophilic diol **2**, along with some preliminary studies of the reactivity of **2** in water. This diol is of potential as a versatile building block in organic synthesis. The two electrophilic sites at C1 and C6 are of orthogonal reactivity and can be used for stepwise functionalization into more complex structures. The highly functionalized, six-carbon chain also contains a double bond that can be used for metal-mediated allylation reactions or for further oxidation, an allylic alcohol that should be useful in directing such reactions to one side or the other of the olefin, and a halohydrin that can give a terminal epoxide for subsequent ring-opening reactions. Despite its attractive features, the synthesis and potential applications of **2** have so far eluded investigation, presumably because of the ease with which it polymerizes in organic solvents. Remarkably, however, we have observed that its stability towards polymerization in water is high, and it should thus be synthetically useful in aqueous media (Scheme 1).

1,6-Bishalodienes are poorly represented in the literature. In fact, the only report of **1** that we are aware of is on the manufacturing of polyenes.[2] Nevertheless, after recognizing the potential of biselectrophilic dienes as versatile, prochiral scaffolds for stereoselective synthesis in water, we decided to investigate the asymmetric dihydroxylation (AD) of **1**, which is easily accessible in one step from commercially available 1,5-hexadiene-3,4-diol.[2] The AD of **1** or similar bishalodienes has to the best of our knowledge not been reported before. Dihydroxylations of simple allylic halides have been studied, however, and they are usually troubled by side reactions such as hydrolysis of the starting material to the allylic alcohol and ring closure of the halohydrin product to give an epoxy alcohol. These pathways can be suppressed by use of a $NaHCO_3$-buffered AD-mix, which Sharpless and coworkers report to give 75–90% yields for allylic chlorides and 10–20% lower yields for the corresponding bromides.[3,4] When we applied this protocol to **1**, we indeed observed a slow turnover of starting material into diol (TLC, not complete after 48 h). However, the reported work-up protocol failed to give the desired product and only minor amounts of polymerized material could be isolated. Fortunately, the work-up procedure could be reduced to simple dilution with water and extraction with ethyl acetate. This gave a crude product that contained the desired diol **2** and the terminal epoxide **3** in a 9 : 1 ratio (Scheme 2).

In comparison, the standard, non-buffered AD-mix protocol gave **2** and **3** in a ratio of 3 : 1. Flash column chromatography easily removed small amounts of residual methansulfonamide, but diol **2** and epoxide **3** were inseparable by this method. In order to avoid tedious and costly separation processes we decided to focus



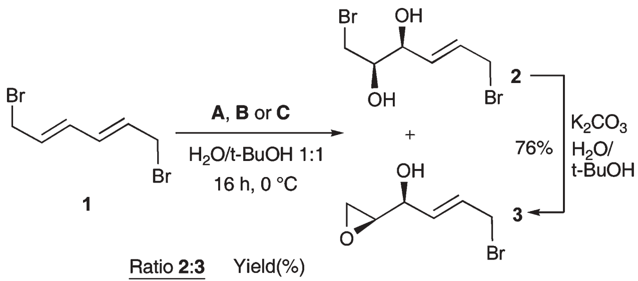
Scheme 1 The densely functionalized biselectrophile **2** has unique potential for aqueous synthesis.

Ulf M. Lindström

Dr Lindström received his PhD in 2000 at Stockholm University, Sweden. In 2000–2001, he was a post-doctoral associate in the lab of Eric T. Kool at Stanford University, California. His independent research career was initiated in early 2002 when he returned to Sweden and Lund University. In 2004 he was promoted to Associate Professor. His research interest is in the development of organic synthesis using water as reaction solvent, with particular emphasis on the discovery of new reactions, ligands and catalysts, and their application in total syntheses of attractive targets.

---

† This work was presented at the Green Solvents for Synthesis Meeting, held in Bruchsal, Germany, 3–6 October 2004.
*ulf.lindstrom@bioorganic.lth.se



	Ratio **2**:**3**	Yield(%)
(**A**)	3 : 1	60
(**B**)	9 : 1	55
(**C**)	>50 : 1	70

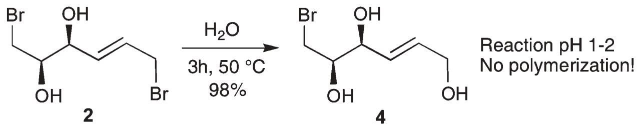
Scheme 2 Asymmetric dihydroxylation of **1**. Yield refers to combined, isolated yield of **2** and **3**. Conditions: **A**) AD-mix α **B**) AD-mix α + $NaHCO_3$ **C**) AD-mix α + $NaHCO_3$ + 1.6% OsO_4 + 3.0% $(DHQ)_2PHAL$.

on further suppressing unwanted side reactions. Careful optimization led to a procedure that employed slightly more OsO_4-catalyst (2.0%) and chiral ligand (4.0%), as well as a 3 : 2 ratio of K_2CO_3–$NaHCO_3$. This resulted in a considerably faster dihydroxylation reaction (complete in 16 h), thus minimizing the formation of epoxide, and using the modified work-up we could obtain the desired diol in 70% yield (**2** : **3** > 50 : 1, >95% purity by NMR) and excellent enantiomeric excess (96.5% ee).[5] This is consistent with the high ee's for *trans* disubstituted allylic chlorides reported by Sharpless and coworkers.[3b] Single recrystallization from hexane–toluene 4 : 1 afforded pure **2** in >99.5% ee. The absolute configuration of **2** was assigned with the help of Sharpless and coworkers' mnemonic device for predicting facial selectivity in dihydroxylation of alkenes.[6] Epoxide **3** could be prepared from **2** in 76% yield with 1 equivalent of K_2CO_3 in H_2O–*t*-BuOH (1 : 1).[7]

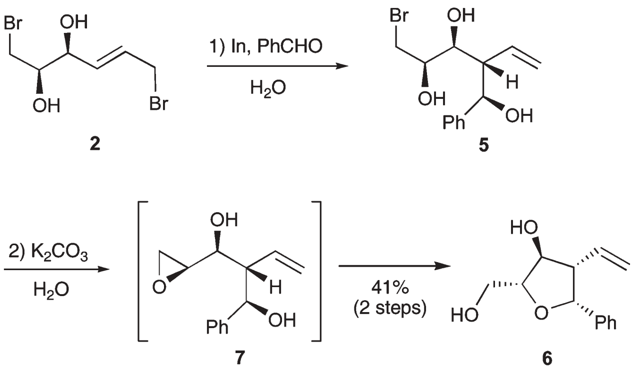
The orthogonal reactivity of the two electrophilic sites at C1 and C6 was confirmed by selective hydrolysis at the allylic position. Hence, stirring **2** in water for 3 h at 50 °C afforded **4** in 98% yield (>90% pure) following solid phase extraction (Scheme 3). It is noteworthy that during the course of the hydrolysis reaction the pH drops to about 1–2 as hydrogen bromide is formed. Still, no polymerization is observed even after 24 h. In organic media, however, compounds **2** and **4** decompose readily in the presence of even a catalytic amount of acid. This should serve to explain their limited use in organic synthesis.

To further probe the synthetic usefulness of **2** and its potential for aqueous asymmetric syntheses of more complex and attractive target structures, we investigated an indium mediated allylation of benzaldehyde. This is one of the most studied C–C bond forming reactions in water.[8] Nevertheless, the scope of this reaction in aqueous synthesis remains somewhat unclear as the vast majority of reports have been on the use of simple allylic halides.[9] Stirring **2** with equimolar amounts of indium and benzaldehyde in D_2O for 4 h gave the *anti* allylation product **5** with 91% diastereoselectivity over the other *anti* adduct (Scheme 4). No *syn* product was detected, which is consistent with the high *anti*-selectivities reported for indium mediated allylation reactions of benzaldehyde with allyl bromides containing a substituted side chain.[8]

Due to difficulties in isolating **5** in pure form, we decided to convert it directly into the more stable, cyclized tetrahydrofuran derivative **6**. Tetrahydrofurans are common subunits in many natural products and pharmacologically relevant.[10] Thus, the stereoselective preparation of functionalized THF derivatives is an ongoing concern.[11] Gratifyingly, adding 3 equivalents of K_2CO_3 to the same flask and heating for 2 h at 75 °C gave the tetrasubstituted THF, **6**, in 41% yield over 2 steps. The cyclization presumably proceeds *via* epoxide **7** initially formed from the halohydrin as shown in Scheme 2. A more elaborate study of this allylation/cyclization procedure, including its mechanistic aspects, is underway and will be described in full detail at a later stage. The absolute configuration of **6** was deduced from the configuration of the starting diol in combination with NOE experiments where, for example, strong interactions between the benzylic and allylic methine hydrogens confirmed the proposed structure.



Scheme 3 Orthogonal reactivity of the two electrophilic positions in **2**.



Scheme 4 Allylation/cyclization procedure for the preparation of **6**.

In summary, we have developed a procedure for the asymmetric dihydroxylation of 1,6-dibromohexadiene. The resulting dibromodiol is an attractive chiral building block for stereoselective synthesis in water as it displays highly useful reactivity in this media. Diastereoselective C–C bond formation to give more complex structures can be achieved as demonstrated by an indium-mediated allylation of benzaldehyde. Treatment of the allylation product with base gave an optically pure, highly substituted tetrahydrofuran in a three-step, two-pot procedure from cheap, achiral starting material. Traditional asymmetric syntheses of such structures in organic solvents will almost certainly require extensive use of various protecting groups, which inevitably leads to extra synthetic steps and more waste products. Our results promote the idea of water as a solvent that is not only cheap and green, but which may also be the solvent of choice in terms of efficiency. Our focus is now on developing the scope of 1,6-dibromodienes in aqueous asymmetric synthesis. This may lead to efficient, multistep syntheses in water, with minimal use of hazardous solvents, protecting group manipulations and chromatographic separations.

Experimental

^1H and ^{13}C NMR spectra were recorded on Bruker DRX 300 or 400 MHz using the residual peak of $CHCl_3$ (δ 7.26) in $CDCl_3$ as reference. Optical rotations, $[\alpha]_D$, were measured on a Perkin-Elmer 341 polarimeter at the sodium D line and at ambient temperature. High resolution mass spectra were recorded on a JEOL SX-102 spectrometer. Analytical thin layer chromatography was performed on Merck silica gel 60 F_{254} plates, and the plates were visualized with UV light and the phosphomolybdic acid–cerium sulfate staining reagent. Reverse solid phase filtration was performed on Sep-Pak columns purchased from Waters. Commercial reagents were used as received from the supplier.

(2*R*,3*S*,4*E*)-1,6-Dibromo-hex-4-en-2,3-diol (2)

To a solution of AD-mix α (4.8 g), potassium osmate dihydrate (19.6 mg, 0.054 mmol), $(DHQ)_2PHAL$ (78 mg, 0.100 mmol), sodium bicarbonate (1.4 g, 16.7 mmol) and methansulfonamide (320 mg, 3.34 mmol) in *tert*-butanol–water 1 : 1 (60 mL) was added (*E*,*E*)-1,6-dibromohexa-2,4-diene,[2] **1** (800 mg, 3.34 mmol), in one portion at 0 °C. The mixture was stirred vigorously with a mechanical stirrer for 16 h at 0 °C. Iced water (30 mL) was then added and stirring continued for 15 min at 0 °C. Ethyl acetate (50 mL) was added and after stirring for an additional 10 min at 0 °C, the phases were separated. The aqueous phase was extracted once again with ethyl acetate (50 mL), and the combined organics washed with brine and dried over sodium sulfate. Concentration afforded a crude product which was taken up in chloroform and the insoluble material was removed by filtration. The filtrate was concentrated and the chloroform precipitation procedure was repeated. Concentration then gave 640 mg (2.34 mmol, 70%) of >95% pure **2** according to ^1H NMR. Recrystallization from hexane–toluene (4 : 1) afforded analytically pure **2**, mp 75–76 °C; $[\alpha]_D$ −18.6 (c = 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 6.11 (m, 1H), 5.84 (dd, J = 15.2, 6.5 Hz, 1H), 4.30 (m, 1H), 4.35 (m, 1H), 3.99 (d, J = 7.8 Hz, 2H), 3.75 (m, 1H), 3.60 (dd, J = 10.6, 4.3 Hz, 1H), 3.46 (dd, J = 10.6, 6.5 Hz, 1H), 2.62 (br d, J = 5.4 Hz, 1H), 2.38 (br d, J = 3.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.0, 129.9, 73.5, 72.6, 35.1, 31.3; HRMS (FAB+) calcd for $C_6H_{10}Br_2NaO_2$ (M + Na): 294.8945, found: 294.8943.

(2*E*,4*S*,5*R*)-6-Bromo-hex-2-en-1,4,5-triol (4)

Dibromide **2** (70 mg, 0.255 mmol) was stirred in water (4 mL) for 18 h at room temperature. The acidic solution was neutralized with solid $NaHCO_3$ (21 mg, 0.255 mmol). Filtration through a C18 reverse phase plug (5 g) using water then methanol as eluent afforded 90–95% pure **4** (53 mg, 98%) after concentration of appropriate fractions. This procedure can be completed in only 3 h at 50 °C without compromising the yield. A pure sample was obtained by flash column chromatography on silica gel (ethyl acetate–methanol 95 : 5), mp 77–78 °C; $[\alpha]_D$ −34.1 (c = 5.3 in MeOH); ^1H NMR ($CDCl_3$, 300 MHz) δ 6.05 (ddt, J = 15.7, 5.0, 1.0 Hz, 1H), 5.80 (ddt, J = 15.6, 6.6, 1.6 Hz, 1H), 4.27 (t, J = 5.7 Hz, 1H), 4.23 (d, J = 4.8 Hz, 2H), 3.75 (m, 1H), 3.60 (dd, J = 10.6, 4.3 Hz, 1H), 3.47 (dd, J = 10.6, 6.6 Hz, 1H), 2.72 (br s, 1H), 2.42 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 133.3, 129.0, 73.6, 73.1, 62.6, 35.3; HRMS (ES+) calcd for $C_6H_{11}O_3BrNa$ (M + Na) 232.9792, found 232.9822.

(1*R*)-1,4-anhydro-2-deoxy-1-phenyl-2-vinyl-*D*-arabinitol (6)

Dibromide **2** (40 mg, 0.146 mmol), benzaldehyde (15 µL, 0.146 mmol) and finely powdered indium (17 mg, 0.146 mmol) was stirred in D_2O (1.6 mL) at room temperature. After 4 h 30 min, NMR showed complete reaction. Then, K_2CO_3 (61 mg, 0.438 mmol) was added and the reaction mixture was heated to 75 °C. After 2 h, TLC (heptane–ethyl acetate 1 : 1) showed complete reaction and the mixture was allowed to cool to room temperature. The reaction mixture was applied on a C18 reverse phase column (5 g) and eluted, first with water and then with methanol. The fractions containing product were combined and the methanol was evaporated. The aqueous residue was freeze dried and the crude product purified by flash chromatography on a silica gel column (heptane–ethyl acetate 3 : 1 → 1 : 1), which afforded 18 mg (41%) of pure **6** as an oil, $[\alpha]_D$ −25.6 (c = 5.1 in CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 7.36–7.18 (m, 5H), 5.29 (d, J = 8.1 Hz, 1H), 5.18 (dt, J = 17.0, 9.8 Hz, 1H), 5.04 (dd, J = 17.0, 1.9 Hz, 1H), 4.96 (dd, J = 10.0, 1.9 Hz, 1H), 4.13 (t, J = 6.4 Hz, 1H), 4.00 (m, 1H), 3.89 (m, 2H), 3.06 (dt, J = 8.7, 6.4 Hz, 1H), 2.26 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.7, 135.7, 128.6, 127.9, 127.1, 118.3, 84.6, 82.5, 76.7, 63.0, 57.7; HRMS (ES+) calcd for $C_{13}H_{16}O_3Na$ (M + Na): 243.0997, found: 243.1022.

Acknowledgements

Financial support came from the Swedish Research Council and the Crafoord Foundation. RD acknowledges a post-doc stipend from the Carl Trygger Foundation.

Olle Hidestål, Rui Ding, Ann Almesåker and Ulf M. Lindström*
Organic Chemistry, Center for Chemistry and Chemical Engineering, Lund University, P. O. Box 124, SE-221 00 Lund, Sweden.
E-mail: ulf.lindstrom@bioorganic.lth.se; Fax: (+46) 46 2228209;
Tel: (+46) 46 2228211

References

1 (*a*) U. M. Lindström, *Chem. Rev.*, 2002, **102**, 2751–2771; (*b*) *Organic Synthesis in Water*, ed. P. A. Grieco, Blackie Academic & Professional, London, 1998; (*c*) C. J. Li and T. H. Chan, *Organic Reactions in Aqueous Media*, John Wiley & Sons, New York, 1997.
2 C. W. Spangler, R. K. McCoy, A. A. Dembek, L. S. Sapochak and B. D. Gates, *J. Chem. Soc., Perkin Trans. 1*, 1989, 151–154.
3 (*a*) H. C. Kolb, Y. L. Bennani and K. B. Sharpless, *Tetrahedron: Asymmetry*, 1993, **4**, 133–141; (*b*) K. P. M. Vanhessche, Z. M. Wang and K. B. Sharpless, *Tetrahedron Lett.*, 1994, **35**, 3469–3472.
4 Attempts to synthesize the corresponding 1,6-dichlorodiene failed because polymerization could not be avoided. Only a theoretical report of this compound exists in the literature: G. Park, *Bull. Korean Chem. Soc.*, 2003, **24**, 265–266.
5 Apart from traces of epoxide **3**, the only observable contamination after the modified work-up procedure is 1–5% of methansulfonamide. The ee of **2** was determined by chiral HPLC using a Chiralpak AD–H column with 15% *tert*-butanol in heptane as eluent. The major isomer eluted at 32 min and the minor at 28 min. A reference sample containing both enantiomers was prepared by performing the AD reaction with equal amounts of α- and β-mix. The use of *tert*-butanol as co-eluent is crucial. Other alcohols gave decomposition of **2** on the column.
6 H. C. Kolb, M. S. VanNieuwenhze and K. B. Sharpless, *Chem. Rev.*, 1994, **94**, 2483–2547.
7 Epoxide **3** is more labile than the starting dibromide and any unnecessary storage and handling should be avoided.
8 C. J. Li and T. H. Chan, *Tetrahedron*, 1999, **55**, 11149–11176.
9 For another indium mediated allylation using highly functionalized allyl bromides, see: Y. Canac, E. Levoirier and A. Lubineau, *J. Org. Chem.*, 2001, **66**, 3206–3210.
10 (*a*) H. Araya, M. Sahai, S. Singh, A. K. Singh, M. Yoshida, N. Hara and Y. Fujimoto, *Phytochemistry*, 2002, **61**, 999–1004; (*b*) E. Peris, A. Cavé, E. Estornell, M. C. Zafra-Polo, B. Figadère, D. Cortes and A. Bermejo, *Tetrahedron*, 2002, **58**, 1335–1342; (*c*) S. H. Sung, M. S. Huh and Y. C. Kim, *Chem. Pharm. Bull.*, 2001, **49**, 1192–1194.
11 (*a*) S. M. Miles, S. P. Marsden, R. J. Leatherbarrow and W. J. Coates, *J. Org. Chem.*, 2004, **69**, 6874–6882; (*b*) P. K. Mandal, G. Maiti and S. C. Roy, *J. Org. Chem.*, 1998, **63**, 2829–2834; (*c*) Z. M. Wang and M. Shen, *J. Org. Chem.*, 1998, **63**, 1414–1418.

The Pt(II)-catalyzed Baeyer–Villiger oxidation of cyclohexanone with H_2O_2 in ionic liquids†

Valeria Conte,*[a] Barbara Floris,[a] Pierluca Galloni,[a] Valentina Mirruzzo,[a] Alessandro Scarso,[b] Daniela Sordi[a] and Giorgio Strukul[b]

Received 9th November 2004, Accepted 3rd February 2005
First published as an Advance Article on the web 14th February 2005
DOI: 10.1039/b416923a

The Pt(II)-catalyzed Baeyer–Villiger oxidation of cyclohexanone with H_2O_2 in a two-phase system, H_2O–IL, is a viable procedure, characterized by synthetically interesting yields, better than those of the same reaction in H_2O–halogenated solvents.

Introduction

The Baeyer–Villiger oxidation of ketones to esters has been largely used in organic synthesis, in that it can occur in the presence of a number of functional groups, is stereoselective, and shows a regiochemical preference for the migrating group.[1] The importance of the reaction is demonstrated by the large number of papers that, also recently, dealt with, *inter alia*, the mechanism,[2,3] theoretical investigations,[4–6] the synthesis of α-fluorinated esters,[7] and the stereochemical output.[8–10]

However, in the classical procedure, the Baeyer–Villiger oxidation suffered, from the environmental point of view, from two major drawbacks, because organic peracids and halogenated solvents had to be used. Thus, many attempts have been made to move towards greener procedures, as recently reviewed.[11] New oxidant systems were tested, among which enzymes and hydrogen peroxide were the green choice. Monooxygenases from different sources[12–15] or whole cells[16–19] were used, with interesting results, especially with respect to enantioselective biocatalysis. As for H_2O_2, it needs to be activated. Several heterogeneous catalysts,[20–24] selenium compounds,[25,26] and metal complexes[27–29] have been used. Also, the use of a fluorous biphasic system[30] and a nanoflow system with fluorous lanthanide catalyst[31] were reported. Among metal catalysts, platinum(II) complexes with chelating diphosphines gave good results,[32] although a chlorinated solvent was still necessary. To explore the possibility of moving towards a more sustainable process, we investigated the Baeyer–Villiger oxidation of cyclohexanone (a substrate that reacted with difficulty with the Pt(II) catalysts in 1,2-dichloroethane) with hydrogen peroxide, catalyzed by Pt(II) complexes, in ionic liquids (ILs). In fact, ILs have been proposed as novel and environmentally benign reaction media for several organic syntheses.[33–36] *N*-alkylpyridium and *N*,*N*′-dialkyl imidazolium cations coupled with a variety of inorganic anions have been used as suitable solvents for several organic reactions as well as in catalytic processes: Friedel–Craft reactions,[37,38] Diels–Alder cycloadditions,[39–44] metal-catalyzed hydrogenations,[45–49] epoxidation[50–52] and bromination of double and triple bonds[53] are just a few examples in this quite new field. To the best of our knowledge, only three papers reported Baeyer–Villiger oxidation in commercial ionic liquids, but one[54] used the dangerous *m*-chloroperbenzoic acid as oxidant, while cyclohexanone was unreactive under the conditions of the second.[55] The third paper reports the heterogeneously catalyzed oxidation of arylketones.[56] In the present investigation ILs with differently substituted imidazolium cations and with different anions were tested, with the aim of comparing hydrophobic and hydrophilic ionic liquids.[57]

---

† This work was presented at the Green Solvents for Synthesis Meeting, held in Bruchsal, Germany, 3–6 October 2004.
*valeria.conte@uniroma2.it

Front row from left 1: Floris; 2: Sordi; 4: Conte; 5: Mirruzzo. Back row from left 1: Galloni.

Valeria Conte gained her Laurea degree in Chemistry in 1982 and a PhD in Chemical Sciences in 1987, both at Padova University, under the supervison of Prof. G. Modena. From 1985–86 she was also a PhD student with Prof. J. K. Stille, CSU Fort Collins Co., USA. A CNR Fellow from 1987–1988, she became a CNR researcher at "CNR Centro Meccanismi Reazioni Organiche" Padova University (1988–98), including a period as a NATO-CNR senior fellow at CSU Fort Collins Co., USA (1993). From 1998–2001 she was Associate Professor of Organic Chemistry at Foggia University and is currently Associate Professor of Organic Chemistry at Tor Vergata University, Rome (2001–present). Her main research interests include reaction mechanisms of metal-catalyzed oxidation with peroxides, vanadium dependent bromoperoxidases mimicking systems and oxidation reactions in ionic liquids.

Results and discussion

The oxidation reactions were carried out mostly at room temperature, under an inert atmosphere (argon). $[Pt(dppd)(\mu\text{-}OH)]_2(BF_4)_2$ (dppb = 1,4-bis(diphenylphosphino)butane) was used as catalyst (Fig. 1), since it was shown that, the larger the P–Pt–P angle, the more effective the catalyst.[58]

Actually, the inert atmosphere is not strictly necessary as far as the Baeyer–Villiger oxidation is concerned, but is desirable for prolonging the catalyst life especially in view of a possible recycle. Cyclohexanone was chosen as the substrate, because its reaction in the organic solvent gave poor yields due to extensive formation of 1,1′-dihydroxy dicyclohexylperoxide,[59] as a parallel undesired reaction promoted by the acidity of commercial H_2O_2 solutions. Therefore any improvement is valuable. In this and similar BV reactions, the role of the Pt complex is crucial, since, in its absence, no oxidation occurs.[29]

The reaction was carried out using the different hydrophilic and hydrophobic ILs in order to identify, first of all, which system, homogeneous *versus* a two-phase one, is superior. The two-phase option is obviously due, as in the case of the chlorinated solvents, to the use of aqueous solutions of hydrogen peroxide as primary oxidant. The ILs were chosen on the basis of their availability and stability in the presence of an oxidant and water. It is to be noted that in several cases irreproducible results were obtained by using different samples of commercial ILs. This fact is likely due to an insufficient purity of the samples used. Such an aspect has been already addressed on other occasions by several authors.[57] Therefore, in order to have ILs with appropriate purity we synthesized our solvents with a two step synthesis. The first was a quaternization reaction between an alkyl substituted imidazole and an alkyl bromide, to obtain a solid precursor. The second was a metathesis reaction in which the bromide ion was exchanged with an appropriate anion able to give a liquid product at room temperature. Both these steps were executed following literature procedures[60–64] with appropriate modifications.[65] Characterization of ionic liquids was made by ^1H NMR and their identity was confirmed by comparison with literature data.[53] In the course of our study we used 1-butyl-3-methylimidazolium, $[bmim^+]$, 1-ethyl-3-methylimidazolium, $[emim^+]$, 1-hexyl-3-methylimidazolium, $[hmim^+]$, and 1-butyl-2,3-dimethylimidazolium, $[bm_2im^+]$, cations and tetrafluoborate, $[BF_4^-]$, hexafluorophosphate, $[PF_6^-]$, triflate, $[CF_3SO_3^-]$, and bis(trifluoromethanesulfonyl)imide anions, $[(CF_3SO_2)_2N^-]$. The structures of ILs tested for performing the title reaction are collected in Fig. 2.

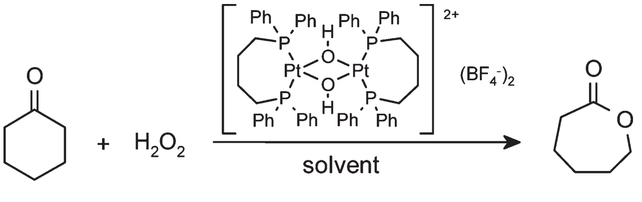


Fig. 1 The Pt(II)-catalyzed Baeyer–Villiger oxidation of cyclohexanone.

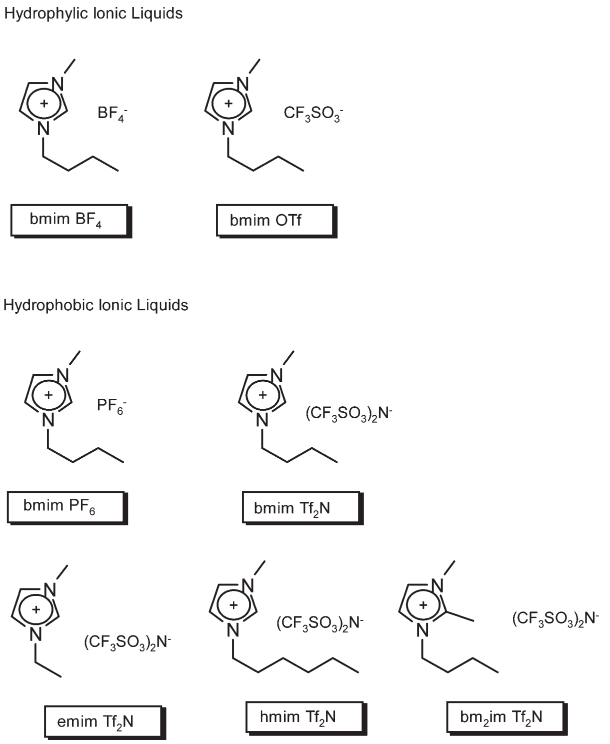


Fig. 2 Ionic liquids used as solvents for the Pt(II)-catalyzed Baeyer–Villiger oxidation of cyclohexanone.

First, the reaction was performed in homogeneous phase, using butylmethylimidazolium tetrafluoborate and triflate. The results are in Table 1, together with the reference reaction in chloroform and the literature for comparison.

The reaction in hydrophilic ILs was faster than that in chloroform, but gave poor results, likely due to a deactivation of the catalyst. Thus, hydrophobic ILs were tested, with the same cation and different anions (Table 2). In this case, the reaction time was even shorter, yields increased, and Tf_2N was the counterion with best results, with a lactone yield twice that in chlorinated solvents. Preliminarily, a $^{31}P\{^1H\}$ NMR experiment was carried out in order to determine the actual presence of $[Pt(dppd)(\mu\text{-}OH)]_2(BF4)_2$ catalyst in the IL. The complex (22 mg) was mixed with bmim Tf_2N (1 ml) followed by 0.31 ml of cyclohexanone. Under these conditions the complex is only sparingly soluble in the IL phase. The NMR spectrum of the IL

Table 1 Pt(II)-catalyzed Baeyer–Villiger oxidation of cyclohexanone with H_2O_2 in hydrophilic ionic liquids, at room temperature

Solvent	Reaction time/min	Yield of lactone (%)	Reactants ratio[a] substr. : H_2O_2 : cat.
bmim BF_4	300	5	200 : 100 : 1.5
bmim OTf	180	4	200 : 100 : 1.5
$CHCl_3$	450	10	200 : 100 : 1.0
CH_2Cl_2[59]	250	*ca.* 10	200 : 100 : 1.0[b]

[a] [cyclohexanone] = 3 M, $[H_2O_2]$ = 1.5 M, [cat] = 2.3×10^{-2} M. [b] [cyclohexanone] = 7.5 M, $[H_2O_2]$ = 3.75 M, [cat] = 7.5×10^{-3} M, cat = $(dppe)PtCF_3$, dppe = diphenylphosphinoethane.

Table 2 Pt(II)-catalyzed Baeyer–Villiger oxidation of cyclohexanone with H_2O_2 in hydrophobic ionic liquids, at room temperature

Solvent	Reaction time/min	Yield of lactone (%)	Reactants ratio[a] substr. : H_2O_2 : cat.
bmim PF_6	60	8	200 : 100 : 1.0
bmim Tf_2N	60	24	200 : 100 : 1.0
$CHCl_3$	450	10	200 : 100 : 1.0

[a] [cyclohexanone] = 3 M, [H_2O_2] = 1.5 M, [cat] = 1.5 × 10^{-2} M.

phase showed the presence of the complex (δ 4.7 ppm, ${}^1J$ P–Pt 3550 Hz).[58] After addition of 35% H_2O_2 (0.13 ml) the mixture was stirred for 18 h. A new sample of the IL phase was dissolved in $CDCl_3$. The new spectrum showed, in addition to the starting complex, the presence of dppb dioxide (δ 34.9 ppm) in approximately a 1 : 1 ratio.

Subsequently, the importance of the cation was checked, keeping Tf_2N as the anion and varying the length and the number of imidazolium alkyl chains. As can be seen from the results in Table 3, the different cations affected the reaction time more than the yield of lactone.

The output of the oxidation was then investigated as a function of the reactants concentration, while keeping their ratio constant (Table 4). Also here, the variation of initial concentrations affected the reaction time more than the caprolactone formation. It should be pointed out that, under the conditions reported in Tables 1–4, blank experiments carried out in the absence of catalyst gave no conversion. Additionally, when in selected experiments carried out at room temperature conversion of the substrate has been quantitatively calculated, it has been found that it never exceeds 35% which compares well with literature data.[58]

Finally, the effect of the catalyst amount, other conditions being equal, was investigated. The results are collected in Table 5. Of course, higher percents of the catalyst sped up the reaction. However, the yields of lactone remained the same, within experimental error.

To summarize the results, it is possible to say that the Pt(II)-catalyzed Baeyer–Villiger oxidation of cyclohexanone with hydrogen peroxide improves when performed in ionic liquids, not only in terms of avoiding halogenated solvents, but also in terms of reduced reaction times and increased yields. The specific imidazolium cation seems relatively important and the anion plays a major role, bis(trifluoromethanesulfonyl)imide being the counterion that consistently gives higher yields.

In order to verify, still at a preliminary stage, the performance of our methodology with other cyclic ketones, 2-methyl-cyclohexanone has been reacted under the conditions described in Table 4, second entry. The results are promising considering that 50% yield was obtained using [$bmim^+$][$(CF_3SO_2)_2N^-$] at room temperature. Further studies with this and other substrates are warranted.

To complete the investigation of the parameters potentially affecting the reactivity, an experiment was performed at 40 °C,

Table 3 Pt(II)-catalyzed Baeyer–Villiger oxidation of cyclohexanone with H_2O_2 in different bis(trifluoromethanesulfonyl)imides, at room temperature

Solvent	Reaction time/min	Yield of lactone (%)	Reactants ratio[a] substr. : H_2O_2 : cat.
emim Tf_2N	215	16	200 : 100 : 1.0
bmim Tf_2N	60	24	200 : 100 : 1.0
hmim Tf_2N	60	19	200 : 100 : 1.0
bm_2im Tf_2N	75	17	200 : 100 : 1.0

[a] [cyclohexanone] = 3 M, [H_2O_2] = 1.5 M, [cat] = 1.5 × 10^{-2} M.

Table 4 Pt(II)-catalyzed Baeyer–Villiger oxidation of cyclohexanone with H_2O_2 bmim Tf_2N, with different concentrations,[a] at room temperature

[ketone]/M	[H_2O_2]/M	10^2 × [cat.]/M	Reaction time/min	Yield of lactone (%)
3.0	1.5	1.50	60	24
0.85	0.5	0.50	120	23
0.48	0.3	0.26	210	18

[a] Substrate : H_2O_2 : catalyst = 200 : 100 : 1.0.

Table 5 Pt(II)-catalyzed Baeyer–Villiger oxidation of cyclohexanone with H_2O_2 in different ILs, with different amount of catalyst, at room temperature

Solvent	Reactants ratio[a]	10^2 × [cat.]/M	React. time/min	Yield of lactone (%)
bmim PF_6	(A)	1.5	60	8
	(B)	2.3	30	9
emim Tf_2N	(A)	1.5	215	16
	(B)	2.3	120	15
bmim Tf_2N	(A)	1.5	60	24
	(B)	2.3	30	25

[a] [cyclohexanone] = 3 M, [H_2O_2] = 1.5 M; (A), substrate : H_2O_2 : catalyst = 200 : 100 : 1.0; (B), substr. : H_2O_2 : cat. = 200 : 100 : 1.5.

Table 6 Pt(II)-catalyzed Baeyer–Villiger oxidation of cyclohexanone with H_2O_2 in bmim Tf_2N at different temperatures[a]

Temperature/°C	Reaction time/min	Yield of lactone (%)
20	120	23
40	120	47
40	120	31[b]

[a] [cyclohexanone] = 0.85 M, [H_2O_2] = 0.5 M, [catalyst] = 5 × 10^{-3} M. [b] Second run with the same IL–catalyst sample.

where the yield in lactone increased up to 47%, within 120 min (Table 6). The reaction reported in the second entry of Table 6 was replicated three more times with fresh reagents and identical results within experimental error. The data so obtained are not reported in the Table.

Moreover, we attempted a recycle of the IL–catalyst system. After 2 hours at 40 °C, the reaction mixture was extracted with diethyl ether, dried under vacuum, added to the same amount of cyclohexanone and H_2O_2. From the second run, 31% lactone was still recovered (see Table 6, second run with the same IL–catalyst sample).

In conclusion, the Pt(II)-catalyzed oxidation of cyclohexanone by hydrogen peroxide significantly improved when performed in ionic liquids, resulting in a reaction that was faster and more efficient than in organic solvents. It is difficult to attribute such an improvement to a particular macroscopic property of the ILs used, because the different imidazolium cations used behaved similarly. The yield of lactone increased with temperature and, despite the sensitivity of the catalyst to prolonged exposure to hydrogen peroxide, recycling of the IL–catalyst system was practicable. It is reasonable to expect even better results with more reactive ketones.

Experimental

The ionic liquids, synthesized *ad hoc*, were dried under vacuum (0.5 mm Hg) at 80 °C for 2–4 h and fluxed with argon before use. The reaction was followed by gas chromatography, using decane as the external standard. Response factors for cyclohexanone and caprolactone were obtained as the slope of the straight line obtained plotting $\text{Area}_{\text{ketone}}/\text{Area}_{\text{decane}}$ (or $\text{Area}_{\text{lactone}}/\text{Area}_{\text{decane}}$) values *vs.* [ketone]/[decane] (or [lactone]/[decane]) values, obtained from a number of solutions of known concentration. All measures were repeated at least three times.

In a typical experiment, the Pt catalyst was weighed in a Schlenk tube, under argon atmosphere, and was added to 1 mL IL and a known volume of cyclohexanone, previously fluxed with argon. A 100 μL sample was taken and added to a 1 mL flask contaning a known amount of decane, dissolved with chloroform, and examined by GC, in order to obtain the initial concentration of the substrate. A known volume of titrated 35% H_2O_2 was added and the reaction was followed by GC, monitoring the decrease of ketone and the increase of lactone, until the concentration of the latter reached a plateau. All the reactions were repeated at least three times and were reproducible within experimental error.

Acknowledgements

Financial support from MIUR, Prin 2003 Project "Development of new recyclable catalysts for oxidation processes with hydrogen peroxide" is gratefully acknowledged.

Valeria Conte,*[a] Barbara Floris,[a] Pierluca Galloni,[a] Valentina Mirruzzo,[a] Alessandro Scarso,[b] Daniela Sordi[a] and Giorgio Strukul[b]
[a]*Dipartimento di Scienze e Tecnologie Chimiche, Università di Roma "Tor Vergata", via della Ricerca Scientifica, 00133, Roma, Italy. E-mail: valeria.conte@uniroma2.it; Fax: +39 06 72594 328; Tel: +39 06 72594 014*
[b]*Dipartimento di Chimica, Università di Venezia, Dorsoduro 2137, 30123 Venezia, Italy. E-mail: strukul@unive.it; Fax: +39 041 2348517; Tel: +39 041 2348931*

References

1 G. R. Krow, in *Comprehensive Organic Synthesis*, ed. B. M. Trost and I. Fleming, Pergamon Press, Oxford, 1991, Vol. **7**, pp. 671–688.
2 C. M. Crudden, A. C. Chen and L. A. Calhoun, *Angew. Chem., Int. Ed.*, 2000, **39**, 2851–2855.
3 A. Berkessel, M. R. M. Andreae, H. Schmickler and J. Lex, *Angew. Chem., Int. Ed.*, 2002, **41**, 4481–4484.
4 Y. Itoh, M. Yamanaka and K. Mikami, *Org. Lett.*, 2003, **5**, 4803–4806.
5 R. R. Sever and T. W. Root, *J. Phys. Chem. B*, 2003, **107**, 10521–10530.
6 R. R. Sever and T. W. Root, *J. Phys. Chem. B*, 2003, **107**, 10848–10862.
7 S. Kobayashi, H. Tanaka, H. Amii and K. Uneyama, *Tetrahedron*, 2003, **59**, 1547–1552.
8 S. Stončius, U. Berg and E. Butkus, *Tetrahedron: Asymmetry*, 2004, **15**, 2405–2413.
9 K. Ito, A. Ishii, T. Kuroda and T. Katsuki, *Synlett.*, 2003, 643–646.
10 S.-I. Murahashi, S. Ono and Y. Imada, *Angew. Chem., Int. Ed.*, 2002, **41**, 2366–2368.
11 G.-J. Ten Brink, I. W. C. E. Arends and R. A. Sheldon, *Chem. Rev.*, 2004, **104**, 4105–4123.
12 M. T. Reetz, B. Brunner, T. Schneider, F. Schulz, C. M. Clouthier and M. M. Kayser, *Angew. Chem., Int. Ed.*, 2004, **43**, 4075–4078 and references therein.
13 M. T. Reetz, F. Daligault, B. Brunner, H. Hinrichs and A. Deege, *Angew. Chem., Int. Ed.*, 2004, **43**, 4078–4081.
14 S. Wang, M. M. Kayser, H. Iwaki and P. C. K. Lau, *J. Mol. Catal. B: Enzym.*, 2003, **22**, 211–218.
15 B. G. Kyte, P. Rouvière, Q. Cheng and J. D. Stewart, *J. Org. Chem.*, 2004, **69**, 12–17.
16 J. D. Carballeira, E. Álvarez and J. V. Sinisterra, *J. Mol. Catal. B: Enzym.*, 2004, **28**, 25–32.
17 M. D. Mihovilovic, F. Rudroff, W. Kandioller, B. Grötzl, P. Stanetty and H. Spreitzer, *Synlett.*, 2003, 1973–1976.
18 M. C. Gutiérrez, V. Alphand and R. Furstoss, *J. Mol. Catal. B: Enzym.*, 2003, **21**, 231–238.
19 P. L. A. Overbeeke, P. Schenkels, F. Secundo and J. A. Jongejan, *J. Mol. Catal. B: Enzym.*, 2003, **21**, 51–53.
20 R. Duchateau, T. W. Dijkstra, J. R. Severn, R. A. van Santen and I. V. Korobkov, *Dalton Trans.*, 2004, 2677–2682.
21 U. R. Pillai and E. Shale-Demessie, *J. Mol. Cat. A: Chem.*, 2003, **191**, 93–100.
22 A. Corma, M. T. Navarro and M. Renz, *J. Catal.*, 2003, **219**, 242–246.
23 M. Renz, T. Blasco, A. Corma, V. Fornés, R. Jensen and L. Nemeth, *Chem. Eur. J.*, 2002, **8**, 4708–4717.
24 C. Palazzi, F. Pinna and G. Strukul, *J. Mol. Cat. A: Chem.*, 2000, **151**, 245–252.
25 Y. Miyake, Y. Nishibayashi and S. Uemura, *Bull. Chem. Soc. Jpn.*, 2002, **75**, 2233–2237.
26 G.-J. Ten Brink, J.-H. Vis, I. W. C. E. Arends and R. A. Sheldon, *J. Org. Chem.*, 2001, **66**, 2429–2433.
27 C.-M. Che and J.-S. Huang, *Coord. Chem. Rev.*, 2003, **242**, 97–113 and references therein.
28 G. Strukul, *Top. Catal.*, 2002, **19**, 33–42.
29 G. Strukul, *Angew. Chem., Int. Ed.*, 1998, **37**, 1198–1209.
30 X. Hao, O. Yamazaki, A. Yoshida and J. Nishikido, *Tetrahedron Lett.*, 2003, **44**, 4977–4980.
31 K. Mikami, Md. N. Islam, M. Yamanaka, Y. Itoh, M. Shinoda and K. Kudo, *Tetrahedron Lett.*, 2004, **45**, 3681–3683.
32 A. Brunetta and G. Strukul, *Eur. J. Inorg. Chem.*, 2004, 1030–1038 and references therein.
33 C. Chiappe and D. Pieraccini, *J. Phys. Org. Chem.*, 2005, in press.
34 T. Welton, *Chem. Rev.*, 1999, **99**, 2071–2083.
35 P. Wasserscheid and W. Keim, *Angew. Chem. Int., Ed.*, 2000, **39**, 3772–3789.

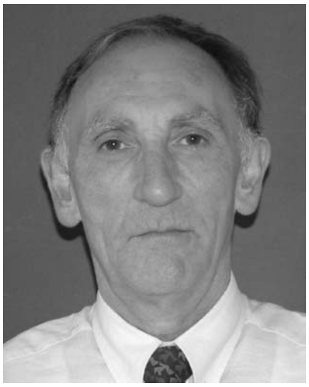
36 R.A. Sheldon, *Chem. Commun.*, 2001, 2399–2407.
37 P. U. Naik, S. J. Nara, J. R. Harjani and M. M. Salunkhe, *Can. J. Chem.*, 2003, **10**, 1057–1060.
38 J. A. Boon, J. A. Levisky, J. L. Pflug and J. S. Wilkes, *J. Org. Chem.*, 1986, **51**, 480–483.
39 I. Meracz and T. Oh, *Tetrahedron Lett.*, 2003, **44**, 6465–6468.
40 A. Behr, F. Naendrup and S. Nave, *Eng. Life Sci.*, 2003, **8**, 325–327.
41 J. S. Yadav, B. V. S. Reddy, J. S. S. Reddy and R. S. Rao, *Tetrahedron*, 2003, **59**, 1599–1604.
42 J. S. Yadav, B. V. S. Reddy, K. U. Gayathri and A. R. Prasad, *Synthesis*, 2002, 2537–2541.
43 I. Hemeon, C. Deamicis, H. Jenkins, P. Scammells and R. D. Singer, *Synlett.*, 2002, 1815–1818.
44 J. Howarth, K. Hanlon, D. Fayne and P. Mc Cormac, *Tetrahedron Lett.*, 1997, **38**, 3097–3100.
45 E. T. Silveira, A. P. Umpierre, L. M. Rossi, G. Machado, J. Morais, G. V. Soares, I. J. R. Baumvol, S. R. Teixeira, P. F. P. Fichtner and J. Dupont, *Chem. Eur. J.*, 2004, **10**, 3734–3740.
46 G. S. Fonseca, A. P. Umpierre, P. F. P. Fichtner, S. R. Teixeira and J. Dupont, *Chem. Eur. J.*, 2003, **9**, 3263–3269.
47 P. J. Dyson, *Appl. Organomet. Chem.*, 2002, **16**, 495–500.
48 C. P. Menhert, E. J. Mozeleski and R. A. Cook, *Chem. Commun.*, 2002, 3010–3011.
49 Y. Chauvin, L. Mussmann and H. Oliver, *Angew. Chem., Int. Ed.*, 1995, **34**, 2698–2700.
50 O. Bortolini, V. Conte, C. Chiappe, G. Fantin, M. Fogagnolo and S. Maietti, *Green Chem.*, 2002, **4**, 94–96.
51 O. Bortolini, S. Campestrini, V. Conte, G. Fantin, M. Fogagnolo and S. Maietti, *Eur. J. Org. Chem.*, 2003, 4804–4809.
52 C. E. Song and E. J. Roh, *Chem. Commun.*, 2000, 837–838.
53 C. Chiappe, V. Conte and D. Pieraccini, *Eur. J. Org. Chem.*, 2002, 2831–2837.
54 J. S. Yadav, B. V. S. Reddy, A. K. Basak and A. V. Narsaiah, *Chem. Lett.*, 2004, **33**, 248–249.
55 R. Bernini, A. Coratti, G. Fabrizi and A. Goggiamani, *Tetrahedron Lett.*, 2003, **44**, 8991–8994.
56 S. P. Panchgalle, U. R. Kalkote, P. S. Niphadkar, P. N. Joshi, S. P. Chavan and G. M. Chaphekar, *Green Chem.*, 2004, **6**, 308–309.
57 P. Wasserscheid and T. Welton, *Ionic Liquids in Synthesis*, Wiley-VCH, Weinheim, 2003.
58 R. Gavagnin, M. Cataldo, F. Pinna and G. Strukul, *Organometallics*, 1998, **17**, 661–667.
59 M. Del Todesco Frisone, F. Pinna and G. Strukul, *Organometallics*, 1993, **12**, 148–156.
60 V. Farmer and T. Welton, *Green Chem.*, 2002, **4**, 97–102.
61 G. S. Owens and M. M. Abu Omar, *J. Mol. Cat. A: Chem.*, 2002, **187**, 215–225.
62 P. A. Z. Suarez, J. E. L. Dullius, S. Einloft, R. F. de Souza and J. Dupont, *Polyhedron*, 1996, **15**, 1217–1219.
63 P. A. Z. Suarez, S. Einloft, J. E. L. Dullius, R. F. De Souza and J. Dupont, *J. Chim. Phys.*, 1998, 1626–1639.
64 L. Cammarata, S. G. Kazarian, P. A. Salter and T. Welton, *Phys. Chem. Chem. Phys.*, 2001, **3**, 5192–5200.
65 V. Conte, B. Floris, P. Galloni, V. Mirruzzo, A. Silvagni and D. Sordi, submitted.

Green solvents for sustainable organic synthesis: state of the art†

Roger A. Sheldon

Received 2nd December 2004, Accepted 17th February 2005
First published as an Advance Article on the web 8th March 2005
DOI: 10.1039/b418069k

The growing awareness of the pressing need for greener, more sustainable technologies has focused attention on the use of atom efficient catalytic methodologies for the manufacture of fine chemicals and pharmaceuticals. Another aspect which is receiving increasing attention is the use of alternative reaction media that circumvent the problems associated with many of the traditional volatile organic solvents. The use of nonconventional reaction media also provides opportunities for facilitating the recovery and recycling of the catalyst. The state of the art in the use of alternative reaction media for green, sustainable organic synthesis is reviewed. Liquid–liquid biphasic catalysis provides an industrially attractive method for the recovery and recycling of catalysts as an alternative to the more traditional solid heterogeneous catalysts. Various approaches to liquid–liquid biphasic catalysis—aqueous biphasic, fluorous biphasic, supercritical carbon dioxide, ionic liquids and various combinations thereof—are reviewed and compared. "The best solvent is no solvent" but if a solvent is needed then water has a lot to recommend it and catalysis in aqueous biphasic systems is an industrially attractive methodology which has found broad application. Similarly, supercritical carbon dioxide is an interesting reaction medium in the context of green chemistry and catalysis in various mono- and biphasic systems involving this solvent are reviewed. Fluorous biphasic systems and ionic liquids also have advantages in certain situations and the advantages and limitations of these media are compared. The ultimate in clean catalytic technologies is to telescope multistep syntheses into one-pot in the form of catalytic cascade processes. Examples of such catalytic cascades involving both chemo- and biocatalytic conversions are presented. Biocatalysis has a distinct advantage in this context in that the reactions all take place at or close to ambient temperature and pressure. In emulation of natural processes, where several different enzymes are compartmentalised in the cell, it can be advantageous to immobilise the various catalysts in such a cascade process. In this context, a novel and effective method for the immobilisation of enzymes as cross-linked enzyme aggregates (CLEAs) is discussed and the use of a combi CLEA, containing two enzymes, for the one-pot conversion of benzaldehyde to *S*-mandelic acid is reported.



Roger Sheldon

Roger Sheldon (1942) received a PhD in organic chemistry from the University of Leicester (UK) in 1967. This was followed by post-doctoral studies with Prof. Jay Kochi in the US. From 1969 to 1980 he was with Shell Research in Amsterdam and from 1980 to 1990 he was R&D Director of DSM Andeno. In 1991 he moved to his present position as Professor of Biocatalysis and Organic Chemistry at the Delft University of Technology (The Netherlands). His primary research interests are in the application of catalytic methodologies—homogeneous, heterogeneous and enzymatic—in organic synthesis, particularly in relation to fine chemicals production. He developed the concept of E factors for assessing the environmental impact of chemical processes.

Introduction

It is widely acknowledged that there is a growing need for more environmentally acceptable processes in the chemical industry. This trend towards what has become known as 'Green Chemistry' or 'Sustainable Technology' necessitates a paradigm shift from traditional concepts of process efficiency, that focus largely on chemical yield, to one that assigns economic value to eliminating waste at source and avoiding the use of toxic and/or hazardous substances.

A reasonable working definition of green chemistry can be formulated as follows: *green chemistry efficiently utilises (preferably renewable) raw materials, eliminates waste and avoids the use of toxic and/or hazardous reagents and solvents in the manufacture and application of chemical products.*

A useful measure of the potential environmental acceptability of chemical processes is the E factor,[1] defined as the mass ratio of waste to desired product. The sheer magnitude of the waste problem in chemicals manufacture is readily apparent from a consideration of typical E factors in various segments of the chemical industry (Table 1). The E factor is the actual amount of waste produced in the process, defined as everything but the desired product. It takes the chemical yield into account and includes reagents, solvents losses, all process aids

---

† This work was presented at the Green Solvents for Synthesis Meeting, held in Bruchsal, Germany, 3–6 October 2004.

Table 1 E Factors in the chemical industry

	Tonnage	E = kg waste/kg product
Bulk chemicals	10^4–10^6	<1–5
Fine chemical industry	10^2–10^4	5– >50
Pharmaceutical industry	10–10^3	25– >100

and, in principle, even fuel (although this is often difficult to quantify). There is one exception: (process) water is generally not taken into account.

The waste generated in the manufacture of organic compounds consists primarily of inorganic salts. This is a direct consequence of the use of stoichiometric inorganic reagents in organic synthesis. In particular, fine chemicals and pharmaceuticals manufacture is rampant with antiquated 'stoichiometric' technologies. Examples, which readily come to mind are stoichiometric reductions with metals (Na, Mg, Zn, Fe) and metal hydride reagents ($LiAlH_4$, $NaBH_4$), oxidations with permanganate, manganese dioxide and chromium(VI) reagents and a wide variety of reactions, *e.g.* sulfonations, nitrations, halogenations, diazotisations and Friedel–Crafts acylations, employing stoichiometric amounts of mineral acids (H_2SO_4, HF, H_3PO_4) and Lewis acids ($AlCl_3$, $ZnCl_2$, BF_3).

The solution is evident: substitution of classical stoichiometric methodologies with cleaner catalytic alternatives. Indeed, a major challenge in (fine) chemicals manufacture is to develop processes based on H_2, O_2, H_2O_2, CO, CO_2 and NH_3 as the direct source of H, O, C and N. Catalytic hydrogenation, carbonylation, hydroformylation and oxidation are good examples of highly atom efficient, low-salt processes (Fig. 1).

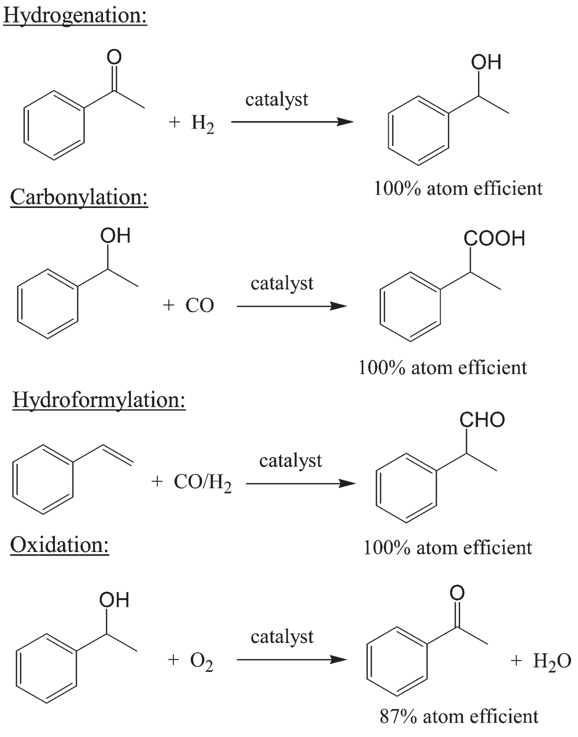


Fig. 1 Atom efficient processes.

It is also worth noting in this context that there is currently much emphasis on the use of renewable raw materials (biomass) as a future source of energy, polymers and bulk and fine chemicals.[2] The biomass is derived from carbon dioxide and water, with the aid of solar energy, *via* photosynthesis. Hence, the basic raw materials of the future will be carbon dioxide, water, oxygen and nitrogen, with conversion of biomass in biorefineries replacing the conversion of fossil fuels in conventional oil refineries.

The question of solvents: alternative reaction media

Another important issue in green chemistry is the use of organic solvents. It has been estimated by GlaxoSmithKline workers[3] that *ca.* 85% of the total mass of chemicals involved in pharmaceutical manufacture comprises solvents, and recovery efficiencies are typically 50–80%. In the redesign of the sertraline manufacturing process,[4] for which Pfizer received a Presidential Green Chemistry Challenge Award in 2002, among other improvements a three step sequence was streamlined to a single step employing ethanol as the sole solvent. This eliminated the need to use, distil and recover four solvents (methylene chloride, tetrahydrofuran, toluene and hexane) employed in the original process.

In the context of green chemistry there are several issues which influence the choice of solvent. It should be relatively nontoxic and relatively nonhazardous, *e.g.* not inflammable or corrosive. The solvent should also be contained, that is it should not be released to the environment. Solvent use is being subjected to close scrutiny and increasingly stringent environmental legislation and the FDA has issued guidelines which can be found on their website (http://www.fda.gov/cder/guidance/index.htm).

Removal of residual solvent from products is usually achieved by evaporation or distillation and most popular solvents are, therefore, highly volatile. Spillage and evaporation inevitably leads to atmospheric pollution, a major environmental issue of global proportions. Moreover, worker exposure to volatile organic compounds (VOCs) is a serious health issue. Many chlorinated hydrocarbon solvents have already been banned or are likely to be in the near future. Unfortunately, many of these solvents are exactly those that have otherwise desirable properties and are, therefore, widely popular for performing organic reactions. Another class of solvents which presents environmental problems comprises the polar aprotic solvents, such as dimethylformamide and dimethyl sulfoxide, that are the solvents of choice for, *e.g.* many nucleophilic substitutions. They are high boiling and not easily removed by distillation. They are also water-miscible which enables their separation by washing with water. Unfortunately, this inevitably leads to contaminated aqueous effluent.

These issues surrounding a wide range of volatile and nonvolatile, polar aprotic solvents have stimulated the fine chemical and pharmaceutical industries to seek more benign alternatives. There is a marked trend away from hydrocarbons and chlorinated hydrocarbons towards lower alcohols, esters and, in some cases, ethers. Inexpensive natural products such as ethanol have the added advantage of being readily biodegradable and ethyl lactate, produced by combining two innocuous natural products, is currently being touted as an environmentally attractive solvent for chemical reactions.

In this context it is worth mentioning that poly(ethylene glycol) (PEG) and poly(propylene glycol) (PPG) have attracted interest as novel solvents for catalytic processes. They are both relatively inexpensive and readily available materials. They are essentially nontoxic (PPG finds use as a solvent for pharmaceutical and cosmetic preparations and both PPG and PEG are approved for use in beverages) and biodegradable. Furthermore, they are, depending on the molecular weight, immiscible with water, nonvolatile, thermally robust, and can in principle be recycled after removal of the product. Hence, combinations of PEG or PPG with, *e.g.* water or $scCO_2$ are of interest as media for biphasic catalysis (see later).

PEG-200 and/or PEG-400 (the number refers to the average molecular weight), for example, have been used for the polyoxometalate catalysed aerobic oxidation of benzylic alcohols,[5] the Wacker oxidation of propylene to acetone[5] and Heck reactions.[6]

Alternative reaction media and multiphasic catalysis

The conclusion is clear: the problem with solvents is not so much their use but the seemingly inherent inefficiencies associated with their containment, recovery and reuse. Alternative solvents should, therefore, provide for their efficient removal from the product and reuse.

The subject of alternative reaction media also touches on another issue: recovery and reuse of the catalyst. This is desirable from both an environmental and an economic viewpoint (many of the catalysts used in fine chemicals manufacture contain highly expensive noble metals and/or chiral ligands). If a catalyst is an insoluble solid, that is, a heterogeneous catalyst, it can easily be separated by centrifugation or filtration. In contrast, if it is a homogeneous catalyst, dissolved in the reaction medium, this presents more of a problem and offsets the major advantages of homogeneous catalysts, such as high activities and selectivities (see Table 2). A serious shortcoming of homogeneous catalysis is the cumbersome separation of the (expensive) catalyst from reaction products and the quantitative recovery of the catalyst in an active form. Separation by distillation of reaction products from the catalyst generally leads to heavy ends which remain in the catalyst phase and eventually deactivate it. In the manufacture of pharmaceuticals quantitative separation of the catalyst is important in order to avoid contamination of the product. Consequently there have been many attempts to heterogenise homogeneous catalysts by attachment to organic or inorganic supports. However, these approaches have, generally speaking, not resulted in commercially viable processes, for a number of reasons, such as leaching of the metal, poor catalyst productivities, irreproducible activities and selectivities and degradation of the support.

This need for efficient separation of product and catalyst, while maintaining the advantages of a homogeneous catalyst, has led to the concept of liquid–liquid biphasic catalysis, whereby the catalyst is dissolved in one phase and the reactants and product(s) in the second liquid phase. The catalyst is recovered and recycled by simple phase separation. Preferably, the catalyst solution remains in the reactor and is reused with a fresh batch of reactants without further treatment or, ideally, it is adapted to continuous operation. Obviously, both solvents are subject to the same restrictions as discussed above for monophasic systems. Several different combinations have been intensely studied in recent years, including *water (aqueous biphasic), supercritical CO_2, fluorous biphasic, and ionic liquids*. It is worth noting that the use of water and supercritical carbon dioxide as reaction media is consistent with the above mentioned trend towards the use of renewable, biomass-based raw materials, which are ultimately derived from carbon dioxide and water.

Aqueous biphasic catalysis

The best solvent is no solvent and if a solvent (diluent) is needed then water is preferred. Water is nontoxic, nonflammable, abundantly available and inexpensive. Moreover, owing to its highly polar character one can expect novel reactivities and selectivities for organometallic catalysis in water. Furthermore, this provides an opportunity to overcome a serious shortcoming of homogeneous catalysts, namely the cumbersome recovery and recycling of the catalyst. Thus, performing the reaction in an aqueous biphasic system, whereby the catalyst resides in the water phase and the product is dissolved in the organic phase,[7] allows for recovery and recycling of the catalyst by simple phase separation.

An example of a large scale application of this concept is the Ruhrchemie/Rhône-Poulenc process for the hydroformylation of propylene to *n*-butanal (Fig. 2), which employs a water-soluble rhodium(I) complex of trisulfonated triphenylphosphine (tppts) as the catalyst.[8]

Pioneering studies of aqueous biphasic catalysis with water soluble organometallic complexes were performed by Joo and coworkers, in hydrogenation[9] and Kuntz, in hydroformylation.[10] Kuntz, for example, synthesised the water soluble ligand, tppts, and showed that its rhodium complex catalysed

Table 2 Heterogeneous *vs.* homogeneous catalysis

	Homogeneous	Heterogeneous
Advantages	- Mild reaction conditions - High activity and selectivity - Efficient heat transfer	- Facile separation of catalyst and products - Continuous processing
Disadvantages	- Cumbersome separation and recycling of catalyst - Product contamination - Not readily adapted to continuous processing	- Heat transfer problems - Low activity and selectivity

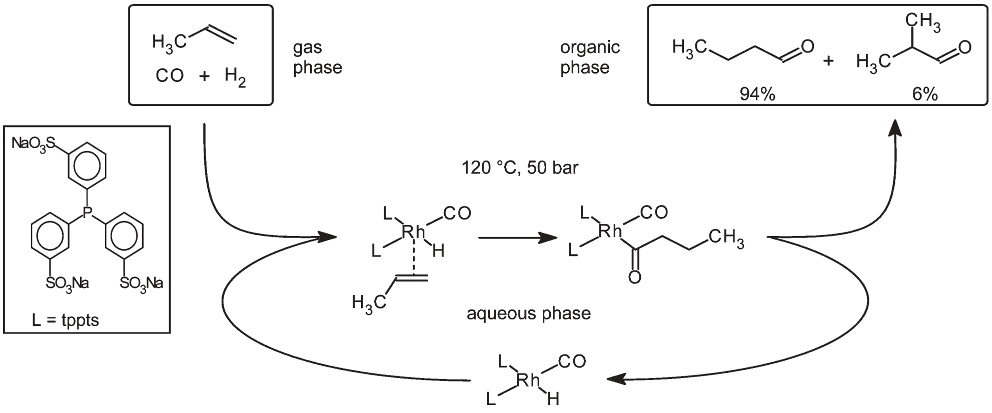


Fig. 2 Rhône-Poulenc/Ruhrchemie process for aqueous biphasic hydroformylation.

hydroformylations in water, thus laying the foundations for the Rhône-Poulenc/Ruhrchemie process for aqueous biphasic hydroformylation mentioned above.

Two decades later, we were interested in palladium catalysed carbonylations in water, with a view to carbonylating carbohydrates as renewable raw materials.[11] To this end, we synthesised the palladium(0) equivalent of the above mentioned rhodium–tppts complex[12] by allowing an aqueous solution of $PdCl_2$ and tppts (4 equiv.) to stand at room temperature for eight days. This resulted in the formation of $Pd(tppts)_3$ together with one equivalent of the corresponding phosphine oxide. Labelling experiments showed that the oxygen was derived from a water molecule (Fig. 3). In contrast, when the solution of $PdCl_2$ and tppts was subjected to 2 bar CO pressure, at room temperature, the $Pd(tppts)_3$ complex was formed in quantitative yield in 5 minutes. Hence, the carbonylation catalyst is rapidly formed, *in situ*, by mixing the ligand and a Pd(II) salt with CO in an aqueous medium.

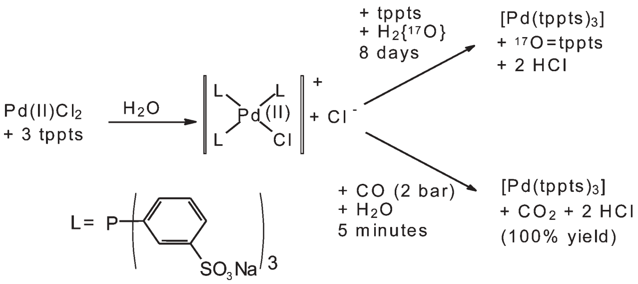


Fig. 3 Reaction of $PdCl_2$ with tppts in water.

The $Pd(tppts)_3$ complex was shown to catalyse the carbonylation of hydroxymethyl furfural (a model, carbohydrate-like substrate) in the presence of a Brønsted acid cocatalyst (Fig. 4). We subsequently showed that the same system catalysed the carbonylation of benzyl alcohol to phenylacetic acid (Fig. 4) in quantitative selectivity.[13] The same methodology was also applied to the synthesis of ibuprofen by aqueous biphasic carbonylation of 1-(4-isobutylphenyl)ethanol (Fig. 4).[14] The reaction is proposed to involve the formation of an intermediate carbenium ion (hence the need for an acid cocatalyst) which reacts with the Pd(0) complex to afford an alkylpalladium(II) species.[15]

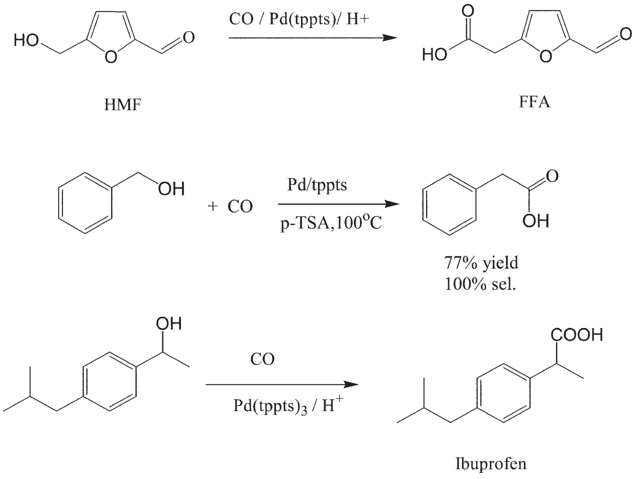


Fig. 4 Alcohol carbonylation in an aqueous biphasic system.

Similarly, Pd–tppts was used by Kohlpaintner and Beller (Hoechst)[16] as the catalyst in the synthesis of phenylacetic acid by biphasic carbonylation of benzyl chloride as an alternative to the classical synthesis *via* reaction with sodium cyanide (Fig. 5). Although the new process still produces one equivalent of sodium chloride, this is substantially less salt generation than in the original process. Moreover, sodium cyanide is about seven times more expensive per kg than carbon monoxide.

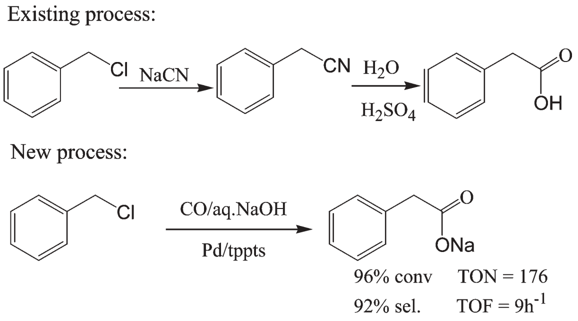


Fig. 5 Aqueous biphasic carbonylation.

We,[17] and others[18] subsequently showed that the same system, Pd–tppts, catalyses the aqueous biphasic hydrocarboxylation of olefins. When a sulfonated diphosphine is used as the ligand the complex formed with palladium(0) catalyses the alternating copolymerisation of ethylene and CO to give the engineering thermoplastic polyketone, Carilon.[19,20] Indeed, when a well-defined complex was used exceptionally high activities were observed,[20] with turnover frequencies (TOFs) higher than the conventional catalyst in methanol as solvent.

Oxidations

The palladium(II) complex of sulfonated bathophenanthroline was used in a highly effective aqueous biphasic aerobic oxidation of primary and secondary alcohols to the corresponding aldehydes or carboxylic acids and ketones respectively (Fig. 6).[21] No organic solvent was necessary, unless the substrate is a solid, and turnover frequencies of the order of 100 h^{-1} were observed. The catalyst could be recovered and recycled by simple phase separation (the aqueous phase is the bottom layer and can be left in the reactor for the next batch). The method constitutes an excellent example of a green catalytic oxidation with oxygen (air) as the oxidant, no organic solvent and a stable recyclable catalyst. The only disadvantage of the use of water as a solvent for aerobic oxidations is the low solubility of oxygen in water. Combined with the necessity (for safety reasons) of diluting the oxygen with nitrogen, this means that a pressure of 10–30 bar is needed to provide a sufficient concentration of oxygen in the aqueous phase.

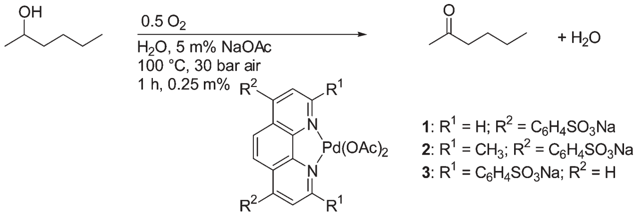


Fig. 6 Aqueous biphasic Pd catalysed aerobic oxidation of alcohols.

Alternatively, the use of hydrogen peroxide as the terminal oxidant is eminently compatible with the use of water as the reaction medium and hydrogen peroxide has been used, in aqueous biphasic systems, for the oxidation of alcohols to aldehydes or ketones, the epoxidation of olefins and the oxidative cleavage of olefins or ketones to carboxylic acids, *e.g.* cyclohexene to adipic acid (Fig. 7).[22]

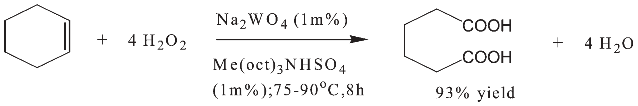


Fig. 7 Green synthesis of adipic acid.

Biocatalysis

Biocatalysis has many attractive features in the context of green chemistry: mild reaction conditions (physiological pH and temperature), an environmentally compatible catalyst (an enzyme) and solvent (often water) combined with high activities and chemo-, regio- and stereoselectivities in multifunctional molecules. Furthermore, the use of enzymes generally circumvents the need for functional group activation and avoids the protection and deprotection steps required in traditional organic syntheses. This affords processes which are shorter, generate less waste and are, therefore, both environmentally and economically more attractive than conventional routes.

The time is ripe for the widespread application of biocatalysis in industrial organic synthesis and according to a recent estimate[23] more than 130 processes have been commercialised. Advances in recombinant DNA techniques have made it, in principle, possible to produce virtually any enzyme for a commercially acceptable price. Advances in protein engineering have made it possible, using techniques such as site directed mutagenesis and *in vitro* evolution, to manipulate enzymes such that they exhibit the desired substrate specificity, activity, stability, pH profile, *etc.*[24] Furthermore, the development of effective immobilisation techniques has paved the way for optimising the performance and recovery and recycling of enzymes.

An illustrative example of the benefits to be gained by replacing conventional chemistry by biocatalysis is provided by the manufacture of 6-aminopenicillanic acid (6-APA), a key raw material for semi-synthetic penicillin and cephalosporin antibiotics, by hydrolysis of penicillin G.[25] Up until the mid-1980s a chemical procedure was used for this hydrolysis (Fig. 8). It involved the use of environmentally unattractive reagents, a chlorinated hydrocarbon solvent (CH_2Cl_2) and a reaction temperature of −40 °C. Thus, 0.6 kg Me_3SiCl, 1.2 kg PCl_5, 1.6 kg $PhNMe_2$, 0.2 kg NH_3, 8.4 l of *n*-BuOH and 8.4 l of CH_2Cl_2 were required to produce 1 kg of 6-APA. In contrast, enzymatic cleavage of penicillin G is performed in water at 37 °C and the only reagent used is NH_3 (0.09 kg per kg of 6-APA), to adjust the pH. The enzymatic process currently accounts for the majority of the several thousand tons of 6-APA produced annually on a world-wide basis.

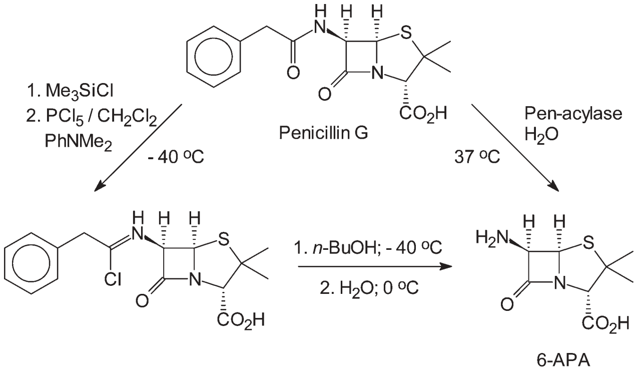


Fig. 8 Enzymatic *versus* chemical deacylation of penicillin G.

Another advantage of biocatalysis is the high degree of chemo-, regio- and stereoselectivities which are difficult or impossible to achieve by chemical means. A pertinent example is the production of the artificial sweetener, aspartame. The enzymatic process, operated by the Holland Sweetener Company (a joint venture of DSM and Tosoh) is completely regio- and enantiospecific (Fig. 9).[26]

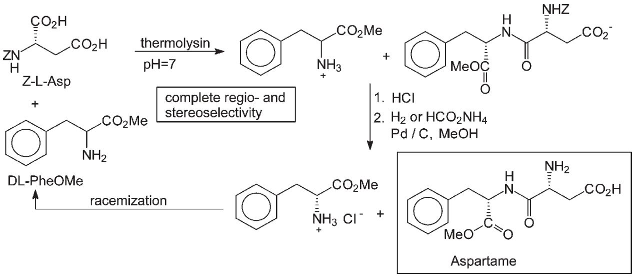


Fig. 9 Enzymatic synthesis of aspartame.

DuPont has developed a process for the manufacture of glyoxylic acid, a large volume fine chemical, by aerobic oxidation of glycolic acid (Fig. 10), mediated by resting whole cells of a recombinant methylotrophic yeast.[27] The glycolic acid is readily available from acid-catalysed carbonylation of formaldehyde. Traditionally, glyoxylic acid was produced by nitric acid oxidation of acetaldehyde or glyoxal, processes with high E factors. The key enzyme in the biocatalytic process is an oxidase which utilises dioxygen as the oxidant, producing one equivalent of hydrogen peroxide, without the need for cofactor regeneration.

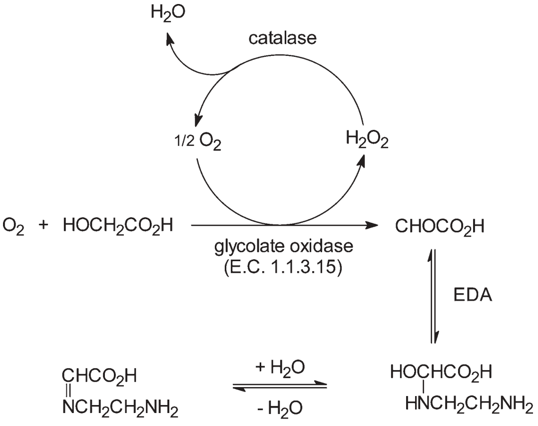


Fig. 10 Biocatalytic production of glyoxylic acid using whole cells of recombinant *Pichia pastoris*; pH 8.9–9.5/8 bar O_2/5 °C/2 h.

Another class of enzymes which catalyse the oxidation of alcohols comprises the alcohol dehydrogenases. However, in this case cofactor regeneration is required, which is an impediment to commercialisation. Recently, a highly enantioselective alcohol dehydrogenase, showing broad substrate specificity and exceptionally high tolerance for organic solvents, was isolated from *Rhodococcus ruber* DSM 4451.[28] The enzyme maintains a high activity at concentrations of up to 20% (v/v) acetone and 50% (v/v) 2-propanol. This enables the use of the enzyme, conveniently as whole microbial cells, as a catalyst for (enantioselective) Oppenauer oxidation of a broad range of alcohols, using acetone (20% v/v in phosphate buffer at pH 8) as the oxidant (Fig. 11), with substrate concentrations up to 1.8 mol l^{-1} (237 g l^{-1} for octan-2-ol). Alternatively, the reaction could be performed in a reduction mode, using a prochiral ketone as substrate and up to 50% v/v

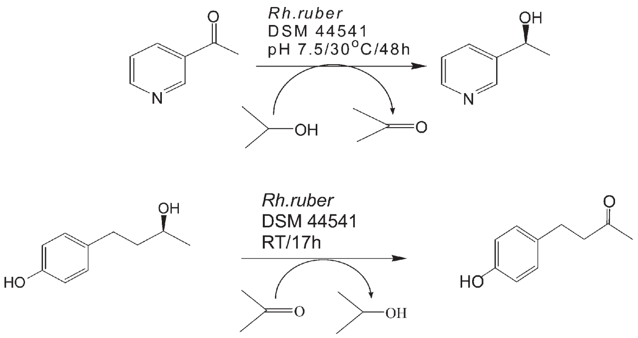


Fig. 11 Biocatalytic Oppenauer oxidations and Meerwein Ponndorf Verley reductions.

isopropanol as the reductant, affording the corresponding (*S*)-alcohol in 99% ee at conversions ranging from 65–92%.

Supercritical carbon dioxide as a reaction medium

Other nonclassical reaction media have, in recent years, attracted increasing attention from the viewpoint of avoiding environmentally unattractive solvents and/or facilitating catalyst recovery and recycling.[29] For example, supercritical carbon dioxide has been receiving increasing attention as an alternative reaction medium in recent years.[30] Several features of $scCO_2$ make it an interesting solvent in the context of green chemistry and catalysis. For carbon dioxide the critical pressure and temperature are moderate: 74 bar and 31 °C, respectively. Hence, the amount of energy required to generate supercritical carbon dioxide is relatively small. In addition, carbon dioxide is nontoxic, chemically inert towards many substances, nonflammable, and simple depressurisation results in its removal. It is miscible with, *e.g.* hydrogen, making it an interesting solvent for hydrogenation and hydroformylation (see below). Furthermore, the physical properties of $scCO_2$, *e.g.* polarity, can be tuned by manipulation of the temperature and pressure. Although it is a greenhouse gas its use involves no net addition to the atmosphere; it is borrowed as it were. Its main uses are as a replacement for VOCs in extraction processes. For example it is widely used for the decaffeination of coffee where it replaced the use of a chlorinated hydrocarbon. The pre-existence of an established SCF extraction industry meant that the necessary equipment was already available.

Hydrogenation and hydroformylation

The use of $scCO_2$ as a solvent for catalytic hydrogenation was pioneered by Poliakoff and has been commercialised by Thomas Swan and Co. for the manufacture of trimethyl cyclohexanone by Pd catalysed hydrogenation of isophorone (Fig. 12).[31] The miscibility of $scCO_2$ with hydrogen results in high diffusion rates, and provides the basis for achieving much

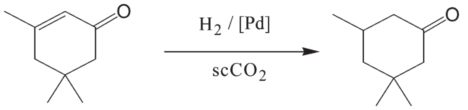


Fig. 12 Hydrogenation of isophorone in $scCO_2$.

higher reaction rates than in conventional solvents. The high reaction rates allow for the use of exceptionally small flow reactors. Chemoselectivities with multifunctional compounds could be adjusted by minor variations in reaction parameters. Similarly, $scCO_2$ has been used for olefin hydroformylation using an immobilised rhodium catalyst.[32]

Oxidations

Just as with water, $scCO_2$ is also an ideal inert solvent for performing catalytic aerobic oxidations; it is nonflammable and completely miscible with oxygen. Recently, much interest has also been focused on catalytic oxidations with hydrogen peroxide, generated *in situ* by Pd-catalysed reaction of hydrogen with oxygen, in $scCO_2$–water mixtures.[33] The system was used effectively for the direct epoxidation of propylene to propylene oxide over a Pd/TS-1 catalyst.[34] These reactions probably involve the intermediate formation of peroxycarbonic acid by reaction of H_2O_2 with CO_2 (Fig. 13).

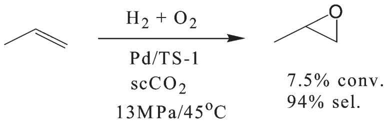


Fig. 13 Epoxidation of propylene with H_2–O_2 in $scCO_2$.

Biocatalysis

$scCO_2$ is also an interesting solvent for performing bioconversions. The first reports of biocatalysis in $scCO_2$ date back to 1985[35] and in the intervening two decades the subject has been extensively studied.[36] Enzymes are generally more stable in $scCO_2$ than in water and the *Candida antarctica* lipase (Novozym 435)-catalysed resolution of 1-phenylethanol was successfully performed at temperatures exceeding 100 °C in this solvent.[37] Matsuda *et al.* found that the enantioselectivity of alcohol acylations catalysed by Novozyme 435 in $scCO_2$ could be controlled by adjusting the pressure and temperature.[38] The same group recently reported a continuous flow system in $scCO_2$ for the enzymatic resolution of chiral secondary alcohols *via* Novozyme 435 catalysed acylation with vinyl acetate (Fig. 14).[39] For example, the kinetic resolution of 1-phenyl ethanol at 9 MPa CO_2 and 40 °C afforded the (*R*)-acetate in 99.8% ee and the (*S*)-alcohol in 90.6% ee at 48% conversion (E = 1800).

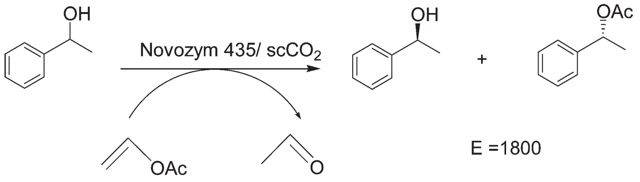


Fig. 14 Kinetic resolution of secondary alcohols with Novozyme 435 in $scCO_2$.

Similarly, the enantioselective reduction of prochiral ketones catalysed by whole cells of *Geotrichum candidum* proceeded smoothly in $scCO_2$ in a semi-continuous flow system (Fig. 15).[40]

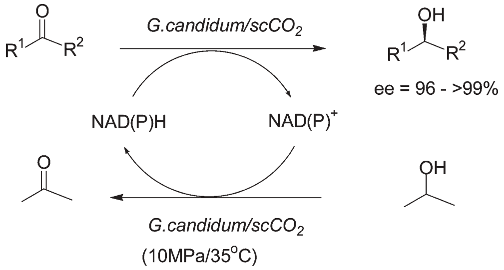


Fig. 15 Enantioselective reduction of prochiral ketones with immobilised resting cells of *Geotrichum candidum* in $scCO_2$.

Enzyme catalysed oxidations with O_2 have also been successfully performed in $scCO_2$ *e.g.* using cholesterol oxidase[41] and polyphenol oxidase.[35b] The use of $scCO_2$ as a solvent for biotransformations clearly has considerable potential and we expect that it will find more applications in the future.

Fluorous biphasic systems

Fluorous biphasic catalysis was pioneered by Horváth and Rabai[42] who coined the term 'fluorous' by analogy with 'aqueous', to describe highly fluorinated alkanes, ethers and tertiary amines. Such fluorous compounds differ markedly from the corresponding hydrocarbon molecules and are, consequently, immiscible with many common organic solvents at ambient temperature although they can become miscible at elevated temperatures. Hence, this provides a basis for performing biphasic catalysis or, alternatively, monophasic catalysis at elevated temperatures with biphasic product–catalyst separation at lower temperatures.[43] A variety of fluorous solvents are commercially available (see Fig. 16 for examples), albeit rather expensive compared with common organic solvents (or water).

In order to perform fluorous biphasic catalysis the (organometallic) catalyst needs to be solubilised in the fluorous phase by deploying "fluorophilic" ligands, analogous to the hydrophilic ligands used in aqueous biphasic catalysis. This is accomplished by incorporating so-called "fluorous ponytails".

Hydroformylation of higher olefins in an aqueous biphasic system is problematic owing to the lack of solubility of the substrate in the aqueous phase. On the other hand, hydroformylation in an organic medium presents the problem of separating the long-chain aldehydes from the catalyst. In contrast, this is not a problem with a fluorous biphasic system where at the elevated reaction temperature the mixture becomes a single phase. Cooling the reaction mixture to room temperature results in a separation into a fluorous phase, containing the catalyst, and an organic phase, containing the

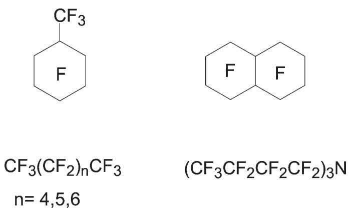


Fig. 16 Examples of fluorous solvents.

aldehyde products. This concept was applied by Horvath and Rabai, to the hydroformylation of 1-decene in a 1 : 1 mixture of $C_6F_{11}CF_3$ and toluene.[42] The catalyst was prepared *in situ* from $Rh(CO)_2(acac)$ and $P[CH_2CH_2(CF_2)_5CF_3]_3$, (P/Rh = 40). Upon completion of the reaction the reactor was cooled to room temperature and phase separation occurred. When the upper, organic phase was returned to the reactor, with fresh reactants, negligible reaction was observed, demonstrating that catalytically active rhodium species are not leached into the organic phase. It was subsequently shown[44,45] that recycling of the catalyst phase, in nine consecutive runs, afforded a total turnover number (TON) of more than 35 000. The rhodium losses amounted to 4.2%, which constitutes *ca.* 1 ppm per mole of aldehyde. Unfortunately there was some leaching of the free ligand into the organic phase, resulting in a slight decrease in (n : iso) selectivity (from *ca.* 92 : 8 to 89 : 11), which is dependent on the ligand–Rh ratio. The three different concepts for olefin hydroformylation—organic solvent, aqueous biphasic and fluorous biphasic—are compared in Fig. 17.

The successful demonstration of the fluorous biphasic concept for performing organometallic catalysis sparked extensive interest in the methodology and it has subsequently been applied to a wide variety of catalytic reactions.[43] Fluorous solvents are particularly suitable for performing aerobic oxidations based on the high solubility of oxygen in fluorocarbons. A few examples of catalytic oxidations in fluorous media have been reported. For example, the aerobic oxidation of alcohols was performed in a fluorous medium, using a copper complex with perfluorinated ligands.[46] Catalytic oxidations with hydrogen peroxide have also been performed in fluorous media.[47]

Notwithstanding the seemingly enormous potential of the fluorous biphasic catalysis concept, as yet a commercial application has not been forthcoming. Presumably the cost of the solvents and ligands is a significant hurdle. Furthermore, although the catalyst and products are well-partitioned over the two phases, there is a finite solubility of the catalyst in the organic phase which has to be coped with. Perhaps an even more serious problem is the extremely long lifetime of fluorocarbons in the environment which, even though they are chemically inert, essentially nontoxic and are not, in contrast to their cousins the CFCs, ozone-depleting agents, is still a matter for genuine concern.

In this context it is interesting to note the recent reports of *fluorous catalysis without fluorous solvents*.[48] The thermomorphic fluorous phosphines, $P[(CH_2)_m(CF_2)_7CF_3]_3$ (m = 2 or 3) exhibit *ca.* 600 fold increases in n-octane solubility between −20 and 80 °C. They catalyse the addition of alcohols to methyl propiolate in a monophasic system at 65 °C and can be recovered by precipitation on cooling. Similarly, we found that a perfluorinated ketone could be used as a catalyst for olefin epoxidations with hydrogen peroxide in organic solvents and subsequently recovered by cooling the reaction mixture to precipitate the ketone.[49]

Ionic liquids

Ionic liquids are quite simply liquids that are composed entirely of ions.[50] They are generally salts of organic cations, *e.g.* tetraalkylammonium, alkylpyridinium, 1,3-dialkylimidazolium, tetraalkylphosphonium (Fig. 18). Room temperature ionic liquids exhibit certain properties which make them attractive media for performing green catalytic reactions. They have essentially no vapour pressure and are thermally robust with liquid ranges of *e.g.*, 300 °C, compared to 100 °C for water. Polarity and hydrophilicity/hydrophobicity can be tuned by a suitable combination of cation and anion, which has earned them the accolade, 'designer solvents'.

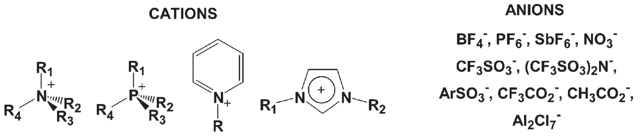


Fig. 18 Examples of ionic liquids.

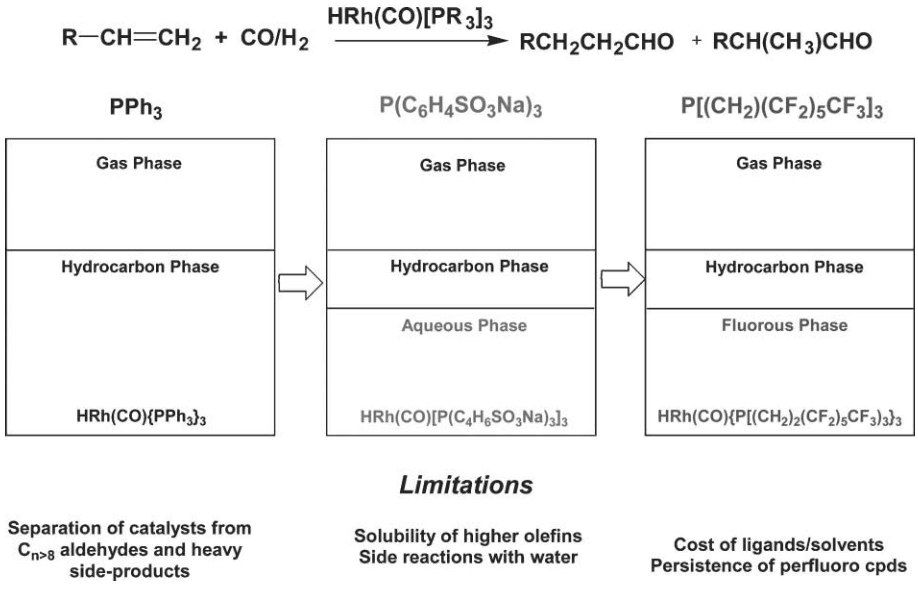
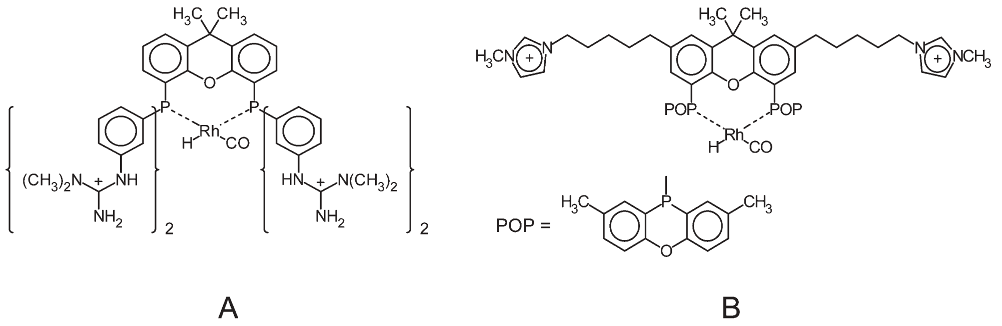


Fig. 17 Different concepts for olefin hydroformylation.



Catalyst	TOF(h^{-1})	n/iso ratio
(tppts)2(CO)RhH	80	2.6
A	50	20
B	320	49

Fig. 19 Hydroformylation of 1-octene in [bmim][PF_6] at 100 °C and 30 bar.

Ionic liquids have been extensively studied in the last few years as media for organic synthesis and catalysis in particular.[51] For example, the hydroformylation of higher olefins, such as 1-octene, was performed in ionic liquids.[52] Good activities were observed with rhodium in combination with the water-soluble ligand, tppts, described above but the selectivity was low (n/iso ratio = 2.6). In order to achieve both high activities and selectivities special ligands had to be designed (Fig. 19). No detectable (less than 0.07%) Rh leaching was observed and the IL phase containing the catalyst could be recycled after separating the product which formed a separate phase. However, the need for rather exotic ligands will presumably translate to higher costs for this process compared to aqueous biphasic hydroformylation, for example.

In the last few years increasing attention has been devoted to conducting biocatalytic transformations in ionic liquids.[53] The first report of enzyme (lipase) catalysed reactions in water-free ionic liquids dates from 2000 and involved transesterification, ammoniolysis and perhydrolysis reactions catalysed by *Candida antarctica* lipase B, usually in its immobilised form, Novozyme 435 (Fig. 20).[54]

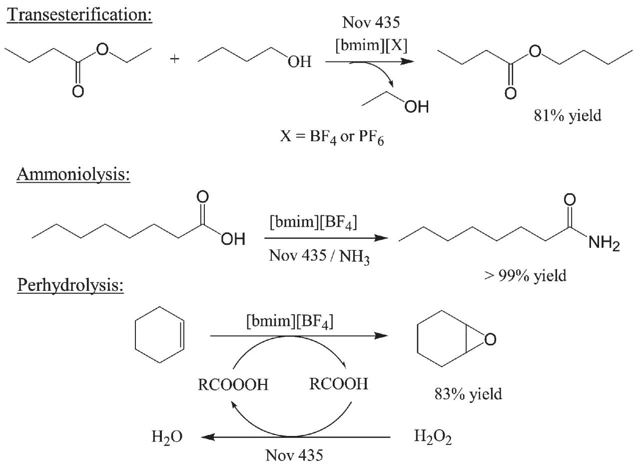


Fig. 20 *Candida antarctica* lipase B (Nov435) catalysed transformations in water-free ionic liquids.[54]

The use of ionic liquids as reaction media for biotransformations has several potential benefits compared to conventional organic solvents, *e.g.*, higher operational stabilities and enantioselectivities[53] and activities are generally at least as high as those observed in organic solvents. They are particularly attractive for performing bioconversions with substrates which are very sparingly soluble in conventional organic solvents, *e.g.*, carbohydrates[55]and nucleosides.

Notwithstanding the advantages of ionic liquids as reaction media for catalytic processes, they have yet to be widely applied in industry. The reasons for this are probably related to their high prices and the paucity of data with regard to their toxicity and biodegradability. The replacement of conventional VOCs with ionic liquids is an obvious improvement with regard to atmospheric emissions but small amounts of ionic liquids will inevitably end up in the environment, *e.g.*, in ground water. Consequently, it is important to establish their effect on the environment. Indeed, the current trend in ionic liquid research is towards the development of nontoxic, biodegradable ionic liquids, *e.g.* based on renewable raw materials.[56]

Biphasic systems with supercritical carbon dioxide

One problem associated with the use of ILs is recovery of the product and recycling of the catalyst. If this is achieved by extraction with a volatile organic solvent then it is questionable what the overall gain is. An attractive alternative is to use $scCO_2$ as the second phase, whereby the catalyst remains in the IL phase and the product is extracted into the $scCO_2$ phase. This concept has been successfully applied to both homogeneous metal catalysis[57] and biocatalytic conversions.[58] We have recently applied the concept of using a 'miscibility switch' for performing catalytic reactions in IL–$scCO_2$ mixtures.[59]

Other combinations with $scCO_2$ have also been considered which dispense with the need for an ionic liquid altogether. For example, a biphasic water–$scCO_2$ system, whereby the catalyst, *e.g.* a metal complex of tppts, resides in the water phase and the product is removed in the $scCO_2$ phase.[30] The system has its limitations: the catalyst needs to be water soluble and all reaction components must be stable towards the acidic pH (3) of carbonic acid. More recently, an attractive system comprising a biphasic mixture of poly(ethylene glycol) (PEG) to dissolve the catalyst and $scCO_2$ as the extractive phase was used for the $RhCl(Ph_3P)_3$-catalysed hydrogenation of styrene.[60] PEGs have the advantage over ILs that they are much less expensive and are nontoxic (analogous to CO_2, they are approved for use in foods and beverages). They are, moreover, miscible with common organic ligands and in the above example the catalyst was stable and recyclable in the PEG phase.

Thermoregulated biphasic catalysis

Another approach to facilitating catalyst separation while maintaining the benefits of homogeneous catalysis involves the use of thermoregulated biphasic catalysis,[61] whereby the catalyst is dissolved in a particular solvent at one temperature and insoluble at another. For example, a diphosphine ligand attached to an ethylene oxide–propylene oxide block copolymer (Fig. 21) afforded rhodium complexes that are soluble in water at room temperature but precipitate on warming to 40 °C. The driving force for this inverted temperature dependence on solubility is dehydration of the ligand on heating. Hence, a rhodium catalysed reaction, such as hydrogenation or hydroformylation can be performed at room temperature in a single phase and the catalyst separated by precipitation at a higher temperature. An added advantage is that runaway conditions are never achieved since the catalyst precipitates and the reaction stops on raising the temperature. This principle has also been applied to biotransformations by attaching enzymes to EO–PO block copolymers.[62]

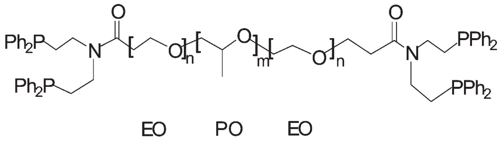


Fig. 21 Ligand for thermoregulated biphasic catalysis.

Catalytic cascade processes

The widespread application of chemo- and biocatalytic methodologies in the manufacture of fine chemicals is resulting in a gradual disappearance of the traditional barriers between the subdisciplines of homogeneous and heterogeneous catalysis and biocatalysis. The key to successful implementation of catalytic methodologies is integration of catalytic steps in multistep organic syntheses and downstream processing. The ultimate in integration is to combine several catalytic steps into a one-pot, multi-step catalytic cascade process.[63] This is truly emulating nature where metabolic pathways conducted in living cells involve an elegant orchestration of a series of biocatalytic steps into an exquisite multicatalyst cascade, without the need for separation of intermediates. Such 'telescoping' of multistep syntheses into a one-pot catalytic cascade has several advantages—fewer unit operations, less solvent, and reactor volume, shorter cycle times, higher volumetric and space time yields and less waste (lower E factor)—which translates to substantial economic and environmental benefits. Furthermore, coupling of reactions together can be used to drive equilibria towards the products, thus avoiding the need for excess reagents. On the other hand, there are several problems associated with the construction of catalytic cascades: catalysts are often incompatible with each other (*e.g.* an enzyme and a metal catalyst), rates are very different and it is difficult to find optimum conditions of pH, temperature, solvent, *etc*. Catalyst recovery and recycle is complicated and downstream processing is difficult. Nature solves this problem by compartmentalisation of the various biocatalysts. Hence, compartmentalisation *via* immobilisation is conceivably a way of solving these problems in cascade processes. It is also worth noting that biocatalytic processes generally proceed under roughly the same conditions—in water at around ambient temperature and pressure—which facilitates the cascading process.

An example of a one-pot, three-step catalytic cascade is shown in Fig. 22. In the first step galactose oxidase catalyses the selective oxidation of the primary alcohol group of galactose to the corresponding hydrated aldehyde. This is followed by L-proline catalysed elimination of water and catalytic hydrogenation, affording the deoxy sugar.[64]

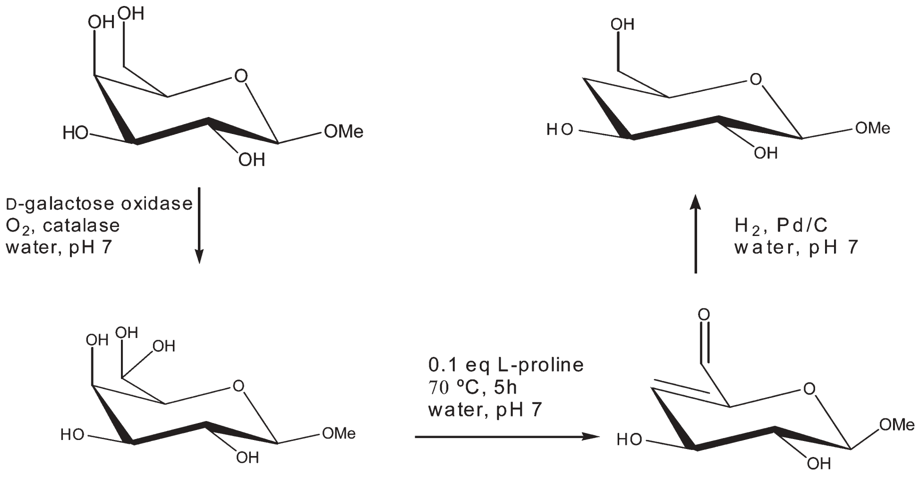


Fig. 22 One-pot, three-step synthesis of a deoxy sugar.

Similarly, we recently combined an asymmetric hydrogenation with a supported chiral Rh catalyst followed by an enzymatic hydrolysis of the product into a one-pot cascade process in water as the only solvent (Fig. 23).[65]

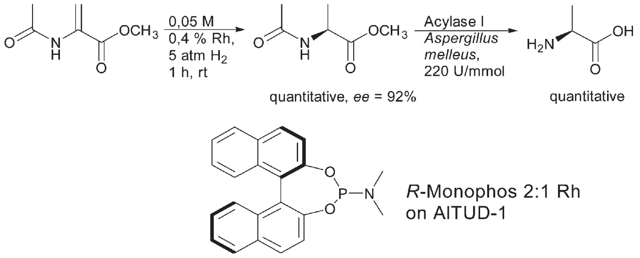


Fig. 23 Chemoenzymatic synthesis of an amino acid.

In the context of immobilisation of multiple enzymes for biocatalytic cascades the so-called Cross-Linked Enzyme Aggregates (CLEAs) are of interest.[66] They exhibit high activity retention and stability and can be readily recovered and recycled without any loss of activity. Furthermore, the method is exquisitely simple—precipitation from an aqueous buffer followed by cross-linking with, for example, glutaraldehyde—and is applicable to a broad range of enzymes. It does not require highly pure enzyme preparations and it actually constitutes a combination of purification and immobilisation into one step. The methodology can also be applied to the co-immobilisation of two or more enzymes to give 'combi CLEAs' which are more effective than mixtures of the individual CLEAs. These are ideally suited to conducting enzymatic cascade reactions in water, where an equilibrium can be shifted by removing the product in a consecutive biotransformation. For example, we have used a combi CLEA containing an *S*-selective nitrilase (from *Manihot esculenta*) and a nonselective nitrilase, in DIPE–water (90 : 10) at pH 5.5, 1 h, for the one-pot conversion of benzaldehyde to *S*-mandelic acid (Fig. 24) in high yield and enantioselectivity.[67]

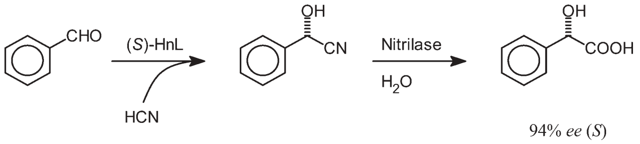


Fig. 24 One-pot conversion of benzaldehyde to *S*-mandelic acid with a combi CLEA.

Conclusions and prospects

The employment of catalytic methodologies—homogeneous, heterogeneous and enzymatic—in nonconventional reaction media holds much promise for the development of a sustainable chemical manufacturing industry. Water, for example, is cheap, abundantly available, nontoxic and nonflammable and the use of aqueous biphasic catalysis provides an ideal basis for recovery and recycling of the (water-soluble) catalyst. Water is also the ideal solvent for many processes catalysed by nature's catalysts, enzymes. Hence, the use of water as a reaction medium meshes well with the current trend towards a sustainable chemical industry based on the utilisation of renewable raw materials rather than fossil fuels as the basic feedstock.

Supercritical carbon dioxide also has many potential benefits in the context of sustainability. In common with water, it is cheap, abundantly available, nontoxic and nonflammable. It is also an eminently suitable solvent for homogeneous, heterogeneous and biocatalytic processes and is readily separated from the catalyst and products by simple release of pressure. Reaction rates are very high in $scCO_2$, owing to its intermediate properties, between a gas and a liquid. Biphasic systems involving $scCO_2$ with, for example an ionic liquid or polyethylene glycol, also hold promise as reaction media for a variety of catalytic processes integrated with product separation and catalyst recycling.

Fluorous biphasic systems and ionic liquids are potentially attractive alternatives for performing conversions which are not feasible in water or supercritical carbon dioxide. Both types of solvent suffer from the (perceived or real) disadvantages of high price and/or limited availability coupled with issues of biodegradability and/or aquatic toxicity. They undoubtedly have commercial potential in niche applications.

The ultimate in sustainable catalytic processes is the integration of chemocatalytic and/or biocatalytic steps into catalytic cascade processes that emulate the metabolic pathways of the cell factory. One-pot syntheses *via* catalytic cascade processes, involving chemo- and biocatalysis, and based on water and carbon dioxide as basic raw materials and reaction media, would seem to provide the ideal basis for a sustainable chemical industry.

Roger A. Sheldon
Biocatalysis and Organic Chemistry, Delft University of Technology, Delft 2628 BL, The Netherlands. E-mail: R.A.Sheldon@tnw.tudelft.nl

References

1 R. A. Sheldon, *C. R. Acad. Sci., Ser. IIc: Chim.*, 2000, **3**, 541–551; R. A. Sheldon, *Chem. Ind. (London)*, 1997, 12–15; R. A. Sheldon, *Pure Appl. Chem.*, 2000, **72**, 1233–1246; R. A. Sheldon, *Russ. Chem. J.*, 2000, **44**, 9–20.
2 White Biotechnology: Gateway to a more Sustainable Future, Europabio Report, 2003, http://www.europabio.org.
3 D. J. C. Constable, A. D. Curzons and V. L. Cunningham, *Green Chem.*, 2002, **4**, 521–527.
4 A. M. Rouhi, *Chem. Eng. News*, April 2002, 31–32; G. P. Taber, D. M. Pfistere and J. C. Colberg, *Org. Proc. Res. Dev.*, 2004, **8**, 385–388.
5 A. Haimov and R. Neumann, *Chem. Commun.*, 2002, 876–877; see also H. Alper, K. Januszkiewicz and D. J. H. Smith, *Tetrahedron Lett.*, 1985, **26**, 2263–2264.
6 S. Chanrasekhar, Ch. Narsihmulu, S. S. Sultana and N. R. Reddy, *Org. Lett.*, 2002, **4**, 4399–4401.
7 G. Papadogianakis and R. A. Sheldon, in *Catalysis*, **Vol. 13**, Specialist Periodical Report, Royal Society of Chemistry, Cambridge, UK, 1997, pp. 114–193; *Aqueous Phase Organometallic Catalysis. Concepts and Applications*, ed. B. Cornils and W. A. Herrmann, Wiley-VCH, Weinheim, 1998.
8 B. Cornils and E. Wiebus, *Recl. Trav. Chim. Pays-Bas*, 1996, **115**, 211–215.
9 F. Joo and M. T. Beck, *React. Kinet. Catal. Lett.*, 1975, **2**, 257–263; F. Joo and Z. Toth, *J. Mol. Catal.*, 1980, **8**, 369–383.
10 E. G. Kuntz, *CHEMTECH*, 1987, **17**, 570–575; E. G. Kuntz, *French Pat.*, 2 314 910, 1975.
11 G. Papadogianakis, L. Maat and R. A. Sheldon, *J. Chem. Soc., Chem. Commun.*, 1994, 1887–1888.
12 G. Papadogianakis, J. A. Peters, L. Maat and R. A. Sheldon, *J. Chem. Soc., Chem. Commun.*, 1995, 1105–1106.
13 G. Papadogianakis, L. Maat and R. A. Sheldon, *J. Mol. Catal. A: Chem.*, 1997, **116**, 179–190.

14 G. Papadogianakis, L. Maat and R. A. Sheldon, *J. Chem. Technol. Biotechnol.*, 1997, **70**, 83–91.
15 G. Verspui, I. I. Moiseev and R. A. Sheldon, *J. Organomet. Chem.*, 1999, **586**, 196–199.
16 W. Kohlpaintner and M. Beller, *J. Mol. Catal. A: Chem.*, 1997, **116**, 259–267.
17 G. Papadogianakis, G. Verspui, L. Maat and R. A. Sheldon, *Catal. Lett.*, 1997, **47**, 43–46.
18 S. Tilloy, E. Monflier, E. Bertoux, Y. Castanet and A. Mortreux, *New J. Chem.*, 1997, **21**, 529–531.
19 G. Verspui, G. Papadogianakis and R. A. Sheldon, *Chem. Commun.*, 1998, 401–402; G. Verspui, F. Schanssema and R. A. Sheldon, *Appl. Catal., A: Gen.*, 2000, **198**, 5–11.
20 G. Verspui, F. Schanssema and R. A. Sheldon, *Angew. Chem., Int. Ed.*, 2000, **39**, 804–806.
21 G. J. ten Brink, I. W. C. E. Arends and R. A. Sheldon, *Science*, 2000, **287**, 1636–1639.
22 R. Noyori, M. Aoki and K. Sato, *Chem. Commun.*, 2003, 1977–1986 and references cited therein.
23 A. J. J. Straathof, S. Panke and A. Schmid, *Curr. Opin. Biotechnol.*, 2002, **13**, 548–556.
24 K. A. Powell, S. W. Ramer, S. B. del Cardayré, W. P. C. Stemmer, M. B. Tobin, P. F. Longchamp and G. W. Huisman, *Angew. Chem., Int. Ed.*, 2001, **40**, 3948–3959.
25 M. A. Wegman, M. H. A. Janssen, F. van Rantwijk and R. A. Sheldon, *Adv. Synth. Catal.*, 2001, **343**, 559–576.
26 K. Oyama, *The industrial production of aspartame*, in *Chirality in Industry*, ed. A. N. Collins, G. N. Sheldrake and J. Crosby, Wiley, New York, 1992, pp. 237–248.
27 J. E. Gavagan, S. K. Fager, J. E. Seip, M. S. Payne, D. L. Anton and R. DiCosimo, *J. Org. Chem.*, 1995, **60**, 3957–3963.
28 W. Stampfer, B. Kosjek, C. Moitzi, W. Kroutil and K. Faber, *Angew. Chem., Int. Ed.*, 2002, **41**, 1014–1017.
29 *Special Issue on Green Solvents for Catalysis*, ed. W. Leitner, K. R. Seddon, P. Wasserscheid, *Green Chem.*, 2003, **5**, 99–284; see also P. G. Jessop, R. R. Stanley, R. A. Brown, C. A. Eckert, C. L. Liotta, T. T. Ngo and P. Pollet, *Green Chem.*, 2003, **5**, 123–128; J. Liu, M. J. Lazzaroni, J. P. Hallett, A. S. Bommarius, C. L. Liotta and C. A. Eckert, *Ind. Eng. Chem. Res.*, 2004, **43**, 1586–1590; C. A. Eckert, C. L. Liotta, D. Bush, J. S. Brown and J. P. Hallett, *J. Phys. Chem. B*, 2004, **108**, 18108–18118.
30 W. Leitner, *Top. Curr. Chem.*, 1999, **206**, 107–132; W. Leitner, *Acc. Chem. Res.*, 2002, **35**, 746–756; E. J. Beckman, *J. Supercrit. Fluids*, 2004, **28**, 121–191.
31 P. Licence, J. Ke, M. Sokolova, S. K. Ross and M. Poliakoff, *Green Chem.*, 2003, **5**, 99–104 for a seminal paper on asymmetric hydrogenation in scCO$_2$ see: M. J. Burk, S. Feng, M. F. Gross and W. J. Tumas, *J. Am. Chem. Soc.*, 1995, **117**, 8277–8278.
32 N. J. Meehan, A. J. Sandee, J. N. H. Reek, P. C. J. Kamer, P. W. N. M. van Leeuwen and M. Poliakoff, *Chem. Commun.*, 2000, 1497–1498.
33 E. J. Beckmann, *Green Chem.*, 2003, **5**, 332–336.
34 T. Danciu, E. J. Beckman, D. Hancu, R. Cochran, R. Grey, D. Hajnik and J. Jewson, *Angew. Chem., Int. Ed.*, 2003, **42**, 1140–1142.
35 (*a*) T. W. Randolph, H. W. Blanch, J. M. Prausnitz and C. R. Wilke, *Biotechnol. Lett.*, 1985, **7**, 325–328; (*b*) D. A. Hammond, M. Karel, A. M. Klibanov and V. J. Krukonis, *Appl. Biochem. Biotechnol.*, 1985, **11**, 393–400; (*c*) K. Nakamura, Y. M. Chi, Y. Yamada and T. Yano, *Chem. Eng. Commun.*, 1986, **45**, 207.
36 T. Matsuda, T. Harada and K. Nakamura, *Green Chem.*, 2004, **6**, 440–444.
37 A. Overmeyer, S. Schrader-Lippelt, V. Kascher and G. Brunner, *Biotechnol. Lett.*, 1999, **21**, 65–69.
38 T. Matsuda, R. Kanamaru, K. Watanabe, T. Harada and K. Nakamura, *Tetrahedron Lett.*, 2001, **42**, 8319–8321; T. Matsuda, R. Kanamaru, K. Watanabe, T. Kamitanaka, T. Harada and K. Nakamura, *Tetrahedron: Asymmetry*, 2003, **14**, 2087–2091.
39 T. Matsuda, K. Watanabe, T. Harada, K. Nakamura, Y. Arita, Y. Misumi, S. Ichikawa and T. Ikariya, *Chem. Commun.*, 2004, 2286–2287.
40 T. Matsuda, K. Watanabe, T. Kamitanaka, T. Harada and K. Nakamura, *Chem. Commun.*, 2003, 1198–1199.
41 T. W. Randolph, D. S. Clark, H. W. Blanch and J. M. Prausnitz, *Science*, 1988, **239**, 387–390.
42 I. T. Horváth and J. Rabai, *Science*, 1994, **266**, 72–75; I. T. Horváth, *Acc. Chem. Res.*, 1998, **31**, 641–650.
43 *Handbook of Fluorous Chemistry*, ed. J. A. Gladysz, D. P. Curran and I. T. Horváth, Wiley, Weinheim, 2004.
44 I. T. Horváth, G. Kiss, R. A. Cook, J. E. Bond, P. A. Stevens, J. Rábai and E. J. Mozeleski, *J. Am. Chem. Soc.*, 1998, **120**, 3133–3143.
45 See also D. F. Foster, D. Gudmunsen, D. J. Adams, A. M. Stuart, E. G. Hope, D. J. Cole-Hamilton, G. P. Schwarz and P. Pogorzelec, *Tetrahedron*, 2002, **58**, 3901–3910.
46 B. Betzemeier, M. Cavazinne, S. Quici and P. Knochel, *Tetrahedron Lett.*, 2000, **41**, 4343–4346.
47 G.-J. ten Brink, J. M. Vis, I. W. C. E. Arends and R. A. Sheldon, *Tetrahedron*, 2002, **58**, 3977–3983; G.-J. ten Brink, J. M. Vis, I. W. C. E. Arends and R. A. Sheldon, *J. Org. Chem.*, 2001, **66**, 2429–2433; G.-J. ten Brink, B. C. M. Fernandes, M. C. A. van Vliet, I. W. C. E. Arends and R. A. Sheldon, *J. Chem. Soc., Perkin Trans. 1*, 2001, 224–228.
48 M. Wende, R. Meier and J. A. Gladysz, *J. Am. Chem. Soc.*, 2001, **123**, 11490–11491; M. Wende and J. A. Gladysz, *J. Am. Chem. Soc.*, 2003, **125**, 5861–5872.
49 M. C. A. van Vliet, I. W. C. E. Arends and R. A. Sheldon, *Chem. Commun.*, 1999, 263–264.
50 *Ionic Liquids as Green Solvents; Progress and Prospects*, ed. R. D. Rogers and K. R. Seddon, ACS Symp. Ser. 856, American Chemical Society, Washington DC, 2003; *Ionic Liquids in Synthesis*, ed. P. Wasserscheid and T. Welton, Wiley-VCH, Weinheim, 2003.
51 For recent reviews see: R. A. Sheldon, *Chem. Commun.*, 2001, 2399–2407; P. Wasserscheid and W. Keim, *Angew. Chem., Int. Ed.*, 2000, **39**, 3772–3789; J. Dupont, R. F. de Souza and P. A. Z. Suarez, *Chem. Rev.*, 2002, **102**, 3667–3692; C. E. Song, *Chem. Commun.*, 2004, 1033–1043.
52 P. Wasserscheid, H. Waffenschmidt, P. Machnitzki, K. W. Kottsieper and O. Stelzer, *Chem. Commun.*, 2001, 451–452; P. W. N. M. van Leeuwen, P. C. J. Kamer, J. N. H. Reek and P. Dierkes, *Chem. Rev.*, 2000, **100**, 2741–2770; R. P. J. Bronger, S. M. Silva, P. C. J. Kramer and P. W. N. M. van Leeuwen, *Chem. Commun.*, 2002, 3044–3045.
53 For reviews see: F. van Rantwijk, R. Madeira Lau and R. A. Sheldon, *Trends Biotechnol.*, 2003, **21**, 131–138; R. A. Sheldon, R. Madeira Lau, M. J. Sorgedrager, F. van Rantwijk and K. R. Seddon, *Green Chem.*, 2002, **4**, 147–151; U. Kragl, M. Eckstein and N. Kaftzik, *Curr. Opin. Biotechnol.*, 2002, **13**, 565–571.
54 R. Madeira Lau, F. van Rantwijk, K. R. Seddon and R. A. Sheldon, *Org. Lett.*, 2000, **2**, 4189–4191.
55 Q. Liu, M. H. A. Janssen, F. van Rantwijk and R. A. Sheldon, *Green Chem.*, 2005, **7**, 39–42.
56 See, for example, N. Gathergood and P. J. Scammels, *Aust. J. Chem.*, 2002, **55**, 557–560.
57 R. A. Brown, P. Pollet, E. McKoon, C. A. Eckhert, C. L. Liotta and P. G. Jessop, *J. Am. Chem. Soc.*, 2001, **123**, 1254–1255; D. J. Cole-Hamilton, *Science*, 2003, **299**, 1702–1706; F. Liu, M. B. Abrams, R. T. Baker and W. Tumas, *Chem. Commun.*, 2001, 433–434.
58 P. Lozano, T. de Diego, D. Carrié, M. Vaultier and J. L. Iborra, *Chem. Commun.*, 2002, 692–693; M. T. Reetz, W. Wiesenhofer, G. Francio and W. Leitner, *Chem. Commun.*, 2002, 992–993; P. Lozano and T. de Diego, *Biotechnol. Prog.*, 2004, **20**, 661–669.
59 M. C. Kroon, A. Shariati, M. Costantini, J. van Spronsen, G.-J. Witkamp, R. A. Sheldon and C. J. Peters, *J. Chem. Eng. Data*, 2005, **50**, 173–176.
60 D. J. Heldebrandt and P. G. Jessop, *J. Am. Chem. Soc.*, 2003, **125**, 5600–5601.
61 D. E. Bergbreiter, *Chem. Rev.*, 2002, **102**, 3345–3383.
62 A. E. Ivanov, E. Edink, A. Kumar, I. Y. Galaev, A. F. Arendsden, A. Bruggink and B. Mattiasson, *Biotechnol. Prog.*, 2003, **19**, 1167–1175.
63 A. Bruggink, R. Schoevaart and T. Kieboom, *Org. Proc. Res. Dev.*, 2003, **7**, 622–640.
64 R. Schoevaart and T. Kieboom, *Tetrahedron Lett.*, 2002, **43**, 3399–3400.
65 C. Simons, U. Hanefeld, I. W. C. E. Arends, A. J. Minnaard, T. Maschmeyer and R. A. Sheldon, *Chem. Commun.*, 2004, 2830–2831.
66 L. Cao, L. M. van Langen and R. A. Sheldon, *Curr. Opin. Biotechnol.*, 2003, **14**, 387–394.
67 C. Mateo, manuscript in preparation.

High performance NMR in ionic liquids†‡

Ralf Giernoth,* Dennis Bankmann and Nils Schlörer

Received 24th November 2004, Accepted 3rd March 2005
First published as an Advance Article on the web 14th March 2005
DOI: 10.1039/b417783e

Nuclear magnetic resonance techniques for investigations of and in neat ionic liquids have been developed. After thorough optimisation, a resolution comparable to classical solvents is achieved. The technique is usable for a wide range of ILs. Observed nuclei are ^{1}H and ^{13}C and potentially ^{2}H and ^{19}F. Measurements of T_1 values show multipulse experiments to be feasible.

Introduction

The interest in ionic liquids[1] (ILs) as novel solvents is ever increasing. However, to date only a very limited range of analytical techniques for everyday use is available. While the purity of the IL itself can be checked by standard analytical methods like NMR in deuterated solvents and mass spectrometry, the bulk structure of the solvent and its participation in reactions is still not well understood. There is therefore a need for *in situ* techniques.

First attempts to characterize the liquid state structure of ILs have appeared in the literature, employing mass spectrometry,[2–4] infrared spectroscopy,[5,6] and NMR. Magnetic resonance measurements have been applied to investigate self-diffusion coefficients and viscosities,[7] ion-pair formation,[8] proton conductance,[9] and the structural consequences of water traces.[10] However, the few spectra published show limited resolution or are not spectra of neat ILs without any other solvent. Furthermore, the use of deuterated substrates for *in situ* investigations in protonated ILs has been demonstrated.[11]

A range of experiments has been performed on first generation ionic liquids containing chloroaluminate anions.[12–17] These results however do not directly relate to modern ILs.

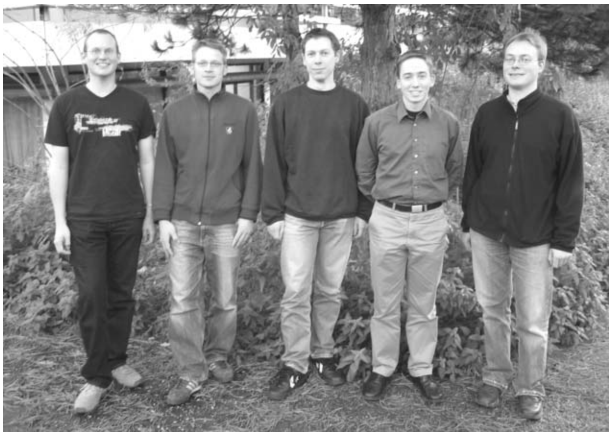
While these investigations have shed light on some structural aspects, a more systematic approach that is compatible with a wide range of ILs is needed to make such methods routinely available to non-spectroscopists. NMR spectroscopy in ILs should provide reproducible results, high sensitivity, and should not require deuterated ILs or substrates for the majority of applications.

The implementation of high resolution nuclear magnetic resonance (NMR) spectroscopy in ionic liquids may help to reveal liquid state structure and reactivity of the solvent, allows for process and purity control in industrial environments, and opens a way towards *in situ* investigations of reactions in ionic liquids.

Results

Setup and lock

As ionic liquids are already quite expensive solvent systems, the use of deuterated ILs is not desirable. The absence of deuteration in commonly used ionic liquids therefore prohibits the use of solvent deuterium nuclei for locking purposes. While the addition of deuterated locking additives to the liquid is possible, these will disturb the bulk structure of the IL or influence reactions. Of course, it is possible to use a coaxial tube insert containing a deuterated substance



Ralf Giernoth (born in 1970) received his PhD from the University of Bonn (Germany) under the supervision of Prof. Joachim Bargon. After two years of post-doctoral research at the University of Oxford (UK) with Dr. John M. Brown as a BASF research fellow, he moved to Cologne (Germany). With an Emmy Noether fellowship (DFG) for young researchers he started to build up his own independent group. His research interests include the synthesis and application of ionic liquids, especially for transition metal catalysis, and the development of in situ spectroscopic methods.

From left to right: Ralf Giernoth, Sven Arenz, Matthias S. Krumm, Dennis Bankmann, and our close cooperation partner Nils Schlörer.

---

† This work was presented at the Green Solvents for Synthesis Meeting, held in Bruchsal, Germany, 3–6 October 2004.
‡ Electronic supplementary information (ESI) available: ^{13}C spectrum of ethanol in [bmim][Tf_2N] and gradient-selected spectra of ILs. See http://www.rsc.org/suppdata/gc/b4/b417783e/
*Ralf.Giernoth@uni-koeln.de

to lock *via* the deuterium channel, but this practice frequently makes the lock signal level a bad indicator for the shim quality.

The fluorine nuclei of the two common IL anions Tf_2N^- and BF_4^- provide an internal ^{19}F lock signal that is more susceptible to changes in field homogeneity. Furthermore, this practice allows for the acquisition of ^2H spectra with ^{19}F lock, which is very helpful for mechanistic studies using H/D labelling, but requires a probe with a separate fluorine channel and a corresponding lock unit and preamplifier.

On standard probes, optimum matching may not be achievable due to the differences in physical properties between ionic liquids and standard laboratory solvents. The mismatching will negatively affect sensitivity, pulse lengths and signal quality. For these reasons, we employ a Bruker TXO probe with ^1H, ^2H, ^{13}C and ^{19}F channels specifically matched to ionic liquids.

Experiments in ionic liquids require comparatively high pulse power levels and lengths as well as high lock power. In our setup, typical 90° pulses for the proton channel at typical pulse power levels were around 16 μs on a 5 mm broadband inverse probe (as compared to 9–10 μs for common NMR solvents). Carbon pulse lengths were typically about 15 μs. Using the 10 mm TXO probe, pulse lengths were about 28 μs for protons and 20 μs for carbon nuclei. All of these values are well within tolerable limits for multipulse experiments. We attribute the high pulse lengths to a comparatively strong absorption of radio frequency radiation by the ionic liquid. During the course of the experiments no sample heating has been observed, however.

Referencing

When applied in the course of *in situ* studies, the chemical shift axis of the NMR spectrum may be conveniently calibrated *via* an arbitrary internal standard. The direct addition of tetramethylsilane (TMS) to the IL as a proton and carbon shift standard is undesirable, though, as it may interact with the system under investigation. A coaxial glass insert containing pure TMS proved suitable for ^1H and ^{13}C external referencing of ^{19}F locked acquisitions, likewise a 1 : 1 mixture of TMS and acetone-d6 for ^2H locking and proton referencing. Due to the attenuation of signals through the ionic liquid medium, the use of a standard solution (*e.g.* 1% TMS in chloroform-d) is not helpful. To compensate for changes in dielectric properties and obtain correct shift values, further referencing against the standards as defined by IUPAC is necessary.[18]

Relaxation

To assess the feasibility of multipulse experiments, proton T_1 values have been determined for a range of imidazolium type ionic liquids with Tf_2N^- and BF_4^- anions *via* inversion recovery experiments. Taking into consideration the typical pulse lengths mentioned above, the results in Fig. 1 show multipulse sequences to be possible. However, T_1 based suppression of the solvent signals from the spectrum, as would be desirable for routine spectroscopy, is precluded by the similarity of solvent and solute relaxation times.

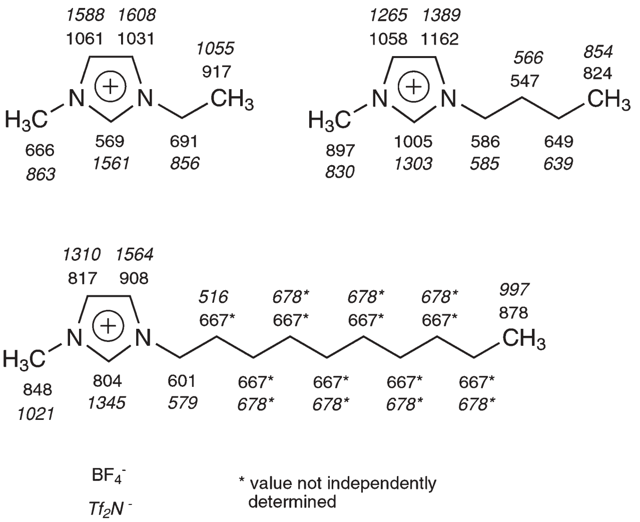


Fig. 1 Proton relaxation data in milliseconds acquired on a 10 mm TXO probe with ^{19}F lock. Values marked with an asterisk have been determined for multiple protons with overlapping signals.

An important trend to notice here is the reduction of T_1 values of the imidazolium ring protons when going from Tf_2N^- to BF_4^- anions. This is in good agreement with the observation of H-bonding of BF_4^- to all three ring protons.[8,10,17,19]

1D spectra of common ILs

The spectra of neat ionic liquids closely resemble those measured in standard NMR solvents. Fig. 2 shows the experimental proton spectrum of [bmim][Tf_2N].

The ^{13}C spectra show a similar appearance and high sensitivity. The acquisition of high S/N-ratio spectra of the IL is possible with less than 8 scans. In all experiments, the CF_3 quartet of the Tf_2N^- anions is clearly visible (Fig. 3).

Resolution and performance

After careful optimisation of shims and pulse lengths, we were able to attain high resolution and good lineshapes routinely. The typical signal widths of about 3–5 Hz (full width at half

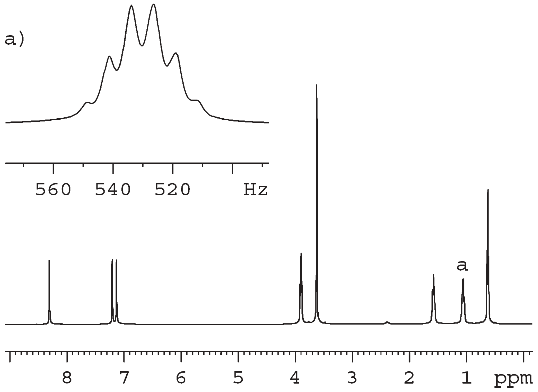


Fig. 2 ^1H spectrum of neat [bmim][Tf_2N] at 298 K acquired on a TXO probe with ^{19}F lock.

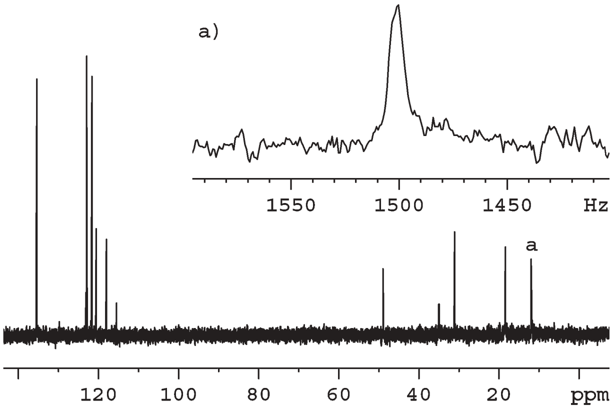


Fig. 3 ^{13}C spectrum of neat [bmim][Tf_2N] at 298 K acquired on a TXO probe with ^{19}F lock.

maximum) in proton spectra at room temperature are still somewhat higher than in classical solvents, which we presume is a result of the higher viscosity of ionic liquids. Performing experiments at temperatures between 278 K and 338 K (Fig. 4) accordingly show decreasing line width with increasing temperature.

Solutes in ionic liquids

As a test substance, we dissolved a drop of ethanol in the ionic liquid [bmim][Tf_2N]. As can be seen from the spectrum in Fig. 5, the CH_2 and CH_3 groups are visible and mostly resolved in the spectrum. The alcohol proton is not visible, however. In the carbon spectrum, both ethanol signals are clearly visible (see supporting information‡).

This experiment shows that the strong signals from the undeuterated solvent do not preclude observation of solutes. The solute signals appear with similar resolution to those of the solvent. Optimisation is expected to increase the resolution and sensitivity further. With the advent of solvent suppression techniques, even weaker signals or signals which are isochronous to solvent signals will become available for observation.

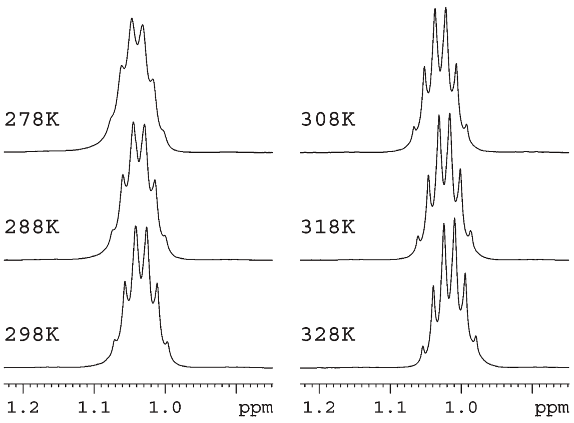


Fig. 4 The CH_2–CH_3 signal of [bmim][Tf_2N] as a function of the sample temperature. The spectra were acquired with ^2H lock on a 5 mm BBI probe.

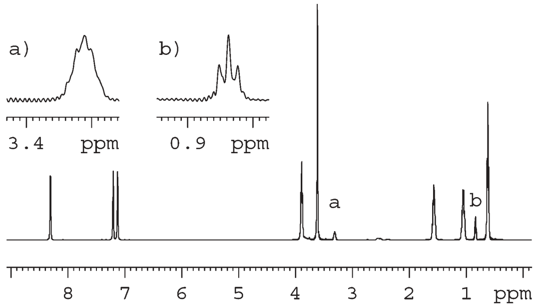


Fig. 5 Proton spectrum of [bmim][Tf_2N] containing one drop of ethanol. The spectrum was acquired with ^2H lock on a 5 mm BBI probe.

Advanced experiments

We were able to carry out 2-dimensional experiments like COSY, HETCOR and gradient-selected experiments like HMQC on a range of neat ILs. The spectra are available in the supporting information‡ for reasons of brevity, as they closely resemble those measured in standard solvents. First multipulse experiments focusing on solutes in ILs could also be realised. The results parallel those in standard solvents. Fig. 6 shows the H,H-COSY spectrum of [bmim][Tf_2N] containing a drop of ethanol. The crosspeaks for the coupling between the CH_2 and CH_3 groups of ethanol can be clearly discerned from the spectrum.

Conclusions

The use of NMR as an *in situ* technique in ionic liquids has been systematically investigated and established. Resolution and appearance of ^1H and ^{13}C spectra of neat ILs have been shown to be similar to those in classical deuterated solvents. Thus, ionic liquids can be regarded as acceptable NMR

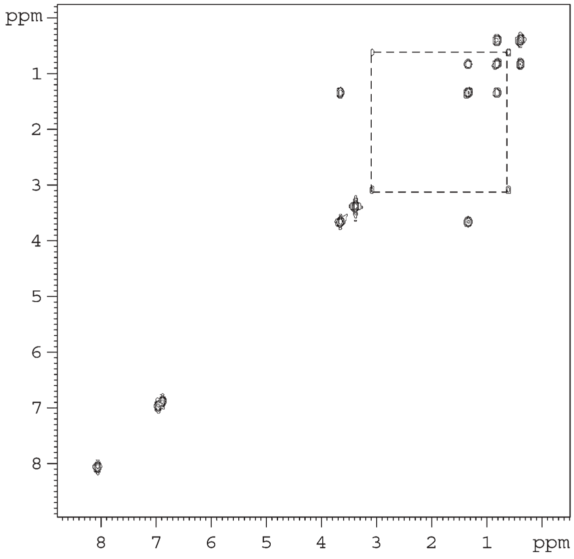


Fig. 6 Gradient COSY spectrum of [bmim][Tf_2N] containing a drop of ethanol. The spectrum was acquired with ^2H lock on a 5 mm BBI probe. The dashed lines indicate the ethanol crosspeaks.

solvents. The synthesis of deuterated ILs for NMR spectroscopy was shown to be avoidable.

We believe that NMR spectroscopy has a high potential for investigating the liquid phase structure of ionic liquids as well as *in situ* investigations of reactions in ionic liquids, especially in cases where the solvent participates. Our current work focuses on advanced NMR techniques including heteronuclear NOE experiments and solvent signal suppression techniques.

Experimental

The fluorine locked experiments were carried out on a Bruker DRX-500 spectrometer (^{1}H base frequency 500 MHz) using a Bruker 10 mm TXO ^{1}H/^{19}F/^{13}C probe with ^{1}H, ^{2}H, ^{13}C and ^{19}F channels. The probe is specifically matched to ionic liquids. Additional experiments were performed on a Bruker 5 mm BBI 1H-BB-D Z-GRD probe with gradient unit. For the one-dimensional experiments the 90° pulse angles were determined and subsequently used in standard pulse sequences. The correlation experiments were performed using standard gradient-selected COSY and HMQC pulse sequences. Unless noted otherwise, the experiments were performed at 298 K using 5 mm NMR tubes (Norell 508-UP). The locking additives were taken from fresh bottles and were injected into 5 mm coaxial inserts under vacuum, frozen with liquid nitrogen and subsequently sealed under vacuum.

The ionic liquids were synthesised according to known literature procedures[20] and dried for 5 h at 70 °C under high vacuum.

Acknowledgements

We thank the Deutsche Forschungsgemeinschaft for financial support of this work through the Emmy Noether programme.

Ralf Giernoth,* Dennis Bankmann and Nils Schlörer
Universität zu Köln, Institut für Organische Chemie, Greinstr. 4, 50939 Köln, Germany. E-mail: Ralf.Giernoth@uni-koeln.de

References

1 *Ionic Liquids in Synthesis*, ed. P. Wasserscheid and T. Welton, Wiley-VCH, Weinheim, 2003.
2 P. Dyson, J. McIndoe and D. Zhao, *Chem. Commun.*, 2003, 508–509.
3 P. Dyson, I. Khalaila, S. Luettgen, J. McIndoe and D. Zhao, *Chem. Commun.*, 2004, 2204–2205.
4 G. Jackson and D. Duckworth, *Chem. Commun.*, 2004, 522–523.
5 C. D. Tran, S. H. D. P. Lacerda and D. Oliveira, *Appl. Spectrosc.*, 2003, **57**, 152–157.
6 L. Cammarata, S. G. Kazarian, P. A. Salter and T. Welton, *Phys. Chem. Chem. Phys.*, 2001, **3**, 5192–5200.
7 A. Noda, K. Hayamizu and M. Watanabe, *J. Phys. Chem. B*, 2001, **105**, 4603–4610.
8 J.-F. Huang, P.-Y. Chen, I.-W. Sun and S. P. Wang, *Inorg. Chim. Acta*, 2001, **320**, 7–11.
9 A. Noda, A. Susan, K. Kudo, S. Mitsushima, K. Hayamizu and M. Watanabe, *J. Phys. Chem. B*, 2003, **107**, 4024–4033.
10 A. Mele, C. D. Tran and S. H. D. P. Lacerda, *Angew. Chem.*, 2003, **115**, 4500–4502; A. Mele, C. D. Tran and S. H. D. P. Lacerda, *Angew. Chem., Int. Ed.*, 2003, **42**, 4364–4366.
11 A. Durazo and M. M. Abu-Omar, *Chem. Commun.*, 2002, 66–67.
12 C. E. Keller and W. R. Carper, *J. Phys. Chem.*, 1994, **98**, 6865–6869.
13 P. C. Trulove, D. K. Sukumaran and R. Osteryoung, *Inorg. Chem.*, 1993, **32**, 4396–4401.
14 Y. S. Fung and S. M. Chau, *Inorg. Chem.*, 1995, **34**, 2371–2376.
15 J. L. E. Campbell, K. E. Johnson and J. R. Torkelson, *Inorg. Chem.*, 1994, **33**, 3340–3345.
16 S. Takahashi, M. L. Saboungi, R. J. Klingler, M. J. Chen and J. W. Rathke, *J. Chem. Soc., Faraday Trans.*, 1993, **89**, 3591–3595.
17 A. Avent, P. Chaloner, M. Day, K. Seddon and T. Welton, *J. Chem. Soc., Dalton Trans.*, 1994, 3405–3413.
18 R. K. Harris, E. D. Becker, S. M. C. D. Menezes, R. Goodfellow and P. Granger, *Pure Appl. Chem.*, 2001, **73**, 1795–1818.
19 J. Antony, D. Mertens, A. Dölle, P. Wasserscheid and W. R. Carper, *ChemPhysChem*, 2003, **4**, 588–594.
20 R. Giernoth and M. Krumm, *Adv. Synth. Catal.*, 2004, **346**, 989–992.

Industrial application of ionic liquids as process aid†

Bernd Weyershausen,* Kerstin Hell and Ute Hesse

Received 1st June 2004, Accepted 24th September 2004
First published as an Advance Article on the web 22nd November 2004
DOI: 10.1039/b408317b

Ionic liquids are no longer just a class of esoteric compounds, but are proving to be valuable and useful in a multitude of different applications. Herein, we report on the development of a hydrosilylation process for the synthesis of organosilicon compounds using ionic liquids for the immobilization, recovery and reuse of the catalyst.

Introduction

Recently, ionic liquids have been extensively evaluated as environmental-friendly or "green" alternatives[1] to conventional organic solvents for a broad range of organic synthetic applications.[2] In addition, ionic liquids have been used *e.g.* as catalysts[3] in organic synthesis, in compositions for stabilizing and/or isolating nucleic acids in or from micro-organisms,[4] as process aids for the synthesis of polynucleotides,[5] as lubricants[6] and for the preparation and stabilization of nanoparticles.[7] Furthermore, after the announcement of the first industrial process involving ionic liquids by BASF (BASIL[8] process) in 2003 the potential of ionic liquids for new chemical processes and technologies is beginning to be recognized.

Bernd Weyershausen studied chemistry and biology at the University of Bonn, Germany. After completion of his diploma thesis at the University of Oviedo, Spain, he earned his doctorate at the University of Bonn in 1998. Supported by a grant of the Alexander von Humboldt Foundation he then worked for one and a half years at The Scripps Research Institute in La Jolla, United States, in the area of the total synthesis of natural products. In 2000 he started his industrial career as a group leader in the R&D department of Degussa's Oligomers & Silicones Business Unit where in 2003 he became head of the section "Silicone Technology" directing about half of the Oligomers & Silicones Business Unit's research capacities. As of January 2005 Bernd Weyershausen will assume responsibilities for Strategic Marketing and New Business Development in Degussa's Industrial Specialties Business Line.

Ionic liquids as process aid

Hydrosilylation

One of the most fundamental and elegant methods of laboratory and industrial synthesis of organomodified polydimethylsiloxanes is the transition metal catalyzed hydrosilylation of CC-double bond containing compounds with SiH-functional polydimethylsiloxanes.[9] Regardless of the broad applicability of the hydrosilylation reaction its technical use still suffers from substantial difficulties. Usually, the reaction is homogeneously catalyzed which means that after completion of the reaction the catalyst either remains within the product or has to be costly removed. From an economic and ecological point of view the recovery and reuse of the expensive precious metal catalyst in homogeneously catalyzed reactions represent serious problems.[10] Therefore, there has been no lack of attempts to reduce the amount of catalyst, which in most cases leads to relatively long reaction times. A technical process based on homogenous catalysis is economically efficient only if in combination with acceptable reaction times the catalyst losses can be kept as small as possible. Hence, there is a demand for processes which allow for the recycling of the catalyst without catalyst losses and the lowest possible stress for the products. In the past, intensive work has been done on immobilization, heterogenization and anchoring of homogenous catalysts for an easy catalyst separation from the products and recovery of the catalyst. Besides *e.g.* the extraction of the catalyst or its adsorption at ion exchangers multiphasic reactions represent another possibility for the separation of product and catalyst phase.

Ionic liquids

In the last few years biphasic reactions employing ionic liquids have gained increasing importance.[11] The ionic liquid generally forms the phase in which the catalyst is dissolved and immobilized. For the first time in 1972, Parshall used an ionic liquid for the immobilization of a transition metal catalyst in a biphasic reaction setup.[12] He described the hydrogenation of CC-double bonds with $PtCl_2$ dissolved in tetraethylammonium chloride associated with tin dichloride ($[Et_4N][SnCl_3]$, mp 78 °C) at temperatures between 60 and 100 °C. "A substantial advantage of the molten salt medium—over conventional organic solvents—... is that the product may be separated by decantation or simple distillation". The use of ionic liquids as

---

† This work was presented at the Green Solvents for Synthesis Meeting, held in Bruchsal, Germany, 3–6 October 2004.
*bernd.weyershausen@degussa.com

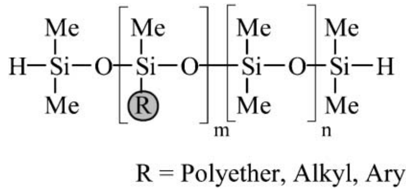


Fig. 1 Organomodified polydimethylsiloxanes (OMS) offer a high synthetical and structural flexibility.

novel media for transition metal catalysis started to receive increasing attention, when in 1992 Wilkes reported on the synthesis of novel non-chloroaluminate, room temperature liquid salts with significantly enhanced stability towards hydrolysis, such as tetrafluoroborate salts.[13] Some of the first succesful examples for catalytic reactions in non-chloroaluminate ionic liquids include the rhodium-catalyzed hydrogenation[14] and hydroformylation[15] of olefins. However, very often catalyst leaching into the organic and/or the product phase is observed, as the transition metal catalyst is not completely retained in the polar ionic liquid phase. Current approaches to circumvent this problem include the modification of the catalyst, the modification of the ligands[15] and the development of task specific ionic liquids.[16]

Organomodified siloxanes

The hydrosilylation of CC-double bond containing compounds with SiH-functional polydimethylsiloxanes is a widely applied reaction in industrial synthesis for the production of organosilicon compounds (Fig. 1) on a technical scale.[9]

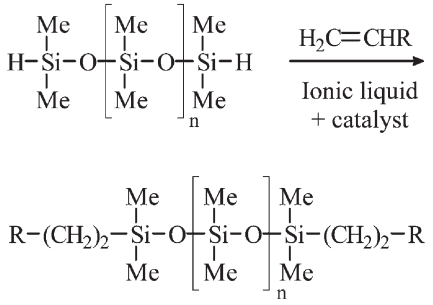
Apart from our general investigations of the hydrosilylation reaction, we became interested in ionic liquids and their potential to be used in hydrosilylation reactions as a means for catalyst heterogenization. In particular, we aimed at the synthesis of polyethersiloxanes. Polyethersiloxanes constitute an important class of surface active compounds which find use in a broad range of industrial applications.[17]

Results and discussion

Herein, we report on a novel process for the synthesis of organomodified polydimethylsiloxanes employing ionic liquids for the heterogenization and/or immobilization of the precious metal catalyst.[18] The advantage of this novel hydrosilylation process is that standard hydrosilylation catalysts can be used without the need of prior modification to prevent catalyst leaching. This is the first known example of a hydrosilylation of olefinic compounds using ionic liquids (Scheme 1).

However, a method for the transition metal catalyzed hydroboration and hydrosilylation of alkynes in ionic liquids has been recently described.[19] Employing the novel hydrosilylation process using ionic liquids a broad range of different organomodified polydimethylsiloxanes was synthesized. The procedure is rather simple and can be described as one pot synthesis (Fig. 2).

For our investigations we chose SiH-functional polydimethylsiloxanes with different chain lengths and functionality patterns and polyethers with different ethylene (EO) and propylene (PO) oxide contents, as well as one small non-polyether olefin (AGE) in order to evaluate the influence of the hydrophilicity/hydrophobicity of the substrates and corresponding products on the catalytic performance of the various catalyst/ionic liquid solutions and even more importantly, on the separation behaviour of the ionic liquid at the end of the reaction. A clean separation of the ionic liquid from the products is the necessary condition to examine the partitioning of the catalyst between the two phases. Naturally, without a clean separation and a much better solubility of the catalyst in the ionic liquid phase than in the product phase a complete retention of the catalyst in the ionic liquid and the desired recovery of the catalyst cannot be achieved. Fig. 3 depicts some of the various polydimethylsiloxanes, olefins, ionic liquids and catalysts used in our investigations; only the ionic liquids and catalysts are shown which gave satisfactory results.



Scheme 1 Hydrosilylation of olefins (*e.g.* polyethers).

The hydrophobicity of the organosilicon products increases with increasing chain length and decreasing SiH-functionalization of the SiH-functional polydimethylsiloxane. The polyethers are more hydrophobic the higher the content of propylene oxide. Now, one would expect that the ionic liquid due to its ionic nature separates more easily from the organosilicon products the more hydrophobic the latter are. During our studies this anticipation was proven to be correct. Table 1 summarizes the results of our investigations.

It turned out that for successful recovery of the catalyst and its reusability it is crucial to find an appropriate combination of a catalyst and an ionic liquid which has to be harmonized with the hydrophilicity/hydrophobicity of the product. First of all, not every catalyst is soluble in each ionic liquid and

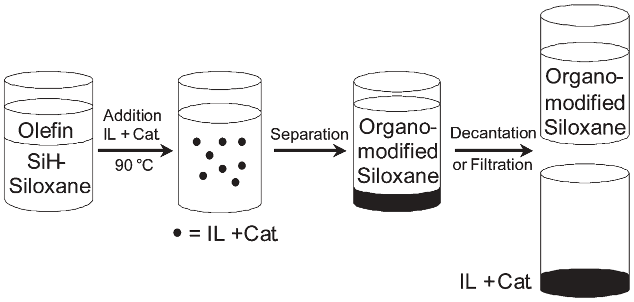


Fig. 2 Schematic representation of the hydrosilylation process using ionic liquids.

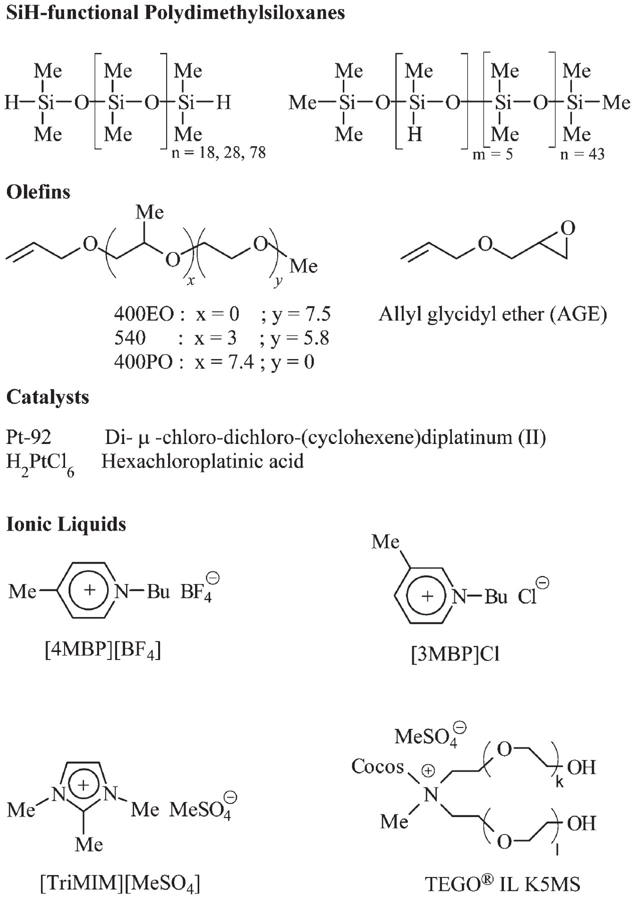


Fig. 3 Raw materials used in the study.

secondly, not every ionic liquid separates as facile as desired from the product phase. However, we were able to identify at least one suitable catalyst/ionic liquid combination for the synthesis of each polyethersiloxane (see Table 1). In some cases more than one catalyst/ionic liquid combination gave good results (see entries nos. 3 and 4, Table 1). It is notworthy that all of the polyethersiloxanes synthesized in this way exhibit very different polarities.

Hydrosilylation reactions with ionic liquids derived from 1-alkylimidazole, *i.e.* in 2-position unsubstituted 1,3-dialkylimidazolium salts, did not give the desired polyethersiloxanes. We assume that the proton in the 2-position of the 1,3-dialkyl-imidazolium salts reacts with the SiH-group of the SiH-functional polydimethylsiloxanes under formation of the corresponding 1,3-dialkylimidazolylidene which deactivates the hydrosilylation catalyst by coordination to the metal center.

Experimental

Typically, the reaction is performed in a liquid–liquid biphasic system where the substrates and products (upper phase) are not miscible with the catalyst/ionic liquid solution (lower phase). The SiH-functional polydimethylsiloxane and 1.3 equiv. of the olefin are placed into the reaction vessel and heated up to 90 °C. Then the precious metal catalyst (20 mass-ppm: metal content of the catalyst based on total weight of combined raw materials) and the ionic liquid (1 mass% based on total weight of combined raw materials) are added. After complete SiH-conversion the reaction mixture is cooled to room temperature and the products are removed from the reaction mixture by either simple decantation or filtration (in the case of non-room temperature ionic liquids). The recovered catalyst/ionic liquid solution can be reused several times without any significant change in catalytic activity. A treatment or workup of the ionic liquid–catalyst solution after each reaction cycle is not necessary. The metal content of the products was analyzed by ICP-OES (*Inductively coupled plasma optical emission spectroscopy*) and the chemical identity of the organomodified polydimethylsiloxane was verified by NMR spectroscopy (^{1}H-, ^{13}C- and ^{29}Si-NMR).

Example 1

The reaction vessel was charged with 71 g [0.1 val (equivalent weight)] of an α,ω-(SiH)-polydimethylsiloxane with a total chain length of 20 Si-atoms and 58.7 g (0.13 mol) of a polyether with an average molecular weight of 400 g mol^{-1} (ethylene glycol content = 100%). The reaction mixture was heated to 90 °C before 5 mg (20 ppm) of di-μ-chloro-dichloro-bis(cyclohexene)diplatinum(II) (Pt-92) dissolved in 1.3 g of 1,2,3-trimethylimidazolium methylsulfate were added. After 5 h the reaction mixture was allowed to cool to room temperature and the polyethersiloxane was filtered off the catalyst/ionic liquid phase. The polyethersiloxane was obtained as a colorless liquid. The catalyst/ionic liquid phase was reused five times without any loss of activity.

Table 1 Results of hydrosilylation reactions of olefins with SiH-functional polydimethylsiloxanes using ionic liquids

Entry	Catalyst	IL	SiH-siloxane	Olefin	Conversion (%/h)	Metal (ppm)[a]
1	Pt-92	[TriMIM][MeSO$_4$][b]	$n = 18$	400EO	>99/5	<1
2	H_2PtCl_6	[3MBP]Cl[c]	$n = 18$	540	>99/3	<1
3	H_2PtCl_6	[4MBP][BF$_4$][d]	$n = 18$	400PO	>99/1	<1
4	H_2PtCl_6	[TriMIM][MeSO$_4$]	$n = 18$	400PO	93/5	<1
5	H_2PtCl_6	[TriMIM][MeSO$_4$]	$n = 78$	AGE	>99/3	<1
6	Pt-92	[TriMIM][MeSO$_4$]	$n = 28$	AGE	>99/1	<1
7	H_2PtCl_6	[TriMIM][MeSO$_4$]	$m = 5$	400PO	>99/1	<1
8	H_2PtCl_6	[TriMIM][MeSO$_4$]	$m = 5$	AGE	>99/3	2
9	H_2PtCl_6	TEGO IL K5 MS[e]	$n = 78$	540	>99/1	5

[a] Detectable platinum content of the product. [b] 1,2,3-Trimethylimidazolium methylsulfate. [c] 3-Methyl-1-butylpyridinium chloride. [d] 4-Methyl-1-butylpyridinium tetrafluoroborate. [e] Cocos pentaethoxy methylammonium methylsulfate.

Example 2

The reaction vessel was charged with 14.2 g (0.02 val) of an α,ω-(SiH)-polydimethylsiloxane with a total chain length of 20 Si-atoms and 14.6 g (0.026 mol) of a polyether with an average molecular weight of 500 g mol^{-1} (propylene glycol content = 40%). The reaction mixture was heated to 90 °C before 1.6 mg (20 ppm) of hexachloroplatinic(IV)acid (Speyer-catalyst) dissolved in 0.3 g of 3-methyl-1-butylpyridinium chloride were added. After 3 h the reaction mixture was allowed to cool to room temperature and the polyethersiloxane was separated from the catalyst/ionic liquid phase. The polyethersiloxane was obtained as a slightly yellow liquid.

Example 3

The reaction vessel was charged with 14.2 g (0.02 val) of an α,ω-(SiH)-polydimethylsiloxane with a total chain length of 20 Si-atoms and 12.66 g (0.026 mol) of a polyether with an average molecular weight of 400 g mol^{-1} (ethylene glycol content = 100%). The reaction mixture was heated to 90 °C and 1.5 mg (20 ppm) of hexachloroplatinic(IV)acid (Speyer-catalyst) dissolved in 0.3 g of 4-methyl-1-butylpyridinium tetrafluoro-borate were added. After 1 h the reaction mixture was allowed to cool to room temperature and the polyethersiloxane was separated from the catalyst/ionic liquid phase. The polyethersiloxane was obtained as a colorless liquid.

Example 4

The reaction vessel was charged with 28.4 g (0.04 val) of an α,ω-(SiH)-polydimethylsiloxane with a total chain length of 20 Si-atoms and 21.74 g (0.052 mol) of a polyether with an average molecular weight of 400 g mol^{-1} (propylene glycol content = 100%). The reaction mixture was heated to 90 °C and 1.5 mg (10 ppm) of hexachloroplatinic(IV)acid (Speyer-catalyst) dissolved in 0.5 g of 1,2,3-trimethylimidazolium methylsulfate were added. After 5 h the reaction mixture was allowed to cool to room temperature and the polyethersiloxane was separated from the catalyst/ionic liquid phase. The polyethersiloxane was obtained as a colorless liquid.

Example 5

The reaction vessel was charged with 147.1 g (0.05 val) of an α,ω-(SiH)-polydimethylsiloxane with a total chain length of 80 Si-atoms and 7.4 g (0.065 mol) of allyl glycidyl ether. The reaction mixture was heated to 115 °C and 8 mg (20 ppm) of hexachloroplatinic(IV)acid (Speyer-catalyst) dissolved in 1.5 g of 1,2,3-trimethylimidazolium methylsulfate were added. After 3 h the reaction mixture was allowed to cool to room temperature and the polyethersiloxane was separated from the catalyst/ionic liquid phase. The epoxy-functional poly-ethersiloxane was obtained as a colorless liquid.

Example 6

The reaction vessel was charged with 55.2 g (0.05 val) of an α,ω-(SiH)-polydimethylsiloxane with a total chain length of 30 Si-atoms and 7.4 g (0.065 mol) of allyl glycidyl ether. The reaction mixture was heated to 115 °C and 2.6 mg (20 ppm) of hexachloroplatinic(IV)acid (Speyer-catalyst) dissolved in 0.6 g of 1,2,3-trimethylimidazolium methylsulfate were added. After 3 h the reaction mixture was allowed to cool to room temperature and the polyethersiloxane was separated from the catalyst/ionic liquid phase. The epoxy-functional polyethersiloxane was obtained as a colorless liquid.

Example 7

The reaction vessel was charged with 15.15 g (0.02 val) of an comblike-(SiH)-polydimethylsiloxane with a total chain length of 50 Si-atoms bearing 5 lateral (SiH)-functionalities 12.6 g (0.026 mol) of a polyether with an average molecular weight of 400 g mol^{-1} (propylene glycol content = 100%). The reaction mixture was heated to 90 °C and 1.5 mg (20 ppm) of hexachloroplatinic(IV)acid (Speyer-catalyst) dissolved in 0.3 g of 1,2,3-trimethylimidazolium methylsulfate were added. After 1 h the reaction mixture was allowed to cool to room temperature and the polyethersiloxane was separated from the catalyst/ionic liquid phase. The polyethersiloxane was obtained as a colorless liquid.

Example 8

The reaction vessel was charged with 22.7 g (0.03 val) of an comblike-(SiH)-polydimethylsiloxane with a total chain lenght of 50 Si-atoms bearing 5 lateral (SiH)-functionalities 4.5 g (0.039 mol) of allyl glycidyl ether. The reaction mixture was heated to 115 °C and 1.4 mg (20 ppm) of hexachloroplatinic(IV)acid (Speyer-catalyst) dissolved in 0.3 g of 1,2,3-trimethylimidazolium methylsulfate were added. After 3 h the reaction mixture was allowed to cool to room temperature and the polyethersiloxane was separated from the catalyst/ionic liquid phase. The epoxy-functional polyethersiloxane was obtained as a colorless liquid.

Example 9

The reaction vessel was charged with 250 g (0.085 val) of an α,ω-(SiH)-polydimethylsiloxane with a total chain length of 80 Si-atoms and 62.1 g (0.11 mol) of a polyether with an average molecular weight of 500 g mol^{-1} (propylene glycol content = 40%). The reaction mixture was heated to 90 °C before 16.6 mg (20 ppm) of hexachloroplatinic(IV)acid (Speyer-catalyst) dissolved in 3.1 g of TEGO IL K5MS (cocos pentaethoxy methylammonium methyl sulfate) were added. After 1 h the reaction mixture was allowed to cool to room temperature and the polyethersiloxane was separated from the catalyst/ionic liquid phase. The polyethersiloxane was obtained as a colorless liquid.

Summary

A novel transition metal catalyzed hydrosilylation process is described. The use of an ionic liquid in this process allows for the immobilization, heterogenization and recovery of the expensive precious metal catalyst, as well as its direct reuse in a subsequent hydrosilylation reaction. From an economic and ecological point of view this process perfectly fits in the concept of "sustainable chemistry". Future research activities will aim at the prolongation of the catalyst life-time. In this respect, it is necessary to gain a deeper understanding of the catalytically active species in the catalyst/ionic liquid solution.

Bernd Weyershausen,* Kerstin Hell and Ute Hesse
Degussa AG, Goldschmidtstr. 100, 45127 Essen, Germany.
E-mail: bernd.weyershausen@degussa.com; Fax: +49-201-173 1839;
Tel: +49-201-173 1655

References

1 R. D. Rogers and K. R. Seddon, *Science*, 2003, **302**, 792.
2 P. Wasserscheid and T. Welton, *Ionic Liquids in Synthesis*, VCH, Weinheim, 2002; R. D. Rogers, K. R. Seddon and S. Volkov, *Green Industrial Applications of Ionic Liquids*, NATO Science Series II. Mathematics, Physics and Chemistry, Kluwer, Dordrecht, 2003, vol. 92; R. D. Rogers and K. R. Seddon, *Ionic Liquids: Industrial Applications to Green Chemistry*, ACS Symposium Series 818, ACS, Washington DC, 2002.
3 H. J. Laas, R. Halpaap, F. Richter and J. Köcher, *Ionic liquids (as catalysts for the oligomerization of isocyanates), Germ. Pat. Appl.*, DE 102 19 227, 30.4.2002, Bayer AG.
4 U. Oelmüller and T. Wille, *Use of compositions consisting of cationic compounds and proton donors for stabilizing and/or isolating nucleic acids in or from micro-organisms such as prokaryots, fungi, protozoa or algae, PCT. Pat. Appl.*, WO 02/00600, 20.6.2001, Quiagen GmbH.
5 J. Myerson, M. G. M. Perobost, D. J. Dellinger and G. F. Dellinger, *Method of synthesizing polynucleotides using ionic liquids, US Pat. Appl.*, US 03/0083489, 31.10.2001, Agilsent Technologies, Inc.
6 R. A. Reich, P. A. Stewart, J. Bohaychick and J. A. Urbanski, *Lubr. Eng.*, 2003, **59**, 16; W. Liu, C. Ye, Q. Gong, H. Wang and P. Wang, *Tribol. Lett.*, 2002, **13**, 81; C. Ye, W. Liu, Y. Chen and L. Yu, *Chem. Commun.*, 2001, **21**, 2245.
7 Y. Zhou and M. Antonietti, *J. Am. Chem. Soc.*, 2003, **125**, 14960; V. Calo, A. Nacci, A. Monopoli, S. Laera and N. Cioffi, *J. Org. Chem.*, 2003, **68**, 2929; J. Dupont, G. S. Fonseca, A. P. Umpierre, P. F. P. Fichtner and S. R. Teixeira, *J. Am. Chem. Soc.*, 2002, **124**, 4228; G. S. Fonseca, A. P. Umpierre, P. F. P. Fichtner, S. R. Teixeira and J. Dupont, *Chemistry*, 2003, **9**, 3263.
8 M. Volland, V. Seitz, M. Maase, M. Flores, R. Papp, K. Massonne, V. Stegmann, K. Halbritter, R. Noe, M. Bartsch, W. Siegel, M. Becker and O. Huttenloch, *Method for the separation of acids from chemical reaction mixtures by means of ionic fluids, PCT Int. Appl.*, WO03/06225, 31.7.2003, BASF AG; M. Freemantle, *Chem. Eng. News*, 2003, **81**, 9.
9 B. Marcniec, *Applied Homogeneous Catalysis with Organometallic Compounds*, ed. B. Cornils and W. A. Herrmann, VCH, Weinheim, 1996, vol. 1, p. 487.
10 B. Cornils and W. A. Herrmann, *Applied Homogeneous Catalysis with Organometallic Compounds*, ed. B. Cornils and W. A. Herrmann, VCH, Weinheim, 1996, vol. 2, p. 573.
11 P. Wasserscheid, *Transition Metal Catalysis*, in *Ionic Liquids in Ionic Liquids in Synthesis*, ed. P. Wasserscheid and T. Welton, VCH, Weinheim, 2002, p. 213.
12 G. W. Parshall, *J. Am. Chem. Soc.*, 1972, **94**, 8716.
13 J. S. Wilkes and M. J. Zaworotko, *J. Chem. Soc., Chem. Commun.*, 1992, 965.
14 P. A. Z. Suarez, J. E. L. Dullius, S. Einloft and R. F. de Souza, *Polyhedron*, 1996, **15**, 1217.
15 Y. Chauvin, L. Mußmann and H. Olivier, *Angew. Chem. Int. Ed.*, 1995, **34**, 1149.
16 J. H. Davis, *Synthesis of Task-specific Ionic Liquids*, in *Ionic Liquids in Synthesis*, ed. P. Wasserscheid and T. Welton, VCH, Weinheim, 2002, p. 33.
17 http://www.degussa.com/en/structure/performance_materials/-oligomers silicones.html.
18 K. Hell, U. Hesse and B. Weyershausen, *Production of organopolysiloxanes using ionic liquids, Eur. Pat. Appl.*, EP1382630, 21.1.2004, Goldschmidt AG.
19 S. Aubin, F. Le Floch, D. Carrie, J. P. Guegan and M. Vaultier, *ACS Symp. Ser. (Ionic Liquids)*, 2002, **818**, 334.

Continuous reactions in supercritical fluids; a cleaner, more selective synthesis of thymol in supercritical CO_2†‡

Rodrigo Amandi,[a] Jason R. Hyde,[a] Stephen K. Ross,[b] Tobias J. Lotz[c] and Martyn Poliakoff*[a]

Received 17th December 2004, Accepted 7th March 2005
First published as an Advance Article on the web 11th April 2005
DOI: 10.1039/b418983c

Continuous fixed-bed catalytic Friedel–Crafts alkylation of *m*-cresol with different alkylating agents, isopropanol (IPA) and propylene, has been carried out using supercritical CO_2, $scCO_2$, as an alternative and more environmentally friendly reaction medium, for the synthesis of the fine chemical thymol. Both a solid Lewis acid catalyst (γ-Al_2O_3) and a solid Brønsted acid catalyst (Nafion® SAC-13) have been investigated over a range of reaction conditions to optimise yield and selectivity for thymol. The reaction product distribution was found to be related to the type of catalyst employed. This is likely to have been due to the different reaction pathways through which the reaction occurred, a direct Friedel–Crafts alkylation in the case of Brønsted type acids and a Fries rearrangement when employing the Lewis catalyst. The new technique of 2DCOR-GC analysis was employed to establish the order of formation of the different species generated in the reaction over the two catalysts in $scCO_2$.

Introduction

Friedel–Crafts alkylation of aromatic compounds is among the most fundamental and useful reactions for carbon–carbon bond formation in aromatic rings.[1] However it is one of the more wasteful in terms of by-product formation, atom efficiency and catalyst usage. Minimisation, or preferably, elimination of waste in chemicals manufacture, is a major objective of Green Chemistry. Hence, the development of economically viable and more environmentally acceptable Friedel–Crafts alkylation processes is highly desirable. One possibility is the use of reaction media such as supercritical fluids, particularly supercritical carbon dioxide ($scCO_2$), as a replacement for conventional organic solvents. The use of $scCO_2$ as the reaction medium in the above reactions might offer the following advantages: enhancement of the reaction rate;[2,3] improved heat and mass transfer at the surface of the catalyst[4,5] and there is some evidence for an increase in the catalyst lifetime due to the extraction of coke precursors.[6,7]

When combined with solid acid catalysts, $scCO_2$ forms the basis of a very efficient process. Friedel–Crafts alkylation of aromatics has been successfully conducted in $scCO_2$ in batch reactors by a number of groups.[8,9] Batch reactions in $scCO_2$ are economically difficult to scale-up because of the cost of large high pressure vessels. However, the use of continuous processes reduces the size of the reactor required to generate a given amount of product and increases safety. This type of process[10] has been demonstrated with the opening of the world's first industrial-scale, multi-purpose supercritical flow reactor in July 2002. Continuous fixed-bed catalytic flow reactors have been used in a wide range of supercritical reactions including hydrogenation,[11] hydroformylation,[12] etherification[13] and indeed Friedel–Crafts type alkylation of simple aromatics.[14]

In this work, we describe the successful application of continuous Friedel–Crafts alkylation in the synthesis of the fine chemical thymol (*6-isopropyl-3-methyl-phenol*) **1**. Thymol possesses some important physiological properties, and it is also widely used in perfumery as an important intermediate in the manufacture of menthol, the major component of fragrances with a peppermint odour.[15] Industrially, thymol is

Rodrigo Amandi studied chemistry in San-Pablo CEU University in Madrid, Spain, where he obtained his degree in 1999. Later on in the year he joined the research group of Dr Flaviano Garcia-Alvarado where he investigated the synthesis and characterisation of new cathodic materials for rechargeable lithium batteries. In September 2000, he started his PhD in the Clean Technology Group, at the University of Nottingham, UK, under the supervision of Prof. Martyn Poliakoff. His research was developed in collaboration with the fine chemical manufacturer Thomas Swan & Co. and was focused on the application of supercritical fluids as replacement solvents for the synthesis of fine chemicals. After completion of his PhD, in late 2003, he started a post-doc within the Clean Technology Group funded by the chemical manufacturer Schenectady Pratteln. He is currently employed as a post-doc, in the Institute of Process Engineering at the ETH in Zurich, Switzerland, under the supervision of Prof. Philipp Rudolf von Rohr.

---

† This work was presented in part at the Green Solvents for Synthesis Meeting, held in Bruchsal, Germany, 3–6 October, 2004.
‡ Electronic supplementary information (ESI) available: Synchronous and asynchronous correlation maps for the 2DCOR-GC data presented in Fig. 1. See http://www.rsc.org/suppdata/gc/b4/b418983c/
*Martyn.poliakoff@Nottingham.ac.uk

obtained by the liquid phase isopropylation of *m*-cresol **2** with propene using activated alumina as catalyst.[16] Wimmer *et al.*[17] have described a process for the synthesis of thymol by reacting *m*-cresol with propene, but using wide and medium pore size (pore diameter of 5–7 Å) zeolites.

In the last few years, other types of solid acid catalysts have been employed in the synthesis of thymol, including calcined Mg–Al hydrotalcites,[18] zinc aluminate spinel ($ZnAl_2O_4$)[15] and mesoporous Al-MCM-41 molecular sieves of different Al : Si ratios.[19]

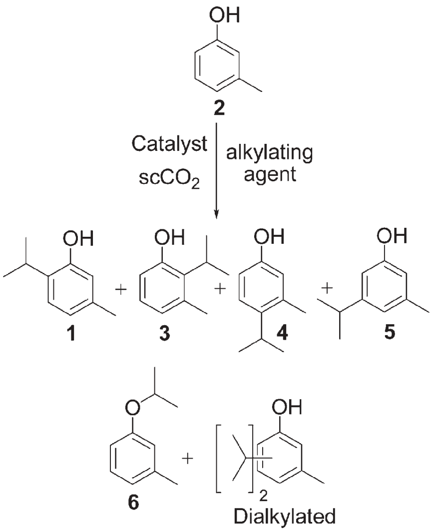
The most important reaction parameter to be controlled in the synthesis of thymol is selectivity towards the product of interest. This is because the boiling points of all the possible isomers generated during the reaction, *2-isopropyl-3-methyl-phenol* **3**, *4-isopropyl-3-methyl-phenol* **4** and *5-isopropyl-3-methyl-phenol* **5** are very similar, making the distillation step needed to separate all the components very difficult indeed; in particular, separation of thymol from **3**. For this reason, generation of unwanted isomers is an issue that must be minimised by careful control of the reaction parameters. Also, an excess of the aromatic species is generally used to decrease the amount of dialkylated and polyalkylated derivatives formed during the reaction.

Results and discussion

Effect of catalyst

The effect of the different reaction parameters, *e.g.* temperature, pressure, concentration of organic material within $scCO_2$ and molar ratio of reactants, has been investigated in depth for both solid catalysts investigated, with the aim of optimising the yield and selectivity for **1**. Table 1 compares the results obtained on the alkylation of **2** with isopropanol (IPA) at the optimum reaction temperature found for both catalysts.

It is clear from Table 1 that the major by-product formed during the reaction, when employing Nafion® SAC-13 is **4**. Further changes in the reaction pressure (100–400 bar), molar ratio of reactants from 3 : 1 to 10 : 1 (**2** : IPA) and concentration of organic material in $scCO_2$ (10–50%w/w) did not have a significant influence on the reaction outcome in terms of yield and selectivity of products. In contrast, when using γ-Al_2O_3 as a solid acid catalyst, the major by-product observed was **3**. Also, a small amount of isopropyl-3-methyl-benzylether **6** was observed when using γ-Al_2O_3. Increasing the reaction temperature above 275 °C, caused a decrease in the yield and selectivity towards thymol as well as an increase in the yield of **4** and **5**. There was a substantial increase in the by-products **3** and **6** when the concentration of organic substrate within $scCO_2$ (see Table 2) was increased with a corresponding decrease in the thymol yield.



Scheme 1 Products formed in the alkylation of **2** over solid acid catalysts in $scCO_2$.

Table 1 % Yield of products and selectivity towards **1** for the Friedel–Crafts alkylation of **2** with IPA over solid acid catalysts in $scCO_2$[a]

	% Yield[d]						
Catalyst	**1**	**3**	**4**	**5**	**6**	Dialkyl.	% Select.[e] **1**
Nafion® SAC-13[b]	52.0	2.5	21.3	4.4	0	6.6	61.2
γ-Al_2O_3[c]	54.0	9.7	1.0	0.4	0.8	2.0	78.6

[a] 200 bar, 3 : 1 molar ratio (**2** : IPA) and 10%w/w of organic material in $scCO_2$. [b] 175 °C. [c] 275 °C. [d] The remaining material was unreacted **2**. [e] Selectivity for **1** was calculated by dividing the number of moles of **1** generated by the sum of the number of moles of **1**, **3**, **4**, **5**, **6** and dialkylated species formed in the reaction.

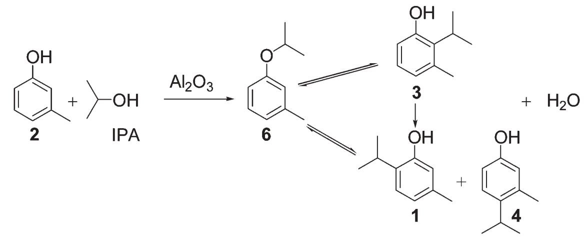
The amount of organic substrate pumped into the supercritical flow system per unit of time, is related to the residence time of reactants across the catalyst bed. As seen from Table 2, the amounts of **3** and **6** generated during the reaction decreased with increasing residence time, but also during this same increase in residence time, an increase in the yield of **1** and **4** were observed. This behaviour suggests that **6** is the first species formed in the reaction, and that **1**, **3** and **4** are formed through a Fries rearrangement process in which **3** (kinetic product) is formed before **1** and **4** (thermodynamic products) according to Scheme 2. The yield of **5** also increased, albeit moderately, with increasing residence time. Formation of **5** is believed to occur *via* an isomerisation process from the more stable species generated in the reaction (**1**, **3** and **4**).[20]

The alkylation of anisole (methyl-phenylether) using IPA and *n*-propanol as the alkylating agents over γ-Al_2O_3, was also attempted. No alkylated derivatives whatsoever were observed across the range of temperature from 100 °C to 250 °C, at 200 bar, 3 : 1 molar ratio of reactants (aromatic : alkylating agent) and a concentration of organic substrate in $scCO_2$ of 10%w/w. The only products detected, were phenol, *o*-cresol,

Table 2 Effect of the concentration of organic material in $scCO_2$ for the alkylation of **2** with IPA over γ-Al_2O_3[a]

	% Yield[b]						
%w/w of organic	**1**	**3**	**4**	**5**	**6**	Dialkyl.	% Select.[b] **1**
5	72.0	1.4	2.4	0.6	0.2	1.8	92.2
10	54.0	9.7	1.0	0.4	0.8	2.0	78.6
20	37.1	15.4	0.9	0.1	1.0	1.4	66.1
50	20.0	13.0	0.6	0	10.0	0.4	44.9

[a] 200 bar, 275 °C and 3 : 1 molar ratio (**2** : IPA). [b] See Table 1 for definition.



Scheme 2 The proposed mechanism for the alkylation of **2** with IPA using γ-Al_2O_3 as the catalyst in $scCO_2$.

m-cresol and *p*-cresol. Formation of these cresols would come from the Fries rearrangement of the starting material, anisole, under the reaction conditions investigated. The fact that a non-hydroxy aromatic cannot be alkylated by IPA using γ-Al_2O_3 as catalyst, is consistent with the Fries rearrangement pathway postulated.

2DCOR-GC analysis was carried out in order to investigate further the proposed mechanism for the formation of thymol. 2DCOR-GC is a new technique developed at Nottingham,[21] which is particularly applicable to unselective reactions monitored by GC. The technique has previously been described in detail.[21] Briefly, 2DCOR-GC uses a set of chromatograms from a system which has been perturbed, for example by changing residence time in a reactor, and uses these chromatograms to generate a 2D map which is rich in information. One of the advantages of 2DCOR-GC is an increase in resolution obtained by stretching chromatograms in a second dimension, which is demonstrated[21] by the resolution between the two isomers of thymol, **1** and **3**, on this particular chromatographic column. In our experiments the reaction residence time was used as the perturbation in order to distinguish in which order the reaction products are produced. Only the synchronous relationships are shown in Fig. 1, because these are sufficient to show that the mechanisms of the two catalysts are clearly very different. One advantage of 2DCOR-GC is that, even at this level of analysis, it is possible to see significant differences between a series of apparently similar chromatograms. Fig. 1a shows the synchronous map produced by the reaction performed with Nafion® SAC-13. A detailed analysis of this correlation map can be found elsewhere.[21] However, it is clear that many products are produced from this reaction. The correlations and their strengths indicate that the reaction is most likely a direct alkylation. A more detailed analysis shows that **6** is formed first, with **3** being produced more rapidly than **1** and **4**. **5** is produced at the slowest rate. By comparison Fig. 1b is the synchronous correlation map obtained from the reaction performed over γ-Al_2O_3 catalyst. It can be seen that this is a cleaner reaction producing fewer products and intermediates. The relationships between **3** and **1** and **4** indicate that all three products most probably originate from **6**; this is consistent with the postulated Fries rearrangement. Again, **3** is produced more rapidly than **1** but in smaller quantities. Since the reaction residence time is the same during the perturbation for both experiments, the lack of **5** production over the γ-Al_2O_3

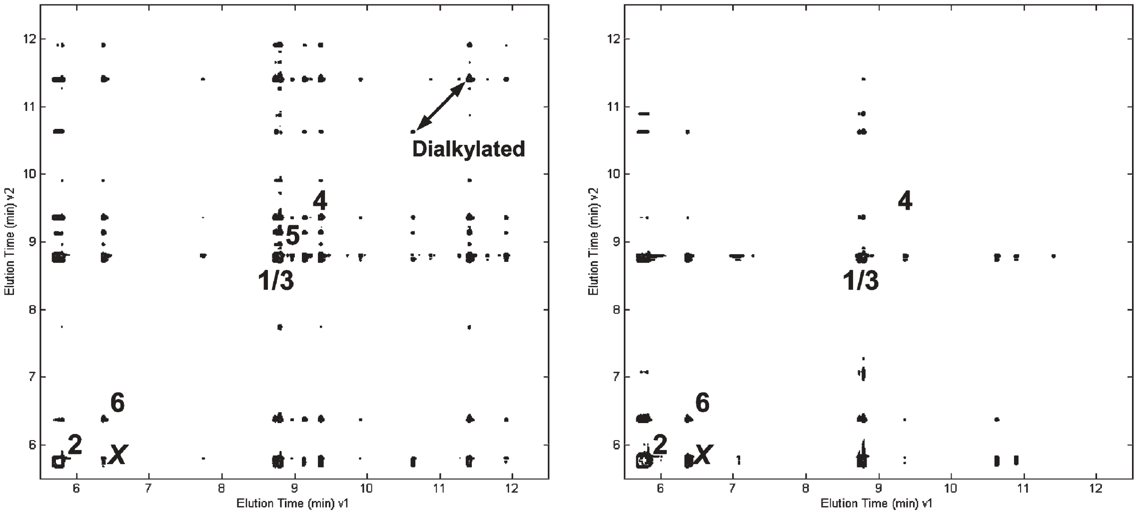


Fig. 1 2DCOR-GC synchronous map produced from the chromatograms recorded using the residence-time perturbed reaction of **2** with IPA over (a) Nafion® SAC-13 catalyst and (b) γ-Al_2O_3 catalyst. 2DCOR-GC can produce two types of correlation maps, synchronous and asynchronous. Only the synchronous maps are shown here. If the mechanisms were related, then, under the same perturbation and level of contouring, the maps would appear identical. Clearly, the maps are different so the mechanisms cannot be identical. The maps are symmetrical about the diagonal axis. Signals along this diagonal, referred to as 'autopeaks', reflect the change in a particular GC signal during the course of the perturbation; a strong autopeak reflects a strong change in signal. The autopeaks are labelled **1**, **2**, *etc* according to Scheme 1 (note that the autopeaks of **1** and **3** almost overlap). Off-diagonal peaks indicate correlations between two signals centred about v_1 and v_2 positions. Thus, the point ***X*** indicates that the correlation between **2** and **6** is weaker in (a) than in (b), because the contour plot for ***X*** is larger in (b). In addition there are more peaks to the right of ***X*** along the bottom of (a) than in equivalent positions in (b). This indicates that **2** is correlated to more products in (a) than in (b), precisely reflecting the greater selectivity of the Lewis acid catalyst in (b). It can be seen that in both cases, **1**, **4** and **3** are synchronously related, but only in (a) is there an autopeak for **5**. In both (a) and (b) it can be seen that **1** and **3** are formed, and can be correlated to **6**, as indicated by the direction of the cross-correlation peaks; this indicates that both species have a common relationship. Both the synchronous and asynchronous maps are available in colour as ESI‡ and a full analysis of the correlation map (a) is given in ref. 18.

catalyst indicates that this reaction is not a direct alkylation, and that transalkylation reactions do not occur within the residence time in the reactor. The 2DCOR-GC analysis presented here supports the proposed routes for production of **1** over the two catalysts.

Further studies focused on increasing the yield and selectivity for **1** using γ-Al_2O_3 as heterogeneous catalyst. To maximise the yield and selectivity for **1**, the residence time across the catalyst bed had to be maximised by increasing the volume of the reactor tube used in the experiments, by increasing its length, as well as by decreasing the bulk flow of CO_2 through the system. Alternatively, a further increase in pressure would have increased the residence time, but as stated before, pressure did not have a major impact on the reaction outcome. Table 3 and Table 4 show the effects of increasing the reactor volume to double its original value and of decreasing the bulk flow of $scCO_2$ respectively.

As expected, by increasing the reactor volume to 20 mL, the yield and selectivity for **1** was increased while decreasing the amount of **3** generated. In contrast, when the flow of CO_2 through the system was decreased to half the initial rate, the reaction outcome was almost unaffected. This was unexpected, because, as explained before, a decrease in the bulk flow of CO_2 should have increased the yield of **1**. Phase measurements (Fig. 2) were carried out to determine if a phase transition was occurring upon decreasing the amount of organic within $scCO_2$.

Under the conditions studied (200 bar, 275 °C), the reaction proceeded in a single phase for both of the concentrations of organic substrate investigated. Thus, a phase transition cannot explain why the reaction outcome did not vary when the bulk flow of CO_2 was decreased. Nevertheless, a possible explanation could be that the water generated when the reaction was conducted at 5%w/w is sufficiently removed by the $scCO_2$ from the catalyst surface. In contrast, at 10%w/w, the water generated in the reaction is too much, and consequently the water removal from the catalyst surface is not sufficient, therefore decreasing the catalyst activity to some extent. To investigate the effect of water on the catalyst performance, water was deliberately added to the mixture of reactants in a 1 : 0.8 : 0.8 molar ratio (**2** : IPA : H_2O). The results are shown in Table 5.

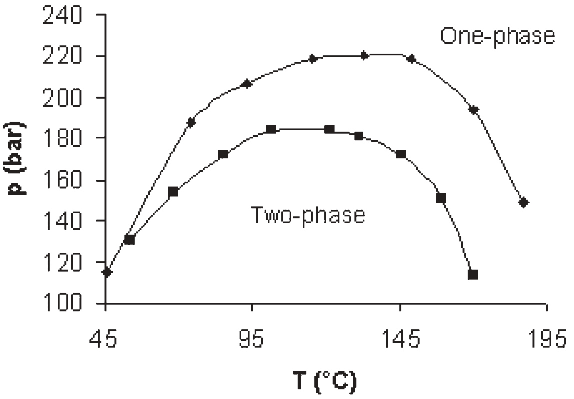


Fig. 2 *p vs. T* phase diagram for the alkylation of **2** with IPA at 1 : 0.8 molar ratio (**2** : IPA) at 5%w/w (■) and 10%w/w (◆). The phase measurements were conducted using a fibre optic probe developed at the University of Nottingham.[22]

Table 3 Influence of the reactor size on the alkylation of **2** with IPA over γ-Al_2O_3 in $scCO_2$[a]

	% Yield						
Reactor volume/mL	**1**	**3**	**4**	**5**	**6**	Dialkyl.	% Select. **1**
10	55.0	1.5	1.1	0.3	0.3	2.9	90.5
20	69.5	1.2	1.0	0.3	0.3	4.2	91.0

[a] 200 bar, 275 °C, 5%w/w of organic in $scCO_2$ and 1 : 0.8 molar ratio (**2** : IPA).

Table 4 Effect of the reaction bulk flow in the synthesis of thymol *via* alkylation of **2** with IPA over γ-Al_2O_3 in $scCO_2$[a]

	% Yield						
Bulk flow/L min^{-1}	**1**	**3**	**4**	**5**	**6**	Dialkyl.	% Select. **1**
0.65	48.5	5.8	0.7	0.2	0.5	3.5	82.3
0.32	46.5	6.5	0.7	0.2	0.5	3.7	80.6

[a] 200 bar, 275 °C, 10%w/w of organic in $scCO_2$ and 1 : 0.8 molar ratio (**2** : IPA).

Table 5 clearly shows that water has an effect on the performance of the catalyst by decreasing the yield and selectivity for **1**. The water generated in the reaction, in addition to the water added to the reactants, was not sufficiently removed by the $scCO_2$, hence a deactivation of the catalyst occurred.

Effect of alkylating agent

The effect of different alkylating agents on the alkylation of *m*-cresol to form thymol was also investigated. To this end, propylene was employed in the alkylation of **2** over γ-Al_2O_3, and the results obtained were compared to those achieved when using IPA. The use of propylene as the alkylating agent avoids the formation of water as a reaction by-product, therefore eliminating the catalyst deactivation previously observed. The effect of temperature was first investigated. The results are displayed in Table 6.

Maximum yield in conjunction with very high selectivity for **1** was achieved at 275 °C. The amount of **3** generated decreased upon increasing the reaction temperature. The yield of **3** at 275 °C, was rather low compared to the amount generated using IPA as the alkylating agent as it was shown in Table 4. In contrast, the yield of polyalkylated species

Table 5 Effect of water on the alkylation of **2** with IPA over γ-Al_2O_3 in $scCO_2$[a]

	% Yield						
	1	**3**	**4**	**5**	**6**	Dialkyl.	% Select. **1**
Added H_2O	46.1	4.4	0.7	0.2	0.4	2.4	85.2
No H_2O	55.0	1.5	1.1	0.3	0.3	2.9	90.5

[a] 200 bar, 275 °C, 5%w/w of organic in $scCO_2$ and 1 : 0.8 molar ratio (**2** : IPA).

Table 6 Effect of the reaction temperature on the alkylation of **2** with propylene over γ-Al_2O_3 in $scCO_2$[a]

	% Yield						
T/°C	**1**	**3**	**4**	**5**	**6**	Dialkyl.	% Select. **1**
200	32.0	8.2	0.3	0.1	0.5	3.6	71.4
250	47.0	1.7	1.1	0.5	0.2	7.3	80.1
275	50.6	1.2	1.6	0.6	0.2	5.2	84.5
300	44.1	1.5	3.2	1.4	0.1	6.4	76.8

[a] 200 bar, 1 : 0.8 molar ratio (**2** : propylene) and 10%w/w of organic material in $scCO_2$.

increased by a large amount and the yield of **4** was also significantly higher.

Further investigations focused on whether an increase in the concentration of organic substrate, **2** and propylene, within $scCO_2$, had the same effect on the catalyst performance as when employing IPA as the alkylating agent (Table 7). However, yield and selectivity for thymol were maintained to similar values even upon increasing the concentration of organic substrate within $scCO_2$ to 40%w/w. This was thought to be related to the higher reactivity of olefins compared to alcohols. Also, the "dry" reaction conditions when employing propylene as the alkylating agent in $scCO_2$, clearly increased the catalytic performance of γ-Al_2O_3, therefore maximising the reaction throughput.

Conclusions

The alkylation of **2** using both IPA and propylene as the alkylating agent, can successfully be carried out in $scCO_2$ as a continuous process to form thymol highly selectively. The choice of catalyst has been shown to be crucial for the selective alkylation of **2** with IPA in $scCO_2$. The use of the Lewis acid γ-Al_2O_3 limited the formation of unwanted products to a great extent compared to the solid Brønsted acid catalyst investigated (Nafion® SAC-13). This was thought to be related to the different reaction mechanisms that were taking place: a direct Friedel–Crafts alkylation reaction when employing Nafion® SAC-13 and a Fries rearrangement process when using γ-Al_2O_3. 2DCOR-GC has proved to be a powerful and useful tool that could be used to elucidate the order of formation of the different species generated during a reaction, and consequently understand the mechanism of the chemical processes that are occurring.

It appears that $scCO_2$ can effectively remove the small quantities of water that are formed in the reaction. However, increasing the amount of organic substrate pumped into the system led to a decrease in catalyst performance as a result of the larger amount of water generated. Employing propylene as the alkylating agent eliminates the water formed as a by-product, and therefore increases the catalytic performance of γ-Al_2O_3 significantly.

Table 7 Effect of the concentration of organic material in $scCO_2$ for the alkylation of **2** with propylene over γ-Al_2O_3[a]

	% Yield						
%w/w of organic	**1**	**3**	**4**	**5**	**6**	Dialkyl.	% Select. **1**
10	50.6	1.2	1.6	0.6	0.2	5.2	84.5
20	50.2	1.6	1.3	0.9	0.2	6.5	83.2
40	49.7	1.3	1.3	0.8	0.2	7.0	82.8

[a] 200 bar, 275 °C and 1 : 0.8 molar ratio (**2** : propylene) in $scCO_2$.

Ideally, the alkylation reaction could be performed using IPA as alkylating agent instead of propene, which is used in current industrial processes, thus, eliminating the handling hazards associated with the use of propene. A final question relates to the precise role of the CO_2 in this reaction. We have performed the reaction of IPA + **2** over the γ-Al_2O_3 catalyst in the absence of CO_2 (1 : 0.8 ratio of **2** : IPA, 0.12 mL min^{-1} flow rate, reactor volume was 10 mL, 200 bar, 272–276 °C). Surprisingly, the overall selectivity (48.2%) for **1** was almost identical to that observed with CO_2 (48.5%). Crucially however, the yield of the two isomers **3** and **4** were doubled. This is of great importance because of the problems of separating **3** and **4** from **2**. Thus, the effect of CO_2 appears to be significant in suppressing the formation of these minor products but the precise mechanism remains unclear.

Continuous flow $scCO_2$ systems have shown a real advantage for the alkylation of aromatic compounds, to produce species of great industrial interest, such as thymol. Further experiments, including catalyst lifetime, need to be carried out to complete full implementation of this process in the chemical industry.

Experimental

A schematic diagram of the supercritical fluid continuous flow apparatus used to carry out all the experiments described in this paper, is shown in Fig. 3. The CO_2 used as the solvent in our reactions was stored as a liquid, in a cylinder next to the apparatus. The liquid CO_2 was fed into a refrigerated reciprocating pump (D) and compressed to reaction pressure *via* pressure multiplication by a compressed air supply. The liquid organic substrate (A) was pumped into the system using a HPLC pump. Alternatively, liquified gaseous reactants were pumped using a JASCO PU-1580-CO2 pump. The $scCO_2$ and the organic substrate were mixed mechanically in a static mixer (B, unheated NPT crosspiece filled with glass beads of 1.5–2 mm diameter) before the mixture reached the reactor (C). Thermocouples placed inside the catalyst bed, in the product(s) stream leaving the reactor and in the heating block were used to monitor the reaction temperature. The reactor used in the majority of our experiments, consisted of a 12 mm (OD) 316-stainless steel tubing with an internal volume of 10 mL. Reactors with larger internal volume were also employed in some of the experiments as indicated. The reaction pressure was dropped stepwise after the reactor, to separate the product(s) from the fluid. A flow meter was connected to the vent line to measure the flow rate of the exhaust gases. The bulk flow of the gaseous CO_2 was set to 0.65 L min^{-1} at 1 bar and 20 °C, corresponding to 1.06 g of CO_2 min^{-1}. Analysis of the samples collected was carried out using GC (Shimadzu GC-17a with an AOC 20i autosampler. The carrier gas used was helium and the detector was a FID. The GC column used was BETA DEX 110 (30 m length,

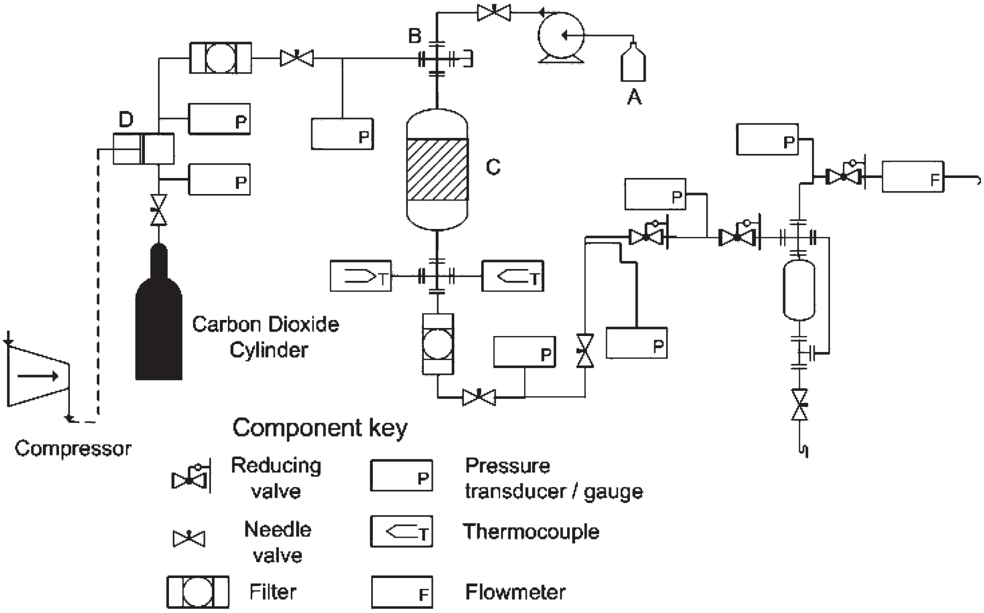


Fig. 3 Schematic of the supercritical fluid continuous flow apparatus employed in this research, where D represents the SCF pump and B the static mixer where the organic substrate (A) and the CO_2 mix before entering the reactor C.

0.25 mm ID and 0.25 μm of film thickness)). The results reported in the tables reflect the general trends of yield and selectivity across all reactor fractions collected during an experiment.

Two solid acid catalysts were employed in our experiments, Nafion® SAC-13 and γ-Al_2O_3. Nafion® SAC-13 (supplied by Aldrich) is a highly porous silica network wherein nanometre sized Nafion® resin particles are entrapped. The composite catalyst SAC-13 contained 13 wt% nanosized Nafion® particles in the porous silica matrix. The surface area of this catalyst is 200 m^2 g^{-1} and its exchange capacity[23] is 0.15 mequiv. g^{-1}. γ-Al_2O_3 had a surface area ranging from 140 to 160 m^2 g^{-1}. Its composition was as follows: Al_2O_3: 95%w/w, SiO_2: 0.035%w/w, Fe_2O_3: 0.025%w/w and Na_2O: 0.008%w/w.

Acknowledgements

We thank Thomas Swan & Co. Ltd., Schenectady Pratteln, EPSRC, EUFP5 project "CPFCO2" and the Marie Curie Programme for funding. We also thank Maia Sokolova for the phase behaviour measurements, Dr E. Garcia-Verdugo for his help and Dr A. Biland for his helpful comments.

Rodrigo Amandi,[a] Jason R. Hyde,[a] Stephen K. Ross,[b] Tobias J. Lotz[c] and Martyn Poliakoff*[a]
[a]*School of Chemistry, University of Nottingham, University Park, Nottingham, UK NG7 2RD.*
E-mail: Martyn.poliakoff@Nottingham.ac.uk
[b]*Thomas Swan & Co. Ltd., Crookhall, Consett, Co. Durham, UK DH8 7ND*
[c]*Schenectady Pratteln GmbH, Kästelliweg 7, Postfach CH-4133 Pratteln 1, Switzerland*

References

1 *Friedel–Crafts and Related Reactions*, ed. G. A. Olah, Wiley, New York, 1963–64, vol. **I–IV**.
2 R. S. Oakes, A. A. Clifford and C. M. Rayner, *J. Chem. Soc., Perkin Trans. 1*, 2001, 917.
3 E. J. Beckman, *J. Supercrit. Fluids*, 2004, **28**, 121.
4 P. G. Jessop and W. Leitner, *Chemical Synthesis Using Supercritical Fluids*, Wiley-VCH, Weinheim, 1999.
5 A. Baiker, *Chem. Rev.*, 1999, **99**, 453.
6 B. Subramaniam, *Appl. Catal., A: Gen.*, 2001, **212**, 199.
7 B. Subramaniam, C. J. Lyon and V. Arunajatesan, *Appl. Catal., B: Environ.*, 2002, **37**, 279.
8 M. A. Harmer and K. W. Hutchenson, *Chem. Commun.*, 2002, 18.
9 J. E. Chateauneuf, J. Foote and K. Nie, *Abstr. Pap. Am. Chem. Soc.*, 2000, **220**, 74.
10 P. Licence, J. Ke, M. Sokolova, S. K. Ross and M. Poliakoff, *Green Chem.*, 2003, **5**, 99.
11 S. van den Hark, M. Harrod and P. Moller, *J. Am. Oil Chem. Soc.*, 1999, **76**, 1363.
12 N. J. Meehan, A. J. Sandee, J. N. H. Reek, P. C. J. Kamer, P. van Leeuwen and M. Poliakoff, *Chem. Commun.*, 2000, 1497.
13 W. K. Gray, F. R. Smail, M. G. Hitzler, S. K. Ross and M. Poliakoff, *J. Am. Chem. Soc.*, 1999, **121**, 10711.
14 T. W. Kuo and C. S. Tan, *Ind. Eng. Chem. Res.*, 2001, **40**, 4724.
15 H. Grabowska, W. Mista, J. Trawczynski, J. Wrzyszcz and M. Zawadzki, *Appl. Catal., A: Gen.*, 2001, **220**, 207.
16 W. Biederman, H. Koller and K. Wedemeyer, *US Pat.*, 4 086 283, 1978.
17 P. Wimmer, H. J. Buysch and L. Puppe, *US Pat.*, 5 030 770, 1991.
18 S. Velu and S. Sivasanker, *Res. Chem. Intermed.*, 1998, **24**, 657.
19 V. Umamaheswari, M. Palanichamy and V. Murugesan, *J. Catal.*, 2002, **210**, 367.
20 A. Klein and K. Wedemeyer, *US Pat.*, 3 968 173, 1976.
21 J. R. Hyde, R. A. Bourne, I. Noda, P. Stephenson and M. Poliakoff, *Anal. Chem.*, 2004, **76**, 6197.
22 M. V. Avdeev, A. N. Konovalov, V. N. Bagratashvili, V. K. Popov, S. I. Tsypina, M. Sokolova, J. Ke and M. Poliakoff, *Phys. Chem. Chem. Phys.*, 2004, 1258.
23 M. A. Harmer and Q. Sun, *Appl. Catal., A: Gen.*, 2001, **221**, 45.

Simultaneous continuous partial oxidation of mixed xylenes in supercritical water†

Eduardo Garcia-Verdugo,*[a] Joan Fraga-Dubreuil,[a] Paul A. Hamley,[a] W. Barry Thomas,[b] Keith Whiston[b] and Martyn Poliakoff*[a]

Received 21st December 2004, Accepted 30th March 2005
First published as an Advance Article on the web 13th April 2005
DOI: 10.1039/b419098j

In this paper we show that a mixture of xylenes can be simultaneously oxidised in supercritical water (scH_2O) in a continuous mode to a mixture of the corresponding carboxylic acids in high combined yield, despite the differences in reactivity of the xylene isomers in conventional oxidation. The single phase environment in scH_2O together with the effect of higher temperatures should increase the reaction rate for each of these oxidation reactions and thus reduce the reactivity differences between the components of the C_8 refinery mixture. Such a process should lead to a considerable reduction in the overall energy input for the oxidation of xylenes. The process in scH_2O described here could simplify the downstream purification processes to a simple crystallization process. This is commercially important, because the purification process can be as expensive as the reaction producing the product. Furthermore, the oxidation of mixed xylenes could avoid the need not only for downstream purification, but also for the upstream separation of the xylene isomers. The use of high temperature water also offers significant cost advantages through enhanced energy recovery, due to a higher process temperature. Finally, the process totally eliminates the use of organic solvents.

Introduction

Selective oxidation is a key process across the whole of the chemical industry. In contrast to the majority of current Green Chemistry research, which is aimed at small tonnage chemical manufacture in the specialty chemicals or pharmaceutical sectors, the field of oxidation of hydrocarbons involves large scale production of chemicals; for instance, 25 Mton p.a. in the case of the oxidation of *p*-xylene to terephthalic acid.[1] Therefore, developing cleaner processes for selective oxidation constitutes a great challenge for Green Chemistry.[2]

An appropriately designed process should decrease waste, minimize the use of hazardous substances, reduce processing time and eliminate the need for down-stream purification.

---

† This work was presented at the Green Solvents for Synthesis Meeting, held in Bruchsal, Germany, 3–6 October 2004.
*Martyn.Poliakoff@nottingham.ac.uk (Martyn Poliakoff)

Eduardo Garcia-Verdugo was born in 1972 in Toledo, Spain. He graduated from the School of Chemistry (Universidad de Valencia) in 1995. He obtained an EU-PhD degree in 2000 from the University Jaume I Castellon in the field of asymmetric supported catalysts. Then, he joined the group of Prof. M. Poliakoff (University of Nottingham) as post-doctoral fellow working in the development of new processes in scH_2O (2000–2004). In 2005, he returned to University Jaume I, where he holds a Ramon y Cajal Fellowship. His research is focused on novel "green" synthetic methods in asymmetric synthesis as well as exploring the use of scEtOH as an alternative solvent for clean organic processes.

Dr. Joan Fraga-Dubreuil was born in Barcelona, Spain in 1976. He studied Physical Sciences at the University of Poitiers, France, where he obtained his MSc degree in Chemistry in 1999. He earned his PhD in organic chemistry in 2002 under the supervision of Prof. J. P. Bazureau at the University of Rennes 1, France. The topic was solvent-less reactions, and the application of ionic liquids as alternative solvents, catalysts and supports for liquid phase organic synthesis assisted by microwave irradiation. In 2003, he was awarded a NATO Postdoctoral Fellowship to work in the field of fluorous biphase catalysis with Prof. I. T. Horváth at Eötvös University, Budapest, Hungary. In 2004, he joined the group of Prof. Martyn Poliakoff at the University of Nottingham, as a postdoctoral researcher. In collaboration with INVISTA Performance Technologies, UK, his current research mainly relates to the synthesis of bulk chemicals, such as polymer intermediates, using supercritical water as an alternative reaction medium.

Furthermore, maximising energy utilization should also be an important consideration in product and process design since many environmental problems can be traced directly back to the combustion of fossil fuels.

Product separation and purification can consume large amounts of energy and plant capacity in many industrial oxidation processes. In general, separation methods are energy intensive, requiring energy as heat or pressure. For instance, in terephthalic acid manufacture, a purification process is required to remove low levels of impurities. Indeed, an additional hydrogenation plant is added to the process to hydrogenate 4-carboxybenzaldehyde back to *p*-toluic acid which can be subsequently separated from the terephthalic acid by fractional crystallization in water.

The manufacture of the isomeric compounds phthalic, isophthalic and terephthalic acid involve three separate manufacturing processes (Fig. 1a). Both terephthalic and isophthalic acids are produced using very similar technology based on oxidation of *p*-, or *m*-xylene by the Amoco Mid-Century process.[3] In the case of *o*-xylene, both liquid and gas-phase oxidation have been used to produce phthalic acid; the by-products from the gas phase process include *o*-toluic acid, phthalide, benzoic acid, and maleic acid. Two distillation stages are required to reach a final purity of at least 99.8%.[4] Each process requires the appropriate purified xylene isomer as feedstock.

These xylenes are obtained by separation of C_8 aromatic hydrocarbons (the thermodynamic refinery product contains 13 parts *o*-xylene, 24 parts *m*-xylene, 18 parts *p*-xylene and 45 parts of ethylbenzene) which presents considerable technical difficulties.[5] *o*-Xylene has a boiling point significantly higher (bp 144 °C) than those of the other components, and can be separated by distillation fairly easily. It is also technically feasible to separate ethylbenzene by distillation but the cost involved is high. Separation of *m*- and *p*-xylene by distillation is quite impractical, as their boiling points are so close together (*m*-xylene 139 °C, *p*-xylene 138 °C, ethylbenzene 136 °C). Until recently, the separation has been achieved by fractional crystallization.[1] The overall separation of C_8 aromatics is therefore as follows. First, the high-boiling compound (*o*-xylene) is separated from a fraction containing ethylbenzene–*p*-xylene–*m*-xylene. Then ethylbenzene, which has a lower boiling point, is removed in a further distillation. The remaining fraction, a 2 : 1 mixture of *m*- : *p*-xylene, is then cooled to between −20 and −75 °C by the evaporation of ethylene, propane or NH_3. After the first crystallization, the *p*-xylene concentration can be as high as 70% and the *m*-xylene in the filtrate is *ca.* 80%. *p*-Xylene is obtained with a purity of

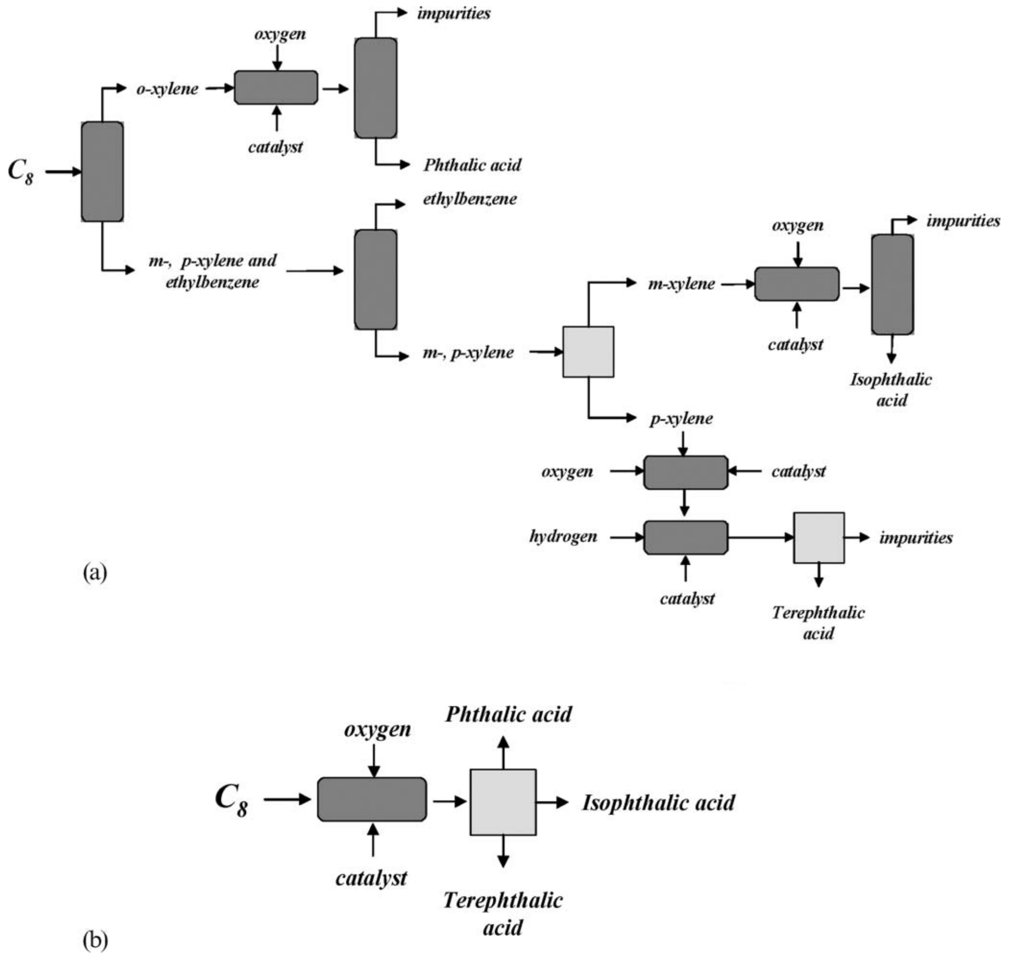


Fig. 1 (a) Separation and oxidation processes of C_8 fraction to produce the related aromatic carboxylic acids. (b) Direct oxidation of C_8 fraction to produce the related aromatic carboxylic acids in scH_2O.

99.5% by means of a series of further melting and crystallization operations, with heat exchangers enabling an optimal utilization of the expensive cooling energy. By contrast, the maximum purity of the *m*-xylene obtained from the filtrates is only 85% (eutectic mixture with *p*-xylene). This mixture is generally recycled by isomerisation to *o*- and *p*-xylene.

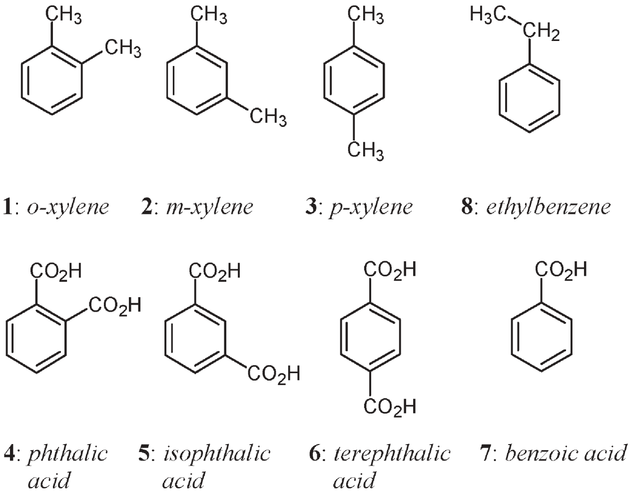
Alternative processes for the production of *p*-xylene are now available; the most widely used involves selective adsorption of *p*-xylene onto a solid adsorbent, followed by the extraction with solvent. *p*-Xylene of about 99.5% purity is recovered from the extract by distillation.[1] Various combinations of separation and isomerisation can be used. The isomerisation may be carried out in the liquid phase in the presence of BF_3–HF or $AlCl_3$–HCl, or, as is more common, in the vapour phase over a cracking type catalyst, *e.g.* silica–alumina, at about 500 °C.

Overall, these processes may be less energy intensive than distillation plus crystallization in accordance with Green Chemistry Principle 6, but they contravene several other Principles.[2]

Thus, although the separation of the C_8 fraction is possible, the production of dicarboxylic acids by oxidation of a mixture in a single process would be highly desirable (Fig. 1b). To date, there are no commercial processes in which the three isomeric dicarboxylic acids can be produced simultaneously from the C_8 refinery feedstock under the same reaction conditions (Fig. 2).

Traditionally, the oxidation of different methylaromatic compounds requires a variety of experimental conditions. In this way, *p*-xylene, *m*-xylene and pseudocumene are oxidised in the liquid phase while *o*-xylene is oxidised in the gas phase using a vanadium phosphorus oxide (VPO) heterogeneous catalyst. The oxidation of *p*-xylene and *m*-xylene are continuous liquid phase processes whilst pseudocumene oxidation requires a batch approach.[3]

By contrast, we have reported the selective oxidation in scH_2O and under similar experimental conditions of different methylaromatic compounds 1,4-dimethylbenzene (*p*-xylene), 1,3-dimethylbenzene (*m*-xylene), 1,2-dimethylbenzene (*o*-xylene), 1,3,5-trimethylbenzene (mesitylene) and 1,2,4-trimethylbenzene (pseudocumene).[6] The oxidation of *p*-xylene in scH_2O generates almost no 4-carboxybenzaldehyde, one of the most problematic impurities in current commercial processes for manufacturing of terephthalic acid.[7] In the case of *o*-xylene oxidation, the selectivity achieved in scH_2O is better than that reported for the equivalent transformation of *o*-xylene in the gas phase, (78% based on *o*-xylene). Therefore, in this paper we show that a mixture of xylenes can be simultaneously oxidised in scH_2O using a continuous mode to a mixture of the corresponding carboxylic acids.



1: *o-xylene* **2**: *m-xylene* **3**: *p-xylene* **8**: *ethylbenzene*

4: *phthalic acid* **5**: *isophthalic acid* **6**: *terephthalic acid* **7**: *benzoic acid*

Fig. 2 The C_8 aromatics and their carboxylic oxidation products.

Results

The continuous oxidation of an equimolecular mixture of the three xylene isomers (33.3 : 33.3 : 33.3% wt/wt of *o*-, *m*- and *p*-xylene) was performed at 380 °C and 230 bar using an aqueous solution of $MnBr_2$ (1700 ppm of Br) as catalyst. The oxygen was generated by thermal decomposition of aqueous H_2O_2. The configuration of the continuous flow reactor which was used has been previously reported.[6,7] The results obtained are summarised in Entry 1 of Tables 1 and 2.

It can be seen that the equimolar mixture of xylenes can be oxidised to the corresponding mixed carboxylic acids with high selectivity and reasonable yields. No partially oxidised intermediates (*i.e.* toluic acid or benzaldehydes) were detected for the any of the isomers. The only side product present was benzoic acid, which in principle can be produced by the decarboxylation of any of the dicarboxylic acids.[8]

The relative composition of the final carboxylic acids mixture was slightly different from that of the feedstock. An equimolar mixture of the three isomers (33.3% of *ortho*-, *meta*- and *para*-xylene, Entry 1, Table 1) led to a carboxylic acid mixture with a lower amount of *o*-phthalic acid than expected (25% observed *vs.* 33.3% *o*-xylene), along with a higher proportion of terephthalic acid (37% *vs.* 33.3% *p*-xylene). The presence of benzoic acid (5%) suggested that the different composition of the product mixture was related to the difference in decarboxylation rate of the dicarboxylic acids. *o*-Phthalic acid is more prone to decarboxylation than either isophthalic or terephthalic acids.[8] Therefore, it seems reasonable that the concentration of *o*-phthalic acid in the final mixture was lower compared to the *para*- and *meta*-isomers, due to decarboxylation. This result is in good agreement with our previous results, in which the oxidation of each xylene isomer was performed separately.[6] The selectivity calculated for the total amount of aromatic dicarboxylic acid (**4**, **5** and **6** in the mixture (w/W_t)) was around 95% compared with 5% for benzoic acid (**7**), similar to the selectivities achieved for oxidation of each isomer separately (Entry 5–7, Table 1).[6–10]

The effect of the catalyst composition on the oxidation of the equimolecular mixture of xylenes was also investigated. In addition to manganese bromide ($MnBr_2$), nickel bromide ($NiBr_2$) and cobalt bromide ($CoBr_2$) were used as catalysts. Tables 3 and 4 summarise the results obtained when the reaction was performed at 380 °C and 220 bar. All the catalysts gave the desired dicarboxylic aromatic diacids, but only in the case of $MnBr_2$ were reasonable yields obtained (60%, Table 4, Entry 1). The least effective catalyst was $NiBr_2$, giving only an 11% yield for the corresponding dicarboxylic acids. The selectivity of the reactions was also affected by the identity of the metal used. $MnBr_2$ was the most selective catalyst with

Table 1 Selectivities observed in the continuous Mn/Br oxidation of mixed xylenes in scH_2O

Entry	*o*- : *m*- : *p*-Xylene[a] (w/W_t)	Selectivity [%][b] di-CA [Total]	**4** [%][c] *ortho*-di-CA	**5** [%][d] *meta*-di-CA	**6** [%][e] *para*-di-CA	**7** [%][f] BA
1	33.3 : 33.3 : 33.3	95	25	33	37	5
2	66 : 17 : 17	93	59	17	17	7
3	17 : 66 : 17	94	10	70	14	6
4	17 : 17 : 66	95	14	17	64	5
5	100 : 0 : 0	94	94	—	—	6
6	0 : 100 : 0	97	—	97	—	3
7	0 : 0 : 100	95	—	—	95	5

[a] Feed composition of the xylene mixture by weight. [b] All calculated by HPLC. (di-CA = dicarboxylic acid). Selectivity for dicarboxylic acid calculated as % = (conc. (mol L^{-1}) **4** + conc. (mol L^{-1}) **5** + conc. (mol L^{-1}) **6**/conc. (mol L^{-1}) **4** + conc. (mol L^{-1}) **5** + conc. (mol L^{-1}) **6** + conc. (mol L^{-1}) **7**) × 100. [c] Selectivity for *ortho*-dicarboxylic acid calculated as % **4** = (conc. (mol L^{-1}) **4**/conc. (mol L^{-1}) **4** + conc. (mol L^{-1}) **5** + conc. (mol L^{-1}) **6** + conc. (mol L^{-1}) **7**) × 100. [d] Selectivity for *meta*-dicarboxylic acid calculated as % **5** = (conc. (mol L^{-1}) **5**/conc. (mol L^{-1}) **4** + conc. (mol L^{-1}) **5** + conc. (mol L^{-1}) **6** + conc. (mol L^{-1}) **7**) × 100. [e] Selectivity for *para*-dicarboxylic acid calculated as% **6** = (conc. (mol L^{-1}) **6**/conc. (mol L^{-1}) **4** + conc. (mol L^{-1}) **5** + conc. (mol L^{-1}) **6** + conc. (mol L^{-1}) **7**) × 100. [f] Selectivity for benzoic acid calculated as % **7** = (conc. (mol L^{-1}) **7**/conc. (mol L^{-1}) **4** + conc. (mol L^{-1}) **5** + conc. (mol L^{-1}) **6** + conc. (mol L^{-1}) **7**) × 100.

Table 2 Yields observed in the continuous Mn/Br oxidation of mixed xylenes in scH_2O

Entry	*o*- : *m*- : *p*-xylene[a] (w/W_t)	Yield[b] di-CA [Total]	**4** [%][c] *ortho*-di-CA	**5** [%][d] *meta*-di-CA	**6** [%][e] *para*-di-CA
1	33.3 : 33.3 : 33.3	59	47	62	69
2	66 : 17 : 17	60	58	65	67
3	17 : 66 : 17	52	34	58	47
4	17 : 17 : 66	47	39	50	48
5	100 : 0 : 0	52	52	—	—
6	0 : 100 : 0	66	—	66	—
7	0 : 0 : 100	61	—	—	61

[a] Feed composition of the xylene mixture by weight. All the reactions were carried out under the same conditions. [b] All calculated by HPLC (di-CA = dicarboxylic acid). Yield of dicarboxylic acid [Total]% = (conc. (mol L^{-1}) **4** + conc. (mol L^{-1}) **5** + conc. (mol L^{-1}) **6**/feed conc. (mol L^{-1}) **1** + feed conc. (mol L^{-1}) **2** + feed conc. (mol L^{-1}) **3**) × 100. [c] Yield of *ortho*-dicarboxylic acid **4** % = (conc. (mol L^{-1}) **4**/feed conc. (mol L^{-1}) **1**) × 100. [d] Yield of *meta*-dicarboxylic acid **5** % = (conc. (mol L^{-1}) **5**/feed conc. (mol L^{-1}) **2**) × 100. [e] Yield of *para*-dicarboxylic acid **6** % = (conc. (mol L^{-1}) **6**/feed conc. (mol L^{-1}) **3**) × 100.

Table 3 Yields for oxidation of the equimolecular mixture using different catalysts

Entry	Catalyst	Yield[a] di-CA [Total]	**4**[b] *ortho*-di-CA	**5**[c] *meta*-di-CA	**6**[c] *para*-di-CA
1	$NiBr_2$	11	13	11	9
2	$CoBr_2$	26	34	23	19
3	$MnBr_2$	59	47	69	62

[a] All calculated by HPLC. All the reactions were carried out under the same conditions. (di-CA = dicarboxylic acid) Yield of dicarboxylic acid [Total]% = (conc. (mol L^{-1}) **4** + conc. (mol L^{-1}) **5** + conc. (mol L^{-1}) **6**/feed conc. (mol L^{-1}) **1** + feed conc. (mol L^{-1}) **2** + feed conc. (mol L^{-1}) **3**) × 100. [b] Yield of *ortho*-dicarboxylic acid **4** % = (conc. (mol L^{-1}) **4**/feed conc. (mol L^{-1}) **1**) × 100. [c] Yield of *meta*-dicarboxylic acid **5** % = (conc. (mol L^{-1}) **5**/feed conc. (mol L^{-1}) **2**) × 100. [d] Yield of *para*-dicarboxylic acid **6** % = (conc. (mol L^{-1}) **6**/feed conc. (mol L^{-1}) **3**) × 100.

only benzoic acid produced as a side product. However, when Ni or Co were used, significant levels of intermediates such as carboxylic benzaldehyde, toluic acid and tolualdehyde were produced (Fig 3).

In order to confirm the result achieved for the equimolar amount of xylene isomers, the oxidation of three different mixtures of xylenes, each rich in one particular isomer, (ratio 66 : 17 : 17% w/W_t) was performed. In each case, our results have shown a high selectivity for the production of the corresponding dicarboxylic acids **4–6**, with no appreciable levels of the incompletely oxidised intermediates such as tolualdehydes, toluic acid and carboxybenzaldehyde (Entry 2–4, Table 1). Although, the selectivity of the reaction seems to be unrelated to the composition of the xylene feedstock, yields showed small changes depending of the concentration of each isomer. The presence of multiple isomers in the mixture can lead to slight differences in the overall reactivity and therefore small variation in yield.

It seems clear that it is possible to carry out the simultaneous oxidation of different mixtures of xylenes in scH_2O to generate the corresponding dicarboxylic aromatic acids with good selectivity and yield. Also, the addition of ethylbenzene may well affect the oxidation rates and therefore change the outcome of the reaction. Preliminary studies were carried out in order to examine this possible effect.

Firstly, ethylbenzene was oxidised by itself using $MnBr_2$ as catalyst under the same temperature and pressure conditions indicated previously. Benzoic acid was produced as the major product in a yield of 89%. This suggests that ethylbenzene can be oxidised more easily than any of the three xylene isomers.

The oxidation of a solution of the three xylene isomers was then carried out. As is shown in Table 5 (entry 1) good selectivities were obtained. These were similar to those obtained for the previous xylene mixture (92% dicarboxylic

Table 4 Selectivity for oxidation of mixed xylenes

		Selectivity				
Entry	*o*- : *m*- : *p*-xylene : ethylbenzene[a] (w/W$_t$)	[%][b] di-CA [Total]	**4** [%][c] *ortho*-di-CA	**5** [%][d] *meta*-di-CA	**6** [%][e] *para*-di-CA	**7** [%][f] BA
1	23 : 44 : 33 : 0[g]	94	18	43	33	6
2	23 : 44 : 33 : 0[h]	84	21	40	31	8
3	13 : 24 : 18 : 45[i]	53	12	23	18	47

[a] Feed composition of the xylene mixture by weight. [b] All calculated by HPLC (di-CA = dicarboxylic acid). Selectivity for dicarboxylic acid calculated as % = (conc. (mol L^{-1}) **4** + conc. (mol L^{-1}) **5** + conc. (mol L^{-1}) **6**/conc. (mol L^{-1}) **4** + conc. (mol L^{-1}) **5** + conc. (mol L^{-1}) **6** + conc. (mol L^{-1}) **7**) × 100. [c] Selectivity for *ortho*-dicarboxylic acid calculated as % **4** = (conc. (mol L^{-1}) **4**/conc. (mol L^{-1}) **4** + conc. (mol L^{-1}) **5** + conc. (mol L^{-1}) **6** + conc. (mol L^{-1}) **7**) × 100. [d] Selectivity for *meta*-dicarboxylic acid calculated as % **5** = (conc. (mol L^{-1}) **5**/conc. (mol L^{-1}) **4** + conc. (mol L^{-1}) **5** + conc. (mol L^{-1}) **6** + conc. (mol L^{-1}) **7**) × 100. [e] Selectivity for *para*-dicarboxylic acid calculated as % **6** = (conc. (mol L^{-1}) **6**/conc. (mol L^{-1}) **4** + conc. (mol L^{-1}) **5** + conc. (mol L^{-1}) **6** + conc. (mol L^{-1}) **7**) × 100. [f] Selectivity for benzoic acid calculated as % **7** = (conc. (mol L^{-1}) **7**/conc. (mol L^{-1}) **4** + conc. (mol L^{-1}) **5** + conc. (mol L^{-1}) **6** + conc. (mol L^{-1}) **7**) × 100. [g] 1.5% organic : water. [h] 2.0% organic : water. [i] 2.0% organic : water. [j] All the reactions were carried out using MnBr$_2$ (1719 ppm of Mn/5000 ppm Br) at 380 °C and 220 bar, at flow rates for each fluid 1.5 times higher than stated in the experimental section. Residence time 3.4 s.

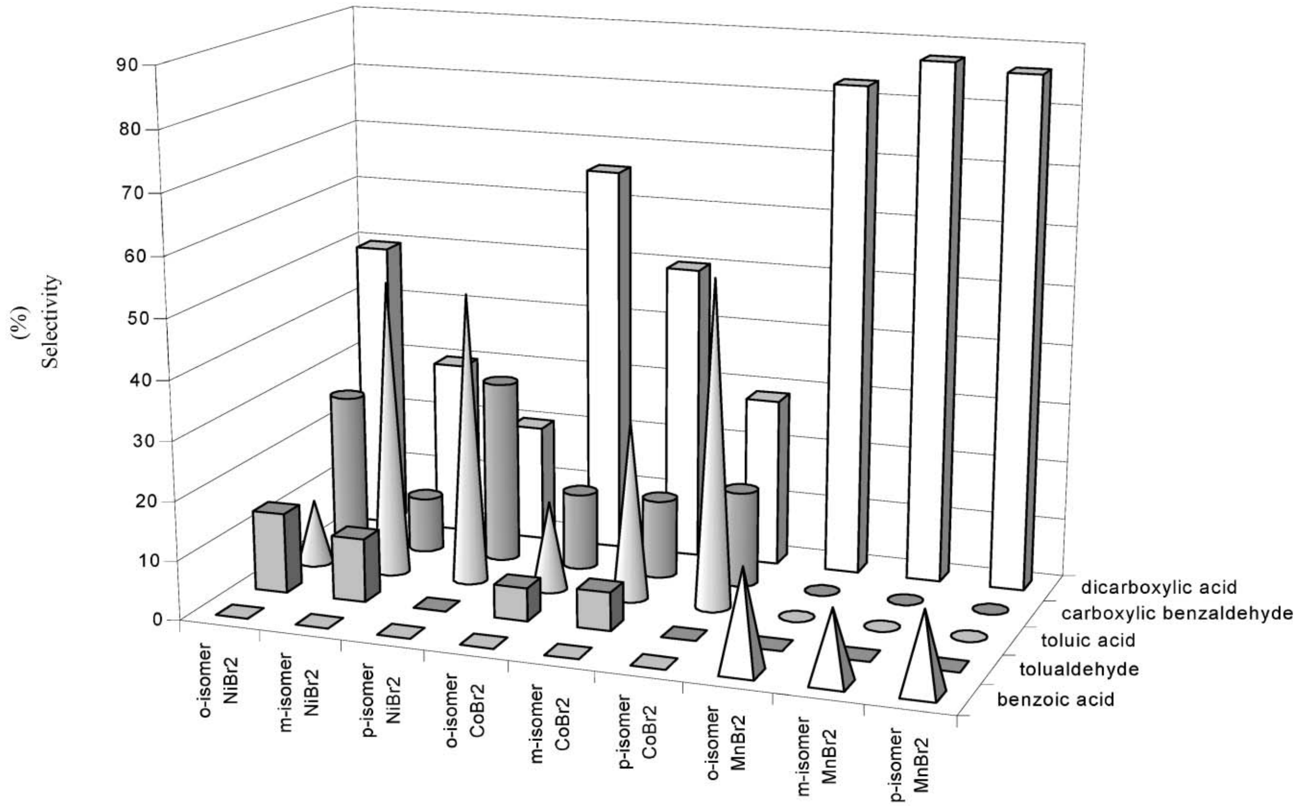


Fig. 3 Effect of the metal on the selectivity for the oxidation of the equimolecular mixture of xylene isomers.

Table 5 Yield for oxidation of mixed xylenes

Entry[a]	*o*- : *m*- : *p*-xylene : ethylbenzene (w/W$_t$)[b]	Yield[f] di-CA [Total]	**4** [%][g] *ortho*-di-CA	**5** [%][h] *meta*-di-CA	**6** [%][i] *para*-di-CA	**7** [%] BA
1	23 : 44 : 33 : 0[c]	45	42	46	46	7[j]
2	23 : 44 : 33 : 0[d]	60	54	60	61	5[j]
3	13 : 24 : 18 : 45[e]	60	57	58	65	68[k]

[a] All calculated by HPLC (di-CA = dicarboxylic acid). All the reactions were carried out using MnBr$_2$ (1719 ppm of Mn/5000 ppm Br) at 380 °C and 220 bar, at flow rates for each fluid 1.5 times higher than stated in the experimental section. [b] Feed composition of the xylene mixture by weight. [c] Residence time 3.4 s and substrate : catalyst ratio. Organic : water ratio 2.25 : 1. [d] Residence time 3.4 s and substrate : catalyst ratio. Organic : water ratio 2.0 : 1. [e] Residence time 3.4 s and substrate : catalyst ratio. Organic : water ratio 2.0 : 1. [f] Yield dicarboxylic acid [Total]% = (conc. (mol L^{-1}) **4** + conc. (mol L^{-1}) **5** + conc. (mol L^{-1}) **6**/feed conc. (mol L^{-1}) **1** + feed conc. (mol L^{-1}) **2** + feed conc. (mol L^{-1}) **3**) × 100. [g] Yield *ortho*-dicarboxylic acid **4** % = (conc. (mol L^{-1}) **4**/feed conc. (mol L^{-1}) **1**) × 100. [h] Yield *meta*-dicarboxylic acid **5**% = (conc. (mol L^{-1}) **5**/feed conc. (mol L^{-1}) **2**) × 100. [i] Yield *para*-dicarboxylic acid **6** % = (conc. (mol L^{-1}) **6**/feed conc. (mol L^{-1}) **3**) × 100. [j] Yield benzoic acid% = (conc. (mol L^{-1}) **7**/feed conc. (mol L^{-1}) **1** + feed conc. (mol L^{-1}) **2** + feed conc. (mol L^{-1}) **3**) × 100. [k] Yield benzoic acid % = (conc. (mol L^{-1}) **7**/feed conc. (mol L^{-1}) **8**) × 100.

acid and 8% of benzoic acid as the unique side product). However, the yields for the dicarboxylic acids of around 45% were slightly lower than some of the results obtained for the other mixtures.

The ratios of the diacid produced were similar to the ratio of the C_8 isomers in the feedstock solution. However, the amount of benzoic acid was again slightly higher than that expected from the composition of the C_8 mixture as a consequence of decarboxylation of the dicarboxylic acid.

Conclusion

We believe that the use of water under high temperature and pressure conditions can provide a suitable solvent for a homogeneous mixture of O_2, organic substrates and a catalyst, thereby overcoming the mass transfer limitations present in either the liquid or the gas-phase. This single phase environment together with the effect of higher temperatures should increase the reaction rate for these oxidation reactions and partially remove the reactivity differences between the components examined. By tuning the experimental conditions used it is possible to perform the simultaneous partial oxidation of these xylene mixtures in high combined yield.

Thus, for the first time, there is a promising process for the oxidation of C_8 aromatics, which does not require the upstream separation of the C_8 isomers. Such a process should lead to a considerable reduction of the overall energy input for the oxidation of xylenes. The process described here generates almost no side products; therefore the downstream purification processes can be simplified to a simple crystallization process[11] which is less energy intensive than the distillation or hydrogenation mentioned above for manufacture of phthalic and terephthalic acid respectively. This is commercially important, because the purification process can be as expensive as the reaction producing the product. Furthermore, the oxidation of mixed xylenes can avoid the need not only for downstream purification, but also for the upstream separation of the xylene isomers. The use of high temperature water also offers significant cost advantages through enhanced energy recovery due to a higher process temperature and the process totally eliminates the use of organic solvents.[12]

Experimental

All the experiments were conducted using a tubular continuous flow reactor. The flow in the reactor was non-turbulent. The continuous oxidation was carried out in scH_2O with metal bromide salt as the catalyst.[6,7] The exotherm was minimised by using relatively dilute solutions (<5% organic w/w). An aqueous solution of H_2O_2 of 2% vol was used as the source of O_2. The H_2O_2 solution was pumped into the system and decomposed in a pre-heater under the required experimental conditions to generate a homogeneous mixture of O_2 and scH_2O.[13] The residence time in the pre-heater was long enough to guarantee total decomposition of H_2O_2 to H_2O and O_2. The residence time calculated from the total reactor volume divided by the volumetric flow rate at reactor temperature, was around 5 seconds. The total volume was taken as the sum of the volume of the tubular reactor, constructed from a 30 cm length of ¼ inch o.d. Hastelloy C276 pipework. The volumetric flow rate was calculated using the physical properties of H_2O at the reaction conditions (T = 380 °C and 230 bar), as published in the International Steam Tables and by the US National Institute of Science and Technology (NIST). The volumetric flow-rate after mixing was 12.26 mL min^{-1}, as follows: H_2O_2: 8.2 mL min^{-1}, Catalyst: 4.0 mL min^{-1}, Organic: 0.06 mL min^{-1}, giving a 1.5% organic : water solution at the mixing point (unless otherwise stated in Tables 4 and 5). To avoid blockage caused by the precipitation of solid products on cooling, a T piece at the bottom of the reactor allowed addition of a flow of NaOH (0.5 M) = 3.4 mL min^{-1}, which rapidly quenched the reaction and formed sodium salts of the acid products. All chemicals were purchased from Aldrich Ltd. and used without further purification.

CAUTION: *this type of oxidation is potentially extremely hazardous, and* ***must*** *be approached with care. A thorough safety assessment must be made*. Before each run, the apparatus was hydrostatically pressure tested when cold, and was then heated with a flow of pure water (5–10 mL/min). Once the operating temperature had been reached, the pumps for organic, H_2O_2 solution, catalyst solution $MnBr_2$ (Catalyst strength: Mn 1719 ppm/Br 5000 ppm) and NaOH (0.5 mol L^{-1}) were started. Typically, an experiment was run for 1–4 h. The products were collected for sequential periods of 15 min and analysed. Every compound (acids and intermediates) was calibrated using the HPLC analysis. The yield was calculated by HPLC as a percentage of the stoichiometric amount expected from the measured amount of organic pumped into the apparatus. The selectivity was calculated by HPLC as a percentage based on the molar amount of a particular component in the solution recovered from the reactor.[6,7] No starting material (xylenes) was detected by HPLC or GC analysis, therefore the missing material was attributed to total oxidation of the aromatic compound to COx gases.

Acknowledgements

Support from the Royal Society, the EPSRC (Grant GR/N06892), the Marie Curie Research Programme (for EVGC) are greatly appreciated. We thank Dr. G. R. Aird, M. Guyler, R. Wilson, P. A. Fields for their help and Invista Performance Technologies for financial support.

Eduardo Garcia-Verdugo,*[a] Joan Fraga-Dubreuil,[a] Paul A. Hamley,[a] W. Barry Thomas,[b] Keith Whiston[b] and Martyn Poliakoff*[a]
[a] *University of Nottingham, Nottingham, UK NG7 2RD.*
E-mail: Martyn.Poliakoff@nottingham.ac.uk
[b] *Invista Performance Technologies, Wilton, Cleveland, UK TS10 4XX*

References

1 (*a*) P. Wiseman, *An Introduction to Industrial Organic Chemistry*, Applied Science Publishers, London, 2nd edn. 1979; (*b*) K. Weissermel and H.-J. Arpe, *Industrial Organic Chemistry*, Verlag Chemie, Weinheim, New York, NY, 3rd edn., 1997.
2 (*a*) L. Rawls, *Chem. Eng. News*, 2003, March 3, 41; (*b*) M. Poliakoff, J. M. Fitzpatrick, T. R. Farren and P. T. Anastas, *Science*, 2002, **297**, 807.

3 W. Partenheimer, *Catal. Today*, 1995, **23**, 69.
4 (*a*) I. V. Zakharov, Y. V. Geletii and V. A. Adamyan, *Kinet. Katal.*, 1991, **32**, 31; (*b*) M. P. Czytko and G. K. Pub, *Ind. Eng. Chem. Prod. Res. Dev.*, 1961, **20**, 481; (*c*) L. J. Csanyi and K. Jaky, *J. Catal.*, 1993, **41**, 721.
5 Kirk-Othmer, *Encyclopedia of Chemical Technology*, Vol. 10, 4th edn., John Wiley & Sons, New York, 1993.
6 E. Garcia-Verdugo, E. Vernadou, W. B. Thomas, K. Whiston, W. Partenheimer, P. A. Hamley and M. Poliakoff, *Adv. Synth. Catal.*, 2004, **2–3**, 307.
7 P. A. Hamley, T. Ilkenhans, J. M. Webster, E. Garcia-Verdugo, E. Vernadou, M. J. Clarke, R. Auerbach, W. B. Thomas, K. Whiston and M. Poliakoff, *Green Chem.*, 2002, **4**, 235.
8 J. B. Dunn, M. L. Burns, S. E. Hunter and P. E. Savage, *J. Supercrit. Fluids*, 2003, **27**, 263.
9 J. B. Dunn, D. I. Urquhart and P. E. Savage, *Adv. Synth. Catal.*, 2002, **344**, 385.
10 (*a*) R. L. Holliday, B. Y. M. Jong and J. W. Kolis, *J. Supercrit. Fluids*, 1998, **12**, 255; (*b*) Y.-L. Kim, J.-D. Kim, J. S. Lim, Y.-W. Lee and S.-C. Yi, *Ind. Eng. Chem. Res.*, 2002, **41**, 5576; (*c*) J. B. Dunn and P. E. Savage, *Ind. Eng. Chem. Res.*, 2002, **41**, 4460.
11 F.-M. Lee, W. Lamshing and R. W. Wytcherley, US Patent 6,054,610, HFM International, Inc.
12 J. B. Dunn and P. E. Savage, *Green Chem.*, 2003, **5**, 649.
13 B. D. Phenix, J. L. DiNaro, J. W. Tester, J. B. Howard and K. A. Smith, *Ind. Eng. Chem. Res.*, 2002, **41**, 624.

Energetic, environmental and economic balances: Spice up your ionic liquid research efficiency†

Dana Kralisch,* Annegret Stark,* Swen Körsten, Günter Kreisel and Bernd Ondruschka

Received 10th November 2004, Accepted 9th March 2005
First published as an Advance Article on the web 30th March 2005
DOI: 10.1039/b417167e

The energy requirement, environmental impact and material costs of the synthesis of ionic liquids, and of their subsequent use as reaction media in the metathesis of 1-octene, are compared to conventional solvents. This preliminary study lays the foundation for an ecological and strategic experimental design. Energetic, environmental and economic assessments over all life-cycle stages allow for the identification of both, disadvantages and opportunities of individual process steps, at an early R&D level. Thus, this approach helps to find new and improved solutions, which comply with the concepts of "Green Chemistry", that cannot be determined by experimental work alone. The potential of innovative methods can be quantitatively compared to current technologies by means of the energy efficiency factor E_{EF}. Interestingly, this study demonstrates that under certain circumstances, a solvent-free reaction mode may not necessarily be ecologically advantageous. Also, the presumption that, due to facile recycling, a bi-phasic reaction mode is always superior to a homogeneous one is questioned: compared to the energy required for the manufacture of a solvent which results in a biphasic reaction mode (*e.g.* an ionic liquid), the energy needed for the separation of a homogeneous reaction mixture by distillation is comparatively small. Thus, efficient recycling of such a solvent must be guaranteed.

Introduction

For some years now, ionic liquids have been commercially available and are starting to show benefits when used in industrial processes.[1] These solvents are, often uncritically, referred to in the context of "Green Chemistry": due to their negligibly low vapour-pressure, gaseous emissions are reduced when used instead of a conventional molecular organic solvent. A reduction of gaseous emission, however, does not automatically relate to a greener process, and many other facets have to be taken into account before such a statement can be made. Surely, considering the number of organic and catalytic reactions investigated in recent years, there is hardly any doubt that an optimal ionic liquid can be found for any envisioned reaction. Advantages may include improved selectivity and reaction rate, catalyst immobilisation, facile solvent recycling (due to biphasic reaction mode), possible solvent design (to achieve optimal reactant solubility), *etc.* Ultimately, it is due to the immense industrial interest which has arisen in the last decade that other questions, which are generally neglected by academic preparative chemists and engineers, have been raised. These questions relate to the many unknowns, such as toxicity,[2] disposal strategies, process costs, recyclability, *etc.*, and their answers will show how well ionic liquids really perform in the context of the Twelve Principles of Green Chemistry.[3]

Dana Kralisch (left) and Annegret Stark (right)

Dana Kralisch studied environmental chemistry at the Friedrich-Schiller-University, Jena, Germany. Following this, she worked for two years as a scientist at the Regional Office of Agriculture of Thuringia, where she concentrated on environmental analyses. Presently, she is employed as research assistant at the Institute of Technical and Environmental Chemistry to pursue her PhD on the ecological assessment of technical processes.

Annegret Stark obtained her PhD from The Queen's University of Belfast in 2001, where she studied oxidation reactions in ionic liquids under the supervision of Prof. K. R. Seddon. She then held a two years Sasol-sponsored postdoctoral position on catalytic reactions in ionic liquids at the University of Stellenbosch, South Africa, in the group of Prof. H. G. Raubenheimer. Since 2003, she has led the ionic liquid research group at the Institute of Technical and Environmental Chemistry, Friedrich-Schiller-University, Jena, Germany.

---

† This work was presented at the Green Solvents for Synthesis Meeting, held in Bruchsal, Germany, 3–6 October 2004.

*dana.kralisch@uni-jena.de (Dana Kralisch)
annegret.stark@uni-jena.de (Annegret Stark)

With this contribution, we attempt to give a first insight into the aspects of energy assessment of both the manufacture of ionic liquids with respect to the solvents and reactants used, and the performance of ionic liquids as solvents in a typical catalytic reaction, namely the metathesis.

The assessment and evaluation of process steps in the context of a life-cycle assessment (LCA) provides a much overlooked tool to identify and prevent ecological disadvantages at an early stage of product and process development. Optimally, life-cycle assessments should accompany experimental work, provide comparative data, and thus lead to new, improved solutions, rather than having to find "end of pipe" remedies. This strategy does not intend to limit the scope of choices of the R&D chemist or engineer at any given stage of the reaction: the overall view of the process might justify opting for a stage which initially appears unfavourable.

However, it should be noted that the intention of this work is not to provide a full life-cycle assessment.[4] This term refers to an exhaustive evaluation of a product from the mining of the primary resources to its disposal, and is usually expressed in impact potentials, such as the global warming potential. This holistic approach is very time-consuming, and the amount of information is limited when applied to the R&D stage, as it is difficult to uncover the weak points in the life-cycle.

Therefore, we have opted for a break-down of the life-cycle assessment into smaller stages. This way, a multitude of information can be obtained. For example, if the production of a specific product in various solvents is considered, their respective supply up to the stage where they enter the process may be assessed. Also, one could consider the work-up of an impure product by extraction, taking into account the supply, extraction efficiency, environmental impact, recyclability and disposal of various solvents. This approach allows for the determination of advantages or disadvantages of all parameters at each process stage.

A variety of other methods have been suggested for the objective assessment of synthetic steps.[5,6] Performance figures, such as the *E*-factor,[7] consider the ratio of waste generated per kilogram product obtained. The advantage of this approach is that the meaning of such ratios is easily imaginable, but the energy input is neglected. Alternatively, the energy efficiency factor (E_{EF}, in MJ kg^{-1}) correlates the cumulative energy demand (CED) for the mining, supply, recycling, disposal *etc.* to the product mass obtained. Therefore, the E_{EF} also reflects the ratio of the material expenditure to product mass. Such data may stem from both, optimised large-scale (*e.g.* the supply of the chemicals) and small-scale (*e.g.* synthesis of a product at R&D level) processes. The meaning of the values obtained is more difficult to picture, but becomes coherent upon comparison.

Our approach takes into account three criteria: the cumulative energy demand (CED), the environmental behaviour of the chemicals used, and economic factors.

The first criterion, *i.e.* the cumulative energy demand, is determined using the life-cycle assessment software Umberto,[8] which allows for the assembly and structuring of material- and energy-flow systems. Thus, complex correlations can be mapped out and individual aspects analysed. Umberto also incorporates the database Ecoinvent,[9] which contains literature references as well as a pool of data for the supply of organic and inorganic chemicals, electrical energy, inert gases, *etc.*, from their primary sources. Some data are also available free of charge, for instance from ref. 10. The CED of chemicals not listed is experimentally determined by measuring the energy requirement for certain process or synthetic steps. Should this not be possible, the CEDs of structurally similar compounds present in the database are used as first approximation. Fig. 1 shows how the CED for the manufacture of a typical ionic liquid, namely 1-butyl-3-methylimidazolium tetrafluoroborate,[11] is compiled using the method described above, which also allows for the comparative analysis of each single life-cycle stage.

One of the possible methods of preparing 1-butyl-3-methylimidazolium tetrafluoroborate encompasses the alkylation of 1-methylimidazole with butyl chloride using solvent 1 (Fig. 1). After the reaction, solvent 1 is removed and recycled, and the reaction mixture, containing 1-butyl-3-methylimidazolium chloride and unreacted starting materials, subjected to an extraction process using solvent 2 and water. In the next reaction step, chloride is exchanged for tetrafluoroborate using aqueous HBF_4, followed by an extraction (water/solvent 3). For all stages, the CED of the supply, recycling and disposal of the chemicals, as well as the energy requirement for heating, stirring, pumping and provision of cooling water is taken into account.

By using this assessment method, individual aspects of the process can be considered separately. For example, the effect of varying the solvent in the extraction of the intermediate product 1-butyl-3-methylimidazolium chloride on the CED can be evaluated, if the CED for the supply, the extraction efficiency and the percentage recyclability of the respective solvent is known. Low conversions or a high solvent requirement are reflected in high CED values for the supply of the chemicals, the synthesis, as well as for the disposal.

As mentioned before, the second criterion of our approach is the comparison of the environmental behaviour of the alternative chemicals (*e.g.* solvents) possible for a process.

This aspect is often difficult to quantify, since there are many, mostly unknown factors which affect the environmental behaviour, and frequently only a limited set of toxicological data is available.

It is therefore necessary to draw upon a qualitative comparison. For this reason, we consider acute and chronic toxicity for humans, acute toxicity for aquatic organisms, persistency in the environment and bioaccumulation.

The third criterion takes into account economic factors in order to allow a rough estimation of the profitability of a process. Optimally, this part of the balance should include all occurring costs, such as the prices of the chemicals, energy, disposal, personnel, equipment and process expenditure, *etc.* Since such data can only be obtained by specialists of economic analyses, we presently limit ourselves to the qualitative comparison of bulk chemical costs, and more detailed determinations are part of our ongoing research. We believe that it is imperative to include this factor into the assessment, since no potential new process, even if it is much "greener" than the existing one, will be implemented, unless it also shows economic benefit.

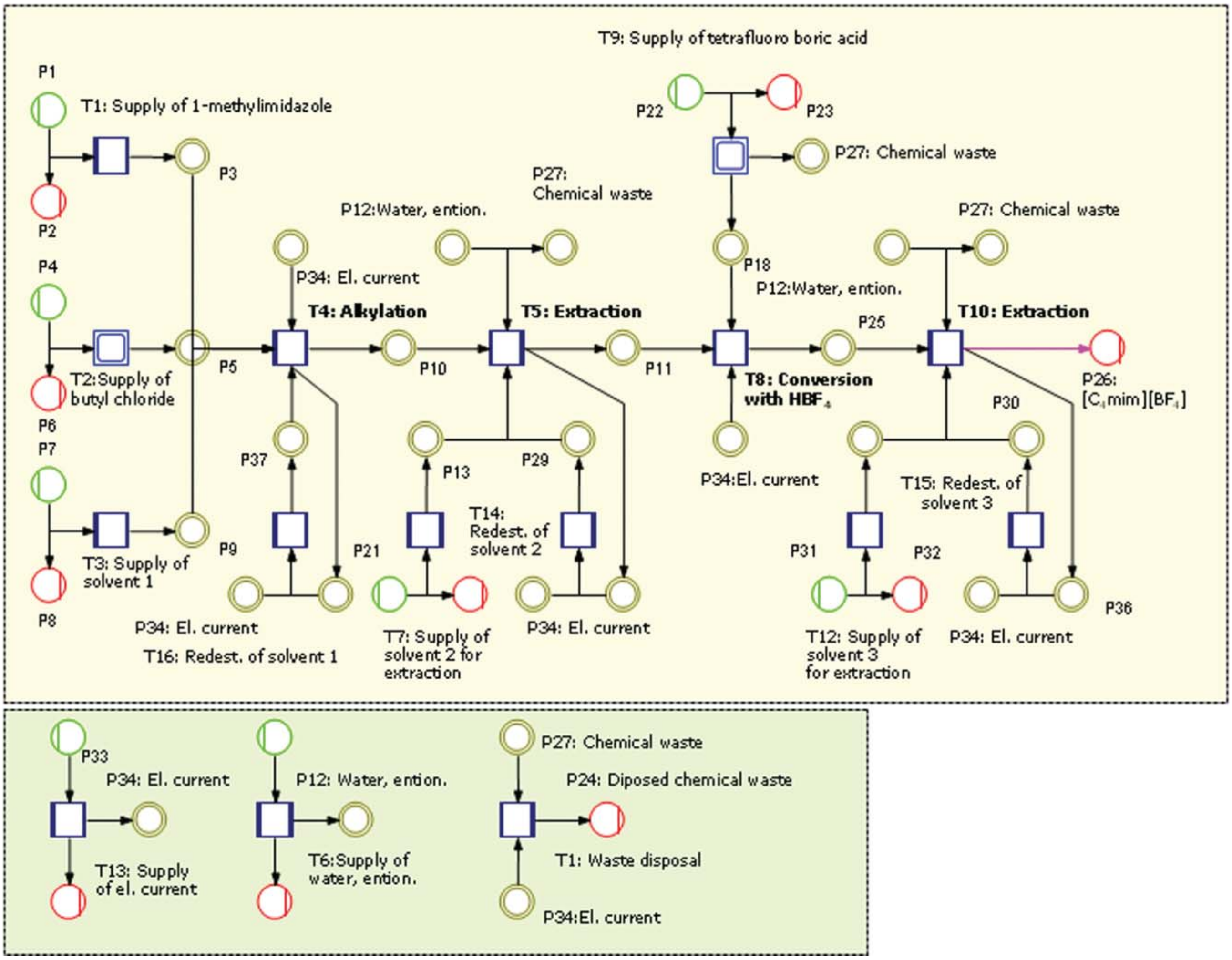


Fig. 1 Material- and energy-flow sheet, assembled using Umberto, for the manufacture of 1-butyl-3-methylimidazolium tetrafluoroborate. Blue squares: places of chemical transition. Green and red circles: input of raw-materials into the network and output of emissions into the environment. Olive-coloured circles: connections. Closed circuits: CED for the distillative purification of organic solvents. Doubly-lined blue squares: port places for subnets. Bottom green block: subnets for the provision of electrical current, supply of distilled water, waste disposal.

Results and discussion

Ionic liquids are conventionally prepared by alkylation of an amine, such as 1-methylimidazole, followed by an anion exchange (Fig. 2).

A review of the literature reveals that the alkylation may be carried out either solvent-free or in the presence of solvents such as water, dichloromethane, trichloroethane, acetone, acetonitrile, methanol, toluene, *etc.*[12] It appears that the choice of solvent is largely based on personal preference rather than on the resulting reaction efficiency. The same can be said about the reaction temperature at which the alkylation is carried out, but 80 °C has apparently been adopted as optimum temperature, although there is, to our knowledge, no report on the optimisation of reaction parameters in the open literature.

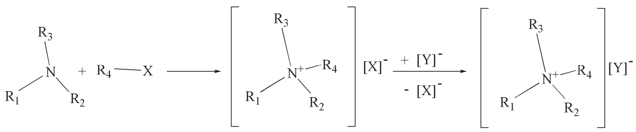
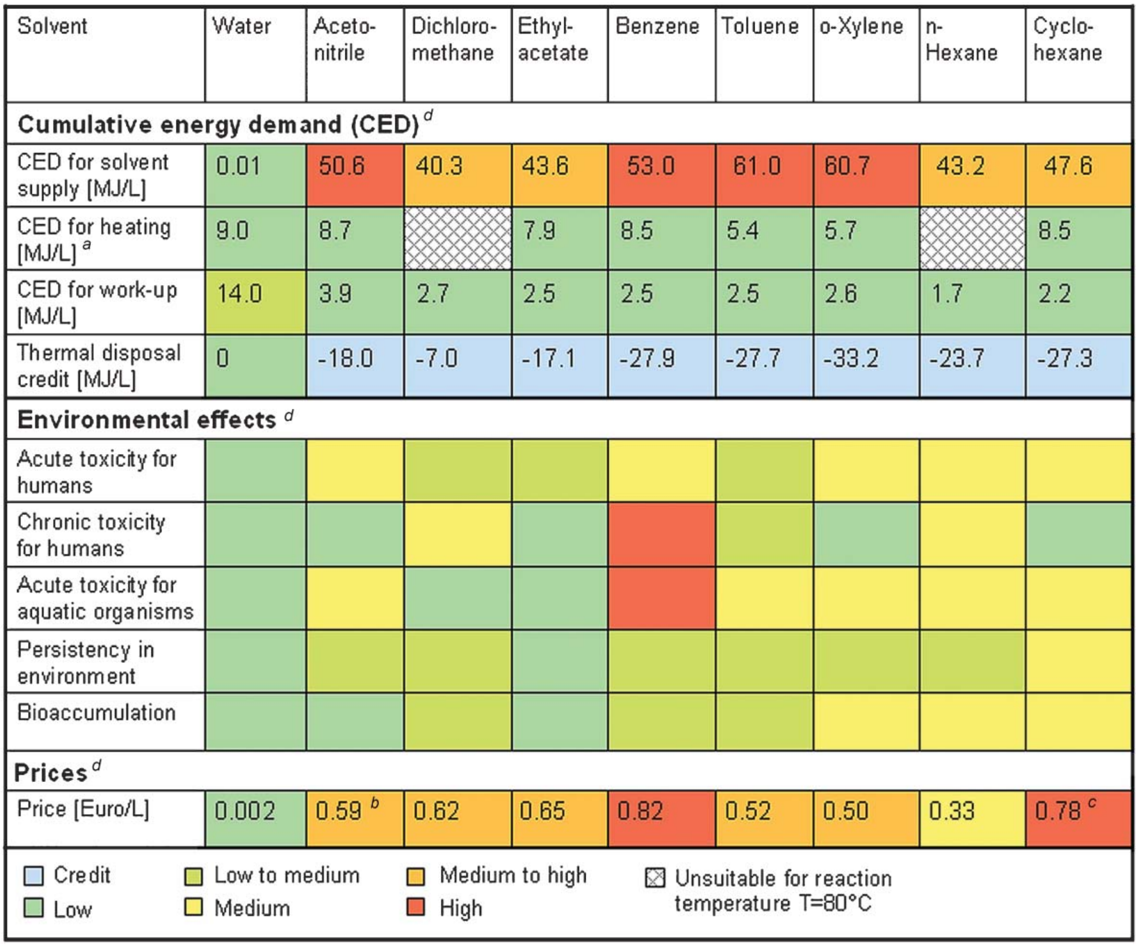


Fig. 2 Preparation of ionic liquids.

Supply of solvents

In a first effort to determine the optimal solvent system for the alkylation reaction, the CEDs of the supply of various solvents were determined (Stage P9, Fig. 1) using the Ecoinvent database of the LCA-software Umberto, and NIST.[13] The CEDs determined are thus not specific to this process but inherent to each solvent's properties. The CED value includes the energy requirement (in MJ L^{-1}) for the supply of the solvent from the raw-materials (coal, oil) in the geological deposits. Since the rate of reaction is very likely dependent on factors such as the polarity of the solvent, polar and unpolar, aromatic and aliphatic solvents were preselected. Table 1, entry 1 shows that the CED is most favourable for water and least for the aromatic solvents and acetonitrile, with the aliphatic solvents, dichloromethane and ethyl acetate ranging in between. A comparison of the environmental effects[14,15] of

Table 1 Cumulative energy demand (CED), environmental effects and prices of various solvents



Solvent	Water	Aceto-nitrile	Dichloro-methane	Ethyl-acetate	Benzene	Toluene	o-Xylene	n-Hexane	Cyclo-hexane
Cumulative energy demand (CED)[d]									
CED for solvent supply [MJ/L]	🟩 0.01	🟥 50.6	🟧 40.3	🟧 43.6	🟥 53.0	🟥 61.0	🟥 60.7	🟧 43.2	🟧 47.6
CED for heating [MJ/L][a]	🟩 9.0	🟩 8.7	⊠	🟩 7.9	🟩 8.5	🟩 5.4	🟩 5.7	⊠	🟩 8.5
CED for work-up [MJ/L]	🟡 14.0	🟩 3.9	🟩 2.7	🟩 2.5	🟩 2.5	🟩 2.5	🟩 2.6	🟩 1.7	🟩 2.2
Thermal disposal credit [MJ/L]	🟩 0	🟦 -18.0	🟦 -7.0	🟦 -17.1	🟦 -27.9	🟦 -27.7	🟦 -33.2	🟦 -23.7	🟦 -27.3
Environmental effects[d]									
Acute toxicity for humans	🟩	🟨	🟡	🟡	🟨	🟡	🟨	🟨	🟨
Chronic toxicity for humans	🟩	🟩	🟨	🟩	🟥	🟡	🟩	🟨	🟩
Acute toxicity for aquatic organisms	🟩	🟨	🟩	🟩	🟥	🟨	🟨	🟨	🟨
Persistency in environment	🟩	🟡	🟡	🟩	🟡	🟡	🟡	🟡	🟨
Bioaccumulation	🟩	🟩	🟡	🟩	🟡	🟡	🟨	🟨	🟨
Prices[d]									
Price [Euro/L]	🟩 0.002	🟧 0.59[b]	🟧 0.62	🟧 0.65	🟥 0.82	🟧 0.52	🟧 0.50	🟨 0.33	🟥 0.78[c]

🟦 Credit 🟡 Low to medium 🟧 Medium to high ⊠ Unsuitable for reaction temperature T=80°C
🟩 Low 🟨 Medium 🟥 High

[a] T = 80 °C, t = 5.75 h. [b] Price extrapolated from Merck catalogue for chemicals and reagents 2003. [c] BASF August 2004. [d] For both the CEDs and prices, the colouring of the squares represent an internal ranking. The colour of the squares referring to the environmental effects are based on direct assignment to toxicological symbols, water pollution class *etc.*

these solvents, as judged from various aspects of toxicity, their persistence in the environment and their bioaccumulation potential (Table 1), reveals that benzene must be avoided, and the hexanes should only be used if advantages prevail in terms of other factors, such as high selectivity, conversion, *etc.* The same applies when considering the price of the respective solvents.[16] In this context, it should be noted that the solvent prices indicated should be analysed qualitatively, as they tend to fluctuate greatly, often up to 20% within a few months.

The CEDs for both heating and work-up of the respective reaction mixture were determined experimentally, and are given (in MJ L^{-1}) in Table 1, entries 2 and 3. The CED for heating reflects the energy required to stir and heat one litre of the respective solvent to 80 °C and to maintain this temperature for 5.75 h. For the CED of the work-up, the energy necessary for the complete removal of the solvent by distillation is taken into account. The assessment of the extraction of the unreacted starting materials from the intermediate product using various solvents, and the conversion to the tetrafluoroborate salt will be carried out in the near future.

As shown in Table 1, the total CED of each solvent for the process at stage P10, Fig. 1 is the sum of the energy required for the supply of the solvent, for the synthesis and work-up, reduced by a thermal credit. This thermal credit originates from the fact that spent solvent (after its removal from the reaction mixture when recycling is not viable or desired) can be thermally disposed off, and the released heating value is used in the process.

Thus, the following conclusion can be drawn: for the manufacture of 1-alkyl-3-methylimidazolium tetrafluoroborate up to the stage where the solvent has been removed from the reaction mixture of the intermediate chloride, aromatic solvents should be avoided due their high cumulated energy demand for their respective supply, high environmental effects and prices. Water, on the other hand, performs best in all three categories. Judging from the compilation of CEDs, the aliphatic solvents *n*-hexane and cyclohexane are superior to ethyl acetate and dichloromethane. On the other hand, when looking at the environmental effects, ethyl acetate should be preferred to the aliphatic solvents.

Conversely, the energy required for the supply of deionised water is relatively low, but extremely high for the work-up. This is mainly due to the high heat capacity of water, which is therefore less appropriate for work-up intensive preparative methods.

Performance of solvents in alkylation

In order to elucidate the performance of the solvents in the alkylation reaction (Stage P10, Fig. 1), experiments were conducted. The alkylation reaction, carried out in various solvents,[12] is known to proceed very slowly, thus samples were taken after 5.75 h. Table 2 illustrates that the polar or aromatic solvents water, acetonitrile, dichloromethane and toluene gave very low to negligible conversions within this time. Xylene (dielectric constant (ε_r) = 2.6), although not examined, is presumed to perform similarly to toluene (ε_r = 2.4). On the other hand, the reaction proceeded faster either in unpolar cyclohexane or in solvent-free mode, and can further be improved upon increasing the reaction time.

It appears as if the reaction rate was dependent on the polarity of the solvent, but the underlying mechanisms are yet unknown and the subject of our ongoing investigations. Thus, of the solvents considered, only cyclohexane remains as a possible candidate, if the use of a solvent was necessary at all (control of exothermic reactions, tuning of viscosity, *etc.*). Since cyclohexane is comparably pricey, other aliphatic solvents will be included in later studies. The chemically similar *n*-hexane should, however, be excluded, due to its relatively high neuro-toxicological potential.

Owing to their low CED, aliphatic solvents with somewhat higher boiling points than optimal reaction temperature should be taken into account for future optimisation. This latter aspect relates to the fact that extra energy is required close to or at the boiling point of a solvent (provisions for condensation), and reactions are therefore better carried out well below its boiling point. For example, acetonitrile, benzene, ethyl acetate and cyclohexane, all possessing boiling points around 80 °C, lead to relatively high CEDs for synthesis (Table 1, entry 2). On the other hand, the boiling point of the optimal solvent may also not be exceedingly high so as to avoid high CEDs during the work-up.

Fig. 3 shows a comparison of the resulting energy efficiency factors for the synthesis of 1 kg of 1-alkyl-3-methylimidazolium chloride by alkylation of 1-methylimidazole in various solvents, subdivided into the factors for the supply of the chemicals (light grey bars), synthesis (white bars) and work-up (dark grey bars).

It should be noted that the disposal of spent compounds is not yet taken into account, since the amount of waste generated over the whole synthetic sequence is still unknown at this point of the synthesis of [C$_4$mim][BF$_4$]. It is obvious that the former life stages, reflected in the energy required to supply the chemicals, play a crucial role in the overall balance, and this aspect is not to be neglected. Therefore, an efficient method for solvent and reactant recycling will have a major impact on the overall balance.

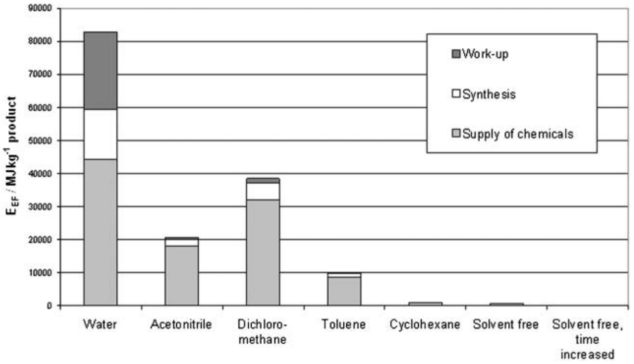


Fig. 3 Comparison of the energy efficiency factors (E_{EF}) for the synthesis of 1-alkyl-3-methylimidazolium chloride in various solvents. E_{EF} (supply of chemicals): light grey bars; E_{EF} (synthesis): white bars; E_{EF} (work-up): dark grey bars.

For the same reason, and since the energy required during synthesis is relatively low, the reaction time should be extended to allow a quantitative reaction. Thus, in the case of the solvent-free reaction, an extension of the reaction time from 5.75 h to 21.75 h decreased the E_{EF} from 740 to 230 MJ kg^{-1}. Interestingly, and against an often voiced opinion, the use of a solvent may be in fact not ecologically disadvantageous: the total CEDs for the synthesis carried out either in cyclohexane (1030 MJ kg^{-1}) or solvent-free differ by only 290 MJ kg^{-1}!

Synthesis of 1-butyl-3-methylimidazolium tetrafluoroborate

In order to determine the energetically most demanding steps in the lab-scale synthesis of an ionic liquid, the synthesis of 1-butyl-3-methylimidazolium tetrafluoroborate ([C$_4$mim][BF$_4$]) was examined in greater detail, using the material- and energy-flow system shown in Fig. 1. It was assumed that 90% of the organic solvents used can be recycled under laboratory conditions. Nominally, all residual waste was thermally disposed off.

Fig. 4 shows two significant reasons for the low energy efficiency of ionic liquids when compared to conventional solvents.

Firstly, the supply of the imidazole starting material requires almost 50% of the total energy, which cannot be substantially decreased by further optimisation of the reaction conditions.

Table 2 Alkylation of 1-methylimidazole with chloroalkanes

Solvent	Water	Acetonitrile	Dichloromethane[a]	Toluene[b]	Cyclohexane	Solvent free[c]	Solvent free[c,d]
Product	[C$_4$mim]Cl	[C$_4$mim]Cl	[C$_4$mim]Cl	[C$_4$mim]Cl	[C$_4$mim]Cl	[C$_6$mim]Cl	[C$_6$mim]Cl
ε_r solvent (T = 20 °C)	80.1	36.6	9.0	2.4	2.0	—	—
Conc/mol L^{-1}	1	1	1	1	1	4	4
Conv. (%)[e]	0.3	2.1	0.9	5.0	35.0	17.1	70.3

[a] Reaction conducted at 66 °C (bp of dichloromethane). [b] Reaction conducted at 127 °C (bp of toluene); no conversion at 80 °C. [c] V = 220 mL. [d] Conversion after 21.75 h. [e] Conditions: V = 300 mL; 1.2 equiv. chloroalkane; T = 80 °C; t = 5.75 h.

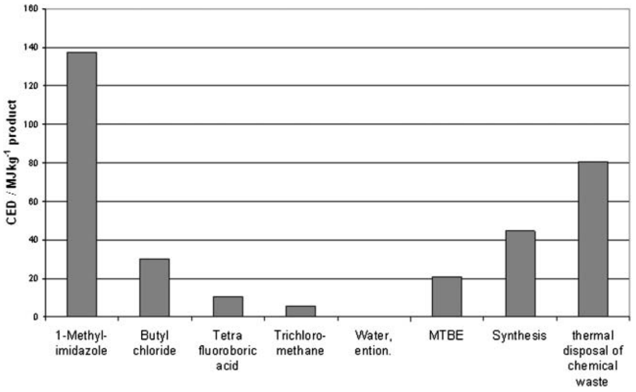


Fig. 4 Estimation of the CEDs for the supply of the reactants (1-methylimidazole, butyl chloride, tetrafluoroboric acid), solvents for extraction (trichloromethane, water, MTBE), synthesis (heating, condensation, stirring), and thermal disposal of chemical wastes.

This finding illustrates again how important it is to continue to scan for alternative ionic liquids with lower energy impact (*e.g.* tetraalkylammonium salts, *vide infra*) which are able to provide a similar performance in the process in question. Secondly, the thermal disposal of the waste also has a considerable impact (mostly due to aqueous wastes), and this aspect must be further optimised.

Variation of reactants

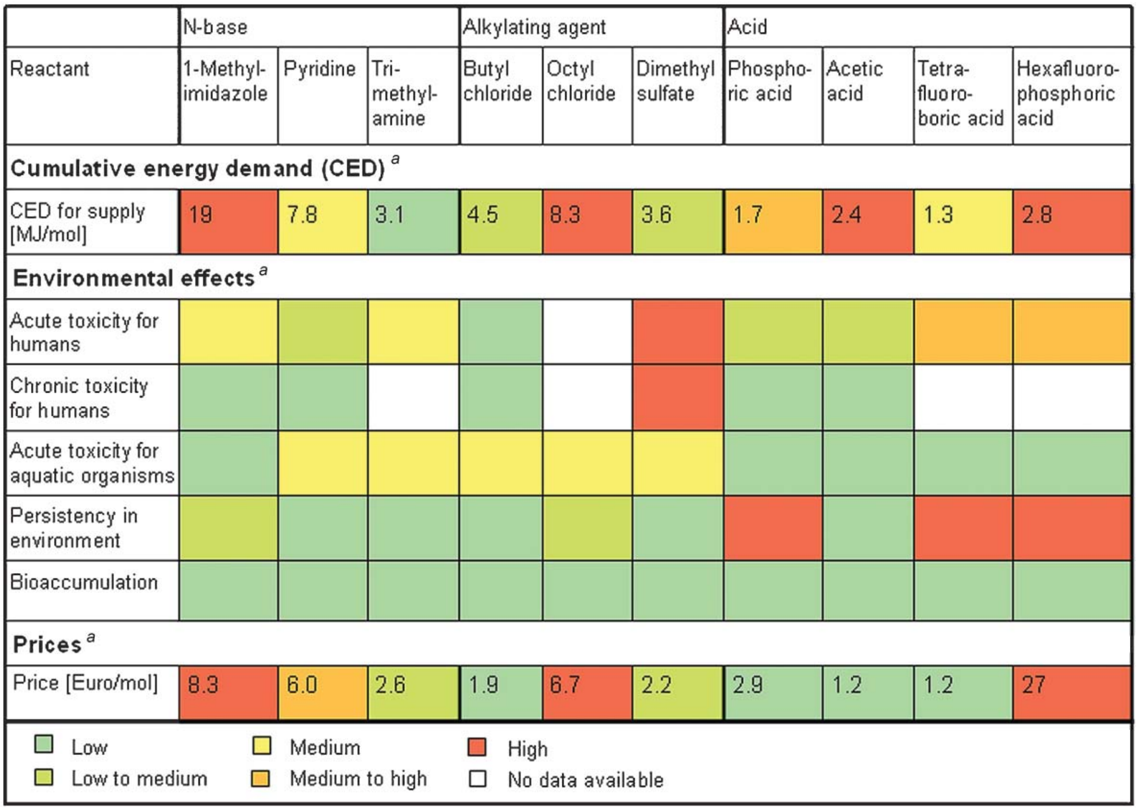
In a similar approach, the reactants used in the manufacture of ionic liquids were considered. In order to conduct such a comparative assessment for a real process, a prior scan of various ionic liquids must be carried out to determine which functionalities the optimal ionic liquid solvent must possess to be applicable. This aspect is important, since the number of available ionic liquids is high and the assessment of all impossible. Once a range of ionic liquids with the necessary properties, such as required polarity, miscibility with reactants or water, co-ordinating properties, melting point, viscosity, density, *etc.*, has been determined, their manufacture can be assessed using the same methodology as outlined above.

Generally, ionic liquids are prepared by alkylation of a base, such as an amine, using an alkylating agent, followed by an anion exchange by means of an acid (Fig. 2). The CEDs for the supply of various N-bases, alkylating agents and acids were compiled using Umberto and are shown in Table 3. It should be noted that they are given in MJ mol^{-1} as opposed to MJ L^{-1} (for solvents, Table 1), since reactants are now concerned.

Upon comparison of the CEDs for the supply of 1-methylimidazole and pyridine, it becomes clear that the manufacture of the bases has a major impact on the total CED.

While pyridine is available directly from charcoal, 1-methylimidazole has already progressed through various synthetic

Table 3 Cumulative energy demand (CED), environmental effects and prices of various N-bases, alkylating agents and acids



	N-base			Alkylating agent			Acid			
Reactant	1-Methyl-imidazole	Pyridine	Tri-methyl-amine	Butyl chloride	Octyl chloride	Dimethyl sulfate	Phospho-ric acid	Acetic acid	Tetra-fluoro-boric acid	Hexafluoro-phosphoric acid
Cumulative energy demand (CED) [a]										
CED for supply [MJ/mol]	🟥 19	🟨 7.8	🟩 3.1	▨ 4.5	🟥 8.3	▨ 3.6	🟧 1.7	🟥 2.4	🟨 1.3	🟥 2.8
Environmental effects [a]										
Acute toxicity for humans	🟨	▨	🟨	🟩	⬜	🟥	▨	▨	🟧	🟧
Chronic toxicity for humans	🟩	🟩	⬜	🟩	⬜	🟥	🟩	🟩	⬜	⬜
Acute toxicity for aquatic organisms	🟩	🟨	🟨	🟨	🟨	🟨	🟩	🟩	🟩	🟩
Persistency in environment	▨	🟩	🟩	🟩	▨	🟩	🟥	🟩	🟥	🟥
Bioaccumulation	🟩	🟩	🟩	🟩	🟩	🟩	🟩	🟩	🟩	🟩
Prices [a]										
Price [Euro/mol]	🟥 8.3	🟧 6.0	▨ 2.6	🟩 1.9	🟥 6.7	▨ 2.2	🟩 2.9	🟩 1.2	🟩 1.2	🟥 27

🟩 Low
▨ Low to medium
🟨 Medium
🟧 Medium to high
🟥 High
⬜ No data available

[a] For both the CEDs for supply and prices of the three groups of reactants, the colouring of the squares represent an internal ranking. The colours of the squares representing the environmental effects are based on direct assignment to toxicological symbols, water pollution class, *etc.*

and separating procedures, and therefore carries a higher initial energetic burden, which is also reflected in the price. Interestingly, the manufacture for tertiary amines such as trimethylamine is low in energy. Unfortunately, ionic liquids based on tertiary amines are often less stable than imidazolium-based ones. However, for certain applications, aliphatic ammonium salts may be useful. In future investigations, we plan to provide more detailed data on other starting materials for the ionic liquid manufacture.

The toxicological properties of the N-bases[14,15] show very little discrepancies: both 1-methylimidazole and trimethylamine are noxious to human health, and pyridine and trimethylamine possess a higher acute toxicity for aquatic organisms. A simulation using EPIWIN[15] indicated a somewhat higher persistency in the environment for 1-methylimidazole.

For the alkylating agents, it appears that shorter alkyl chain homologues are less difficult to produce than longer analogues. It should be noted that dimethylsulfate is best avoided as alkylating agent, due to its high acute and chronic toxicity for humans. However, as stated above, other aspects, such as high reaction rate or selectivity, may justify its use. Table 3 also shows that all examples of acids considered are energetically relatively undemanding in their manufacture compared to the other reactants, and will therefore hardly impact on the overall balance. However, it is important to find alternatives to the frequently used fluorinated anions, such as tetrafluoroborate and hexafluorophosphate: these anions possess both a high acute toxicity for humans, and long persistency in the environment. Additionally, hexafluorophosphoric acid features a high price in the fine chemical catalogue,[17,18] and the supply of fluorinated acids on industrially relevant scale is as yet uncertain.

Metathesis of 1-octene in various solvents

The possibility to conduct a reaction in a biphasic liquid–liquid mode has been frequently praised as advantageous,[19] as it allows for simple phase separation. It is generally agreed that this option reduces the overall costs that occur when a homogeneous solvent–reactant mixture is instead distillatively separated after the reaction. In order to elucidate this, the metathesis of 1-octene to 7-tetradecene, catalysed by Grubb's first generation ruthenium catalyst (Fig. 5) in the presence of an ionic liquid was compared with reactions in conventional solvents.

It should be noted that the reactions carried out with the ionic liquid [C$_4$mim][BF$_4$] are biphasic, whereas those with conventional solvents all give homogeneous solutions.

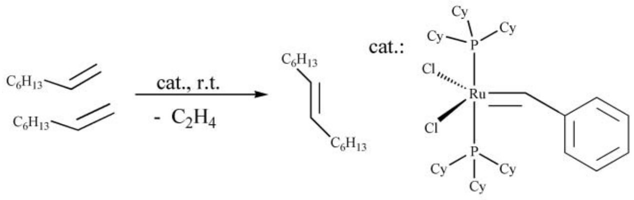


Fig. 5 Metathesis of 1-octene to 7-tetradecene, catalysed by Grubb's first generation ruthenium catalyst.

Fig. 6 shows that in the absence of solvent, *i.e.* in neat 1-octene, the reaction proceeds to almost 50% completion within 200 min. When the reaction is carried out in *n*-hexane or *o*-xylene, the conversion drops significantly. This phenomenon is not due to a lower initial rate of reaction, since even after extended reaction times, a 50% conversion is not achieved. Therefore, the catalyst stability must be diminished, which was also visually observed (darkening of the reaction mixture). Interestingly, the ionic liquid and dichloromethane increased the activity of the catalyst, both giving conversions of >60% within 200 min.

The results of the energy efficiency factor of the metathesis in various solvents, expressed as E_{EF}, are displayed in Fig. 7. Again, the light grey bars relate to the cumulated energy demand of chemical supply in each of the processes, excluding the CED for the catalyst supply. This figure illustrates that in biphasic mode (*i.e.* with an ionic liquid), the energy requirement for the separation of the reaction mixture from the solvent is indeed negligibly low (dark grey bars), while the energy consumed during the synthesis remains at the same order of magnitude as when conducted in homogeneous mode (white bars). However, due to the manufacture of the ionic liquid, its overall balance is four times worse than, for

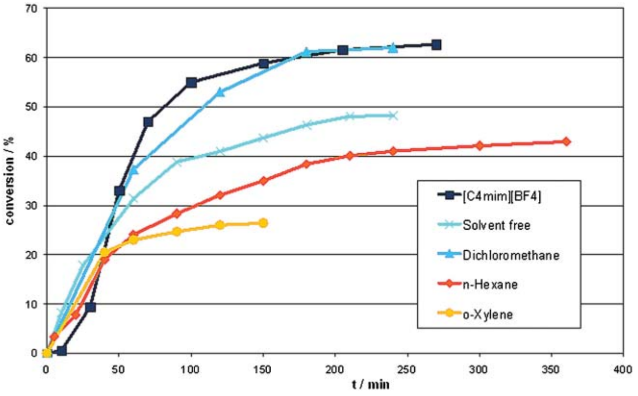


Fig. 6 Conversion of the ruthenium-catalysed metathesis of 1-octene to 7-tetradecene, carried out with various solvents, as a function of time.

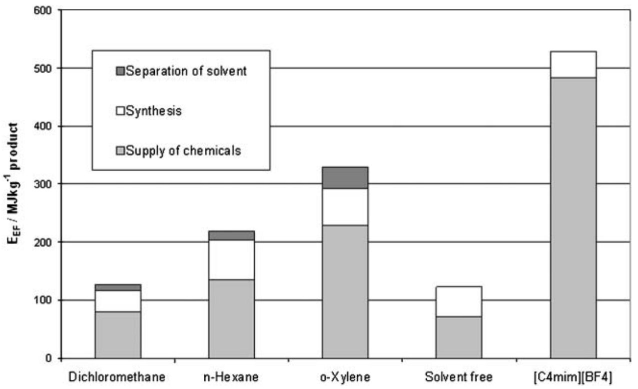


Fig. 7 Comparison of the energy efficiency factors for the metathesis of 1-octene to 7-tetradecene in various solvents. E_{EF} (supply of chemicals): light grey bars; E_{EF} (synthesis): white bars; E_{EF} (separation of solvent): dark grey bars.

example, for dichloromethane. Conversely however, comparison of the results for dichloromethane and the solvent-free synthesis show that the improved reaction rate in dichloromethane does not justify its use in this instance!

Obviously, the biphasic reaction mode obtained by using ionic liquids minimises the overall energy requirements only if the recycling efficiency of the solvent is guaranteed! Unfortunately, there is, to the best of our knowledge, no account published in the open literature yet, in which the efficiency of the recycling of an ionic liquid on a large scale (>1 kg) has been scrutinised.

Conclusions and future prospects

In conclusion, this preliminary study has both answered some questions and raised new issues:

Firstly, the need for further optimisation of the reaction conditions of the synthesis of ionic liquids has been outlined. The nature of a solvent influences the reaction rate of the alkylation step. Under certain circumstances this effect may even justify the use of a solvent from an ecological point of view. Aspects such as the rate of reactions, together with toxicological, energetic and economic considerations should affect the choice of solvent. Many other parameters, such as the reaction temperature, have also not yet been optimised.

Secondly, it has been shown that the imidazole moiety carries the largest energetic burden in the synthesis of ionic liquids. One solution to this problem is the substitution of imidazole with other amines, if the properties of the alternative ionic liquid allow this. Otherwise, alternative synthetic routes to imidazolium salts, which circumvent the use of imidazoles, must be considered.

A third aspect in the ionic liquid synthesis relates to the fact that most ionic liquids presently used contain fluorinated anions, mainly because these render the ionic liquid hydrophobic enough to allow for aqueous extractions following their synthesis. However, it has been shown on the example of tetrafluoroborate and hexafluorophosphate, that such anions possess a long persistency in the environment, and their large scale supply is not guaranteed.

Another point, namely the presumed advantage of biphasic reaction design, was scrutinised. Our results show that it is correct to assume that the energy required for the distillative step when operating homogeneously can thus be avoided. However, disproportionately more energy is necessary for the manufacture of the ionic liquids, and thus this argument can only bear up if efficient recycling is demonstrated. Until this is the case, conventional organic solvents are still the media of choice in this particular catalytic reaction.

An integrated approach, as it is presented here, conveys additional information that is otherwise not obvious. The three factors (CED, environmental behaviour, and economic aspects) together with experimental evidence, may lead to a different choice of process parameters than the one made on synthetic evidence alone.

Presently, we examine other aspects of the preparation of ionic liquids, which have not been assessed in this preliminary study, such as the extractions, supply of alternative amines, waste disposal and recycling issues. Additionally, various algorithms for the assessment of synthesis costs in the laboratory will be established.

Experimental

Supply of solvents

The CED for heating was determined in a 2 L round-bottomed flask, containing a magnetic stir-bar, which was immersed in a heating-jacket and fitted with a reflux condenser. 1 L of the respective solvent was heated to 80 °C and allowed to stir for 5.75 h. The energy for both the stirring and heating were determined using an energy monitoring socket (Energy Monitor 3000, Voltcraft).

The CED for work-up was determined by placing 1 L of the respective solvent on a rotary evaporator fitted with a water-bath (65 °C), and removing the solvent *in vacuo*. The energy for the vacuum pump, heating of the water-bath and condensation (cryostat) was measured using an Energy Monitor 3000, Voltcraft.

Performance of solvents in alkylation

For the determination of conversions, the alkylation of 1-methylimidazole was carried out in a 1 L reactor (RC-1, Mettler), which allows for precise temperature control. 0.3 mol 1-methylimidazole and 0.36 mol alkylating agent (1.2 equivalents) were combined and solvent (water, chloroform, acetonitrile, toluene, cyclohexane) added to give 300 mL (1 M 1-methylimidazole). The reaction mixture was heated to 80 °C at a rate of 10 °C $\min^{-1}$, allowed to stir for 5.75 h, then cooled to room-temperature at a rate of 10 °C $\min^{-1}$, unless indicated otherwise in Table 2. The yield was determined by ^{1}H NMR directly from the reaction mixture. For the solvent-free experiment, 0.9 mol 1-methylimidazole was reacted with a 1.2-fold excess of the hexyl chloride. The yields for the reaction in cyclohexane and solvent-free were determined gravimetrically after complete phase separation and removal of all volatiles *in vacuo* (rotary evaporator, water bath 80 °C, 3 h, 10 mbar).

Synthesis of 1-butyl-3-methylimidazolium tetrafluoroborate

The CEDs for the reaction were determined experimentally using a 500 mL round-bottomed flask, which was immersed in an oil-bath. The reaction mixture, consisting of 1.2 mole 1-methylimidazole and 1.4 mole butyl chloride, was heated to 80 °C and stirred using a magnetic stir-bar (t = 21.75 h). Extraction of the reaction mixture (150 mL deionised water/600 mL MTBE) resulted in an overall yield of 70%. The intermediate 1-butyl-3-methylimidazolium chloride (1 mol) was dissolved in 150 mL water, and stirred at room-temperature for 12 h with a 1.5-fold excess HBF_4 (50% aqueous solution), followed by an aqueous extraction (500 mL deionised water) from trichloromethane solution (150 mL $CHCl_3$). The yield for this ion exchange is 80%.

The CED of 1-methylimidazole was not available from ref. 9 and was therefore estimated from the CED for solvent supply of benzimidazole. This approach is viable due to the similarities in structure and manufacture.

Methathesis of 1-octene in various solvents

Metathesis of 1-octene to 7-tetradecene: 5 mL of solvent (unless otherwise indicated), 5 mL 1-octene (freshly distilled from KOH), and 0.005 g benzylidene-bis(tricyclohexylphosphine) dichlororuthenium (Grubbs' first generation ruthenium catalyst) were combined and stirred at room-temperature. At the times indicated, samples were analysed by gas chromatography (Varian CP-3800, HP 5-column, injector temperature 250 °C, detector temperature 300 °C, programme: 1 min at 60 °C, 10 °C min^{-1} to 100 °C, 20 °C min^{-1} to 200 °C, 2.5 min). All experiments were conducted at least in duplicate, and the error is estimated to be ±5%. For the metathesis, the ionic liquid [C_4mim][BF_4] was used as received (Fluka, puriss.). Specification: water < 200 ppm, halogens < 10 ppm.

Acknowledgements

The authors thank C. Palik, A. Wermann and R. Grunert for their dedicated cooperation, and the referees for useful discussions.

Dana Kralisch,* Annegret Stark,* Swen Körsten, Günter Kreisel and Bernd Ondruschka
Institute for Technical Chemistry and Environmental Chemistry, Friedrich-Schiller-University Jena, Lessingstr. 12, 07743 Jena, Germany. E-mail: dana.kralisch@uni-jena.de; annegret.stark@uni-jena.de; Fax:+49 3641 948402; Tel:+49 3641 948433

References

1 R. D. Rogers and K. R. Seddon, *Science*, 2003, **302**, 792.
2 B. Jastorff, R. Stoermann, J. Ranke, K. Moelter, F. Stock, B. Oberheitmann, W. Hoffmann, J. Hoffmann, M. Nuechter, B. Ondruschka and J. Filser, *Green Chem.*, 2003, **5**, 136; J. Ranke, K. Moelter, F. Stock, U. Bottin-Weber, J. Poczobutt, J. Hoffmann, B. Ondruschka, J. Filser and B. Jastorff, *CPS, Biochemistry*, 2003, 1.
3 P. T. Anastas and J. C. Warner, *Green Chemistry—Theory and Practice*, Oxford University Press, Oxford, 1998, p. 30.
4 DIN EN ISO 14040: 1997; Umweltmanagement, Produkt-Ökobilanz, Prinzipien und allgemeine Anforderungen; DIN Deutsches Institut für Normung e.V., Beuth Verlag, Berlin, 1997.
5 D. J. C. Constable, A. D. Curzons and V. L. Cunningham, *Green Chem.*, 2002, **4**, 521.
6 R. L. Lankey and P. T. Anastas, *Ind. Eng. Chem. Res.*, 2002, **41**, 4498.
7 R. A. Sheldon, *CHEMTECH*, 1994, **3**, 38.
8 Umberto 4.3, 2003; Hamburg: ifu Institut für Umweltinformatik, Heidelberg: ifeu Institut für Energie- und Umweltforschung.
9 Ecoinvent, Data v.1.0; 2003, Swiss Centre for Life Cycle Inventories.
10 ProBas, http://www.probas.umweltbundesamt.de/php/, Umweltbundesamt, September 2004.
11 J. S. Wilkes and M. J. Zaworotko, *J. Chem. Soc., Chem. Commun.*, 1992, 965.
12 J. H. Davis, K. J. Forrester and T. Merrigan, *Tetrahedron Lett.*, 1998, **39**, 8955; J. E. Gordon and S. Rao, *J. Am. Chem. Soc.*, 1978, **100**, 7445; W. T. Ford, R. J. Hauri and D. J. Hart, *J. Org. Chem.*, 1973, **38**, 3916; J. A. Vega, J. J. Vaquero, J. Alverez-Builla, J. Ezquerra and C. Hambouchi, *Tetrahedron*, 1999, **55**, 2317; R. P. Singh, S. Manandhar and J. M. Shreeve, *Tetrahedron Lett.*, 2002, **43**, 9497; WO 9,521,871; US 6596,130; WO 0,115,175; P. Tissot, in *Molten Salt Techniques*, ed. D. G. Lovering and R. J. Gale, Plenum Press, New York, London, 1983.
13 NIST Standard Reference Database, http://webbook.nist.gov/chemistry, Number 69, March 2003.
14 Merck KGaA, Safety data sheets, 2004.
15 EPIWIN, v.3.11, 2000, Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency.
16 Platts, http://www.platts.com, August 2004.
17 Merck KGaA, 2003, Catalogue for chemicals and reagents.
18 Sigma-Aldrich, http://www.sigmaaldrich.com, October 2004.
19 D. J. Adams, P. J. Dyson and S. J. Tavener, *Chemistry in Alternative Reaction Media*, John Wiley Sons Ltd., 2004, p. 40.

Selective laccase-mediated oxidation of sugars derivatives†

Mattia Marzorati,[ab] Bruno Danieli,[a] Dietmar Haltrich[c] and Sergio Riva*[b]

Received 1st November 2004, Accepted 22nd December 2004
First published as an Advance Article on the web 28th January 2005
DOI: 10.1039/b416668j

A laccase from *Trametes pubescens* and the chemical mediator TEMPO have been used to catalyze the regioselective oxidation of the primary hydroxyl groups of sugar derivatives. The efficiency of this system has been initially tested with mono- and disaccharides (*i.e.*, phenyl β-D-glucopyranoside), and the corresponding glycopyranosiduronates have been isolated and characterized. Subsequently, this chemo-enzymatic approach has been exploited to achieve the partial oxidation of a water soluble cellulose sample.

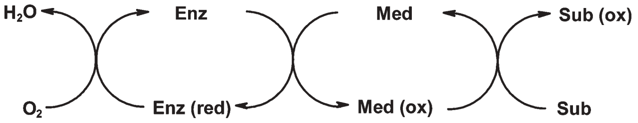
Introduction

Laccases are oxidoreductases belonging to the multinuclear copper-containing oxidases.[1] Their catalytic redox site is a cluster of four copper atoms which is responsible for the monoelectronic oxidation of suitable substrate molecules at the expense of molecular oxygen. In fact, the overall outcome of a catalytic cycle is the reduction of one molecule of oxygen to two molecules of water and the concomitant oxidation of four substrate molecules to give four radicals.[2] Despite the ubiquitous presence of these enzymes in nature (they are involved in the production and in the degradation of lignin in plants and, additionally, they have been widely found in fungi),[3] their synthetic exploitation has been quite neglected, mainly because they have not been commercially available until very recently. The search for new efficient and environmentally benign oxidative processes for the textile and for the pulp and paper industries[4] has increased the interest for these "ideally green" enzymes that work with air and produce water as the only by-product, making them more generally available to the scientific community.

Typical substrates of laccases are phenols and aliphatic or aromatic amines, the reaction products being mixtures of dimers or oligomers derived by the coupling of the reactive radical intermediates. For instance, we have recently exploited these biotransformations to isolate new dimeric derivatives of the hormone β-estradiol[5] and of the phytoalexin resveratrol.[6]

As shown in Scheme 1, laccase oxidation of non-phenolic groups, like primary alcohols or aromatic methyl groups, is also possible thanks to the ancillary action of the so-called "mediators" (*i.e.*, TEMPO, HBT, ABTS):[7] the oxidation step is performed by the oxidized form of a suitable mediator, generated by its interaction with the laccase. Reports on the application of this methodology are related to the oxidation of primary alcohols, benzyl amines or aromatic methyl substituents to the corresponding aldehydes.[8]

Selective chemical oxidation of sugars primary OHs mediated by TEMPO has also been described. In these studies the *in situ* regeneration of the oxidized form of the mediator has been satisfied either by anodic oxidation (in a paper describing the electroorganic oxidation of several mono-, di-, and oligosaccharides)[9] or by the NaOCl–NaBr system (in papers describing the selective oxidation of cyclodextrins,[10] a water-soluble cellulose derivative,[11] and other polysaccharides[12]). The use of NaOCl has been also described in the patent literature dealing with the partial oxidation of cellulose derivatives and of other polysaccharides.[13] The exploitation of oxidative enzymes (among them the laccases) for the same transformations has also been patented,[13,14] but the experimental details are quite scant both in terms of reaction conditions and of product



Scheme 1 Oxidation of a generic non-phenolic substrate (Sub) using the laccase-mediator system.

Sergio Riva is a Senior Research Scientist at the ICRM (Institute of Chemistry of Molecular Recognition, affiliated to the Italian Consiglio Nazionale delle Ricerche), where he has been working since 1984, and has been a "Professore a Contratto" at the University of Modena since 1999. He gained his Laurea in Chemistry from the University of Milano in 1983 and his Diploma di Specialitaã in Organic Synthesis from Milano Politecnico in 1989. He spent one year (1987) at M.I.T. (Cambridge, USA) working with Prof. A. Klibanov. His research activities are documented by more than 130 publications reporting on the isolation and characterization of enzymes (dehydrogenases, laccases, glycosyltransferases, hydrolases, oxynitrilases), and on the use of these biocatalysts for the selective modification of natural compounds.

---

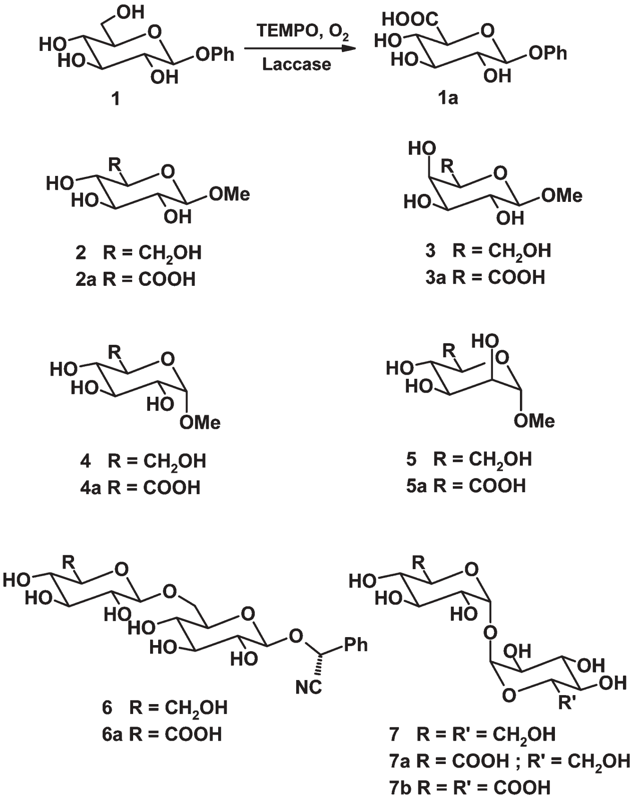
† This work was presented at the Green Solvents for Synthesis Meeting, held in Bruchsal, Germany, 3–6 October 2004.

*Sergio.riva@icrm.cnr.it

characterization. Due to the potential importance of these biotransformations (there is a continued need for new and efficient methods to achieve the selective modification of natural polysaccharides in order to modulate their properties for specific applications in various technical areas), we have investigated the performances of a laccase, isolated from the fungus *Trametes pubescens*,[15] towards the selective oxidation of a series of sugar derivatives to the corresponding glycopyranosiduronic acids, and the results are reported in the following.

Results and discussion

Phenyl β-D-glucopyranoside (**1**) was initially chosen as a model substrate and submitted to the action of *Trametes pubescens* laccase (TpL) in a slightly acidic water solution (20 mM acetate buffer, pH 4.5) containing TEMPO (0.1 equiv.). After 48 h, the corresponding phenyl β-D-glucopyranosiduronic acid (**1a**) was isolated in 50% yields (Scheme 2). Oxidation of the primary C-6 OH to the corresponding carboxylate was clearly confirmed by FT-IR and by ^{1}H- and ^{13}C-NMR analyses. Further control experiments confirmed that the oxidation reaction did not take place in the presence of only one of the two oxidative agents (laccase or TEMPO), and that TEMPO was the best performing mediator in comparison with other compounds described in the literature (ABTS, HBT, VLA, HPI).[7]



Scheme 2 Oxidation of mono- and disaccharides using a laccase and TEMPO.

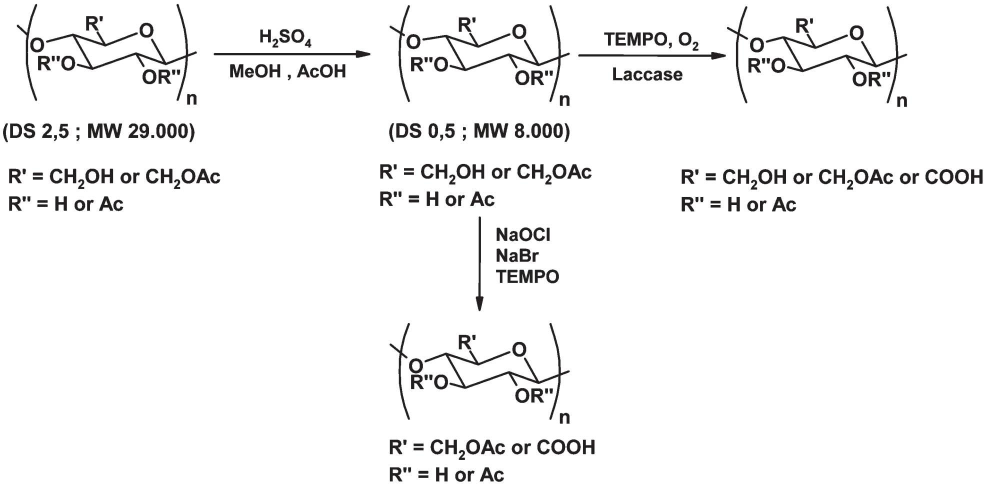
As shown in Table 1, oxidation of other monosaccharide derivatives (**2–5**) gave the corresponding glycopyranosiduronates **2a–5a** as the only isolated products. Oxidation of the disaccharidic glycoside amygdalin (**6**) was also quite efficient, as the gentiobiose unit of **6** possesses only one free primary OH suitable to be transformed into the corresponding carboxylate **6a**. Only one monocarboxylic derivative (**7a**) was isolated by oxidizing α-D-trehalose (**7**), due to the symmetry of this substrate molecule; additionally another much more polar product was detected by TLC (presumably the dicarboxylate **7b**) but could not be isolated by usual flash silica chromatography. Oxidation of sucrose (possessing three non-equivalent primary OHs) and raffinose (with four non-equivalent primary OHs) gave, as expected, much more complex product patterns. The corresponding monocarboxylic derivatives could only be isolated as a mixture, as confirmed by their complex ^{13}C-NMR spectra, in which more than one signal was clearly detected at ∼175 ppm.

Having this preliminary information in hand, we focused our attention on the modification of a polysaccharide. In order to perform the oxidative reactions using the homogeneous conditions previously described, a partially acetylated cellulose derivative was prepared according to a reported protocol (Scheme 3).[11] Fig. 1 shows the ^{13}C-NMR spectra of the starting material (A), of the fully oxidized derivative obtained using an excess of NaOCl (C),[11] and of the partially oxidized product obtained by the action of the TpL-TEMPO system (B). Diagnostic signals are the ones at ∼61 (a) and 63 (b) ppm, due to the primary C-6 OH or C-6 OAc, respectively, and the ones at ∼84 (c) and 81 (d) ppm, due to the C-4 OH adjacent to COOH or to CH_2OH/CH_2OAc, respectively. Oxidation of the primary C-6 OH caused the disappearance of the signal at ∼61 ppm and the concomitant appearance of a signal at ∼84 ppm (signals at ∼175 ppm were not diagnostic, due to the concomitant presence of several acetate moieties on the cellulose skeleton). Fig. 1 shows that, at variance to the chemical oxidation, only a partial modification of the starting material was achieved using the laccase-mediated reaction.

In conclusion, these simple experiments clearly indicate that the laccase–TEMPO system can indeed be used to catalyze the mild regioselective oxidation of sugar primary OHs. Even if the reactions conditions have not been optimized in terms of enzyme units, temperature, time and other parameters, these preliminary results are clearly indicative of the potentiality of this "green" approach for the partial and selective modification of polysaccharides, a process that might be of significant industrial interest.

Table 1 Laccase mediated oxidation of mono- and disaccharides

Substrate	Product (% isolated yields)
1	**1a** (50)
2	**2a** (46)
3	**3a** (44)
4	**4a** (27)
5	**5a** (28)
6	**6a** (47)
7	**7a** (32)



Scheme 3 Preparation and oxidation of water soluble cellulose derivatives.

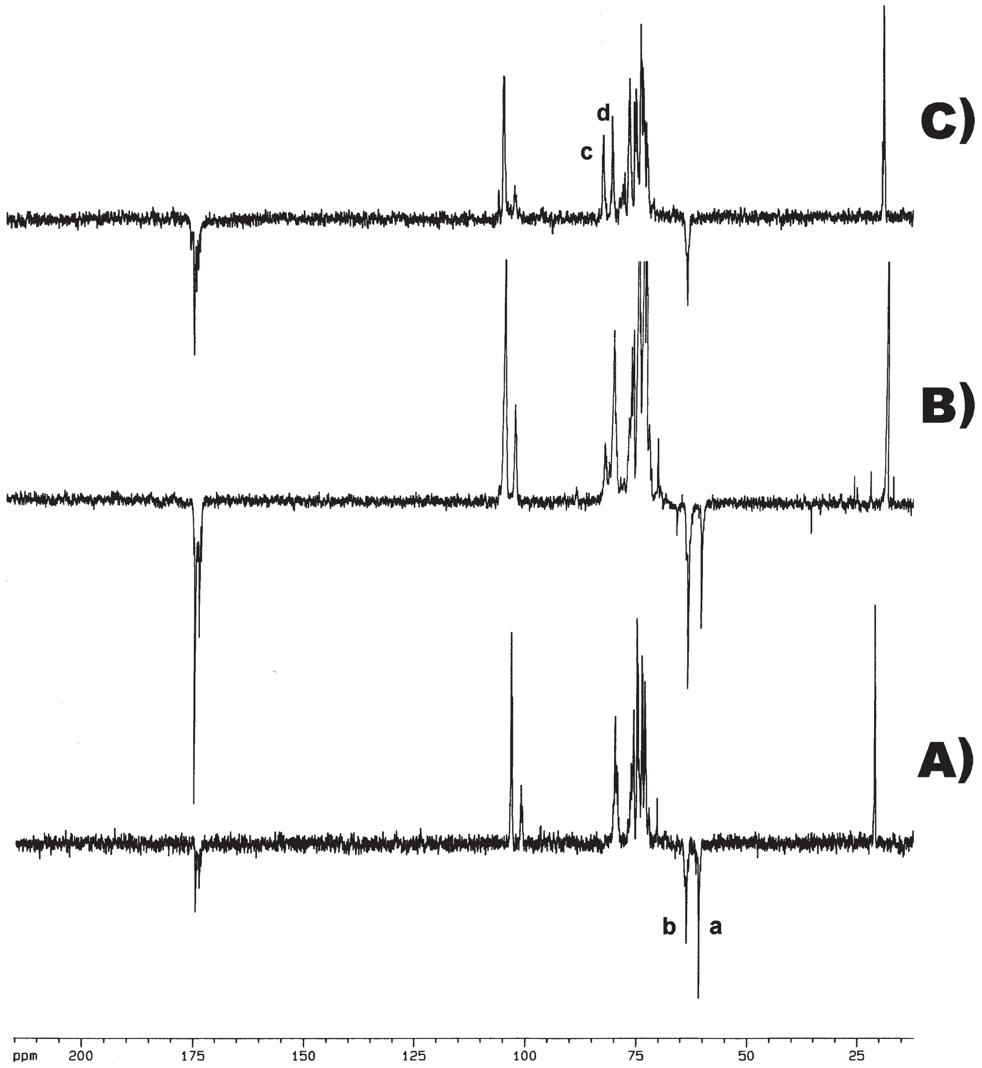


Fig. 1 ^{13}C-NMR spectra of a partially acetylated water soluble cellulose sample (A) and of its oxidized derivatives obtained using either laccase-TEMPO (partial oxidation, B) or NaOCl–NaBr–TEMPO (exhaustive oxidation, C).

Experimental

Materials and methods

Substrates and reagents were from Fluka. TLC analyses were performed on silica plates (Merck 60 F_{254}) and treated with the phosphomolybdic reagent. Purifications were performed by flash chromatography on silica gel (Merck 60, 230–400 Mesh). NMR spectra were recorded on a Bruker AC300 (300 MHz) or on a Bruker AC400 (400 MHz); FT-IR spectra were recorded on a Jasco FT-IR-610 instrument.

Laccase from *Trametes pubescens*

The laccase from *Trametes pubescens* was isolated as previously described,[15] and its activity evaluated by monitoring the oxidation of ABTS (2,2′-azino-bis-(3-ethylbenzothiazoline-6-sulfonic acid) at 436 nm. An enzymatic solution (10 μl) was added to a 1 ml corvette containing 20 mM acetate buffer pH 3.5 (890 μl) and ABTS (100 μl of a 10 mM solution of ABTS in H_2O). One enzyme unit is defined as the amount of laccase that oxidizes 1 μmol of ABTS under this condition (ε_{ABTS} = 29.3 mM^{-1} cm^{-1}).

Oxidation of phenyl β-D-glucopyranoside (1) with T*rametes pubescens* laccase

Phenyl β-D-glucopyranoside (**1**, 110 mg, 0.43 mmol) was dissolved in 10 ml acetate buffer, 20 mM and pH 4.5. TEMPO (10 mg, 0.06 mmol) and 0.5 ml of enzymatic solution (54 U) were added and the reaction was gently shaken at rt for 48 h, monitoring the conversion by TLC (eluent AcOEt–MeOH–H_2O 8 : 2 : 1). The solvent was evaporated and the residue purified by flash chromatography (eluent AcOEt–MeOH–H_2O 8 : 2 : 1 and then 7 : 3 : 1) to give 58 mg (0.21 mmol, 50% yields) of phenyl β-D-glucopyranosiduronic acid (**1a**, confirmed by comparison with an authentic sample commercialized by Fluka).

Amorphous solid; R_f = 0.22 (eluent AcOEt–MeOH–H_2O 8 : 2 : 1); FT-IR: (KBr) 1605 cm^{-1} (stretching C=O). ^{1}H-NMR (CD_3OD) δ: 7.26 (2H, t, J = 7.9 Hz), 7.09 (2H, d, J = 8.2 Hz) and 6.99 (1H, t, J = 7.3 Hz): ArH; 4.94 (1H, d, J = 7 Hz, H-1); 3.83 (1H, d, J = 8.9 Hz, H-5); 3.50 (3H, m, H-2, H-3 and H-4). ^{13}C-NMR (CD_3OD) δ: 176.36 (COOH); 130.75, 123.82, 118.14 and 107.58 (Ar); 102.52 (C-1); 77.91, 76.68, 74.93 and 73.84 (C-2, C-3, C-4, C-5).

Oxidation of methyl β-D-glucopyranoside (2) with *Trametes pubescens* laccase

Methyl β-D-glucopyranoside (**2**, 203 mg, 1.0 mmol) was dissolved in 10 ml acetate buffer, 20 mM and pH 4.5. TEMPO (16 mg, 0.1 mmol) and 3.5 ml of enzymatic solution (60 U) were added and the reaction was gently shaken at rt for 48 h, monitoring the conversion by TLC (eluent AcOEt–MeOH–H_2O 8 : 2 : 1). The solvent was evaporated and the residue purified by flash chromatography (eluent AcOEt–MeOH–H_2O 8 : 2 : 1 and then 7 : 3 : 1) to give 101 mg (0.46 mmol, 46% yields) of methyl β-D-glucopyranosiduronic acid (**2a**, confirmed by comparison with an authentic sample commercialized by Sigma).

Amorphous solid; R_f = 0.20 (eluent AcOEt–MeOH–H_2O 8 : 2 : 1); FT-IR: (KBr) 1612 cm^{-1} (stretching C=O). ^{1}H-NMR (CD_3OD) δ: 4.20 (1H, d, J = 7.7 Hz, H-1); 3.62 (1H, d, J = 9 Hz, H-5); 3.56 (3H, s, OCH_3); 3.44 (2H, m, H-3 and H-4); 3.23 (1H, t, J = 8.2 Hz, H-2).

Oxidation of methyl β-D-galactopyranoside (3) with *Trametes pubescens* laccase

Methyl β-D-galactopyranoside (**3**, 108 mg, 0.56 mmol) was dissolved in 10 ml acetate buffer, 20 mM and pH 4.5. TEMPO (10 mg, 0.06 mmol) and 3.0 ml of enzymatic solution (45 U) were added and the reaction was gently shaken at rt for 48 h, monitoring the conversion by TLC (eluent AcOEt–MeOH–H_2O 8 : 2 : 1). The solvent was evaporated and the residue purified by flash chromatography (eluent AcOEt–MeOH–H_2O 8 : 2 : 1 and then 7 : 3 : 1) to give 51 mg (0.25 mmol, 44% yields) of methyl β-D-galactopyranosiduronic acid (**3a**).

Amorphous solid; R_f = 0.06 (eluent AcOEt–MeOH–H_2O 8 : 2 : 1); FT-IR: (KBr) 1609 cm^{-1} (stretching C=O).^{1}H-NMR (CD_3OD) δ: 4.18 (2H, m, H-1 and H-4); 3.94 (1H, br s, H-5); 3.60 (3H, s, OCH_3); 3,55 (2H, m, H-2, H-3). These spectroscopic data were in accordance with those in the literature.[16]

Oxidation of methyl α-D-glucopyranoside (4) with *Trametes pubescens* laccase

Methyl α-D-glucopyranoside (**4**, 105 mg, 0.54 mmol) was dissolved in 10 ml acetate buffer, 20 mM and pH 4.5. TEMPO (10 mg, 0.06 mmol) and 1.0 ml of enzymatic solution (54 U) were added and the reaction was gently shaken at rt for 48 h, monitoring the conversion by TLC (eluent AcOEt–MeOH–H_2O 8 : 2 : 1). The solvent was evaporated and the residue purified by flash chromatography (eluent AcOEt–MeOH–H_2O 8 : 2 : 1 and then 7 : 3 : 1) to give 30 mg (0.14 mmol, 27% yields) of methyl α-D-glucopyranosiduronic acid (**4a**).[9,17]

Amorphous solid; R_f = 0.07 (eluent AcOEt–MeOH–H_2O 8 : 2 : 1); FT-IR: (KBr) 1618 cm^{-1} (stretching C=O). ^{1}H-NMR (CD_3OD) δ: 4.76 (1H, d, J = 3.7 Hz, H-1); 3.86 (1H, d, J = 10.1 Hz, H-5); 3.67 (1H, t, J = 9.4 Hz, H-3); 3.46 (1H, dd, J_1 = 10.2 Hz, J_2 = 4.7 Hz, H-2); 3.45 (3H, s, OCH_3); 3.44 (1H, t, J = 10.2 Hz, H-4).

Oxidation of methyl α-D-mannopyranoside (5) with *Trametes pubescens* laccase

Methyl α-D-mannopyranoside (**5**, 108 mg, 0.56 mmol) was dissolved in 10 ml acetate buffer, 20 mM and pH 4.5. TEMPO (10 mg, 0.06 mmol) and 1.0 ml of enzymatic solution (54 U) were added and the reaction was gently shaken at rt for 48 h, monitoring the conversion by TLC (eluent AcOEt–MeOH–H_2O 8 : 2 : 1). The solvent was evaporated and the residue purified by flash chromatography (eluent AcOEt–MeOH–H_2O 8 : 2 : 1 and then 7 : 3 : 1) to give 32 mg (0.14 mmol, 28% yields) of methyl α-D-mannopyranosiduronic acid (**5a**).[9,17]

Amorphous solid; R_f = 0.12 (eluent AcOEt–MeOH–H_2O 8 : 2 : 1); FT-IR: (KBr) 1605 cm^{-1} (stretching C=O). ^{1}H-NMR (CD_3OD) δ: 4.79 (1H, d, J = 1.3 Hz, H-1); 3.84 (1H, d, J = 9.6 Hz, H-5); 3.78 (1H, t, J = 8.8 Hz, H-4) 3.77 (1H, dd,

J_1 = 3.3 Hz, J_2 = 1.7 Hz, H-2); 3.71 (1H, dd, J_1 = 8.9 Hz, J_2 = 3.3 Hz, H-3); 3.41 (3H, s, OCH_3).

Oxidation of amygdalin (6) with *Trametes pubescens* laccase

Amygdalin (**6**, 100 mg, 0.22 mmol) was dissolved in 10 ml acetate buffer, 20 mM and pH 4.5. TEMPO (10 mg, 0.06 mmol) and 1.0 ml of enzymatic solution (54 U) were added and the reaction was gently shaken at rt for 48 h, monitoring the conversion by TLC (eluent AcOEt–MeOH–H_2O 8 : 2 : 1). The solvent was evaporated and the residue purified by flash chromatography (eluent AcOEt–MeOH–H_2O 8 : 2 : 1 and then 7 : 3 : 1) to give 48 mg (0.10 mmol, 47% yields) of the monocarboxylic derivative **6a**.

Amorphous solid; $[\alpha]_D = -90.2$ (c = 1, H_2O); R_f .= 0.10 (eluent AcOEt–MeOH–H_2O 8 : 2 : 1); FT-IR: (KBr) 1614 cm^{-1} (stretching C=O).^{1}H-NMR (CD_3OD) δ: 7.64 (2H, m,) and 7.45 (3H, m): ArH; 5.92 (1H, s, C*H*CN); 4.59 (1H, d, J = 7.8 Hz, H-1′); 4.37 (1H, d, J = 7.5 Hz, H-1); 4.26 (1H, dd, J_1 = 12.0 Hz, J_2 = 2.0 Hz, H-6b); 3.87 (1H, dd, J_1 = 12.0 Hz, J_2 = 6.8 Hz, H-6a); 3.67 (1H, d, J = 9.3 Hz, H-5′); 3.3 (3H, m); 3.5 (4H, m,). ^{13}C-NMR (CD_3OD) δ: 175.66 (C-6′); 133.75, 129.44, 128.67 and 127.40 (Ar); 118.28 (*C*N); 103.53 (C-1′); 101.45 (C-1); 74.50 (C-5′); 76.42, 76,29, 73.60, 73.43, 72.34 and 70.34 (C-2, C-3, C-4, C-5, C-2′, C-3′ and C-4′); 68.65 (C-6); 67.58 (*C*HCN).

Oxidation of D-(+)-trehalose (7) with *Trametes pubescens* laccase

D-(+)-Trehalose (**7**, 150 mg, 0.44 mmol) was dissolved in 12 ml acetate buffer, 20 mM and pH 4.5. TEMPO (10 mg, 0.06 mmol) and 1.0 ml of enzymatic solution (54 U) were added and the reaction was gently shaken at rt for 72 h, monitoring the conversion by TLC (eluent AcOEt–MeOH–H_2O 6 : 4 : 1.5). The solvent was evaporated and the residue purified by flash chromatography (eluent AcOEt–MeOH–H_2O 7 : 4 : 1 and then 6 : 6 : 1) to give 51 mg (0.14 mmol, 32% yields) of the monocarboxylic derivative **7a**.

Amorphous solid; $[\alpha]_D$ = 12.8 (c = 0.5, H_2O); R_f = 0.30 (eluent AcOEt–MeOH–H_2O 6 : 4 : 1.5) FT-IR: (KBr) 1609 cm^{-1} (stretching C=O).^{1}H-NMR (CD_3OD) selected data δ: 5.19 (1H, d, J = 3.7 Hz, H-1′); 5.17 (1H, d, J = 3.8 Hz, H-1); 4.17 (1H, d, J = 10 Hz, H-5); 3.8 (4H, m, H-3, H-3′, H-5′, H-6′b); 3.69 (1H, dd, J_1 = 11.8 Hz, J_2 = 5.3 Hz, H-6′a); 3.54 (1H, dd, J_1 = 9.8 Hz, J_2 = 3.8 Hz, H-2); 3.49 (1H, dd, J_1 = 9.7 Hz, J_2 = 4.7 Hz, H-2′); 3.47 (1H, t, J = 10.2 Hz, H-4); 3.32 (1H, m, H-4′). ^{13}C-NMR (CD_3OD) δ: 176.57 (C-6); 93.97 (C-7); 93.79 (C-1); 73.10, 72.87, 72.80, 72.36, 71.77 and 71.62 (C-2, C-3, C-4, C-8, C-9, C-11); 70.63 (C-5); 70.52 (C-10); 61.30 (C-12)

Preparation of water soluble acetyl-cellulose[11]

A sample of acetyl-cellulose (DS = 0.5; 10 g) was dissolved at room temperature in a mixture of MeOH (13 ml) and AcOH (37 ml). Following the addition of 0.69 ml of concentrated H_2SO_4 (0.013 mmol), the solution was stirred at 72 °C for 200 min. Once the solution was again at rt, AcONa (3.4 g, 0.025 mmol) was added to neutralize the sulfuric acid, followed by the addition of 150 mL of AcOEt. The white precipite (cellulose + salts) was dissolved in 100 ml of H_2O, the solution was dialized against 10 l of distilled H_2O in order to eliminate the salts and then lyiophilized to give 8.54 g of acetyl cellulose (with DS ~ 0.5 and MW ~ 8000, according to literature).

^{13}C-NMR (D_2O) selected data δ: 174.83–173.94 (CH_3*C*O); 103.47, 101.21 (C-1); 80.04 ÷ 79.46 (C-4); 63.83 (C-6: *C*H_2OAc); 61.05 (C-6: *C*H_2OH); 21.22 (*C*H_3CO).

Oxidation of water solubile acetyl-cellulose catalyzed by the laccase from *Trametes pubescens*

The previously prepared acetyl cellulose (200 mg, approximately 1.1 mmol of glucose moieties) was dissolved in 10 ml of 20 mM acetate buffer at pH 4.5. TEMPO (15 mg, 0.1 mmol) and 300 U of laccase from *Trametes pubescens* were added and the solution was gently stirred for 2 days. Reaction volume was reduced to ~3 ml by vacuum distillation, isopropanol (35 ml) was added and the mixture was cooled at 4 °C for 1 h. The solid was recovered by centrifugation, washed with *i*-PrOH, redissolved in H_2O (3 ml) and lyophilized to give 160 mg of a white powder.

^{13}C-NMR (D_2O) selected data δ: 176.64–175.04 (CH_3*C*O and COOH); 104.97, 102.61 (C-1); 83.25 (C-4, COOH); 81.47 (C-4, *C*H_2OAc); 65.12 (C-6, *C*H_2OAc); 62.31 (C-6, *C*H_2OH); 22.65 (*C*H_3CO).

Exhaustive oxidation of water soluble acetyl-cellulose with TEMPO–NaBr–NaClO[11]

The previously prepared acetyl cellulose (446 mg, approximately 2 mmol of glucose moieties) was dissolved in H_2O (50 ml) and the solution was adjusted to pH 10 by adding 0.5 M NaOH. Following the addition of TEMPO (5 mg, 0.03 mmol) and NaBr (108 mg), the solution was cooled in an ice bath. A commercial solution of NaOCl (5 ml) was added and the solution stirred for 1 h by adding NaOH (to keep the pH at 10) and NaOCl (approximately 4 ml). MeOH (3 ml) was added, the reaction volume was reduced to ~15 ml by vacuum distillation, isopropanol (200 ml) was added and the mixture was cooled at 4 °C for 1 h. The solid was recoverd by centrifugation, washed with *i*-PrOH, dissolved in H_2O (10 ml) and lyophilized to give 360 mg of a white powder.

^{13}C-NMR (D_2O) selected data δ: 175.55–173.57 (CH_3*C*O and COOH); 104.57, 101.07 (C-1); 81.87 (C-4, COOH); 79.97 (C-4, *C*H_2OAc); 63.73 (C-6, *C*H_2OAc); 22.65 (*C*H_3CO)

Acknowledgements

This work was partly supported by a bilateral project between Italy and Austria (S. R. + D. H.) sponsored by the respective Ministry for Foreign Affairs

Mattia Marzorati,[ab] Bruno Danieli,[a] Dietmar Haltrich[c] and Sergio Riva*[b]
[a]*Dipartimento di Chimica Organica ed Industriale, Università degli Studi di Milano, Via Venezian 21, 20133 Milano, Italy*
[b]*Istituto di Chimica del Riconoscimento Molecolare, C.N.R., Via Mario Bianco 9, 20131 Milano, Italy. E-mail: Sergio.riva@icrm.cnr.it; Fax: + 02 2850 0036; Tel: + 02 2850 0032*
[c]*Department of Food Science and Technology, BOKU, Muthgasse 18, 1190 Wien, Austria*

References

1 (*a*) S. G. Burton, *Curr. Org. Chem.*, 2003, **7**, 1317; (*b*) A. M. Mayer and R. C. Staples, *Phytochemistry*, 2002, **60**, 551.
2 E. I. Solomon, U. M. Sundaram and T. E. Machonkin, *Chem. Rev.*, 1996, **96**, 2563.
3 R. Burbonnais, M. G. Paice, I. D. Reid, P. Lanthier and M. Yaguchi, *Appl. Environ. Microbiol.*, 1995, **61**, 1876.
4 (*a*) Y. M. Galante and C. Formantici, *Curr. Org. Chem.*, 2003, **7**, 1399–1422; (*b*) H. P. Call and I. Mücke, *J. Biotechnol.*, 1997, **53**, 163.
5 A. Intra, S. Nicotra, G. Ottolina, S. Riva and B. Danieli, *Tetrahedron: Asymmetry*, 2004, **15**, 2927.
6 S. Nicotra, M. R. Cramarossa, A. Mucci, U. M. Pagnoni, S. Riva and L. Forti, *Tetrahedron*, 2004, **60**, 595.
7 A. M. Barreca, B. Sjogren, M. Fabbrini, C. Galli and P. Gentili, *Biocatal. Biotransform.*, 2004, **22**, 105 and references therein.
8 (*a*) M. Fabbrini, C. Galli, P. Gentili and D. Macchitella, *Tetrahedron Lett.*, 2001, **42**, 7551; (*b*) A. Potthast, T. Rosenau, C. L. Chen and J. S. Gratzl, *J. Org. Chem.*, 1995, **60**, 4320.
9 K. Schnatbaum and H. J. Schafer, *Synthesis*, 1999, 864.
10 C. Fraschini and M. Vignon, *Carbohydr. Res.*, 2000, **328**, 585.
11 S. Gomez-Bujedo, E. Fleury and M. R. Mignon, *Macromolecules*, 2004, **5**, 565.
12 P. S. Chang and J. F. Robyt, *J. Carbohydr. Chem.*, **15**, 819.
13 J. M. Jetten, R. Van Der Dool, W. Van Hartingsveldt and A. C. Besemer, *Patent*, WO 00/50463.
14 (*a*) L. Viikari, K. Kruus and J. Buchert, *Patent*, WO 99/23117; (*b*) J. Kierulff, *Patent*, WO 99/32652.
15 C. Leitner, J. Hess, C. Galhaup, R. Ludwig, B. Nidetzky, K. Kulbe and D. Haltrich, *Appl. Biochem. Biotechnol.*, 2002, **16**, 223.
16 G. Baisch and R. Ohrlein, *Carbohydr. Res.*, 1998, **312**, 61.
17 P. A. Gorin and M. Mazurek, *Can. J. Chem.*, 1975, **53**, 1212.

PAPER www.rsc.org/greenchem | Green Chemistry

Recycling of a perfluoroalkylated BINOL ligand using fluorous solid-phase extraction†

John Fawcett, Eric. G. Hope, Alison M. Stuart* and Andrew J. West

Received 2nd December 2004, Accepted 3rd February 2005
First published as an Advance Article on the web 25th March 2005
DOI: 10.1039/b418039a

After the asymmetric addition of allyltri-*n*-butyltin to benzaldehyde, a perfluoroalkylated BINOL-Sn complex was separated from the organic product using fluorous reverse phase silica gel. The lightly fluorinated ligand was then recovered by hydrolysis of the R_{f6}-BINOL-Sn complex with dilute hydrochloric acid and was reused three times without loss of activity or enantioselectivity.

Introduction

The fluorous biphase system has been applied successfully to a wide range of homogeneous catalyses with excellent catalyst recovery and reuse being reported.[1] However, it is unlikely to be exploited commercially because of intersolvent leaching problems, the prohibitive expense of the perfluorocarbon solvents and concerns about their environmental persistence. An alternative approach, designed by Curran for high throughput organic synthesis, uses fluorous reverse phase (FRP) silica gel as a solid support for the separation of fluorous-tagged products from non-fluorinated reagents, as well as the removal of perfluoroalkylated reagents from organic products.[1–3] The major advantages of fluorous solid-phase extraction are that fewer and shorter fluorous ponytails are required (<40% fluorine content by molecular weight) compared to liquid–liquid extraction using the FBS (>60% fluorine content by molecular weight) and perfluorocarbon solvents are no longer required for either the reaction or separation step. Recently, we reported the first example of separation, recovery and recycle of a perfluoroalkylated Lewis acid catalyst, $[Ni\{C_6F_{13}C(O)CHC(O)C_6F_{13}\}_2]$, using FRP silica gel after catalyzing the reaction between 2,4-pentanedione and ethylcyanoformate in dichloromethane.[4] We have also extended the applications of this novel separation technique in order to recover and recycle lightly fluorinated BINAP ligands after the ruthenium-catalysed asymmetric hydrogenation of methyl acetoacetate.[5] Here, we demonstrate the efficient separation and recycle of a perfluoroalkylated BINOL ligand using fluorous solid-phase extraction.[6]

Results and discussion

The three step synthesis of the perfluoroalkylated BINOL ligand (**1**; $\mathbf{H_2L}$) is outlined in Scheme 1 and was developed originally for the preparation of fluorous-derivatised BINAP ligands.[5,7] After protecting the binaphtholic groups, the perfluoroalkyl groups were attached directly to the binaphthyl backbone by a copper-mediated cross-coupling reaction using perfluorohexyl iodide. Sodium ethoxide was then used to remove the acetyl protecting groups giving the air-stable R_{f6}-BINOL ligand which partitions preferentially (73 : 27) into the organic phase of a toluene : perfluoro-1,3-dimethylcyclohexane biphase even though it contains 54% fluorine content by molecular weight.

Initially, the reactivity and enantioselectivity of (*R*)-R_{f6}-BINOL (**1**) was evaluated in the asymmetric addition of diethylzinc to benzaldehyde (Scheme 2) and compared directly with (*R*)-BINOL using the methodology developed by Chan and co-workers.[8] An excess of titanium tetraisopropoxide and diethylzinc was used to ensure high conversion and enantioselectivity. Each reaction was repeated three times and the results from both systems proved to be highly reproducible. Although similar conversions were obtained in each case (Table 1), the product enantioselectivities were slightly lower when (*R*)-R_{f6}-BINOL was used in place of (*R*)-BINOL.

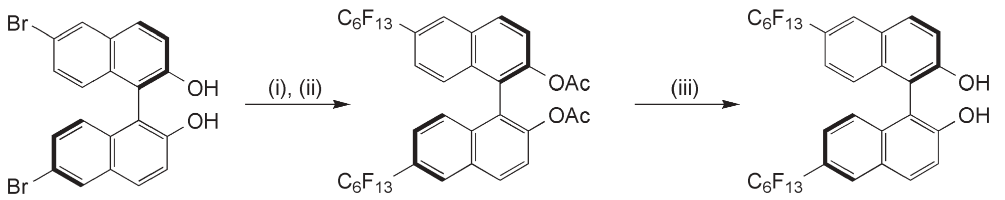
Once it had been established that the fluorinated BINOL ligand was effective in the asymmetric alkylation of benzaldehyde, the separation and recovery of the R_{f6}-BINOL ligand was investigated. At the end of the reaction, dilute hydrochloric acid was added to quench the excess diethylzinc. The organic layer was separated, dried, concentrated *in vacuo* and

Alison Stuart

Alison Stuart studied chemistry at the University of St Andrews and obtained her PhD in organofluorine chemistry with Paul Coe at the University of Birmingham in 1996. After a postdoctoral appointment with Eric Hope at the University of Leicester in fluorous biphase catalysis, she was awarded a two year fellowship with Lloyd's Tercentenary Foundation in 1999 and a Royal Society University Research Fellowship in 2000. Currently, her research is focussed on the applications of fluorous chemistry in organic synthesis as well as homogeneous catalysis.

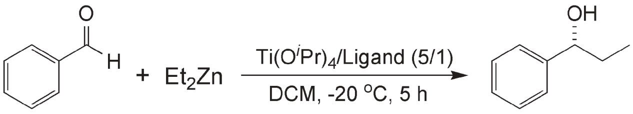
---

† This work was presented at the Green Solvents for Synthesis Meeting, held in Bruchsal, Germany, 3–6 October 2004.
*amc17@le.ac.uk



(1)

Scheme 1 (i) Ac_2O, Et_3N, DMAP, DCM, reflux; (ii) $C_6F_{13}I$, Cu, 2,2′-bipy, DMSO, C_6H_5F, 80 °C; (iii) NaOEt, MeOH, rt.



Scheme 2

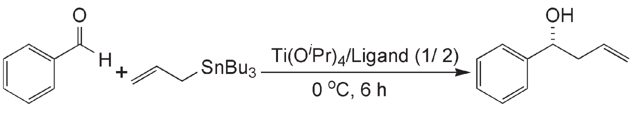
Table 1 Asymmetric addition of diethylzinc to benzaldehyde[a]

Ligand	Conversion (%)[b]	ee (%)[c]
(*R*)-BINOL	88	89
(*R*)-R_{f6}-BINOL	88	74

[a] Benzaldehyde (1.20 mmol), Et_2Zn (3.12 mmol), $Ti(O^iPr)_4$ (0.96 mmol) and ligand (0.21 mmol) in DCM (10 ml), −20 °C, 5 h. [b] Percent conversion determined by ^{1}H NMR spectroscopy. [c] ee determined by chiral gc.

then added to the top of a short column of FRP silica gel. Acetonitrile was used to elute the organic product, but ^{1}H and ^{19}F NMR spectroscopy revealed that the 1-phenyl-propan-1-ol product was contaminated with (*R*)-R_{f6}-BINOL. Unfortunately, it was not possible to separate the alcohol product from the lightly fluorinated analogue of BINOL using fluorous solid-phase extraction because (**1**) is still a relatively polar compound. A highly fluorinated BINOL derivative that contains six fluorous ponytails has, however, been recycled successfully using FRP silica gel after the asymmetric addition of diethylzinc to aromatic aldehydes in high conversions and good enantioselectivities.[9] Unfortunately, the disadvantage of this methodology was that the expensive fluorous solvent, perfluorohexane, was used to recover the highly fluorous BINOL ligand from the column.

We have also investigated the catalytic application of the Ti-R_{f6}-BINOL system in the asymmetric allylation of benzaldehyde using allyltri-*n*-butyltin (Scheme 3). Zhao and co-workers[10] have studied this reaction and obtained good conversions and enantioselectivities in a perfluorohexane–hexane biphase, but reported significant leaching (24%) of the lightly fluorinated BINOL ligand into the organic phase. Initially, we used the conditions developed by Zhao and co-workers with only slight modifications. Dichloromethane was used as the reaction solvent because (*R*)-BINOL is insoluble in hexane. Good conversions were obtained for both (*R*)-BINOL and (*R*)-R_{f6}-BINOL (Table 2), but once again, the enantioselectivity was slightly lower when the fluorinated BINOL ligand was used in dichloromethane. However, by changing the solvent to hexane the enantioselectivity increased to 75% ee demonstrating that the perfluoroalkyl groups do not have a detrimental effect on the abilities of the modifying ligand.



Scheme 3

In the separation and recycling studies both the fluorous and non-fluorous catalyses were carried out in dichloromethane to enable the direct comparison between (*R*)-R_{f6}-BINOL and conventional (*R*)-BINOL. The separation of (*R*)-BINOL from the organic product, 4-phenyl-1-buten-4-ol, was first investigated on conventional silica gel. Since allyltri-*n*-butyltin was added in a stoichiometric amount, it was not necessary to carry out an acid wash and so the crude reaction mixture was concentrated *in vacuo* before being loaded on to the top of a short column of silica gel. The 4-phenyl-1-buten-4-ol product was eluted from the column with acetonitrile and analysis by ^{1}H NMR spectroscopy showed that it was contaminated with an (*R*)-BINOL-containing species that also gave rise to butyl peaks. Tin NMR spectroscopic studies confirmed the presence of tin in this byproduct and all attempts to separate this contaminant from the desired product by solid-phase extraction were unsuccessful. In a further attempt to carry out this separation, the concentrated reaction mixture was left to stand overnight and some crystals suitable for X-ray analysis were formed in the residue. The crystal structure revealed that a monodeprotonated BINOL (HL)-tributyltin polymer was formed; selected bond length and bond angle data are given in Table 3. The structure of the monomeric repeat unit (Fig. 1) shows that tributyltin binds tightly to the deprotonated naphthoxy atom of BINOL and forms a much weaker interaction with the naphthol oxygen atom of an adjacent repeat unit to generate a polymeric chain containing alternating $SnBu_3$ and monodeprotonated BINOL units (Fig. 2). The highly distorted trigonal bipyramidal tin environment, in which the tributyl groups are displaced towards the neutral donor group, is very similar to the coordination geometry adopted by $[SnPh_3(O^iBu)(HO^iBu)]$,[11] which has analogous

Table 2 Asymmetric addition of allyltri-*n*-butyltin to benzaldehyde[a]

Ligand	Solvent	Conversion (%)[b]	ee (%)[c]
(*R*)-BINOL	Dichloromethane	89	79
(*R*)-R_{f6}-BINOL	Dichloromethane	85	66
(*R*)-R_{f6}-BINOL	Hexane	88	75

[a] Benzaldehyde (1 mmol), allyltri-*n*-butyltin (1.1 mmol), $Ti(O^iPr)_4$ (0.1 mmol), ligand (0.2 mmol), 0 °C, 6 h. [b] Percent conversion determined by ^{1}H NMR spectroscopy. [c] ee determined by conversion into the Mosher's acid ester followed by gc analysis.

Table 3 Selected bond lengths (Å) and bond angles (°) for [SnBu$_3$(2-O-2′-HO-1,1′-binaphthol)]$_n$[a]

Sn(1)–C(1)	2.138(5)	C(1)–Sn(1)–O(2)	92.45(19)
Sn(1)–C(5)	2.142(5)	C(5)–Sn(1)–O(2)	95.24(18)
Sn(1)–C(9)	2.171(5)	C(9)–Sn(1)–O(2)	99.4(2)
Sn(1)–O(2)	2.142(4)	C(1)–Sn(1)–C(5)	126.2(2)
Sn(1)–O(1)#1	2.549(4)	C(1)–Sn(1)–C(9)	114.3(2)
O(1)–Sn(1)#2	2.549(4)	C(5)–Sn(1)–C(9)	116.7(2)
O(1)–C(13)	1.383(7)	C(5)–Sn(1)–O(1)#1	80.77(17)
O(2)–C(24)	1.363(6)	C(1)–Sn(1)–O(1)#1	87.55(18)
		O(2)–Sn(1)–O(1)#1	175.01(13)

[a] Symmetry transformations used to generate equivalent atoms: #1 $-x, y - 1/2, -z + 1$; #2 $-x, y + 1/2, -z + 1$.

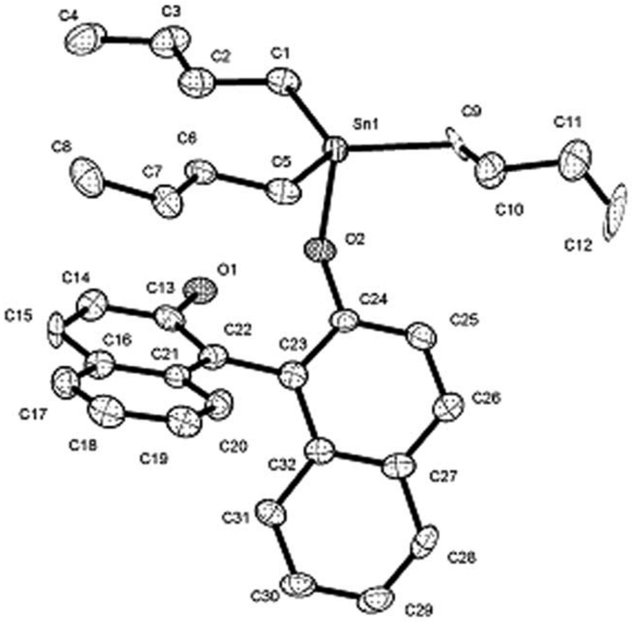


Fig. 1 Crystal structure of [SnBu$_3$(2-O-2′-HO-1,1′-binaphthol)]$_n$ repeat unit. Displacement ellipsoids are shown at the 50% probability level. The H atoms are omitted for clarity.

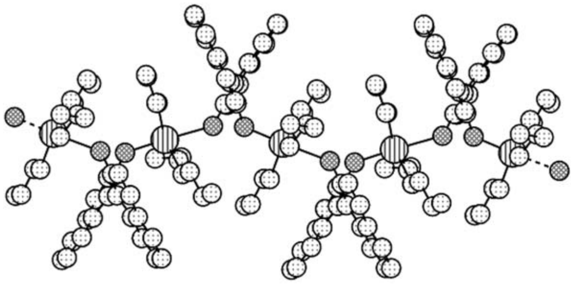


Fig. 2 Extended solid-state structure of [SnBu$_3$(2-O-2′-HO-1,1′-binaphthol)]$_n$. The H atoms are omitted for clarity.

Sn–O distances of 2.065(5) and 2.550(6) Å. The number of crystallographically characterized monodeprotonated BINOL (HL) complexes is relatively small, but the polymeric structure observed here is very similar to that reported recently for [Li((*R*)-HBINOL)(THF)$_2$]$_n$.[12]

After carrying out the asymmetric catalysis with (*R*)-R$_{f6}$-BINOL, the concentrated crude reaction mixture was added to the top of a short column of FRP silica gel. This time elution with acetonitrile gave clean product without any BINOL impurities. After an acid wash of the product, ICP atomic emission spectroscopy revealed that there was only a very small amount of tin (1.24 ppm ≡ 0.02% of the original amount of tin added) and titanium (2.21 ppm ≡ 0.88% of the original amount of titanium added) leaching into the product. Once the product was removed completely from the column with acetonitrile, a solvent switch to diethyl ether was then used to recover the R$_{f6}$-BINOL containing species. From ^{1}H and ^{119}Sn{^{1}H} NMR spectroscopic studies of this material, it is believed that a non-polar, R$_{f6}$-BINOL-Sn polymer is also formed in this system and this accounts for the ability to isolate the organic product without R$_{f6}$-BINOL contamination in contrast to our earlier work on the asymmetric alkylation of benzaldehyde with diethylzinc. When the isolated material was dried and reused in a second catalytic run with fresh aliquots of Ti(O^{i}Pr)$_4$, benzaldehyde and allyltri-*n*-butyltin, only unreacted starting materials were recovered. However, it is possible to recover (*R*)-R$_{f6}$-BINOL from the R$_{f6}$-BINOL-Sn polymer by hydrolysis with 4 M hydrochloric acid and this recovered (*R*)-R$_{f6}$-BINOL ligand was then reused in three further catalytic runs (Table 4).

The data show that similar product conversions are achieved after each run, with a slight fall after the third ligand reuse that is most likely to be caused by mechanical losses of the ligand after each recycle. There is also a small decrease in the product enantioselectivity probably due to a small amount of ligand racemisation. Only very low levels of tin and titanium leaching into the organic product were obtained and the amount of tin and titanium in the product could be removed to below detectable levels by simply passing the product, after separation on the FRP column, through a second short column of silica gel using acetonitrile as the eluant.

A subsequent investigation of alternative solid supports (powdered PTFE, C$_8$ reverse phase silica gel and conventional silica gel) demonstrated that FRP silica gel is essential for the efficient separation of the (*R*)-R$_{f6}$-BINOL-Sn complex from the organic product, since leaching of the R$_{f6}$-BINOL complex into the product was obtained with all of these alternative solid supports. Although the separation procedure was established originally after asymmetric allylation in dichloromethane, exactly the same recycling protocol can be used after catalysis in hexane when the product was obtained in higher enantioselectivity (78% ee). Analysis of the product by ^{1}H NMR spectroscopy and ICP atomic emission spectroscopy showed that it was isolated without any ligand contamination and only low levels of tin (1.18 ppm) and titanium (2.11 ppm) leaching

Table 4 Recycling results for (*R*)-R$_{f6}$-BINOL in dichloromethane

Run	Conversion (%)[a]	ee (%)[b]	Sn (ppm)[c]	Ti (ppm)[c]
1	85	66	1.24 (0.02%)	2.21 (0.88%)
2[d]	85	63	0.75 (0.01%)	1.99 (0.83%)
3[d]	82	58	2.73 (0.04%)	2.86 (1.19%)
4[d]	78	58	4.40 (0.07%)	4.65 (1.93%)

[a] Percent conversion determined by ^{1}H NMR spectroscopy. [b] ee determined by conversion into the Mosher's acid ester followed by gc analysis. [c] Metal content in product determined by ICP analysis, overall percentage shown in brackets. [d] Using ligand from previous run.

were detected. This final test demonstrates that the light fluorous approach can be used successfully in the asymmetric allylation of benzaldehyde to yield the product in high conversion and enantiopurity, whilst allowing the ligand to be isolated, recovered and reused without loss of activity or enantioselectivity.

Experimental

Proton and ^{19}F NMR spectroscopies were carried out on a Bruker ARX 300 spectrometer at 300.14 and 282.41 MHz respectively. Tin NMR spectroscopy was carried out on a Bruker DRX 400 spectrometer at 149.21 MHz. All chemical shifts are quoted in ppm using the high frequency positive convention; ^{1}H NMR spectra were referenced to external $SiMe_4$; ^{19}F NMR spectra to external $CFCl_3$ and ^{119}Sn NMR spectra to external $SnMe_4$. Mass spectra were recorded on a Kratos Concept 1H mass spectrometer. GC analyses were performed using a Perkin Elmer Clarus 500 GC fitted with an SGE CYDEX-B column. Optical rotation measurements were obtained using a Perkin Elmer Polarimeter 341 at 589 nm using a Na–Hal lamp. $Ti(^iOPr)_4$ was obtained from a commercial source (Aldrich), while the BINOL ligands were either purchased from a commercial source (Fluka) or synthesised by literature methods.[5] Fluoroflash® silica gel (40 μm) was purchased from Fluorous Technologies. Dichloromethane and hexane were dried by refluxing over calcium hydride or sodium wire respectively under dinitrogen. The solvents were distilled under nitrogen, stored in a closed ampoule over 4 Å molecular sieves and frozen–pumped–thawed three times to remove all dissolved gases.

General procedure for asymmetric addition of diethylzinc to benzaldehyde

A solution of $Ti(O^iPr)_4$ (157 μl, 0.32 mmol) and BINOL (0.21 mmol, 0.2 equiv.) in dichloromethane (10 ml) was stirred for one hour. An additional portion of $Ti(O^iPr)_4$ was then added (314 μl, 0.64 mmol) as well as the benzaldehyde (107 μl, 1.2 mmol). The solution was then cooled to −20 °C before adding diethylzinc (3.12 mmol, 3.12 ml of 1 M solution in hexane). After stirring the reaction mixture for five hours at −20 °C, it was quenched with 1 M hydrochloric acid (50 ml). The mixture was extracted with diethyl ether, dried, filtered and the solvent removed *in vacuo* to yield the product as a colourless oil contaminated with BINOL ligand. Product ee was determined using chiral GC and the absolute configuration was based on the comparison with the GC traces of the known, commercially available, enantiomerically pure compounds (CYDEX-B 30m, 90 °C for 24 min, 45 °C min^{-1} to 135 °C, hold 5 min. Injector: 220 °C, detector: 250 °C. Flow rate: 3 ml min^{-1}. R_t 25.3 min (*S*)-1-phenyl-propan-1-ol, R_t 25.9 min (*R*)-1-phenyl-propan-1-ol).

Asymmetric addition using (*R*)-BINOL

The general catalysis procedure was followed using (*R*)-BINOL as ligand (0.21 mmol, 60 mg). The product was collected as a colourless oil contaminated with (*R*)-BINOL. *m*/*z* (ES$^-$) 135 [M–H]$^-$ (90%). δ_H 0.81 (3H, t, $^3J_{HH}$ 7.2 Hz, CH_3), 1.69 (2H, m, CH_2), 1.98 (1H, br s, OH), 4.47 (1H, t, $^3J_{HH}$ 6.6 Hz, CH), 7.16–7.29 (5H, m, PhH). Run 1: 90% conversion, 86% ee; Run 2: 85% conversion, 90% ee; Run 3: 90% conversion, 90% ee.

Asymmetric addition using (*R*)-R_{f6}-BINOL

The general catalysis procedure was followed using (*R*)-R_{f6}-BINOL as ligand (0.21 mmol, 194 mg). The product was collected as a colourless oil. *m*/*z* (ES$^-$) 135 [M–H]$^-$ (90%). δ_H 0.81 (3H, t, $^3J_{HH}$ 7.2 Hz, CH_3), 1.69 (2H, m, CH_2), 1.98 (1H, br s, OH), 4.47 (1H, t, $^3J_{HH}$ 6.6 Hz, CH), 7.16–7.29 (5H, m, PhH). Run 1: 90% conversion, 77% ee; Run 2: 86% conversion, 70% ee; Run 3: 88% conversion, 75% ee.

Attempted separation of (*R*)-R_{f6}-BINOL and 1-phenyl-propan-1-ol

The crude product and R_{f6}-BINOL post-reaction mixture in diethyl ether was concentrated *in vacuo* and placed on the top of a 3 cm long column of FRP silica gel (1 cm in diameter). Elution with acetonitrile gave 1-phenyl-propan-1-ol which was contaminated with (*R*)-R_{f6}-BINOL ligand.

General procedure for asymmetric addition of allyltri-*n*-butyltin to benzaldehyde

The BINOL ligand (0.2 mmol) was added to a solution of $Ti(O^iPr)_4$ (0.3 ml, 0.1 mmol) in either hexane (20 ml) or dichloromethane (20 ml) and the mixture was stirred for one hour. After cooling the reaction mixture to 0 °C, benzaldehyde (0.1 ml, 1 mmol) was added. The reaction mixture was stirred for 10 minutes before adding allyltri-*n*-butyltin (0.34 ml, 1.1 mmol) and the reaction mixture was stirred at 0 °C for a further six hours. The solvent was removed under reduced pressure and the crude mixture was then used in the general separation procedure.

Determination of product (4-phenyl-1-buten-4-ol) enantiomeric excess

4-Phenyl-1-buten-4-ol (29 μl, 0.2 mmol) was added to a solution of Mosher's acid chloride (2 ml, 0.1 M solution in dichloromethane, 0.2 mmol) and pyridine (0.2 ml, 2.5 mmol). After stirring the reaction mixture for 30 minutes, 1 M hydrochloric acid was added (3 ml). The organic phase was separated, washed with $NaHCO_3$ (10 ml) and water (10 ml), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to yield a colourless oil which was analysed by chiral GC for diastereomeric content and the absolute configuration was determined to be *R* by comparison of the optical rotation data for 4-phenyl-1-buten-4-ol with the published specific rotation (CYDEX-B, 180 °C for 20 min. Injector: 220 °C, detector: 250 °C. Flow rate: 2 ml min^{-1}. R_t 8.81 min (*R*)-4-phenyl-1-buten-4-ol, Mosher's acid ester; R_t 13.00 min (*S*)-4-phenyl-1-buten-4-ol, Mosher's acid ester).[13]

Crystal data for $[SnBu_3(2\text{-}O\text{-}2'\text{-}HO\text{-}1,1'\text{-binaphthol})]_n$

$C_{32}H_{40}O_2Sn$, M = 575.33, monoclinic, space group $P2_1$, a = 11.2787(12), b = 11.6990(13), c = 11.6960(13) Å,

β = 115.519(2)°, U = 1392.7(3) Å^3, T = 150 K, Z = 2, D_c = 1.372 g cm^{-3}, F(000) = 596, colourless block, dimensions 0.26 × 0.12 × 0.06 mm, μ(Mo–Kα) = 0.943 mm^{-1}. Data were measured on a Bruker SMART diffractometer using graphite-monochromated Mo-Kα radiation (λ = 0.71073 Å), 10765 reflections measured, 5207 unique (R_{int} = 0.0232). An empirical absorption correction based on 6652 reflections (SADABS) was applied, maximum and minimum transmission factors of 0.86 and 0.52 respectively. The structure was solved by Patterson methods and refined using full matrix refinement based on F^2 gave R_1 = 0.0450 for 5031 observed data and wR_2 = 0.1205 for all 5207 data, GOF = 1.076 for 317 parameters. The OH hydrogen was not located or refined, but was included in calculating the molecular weight and density. The highest residual electron density peak (3.94 e Å^{-3}) was located 1.136 Å from the Sn atom. CCDC reference numbers [257732]. See http://www.rsc.org/suppdata/gc/b4/b418039a/ for crystallographic data in .cif or other electronic format.

^{1}H, ^{19}F{^{1}H} and ^{119}Sn{^{1}H} NMR studies of material recovered from column before acid wash

(*R*)-BINOL product. δ_H 0.70 (9H, t, $^3J_{HH}$ 7.2 Hz, CH_3), 0.80 (6H, m, CH_2), 1.05 (6H, m, CH_2), 1.20 (6H, m, CH_2), 5.06 (1H, br s, OH), 7.09 (2H, m, ArH), 7.23 (2H, m, ArH), 7.30 (2H, d, $^3J_{HH}$ 9.0 Hz, ArH), 7.74 (2H, d, $^3J_{HH}$ 8.6 Hz, ArH), 7.76 (2H, d, $^3J_{HH}$ 8.7 Hz, ArH), 7.81 (1H, d, $^3J_{HH}$ 7.9 Hz, ArH), 7.89 (1H, d, $^3J_{HH}$ 9.2 Hz, ArH). δ_{Sn} 105.47 (2Sn, s), 115.63 (1Sn, s).

(*R*)-R$_{f6}$-BINOL product. δ_H 0.82 (9H, t, $^3J_{HH}$ 7.3 Hz, CH_3), 1.06 (6H, m, CH_2), 1.24 (6H, m, CH_2), 1.40 (6H, m, CH_2), 5.21 (1H, br s, OH), 7.01 (2H, d, $^3J_{HH}$ 8.1 Hz, ArH), 7.22 (4H, m, ArH), 7.77 (1H, d, $^3J_{HH}$ 8.8 Hz, ArH), 7.85 (1H, d, $^3J_{HH}$ 7.8 Hz, ArH), 7.99 (2H, d, $^3J_{HH}$ 7.2 Hz, ArH). δ_F −80.79 (6F, t, $^4J_{FF}$ 9.2 Hz, CF_3), −109.59 (4F, m, α-CF_2), −121.44 (8F, m, 2 × CF_2), −122.78 (4F, m, CF_2), −126.12 (4F, m, CF_2). δ_{Sn} 106.20 (2Sn, s), 123.05 (1Sn, s).

Asymmetric addition of allyltri-*n*-butyltin using (*R*)-BINOL

The general catalysis procedure was followed using (*R*)-BINOL (57 mg, 0.2 mmol) as ligand. The product was collected as a colourless oil contaminated with BINOL material. *m*/*z* (ES$^+$) 149 [M+H]$^+$ (23%). δ_H 2.32 (1H, br s, OH), 2.54 (2H, m, CH_2), 4.74 (1H, dd, $^3J_{HH}$ 7.0 Hz, $^3J_{HH}$ 5.8 Hz, CH), 5.15 (1H, m, =CH_2), 5.20 (1H, dm, $^3J_{HH}$ 9.0 Hz, =CH_2), 5.84 (1H, m, HC=), 7.24–7.39 (5H, m, PhH). Run 1: 90% conversion, 82% ee; Run 2: 90% conversion, 78% ee; Run 3: 88% conversion, 78% ee.

Asymmetric addition of allyltri-*n*-butyltin using (*R*)-R$_{f6}$-BINOL

The general catalysis procedure was followed using (*R*)-R$_{f6}$-BINOL (184 mg, 0.2 mmol) as ligand in hexane. The product was collected as a colourless oil. *m*/*z* (ES$^+$) 149 [M+H]$^+$ (26%). δ_H 2.32 (1H, br s, OH), 2.54 (2H, m, CH_2), 4.74 (1H, dd, $^3J_{HH}$ 7.0 Hz, $^3J_{HH}$ 5.8 Hz, CH), 5.15 (1H, m, =CH_2), 5.20 (1H, dm, $^3J_{HH}$ 9.0 Hz, =CH_2), 5.84 (1H, m, HC=), 7.24–7.39 (5H, m, PhH). Run 1: 86% conversion, 74% ee; Run 2: 90% conversion, 78% ee; Run 3: 88% conversion, 74% ee.

General procedure for the separation of BINOL and 4-phenyl-1-buten-4-ol

A standard reaction mixture was concentrated *in vacuo* and the residue placed onto the top of a column of silica gel, FRP silica gel, C$_8$-reverse phase silica gel or powdered PTFE (3 cm long, 1 cm diameter). Acetonitrile was then used as elutant to recover the product. Diethyl ether was used as the second elutant to recover any ligand not eluted with the acetonitrile phase. This was washed with 4 M HCl, the organic layer separated and dried and the solvent removed under reduced pressure to yield free BINOL. Only when both FRP silica gel and (*R*)-R$_{f6}$-BINOL were used was complete separation of the ligand and product possible. After acid washes of the diethyl ether fraction and removal of the solvent, the recovered (*R*)-R$_{f6}$-BINOL was used in three further catalytic runs following the same catalysis procedure. The general separation procedure was then used to recover the ligand and separate the 4-phenyl-1-buten-4-ol product. After each run, the product was washed with 6 M hydrochloric acid and the Sn and Ti levels determined by ICP analysis of the wash. Figures in brackets indicate percentage of metal added at the outset which is present in the product. Run 1: 85% conversion, 66% ee. Sn: 1.24 ppm (0.02%) Ti: 2.21 ppm (0.88%); Run 2: 85% conversion, 63% ee. Sn: 0.75 ppm (0.01%) Ti: 1.99 ppm (0.83%); Run 3: 82% conversion, 58% ee. Sn: 2.73 ppm (0.04%) Ti: 2.86 ppm (1.19%); Run 4: 78% conversion, 58% ee. Sn: 4.40 ppm (0.07%) Ti: 4.65 ppm (1.93%).

Acknowledgements

We thank the Royal Society (EGH, AMS), the EPSRC (AJW) and Merck GmbH (AJW) for financial support.

John Fawcett, Eric. G. Hope, Alison M. Stuart* and Andrew J. West
Department of Chemistry, University of Leicester, Leicester, UK, LE1 7RH. E-mail: amc17@le.ac.uk; Fax: +44 116 252 3789; Tel: +44 116 252 2136

References

1 *Handbook of Fluorous Chemistry*, ed. J. A. Gladysz, D. P. Curran and I. T. Horváth, Wiley-VCH Verlag GmbH & Co. KgaA, Weinheim, Germany, 2004.
2 D. P. Curran, *Synlett*, 2001, 1488.
3 W. Zhang, *Tetrahedron*, 2003, **59**, 4475.
4 B. Croxtall, E. G. Hope and A. M. Stuart, *Chem. Commun.*, 2003, 2430.
5 E. G. Hope, A. M. Stuart and A. J. West, *Green Chem.*, 2004, **6**, 345.
6 J. Vaughan-Spickers, A. M. Stuart, E. G. Hope and A. J. West, *Eur. Patent Appl.*, 2004, EP04022878.5.
7 D. J. Birdsall, E. G. Hope, A. M. Stuart, W. Chen, Y. Hu and J. Xiao, *Tetrahedron Lett.*, 2001, **42**, 8551.
8 F.-Y. Zhang, C.-W. Yip, R. Cao and A. S. C. Chan, *Tetrahedron: Asymmetry*, 1997, **8**, 585.
9 Y. Nakamura, S. Takeuchi and Y. Ohgo, *J. Fluorine Chem.*, 2003, **120**, 121.
10 Y.-Y. Yin, G. Zhao, Z.-S. Qian and W.-X. Yin, *J. Fluorine Chem.*, 2003, **120**, 117.
11 H. Renter and D. Schröder, *Acta Crystallogr. Sect. C: Struct. Commun.*, 1993, **49**, 954.
12 H. C. Aspinall, J. F. Bickley, J. L. M. Dwyer, N. Greeves and A. Steiner, *Angew. Chem., Int. Ed.*, 2000, **39**, 2858.
13 G. E. Keck, K. H. Tarbet and L. S. Geraci, *J. Am. Chem. Soc.*, 1993, **115**, 8467.

Corrosion behaviour of ionic liquids†

Marc Uerdingen,*[a] Claudia Treber,[a] Martina Balser,[b] Günter Schmitt[c] and Christoph Werner[bd]

Received 24th December 2004, Accepted 7th March 2005
First published as an Advance Article on the web 29th March 2005
DOI: 10.1039/b419320m

The corrosion behaviour of carbon steel, austenitic stainless steel, nickel-based alloy C22, copper, brass and aluminium (AlMg3) was investigated in seven ionic liquids (ILs) with different chemical structure under flow conditions at temperatures up to 90 °C. Stainless steel proved resistant in all water-free and water-diluted systems tested. Alloy C22 generally was not attacked, however, it was also moderately corroded in a diluted IL with dimethyl phosphate as anion. For carbon steel and aluminium the corrosivity of IL media strongly depends on the chemical structure of the cationic moiety and the nature of anion in the IL molecule. Anions like tosylate and dimethyl phosphate generally trigger higher corrosivity specifically in water-diluted ILs. In general, the aluminium alloy performed better than carbon steel, specifically in water-free ILs. Copper and brass generally suffer from severe attack in IL media at higher temperatures. However, it was demonstrated that corrosion inhibition is possible.

Introduction

In recent years a growing number of scientists and engineers have been attracted to the fascinating property profile of ionic liquids (ILs) so that a broad range of applications is under current investigation.[1] A few impressive examples demonstrate that ILs have begun the transition from curiosities to commodities.[2] The BASIL™-process[3] and the hydrosilylation process[4] represent this development. Some other processes which have not yet been realised on a technical scale include the DIFASOL-process[5] and the desulfurisation of hydrocarbon feeds.[6]

The specific chemical behaviour and the unique physical properties are the key factors for considering ILs for new and innovative applications. However, for their commercial implementation, ionic liquids have to meet a number of requirements such as purity, the commercial availability, the thermal stability, toxicological issues and last but not least the corrosivity to materials typically used for vessels, pipings and other technical equipment.

Material corrosion can be a risk for plant integrity, reduce plant efficiency, cause plant shutdowns, yield loss or contamination of produced products, waste valuable resources, result in overdesign and may require costly maintenance.

This paper reports on the corrosion behaviour of a number of metallic materials in ILs with different chemical structures in the absence and presence of water. As flow systems are generally encountered in technical processes the experimental programme was designed to study the likelihood of flow enhanced corrosion which may lead to flow induced localised corrosion (FILC), often also called erosion corrosion.

This type of material attack is initiated under turbulent flow conditions when high energy near-wall microturbulences interact with the wall and destruct protective scales, layers or films on the substrate. Therefore the initiation of FILC strongly depends on the mechanical properties of protective scales, layers or films. However, the type and properties of surface layers formed on metallic materials in ionic liquids are widely unknown. More information on this issue is welcome both for scientific and technical reasons.

The study of flow effects on corrosion of metal in ILs has another interesting aspect. Most of the ILs considered today for technical application are imidazolium or quaternary ammonium compounds and some of those are known to influence the fluid dynamics considerably and can increase the critical flow intensities for FILC initiation (at least in the presence of water).[7,8] Would this effect be detectable also for water-free imidazolium based ionic liquids?

Marc Uerdingen

Dr Marc Uerdingen was born in 1972, and studied chemistry at the University of Bonn. He obtained his Masters thesis in 1998 at the Kékulé Institute of Organic Chemistry at the University of Bonn in the group of Prof. Krause. He subsequently conducted his PhD at the Institute of Organic Chemistry at the University of Dortmund, where he finished his PhD studies on "Investigations on Copper Assisted Addition Reaction on Michael Acceptors" in 2001. Since 2002 he has headed the R&D Department of Solvent Innovation GmbH, Cologne, Germany.

---

† This work was presented at the Green Solvents for Synthesis Meeting, held in Bruchsal, Germany, 3–6 October 2004.

*marc.uerdingen@solvent-innovation.com

Experimental

For screening purposes the susceptibility of materials to FILC can be easily evaluated using the "rotating cage" method.[9–11] Here, coupons (generally flat coupons) are mounted between glass powder reinforced PTFE plates (Fig. 1). Upon rotation highly turbulent disturbed flow regimes are encountered at the coupons, specifically at the leading edges. This is welcome because such disturbed flow fields are responsible for FILC initiation. While this method was successfully used for a long time without knowing the exact wall shear stresses existing under given geometric conditions and rotation frequencies, it is today possible to quantify local flow intensities at rotated coupons.[12]

In the experiments reported here 6 coupons (50 × 10 × 2 [mm]) each of carbon steel, austenitic stainless steel (1.4301, equivalent to stainless steel 304), Hastelloy C22 (nickel-based alloy), brass (CuZn40), copper (SF-quality) and aluminium (AlMg3) were mounted into the same "rotating cage" and rotated in a 2 L glass autoclave containing 1.5 L of test liquid with a rotation frequency of 800 rpm (circumferential flow velocity of 2.5 m s^{-1}). The experimental setup is exemplified in Fig. 2. Prior to the experiments all test coupons were cleaned for 5 min subsequently in hexane, acetone, 10% hydrochloric acid, 10% sodium hydroxide solution and methanol. The coupons were air-dried and subjected to weight measurements.

The test liquid was aerated by air-bubbling from a cylinder with pressurised dry air (2 bubbles per second). The test medium was heated to 90 °C with a heating jacket at the glass autoclave at ambient pressure. The exposure time was 4 days. At the end of the experiment the appearance of the coupons was photographically documented and after surface cleaning with a hard brush under flowing water, the mass loss of the coupons determined. From the mass loss an integral surface related mass loss rate [g m^{-2} h^{-1}] and an integral corrosion penetration rate [mm $year^{-1}$] was calculated assuming a linear time law.

The chemical structures of the 7 ILs tested are shown in Scheme 1. Substances **1** to **5** are imidazolium derivatives with different substituents and varying anions (ethyl sulfate, octyl sulfate, tosylate, chloride and dimethyl phosphate). Substances **6** and **7** are quaternary ammonium compounds with different chemical structures and different anions (methyl sulfate and saccharinate).

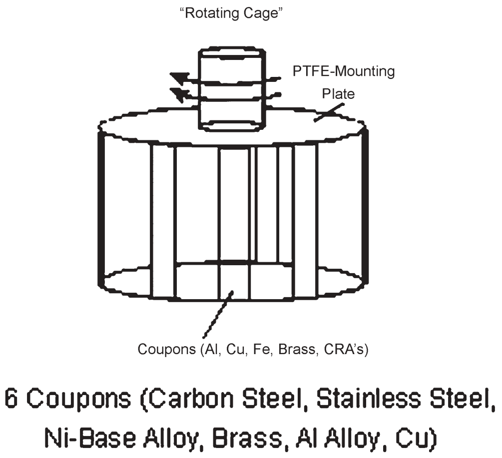


Fig. 1 Sketch of a rotating cage.

Fig. 2 Experimental setup of rotating cage experiments.

Results

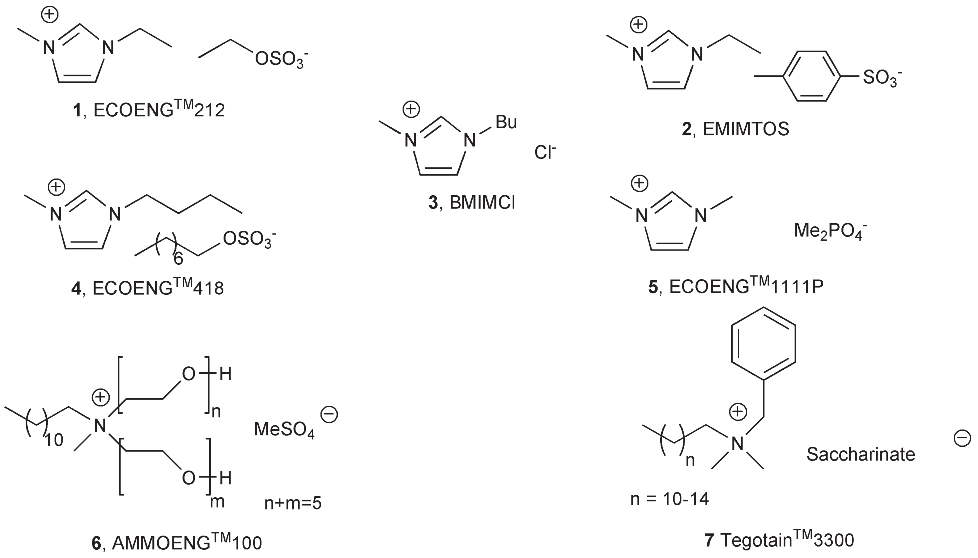
Water-free ionic liquids

Application of the ionic liquids (IL) **1**, **2**, **5** and **6** in water-free quality (water content determined by Karl-Fischer-Titration, less than 1% before aeration) revealed that both the chemical structure of the cation and the type of anion exert dramatic effects on the corrosivity of ILs at 90 °C (Fig. 3). Thus, IL **1** appeared significantly less corrosive than IL **2**, which can be attributed to the type of anion. Clearly the tosylate anion increases the corrosivity, specifically for carbon steel, brass and copper which are attacked with corrosion rates between 15 and 25 mm $year^{-1}$. With ethyl sulfate as the anion, carbon steel is not attacked, while brass and copper still show corrosion rates in the order of 2 mm $year^{-1}$, well above the target corrosion rate of max. 0.1 mm $year^{-1}$ as for stainless steel type 304, aluminium alloy AlMg3, and, as one would expect, the nickel-base alloy C22. This material was not attacked in all experiments but one. In this case IL **5** (imidazolium salt with dimethyl phosphate as anion) had been used in a 10% concentration in water (Fig. 4) and the corrosion rate was determined to be about 0.71 mm $year^{-1}$.

The austenitic stainless steel proved resistant in all IL-containing media tested: water-free or as an aqueous solution. Localised attack (*e.g.* pitting, intergrannular corrosion) could not be observed in any of the experiments. Nevertheless, resistance to localised corrosion of stainless steel in IL-containing media should be investigated in more detail in a separate study.

It was an interesting finding that aluminium alloys like AlMg3 generally performed very well in the water-free ILs (corrosion rates of 0.03 mm $year^{-1}$ and below). As ILs are also discussed as efficient heat exchanger fluids or extraction media, aluminium alloys represent an attractive group of construction materials for those applications.

For comparison Fig. 3 also contains the results obtained under otherwise similar conditions in water with 250 ppm NaCl (reference medium R1) or in an uninhibited 1 : 1 (v/v) mixture of water and ethylene glycol (reference medium R2).



Scheme 1 Ionic liquids tested.[13]

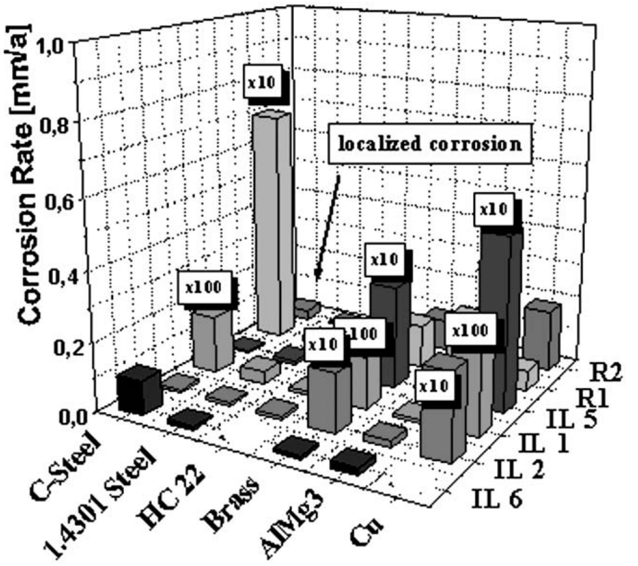


Fig. 3 Materials corrosion in water-free ILs and reference media (R1: water with 250 ppm chloride, R2: uninhibited 1 : 1 water–glycol mixture).

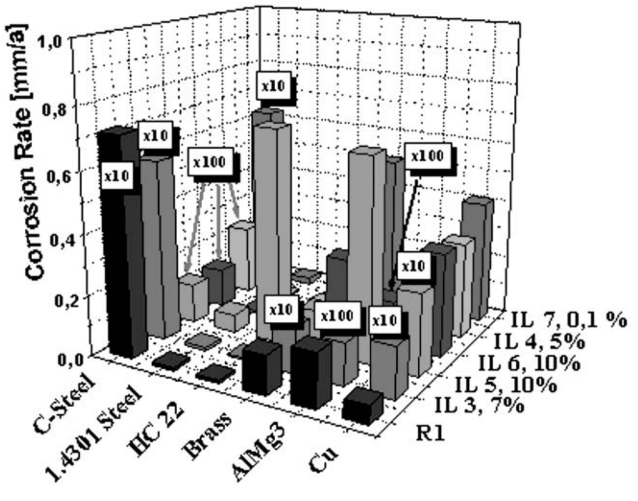


Fig. 4 Increase of corrosivity of ILs by high water-dilution. Comparison with materials corrosion in water with 250 ppm (R1).

Carbon steel experienced a very high corrosion rate (*ca.* 7 mm year^{-1}) in water containing chloride (Fig. 3, R1), while brass and the aluminium alloy marginally surpassed the 0.1 mm year^{-1} target line (brass: 0.13 mm year^{-1}, aluminium: 0.18 mm year^{-1}). In the glycol solution (Fig. 3, R2) only brass and copper exhibited a significant material loss (brass: 0.09 mm year^{-1}; copper: 0.18 mm year^{-1}). This is due to corrosion attack by glycolic acid formed during the 4 days exposure time from glycol oxidation in aerated solutions at temperatures as high as 90 °C. This reaction is known to be catalysed by corroding copper-containing metals. On the carbon steel coupon pitting was observed with a maximum penetration depth of 50 μm.

The corrosivity of IL decreases with decreasing temperature. Thus, at 36 °C none of the materials tested showed any corrosion attack after 4 days of exposure. It should be noted that due to the high viscosity of ILs at lower temperature the rotation speed was only set to 500 rpm in the experiments at 36 °C. However, the lower rotation speed is not expected to have a significant effect under these conditions.

Effect of water content

Addition of only 10% of water can increase the corrosivity of IL media significantly (Fig. 5). For IL **2** this holds specifically for brass and copper, the corrosion rate of which is approximately doubled in the presence of 10% water (brass: increase from 1.8 to 3.8 mm year^{-1}; copper: increase from 2.5 to 5.6 mm year^{-1}). Even the aluminium alloy experienced higher mass loss which, however, still remained below the target mass loss rate (0.06 mm year^{-1}). Stainless steels and the Ni-based alloy C22 also performed well in the 90% solutions of IL **2** and **6**. However, carbon steel was not attacked in IL **2**,

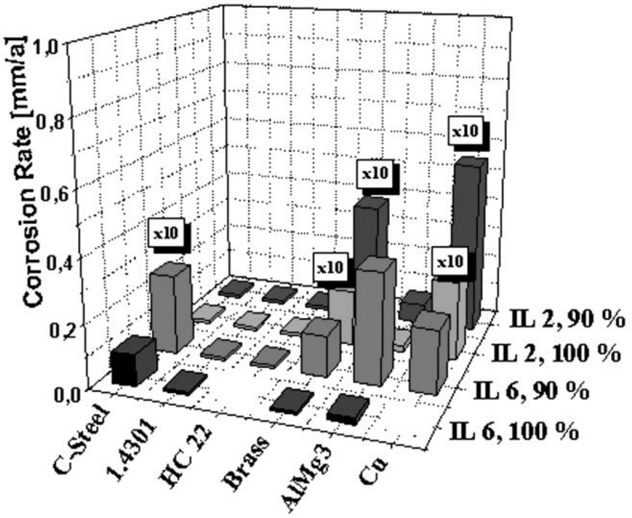


Fig. 5 Increase of IL corrosivity by 10% water-dilution.

but was severely corroded (2.5 mm year^{-1}) in IL **6** with 10% water. While sulfuric acid could possibly be formed in both IL **2** and **6** media *via* hydrolysis of the methyl and ethyl sulfate moieties it seems that the imidazolium ion is a better corrosion inhibitor for steel than the PEG modified quaternary ammonium moiety in IL **6**.

This is supported by results obtained with higher diluted IL **6** solutions (Fig. 6). The corrosion of steel is enhanced dramatically amounting to 12.5 mm year^{-1} in 10% IL **6** solution. Also brass and copper experience higher mass losses with increasing dilution of the IL **6** solution. However, in 10% IL **6** solution corrosion rates of only 0.26 and 0.34 mm year^{-1}, respectively, were observed. The aluminium alloy was affected from dilution of IL **6** with water as well. However, higher dilutions of IL **6** in water seem not to increase the corrosion rate significantly.

Diluted solutions of the ILs proved to be very corrosive for steel, also in the case of ILs **3** to **7** (Fig. 4). In the case of a 10% solution of IL **5** (anion: dimethyl phosphate) even the Ni-based alloy C22 experienced significant materials attack (0.7 mm year^{-1}). In the same solution stainless steel yielded a corrosion rate of 0.06 mm year^{-1} which is well below the 0.1 mm year^{-1} target line, but still higher than observed in all other IL-containing solutions. The aluminium alloy also experienced mass losses corresponding to a corrosion rate of approx. 0.7 mm year^{-1}.

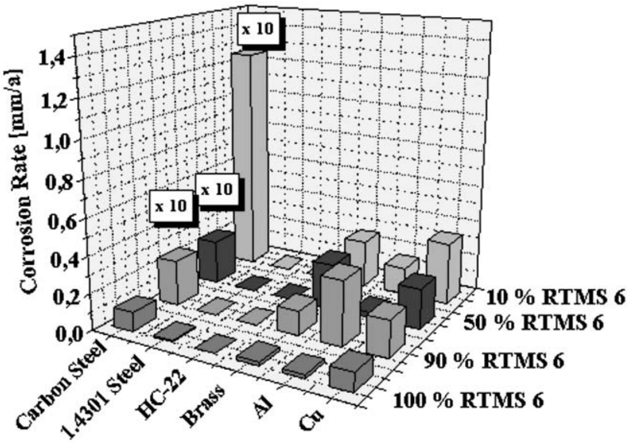


Fig. 6 Effect of water-dilution of IL **6**.

Diluted solutions of the ILs **3** and **4** caused high material attack at the aluminium alloy, while the addition of 0.1% of IL **7** exerted no stimulating effect on the corrosion of aluminium (Fig. 4). Brass and copper experienced moderate mass losses in highly diluted IL solutions. However, in the case of a 7% IL **4** solution the corrosion rate exceeded 1.5 mm year^{-1}. Without having tested accordingly, it still remains to be investigated whether brass and copper undergo stress corrosion cracking in diluted IL solutions of the kind tested in this work.

Corrosion inhibition

The finding that 10% water in IL **6** can already enhance the corrosion rate of metals, specifically carbon steel, prompted us to test whether corrosion inhibitors can be used in these systems to decrease the medium corrosivity. A test run was performed with addition of 2000 ppm of 1*H*-benzotriazole, a well known inhibitor for copper corrosion in neutral aqueous media, to a 90% water containing IL **6** solution (Fig. 7). It appeared that this addition indeed inhibited the copper corrosion significantly, while the carbon steel attack was highly stimulated. Nevertheless, these results indicate that the use of corrosion inhibitors is also possible in IL media. However, for given applications the most effective additives still remain to be evaluated.

Conclusions

The combination of metallic materials, ionic liquid and by-product is essential for the corrosion behaviour. In this investigation we concentrated on various ILs diluted in different water concentrations in the presence of six metals. The corrosivity for a given metal is determined by the chemical structure of the IL cation and the nature of the anion.

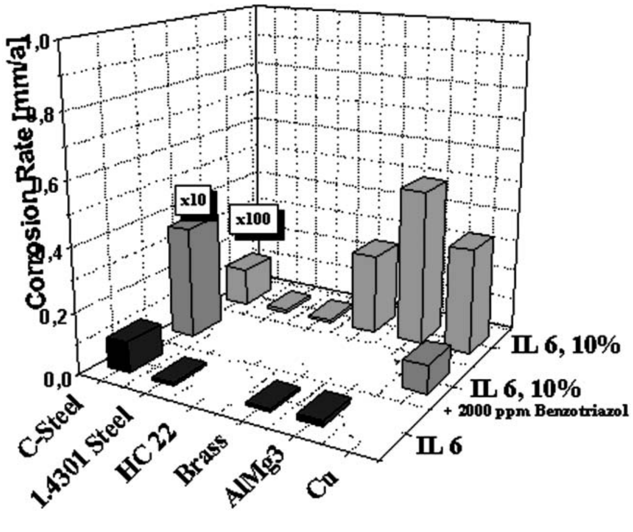


Fig. 7 Effect of benzotriazole addition on materials corrosion in aqueous 10% IL **6** solution (reference: performance in 100% IL **6**).

Negative effects are exerted by the tosylate and dimethyl phosphate anion. Dilution with water could lead to hydrolysis of many anions used in IL production which then produce acids (*e.g.* sulfuric acid, phosphoric acid) and, hence, cause acid corrosion.

The best performance in all IL media tested was observed with stainless steel type 304. The Ni-based alloy C22 in general proved to have a high resistance to IL-containing media. However, only in water-diluted IL **5** containing the dimethyl phosphate ion did this metal experience a relatively high corrosive attack.

The corrosion resistance of carbon steel in water-free ILs strongly depends on the IL anion. Primarily, the tosylate anion has to be avoided. Corrosion problems arise from dilution of ILs with water. Depending on the type of IL, carbon steel may undergo severe corrosion in diluted IL media.

In water-free ILs the aluminium alloy AlMg3 also exhibited a high corrosion resistance. This material can, therefore, be recommended for the technical usage in IL applications. However, dilution with water can cause a considerable increase of medium corrosivity.

Copper and brass exhibit the lowest corrosion resistance in IL-containing media. For this group of metals the question of stress corrosion cracking has still to be investigated.

It was experimentally established that corrosion inhibition is also possible in IL-containing media. 1*H*-benzotriazole was shown to act as an efficient corrosion inhibitor in IL **6** containing 90% water. Under the same conditions this substance stimulates carbon steel corrosion. In mixed installations appropriate inhibitor packages have to be applied.

The results obtained indicate that materials selection for technical equipment used in IL-based chemical processes is a very important issue and requires further investigations with respect to chemical and electrochemical corrosion mechanisms and its relation to the chemical structure and concentration of ILs. IL media, especially water-free or highly concentrated ILs, could represent a corrosion media which so far have not been investigated in detail. Apart from general and flow enhanced corrosion the question of localised attack (pitting, selective corrosion, stress corrosion cracking, hydrogen uptake, *etc.*) has to be investigated for candidate materials. In flow related studies the flow dynamics of ILs should also be investigated.

Furthermore, the corrosivity of metallic materials in typical reaction mixtures of ILs with other chemical compounds (*e.g.* rhodium catalysts as used in hydroformylation reactions[14]) should be investigated. This is specifically important for miniplant technologies.

Acknowledgements

We thank Prof. Dr P. Wasserscheid for helpful discussions and Prof. Dr W. Leitner for the permission to perform this work in the Institute for Technical Chemistry and Petrolchemistry at the Aachen University of Technology.

Marc Uerdingen,*[a] Claudia Treber,[a] Martina Balser,[b] Günter Schmitt[c] and Christoph Werner[bd]
[a]*Solvent Innovation GmbH, Cologne, Germany.*
E-mail: marc.uerdingen@solvent-innovation.com
[b]*Aachen University of Technology, Germany*
[c]*Iserlohn University of Applied Sciences, Germany*
[d]*Enthone GmbH, Langenfeld, Germany*

References

1 *Ionic Liquids in Synthesis*, ed. P. Wasserscheid and T. Welton, 2002, Wiley-VCH, references cited herein.
2 J. H. Davis, Jr. and P. A. Fox, *Chem. Commun.*, 2003, 1209.
3 M. Fremeantle, *Chem. Eng. News*, 2003, **81**, 9.
4 B. Weyershausen, K. Hell and U. Hesse, *Green Chem.*, 2005, **7**, DOI: 10.1039/b408317b.
5 F. Favre, A. Ferestiere, F. Hugues, H. Olivier-Bourbigou and J.-A. Chordoge, *Pet. Tech.*, 2002, **441**, 104–109; D. Commereuc, A. Forestiere, F. Hugues and H. Olivier-Bourbigou, DE 101 52 957 A1; DE 198 29 466 A1.
6 J. Esser, P. Wasserscheid and A. Jess, *Green Chem.*, 2004, **6**, 316–322; A. Bösmann, L. Datsevitch, A. Jess, A. Laiuter, C. Schmitz and P. Wasserscheid, DE 101 55 281.5.
7 G. Schmitt, *Mater. Corros.*, 2001, **52**, 124–136.
8 G. Schmitt, C. Werner and M. Bakalli, *Fluid mechanical interactions of turbulent flowing liquids with the wall—revisited with a new electrochemical tool*, CORROSION'2005, NACE International, Houston TX, 2005, Paper 05-344.
9 G. Schmitt and W. Bruckhoff, *Relevance of laboratory experiments for investigation and mitigation of flow induced localised corrosion in gas production*, CORROSION'88, NACE, Houston TX, 1988, Paper 357.
10 G. Schmitt, W. Bruckhoff, K. Faessler and G. Bluemmel, *Mater. Perform.*, 1991, **30**, 2, 85–90.
11 S. Papavinasam, R. W. Revie, M. Attard, A. Demoz, H. Sun, J. C. Donini and K. H. Michaelian, *Mater. Perform.*, 2000, **39**, 8, 58–60.
12 C. Deslouis, A. Belghazi, Y. T. Al-Janabi, P. Plagemann and G. Schmitt, *Quantifying local wall shear stresses in the rotated cage*, CORROSION'2004, NACE International, Houston TX, 2004, Paper 04727.
13 ECOENG™212 is 1-ethyl-3-methylimidazolium ethylsulfate; ECOENG™418 is 1-butyl-3-metylimidazolium octylsulfate; ECOENG™1111P is 1,3-dimethyl-imidazolium dimethylphosphate; Ammoeng™100 is (C12–C18)alkylpoly-(3)oxyethyldihydroxyethylmethylammonium methylsulfate); all ionic liquids are available from Solvent Innovation, Cologne.
14 R. van Hal, P. Wasserscheid and A. Bösmann, *Green Chem.*, 2002, **4**, 400–404.

Stabilization of Ti-molecular sieve catalysts used in selective sulfoxidation reactions by ionic liquids†

Valentin Cimpeanu,[a] Christopher Hardacre,*[b] Vasile I. Pârvulescu*[c] and Jillian M. Thompson[b]

Received 8th November 2004, Accepted 16th March 2005
First published as an Advance Article on the web 7th April 2005
DOI: 10.1039/b417000h

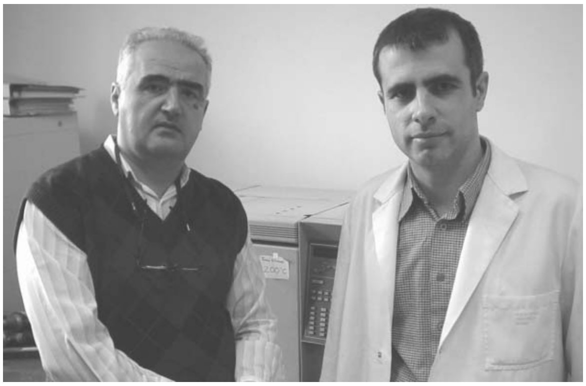
Sulfoxidation reactions of 4,6-dimethyl-2-methylthiopyrimidine have been performed using titanosilicate catalysts in ionic liquids, dioxane and ethanol. The ionic liquid reactions showed superior reactivity compared with molecular solvents. Moreover, on examination of the recycling of the catalyst, a significant increase in the stability of catalyst was found both in terms of recycling activity and leaching of the titanium from the catalyst. The mechanism by which the ionic liquid reduces the solubilisation of the catalysts is explored.

Introduction

Heterogeneous catalysed oxidations are one of the most widely applied and important industrial processes currently used and have recently been reviewed extensively.[1,2] More than 60% of industrial chemicals and intermediates presently produced involve selective oxidations. Within this group, liquid phase oxidation of hydrocarbons, alcohols and thioethers are amongst the most significant. Although selectivity is the main driver behind process development in selective oxidation reactions, the stability and recyclability of the catalyst used is also a vital part of the overall scheme.[2] In liquid phase heterogeneous catalysis, leaching of the active species from the catalyst into the solvent medium is one of the main reasons for catalyst deactivation and poor recyclability. Whilst many factors govern the solubilisation of the catalyst into the liquid phase, one important variable is the nature of the solvent and the interaction with the surface of the catalyst. We describe here the effect of ionic liquids compared with molecular solvents on the leaching of titanium from titanosilicates and hence the recyclability of the catalyst.

Ionic liquids (ILs) have been used in numerous reactions[3] and the first industrial process has been established by BASF.[4] Catalytic studies in ionic liquids have been dominated by investigations into homogeneous catalyst systems whereby the ionic liquid immobilises the catalyst and allows good separation of the solvent–catalyst system from the products.[3] More recently, the combination of heterogeneous catalysts in ionic

Chris Hardacre read Natural Sciences at the University of Cambridge and obtained his PhD in 1994. After SERC and Emmanuel College research fellowships, he was appointed to a Lectureship in Physical Chemistry at the Queenã s University of Belfast in 1995. In 2003, he became a Professor of Physical Chemistry. His current interests lie in understanding heterogeneously catalysed processes and their application in fine chemical synthesis and the use of synchrotron radiation to probe the structure of ionic liquids and understand reactions performed in them.



Vasile Pârvulescu (left) and Valentin Cimpeanu (right).

Valentin Cimpeanu is a PhD student in the University of Bucharest. During his PhD under the supervision of Prof. Pârvulescu, he received a one-year Marie Curie Fellowship at QUILL. His current research interests are focused on sulfoxidation, reactions in ionic liquids and multinuclear NMR.

Vasile Pârvulescu graduated from the University of Bucharest in 1979, and obtained a PhD in 1986 from the Polytechnic University of Bucharest. After several fellowships in the Universite Catholique de Louvain (NATO, PECO) and an A.v. Humboldt fellowship in the Max-Planck Institut in Mulheim, he received a full Professor position at the University of Bucharest. He is author of 121 papers and 215 patents, and his current interests concern heterogeneous diastereoselective reactions and the preparation and investigation of mesoporous catalysts.

---

† This work was presented at the Green Solvents for Synthesis Meeting, held in Bruchsal, Germany, 3–6 October 2004.

liquids has been investigated. In particular, selective hydrogenation,[5,6] selective oxidation,[7] Heck coupling,[8] Friedel–Crafts,[9] and cyclization reactions[10] have been reported. Although the advantages of the ionic liquids have been described in many of these studies, for example increased rates and/or selectivities, in only a few studies has the heterogeneity of the process been examined. For example, in selective hydrogenation reactions using palladium supported on carbon, the system was recyclable over six reactions.[6] However, the simple reuse of a catalyst over several consecutive runs is not sufficient proof for absence of leaching, and a more rigorous approach is needed, such as testing the catalytic ability of the separated liquid phase.[11,12] In this case, no leaching of the palladium was found by ICP and no significant activity of the separated ionic liquid phase was found. In contrast, using zeolites for the Friedel–Crafts acylation of anisole showed clearly that the zeolite simply acted as a reservoir of protons which underwent ion exchange with the ionic liquid cation.[9] This process was totally homogeneously catalysed and although the catalyst could be recycled, this was only possible following a calcination process.

This paper is part of an ongoing study into heterogeneously catalysed ionic liquid processes, in particular the use of Ti-SBA-15 and Ti-Ge-MCM-41 catalysts for sulfoxidation of aliphatic and heterocyclic sulfides.[7,13] Herein the stability of the catalysts in ionic liquids compared with molecular solvents is examined in detail for the selective sulfoxidation of 4,6-dimethyl-2-methylthiopyrimidine to the corresponding sulfoxide rather than overoxidation to the sulfone using hydrogen peroxide as the oxidant, Fig. 1.

Experimental

The Ti-Ge-MCM-41 catalysts were prepared employing a one-pot sol-gel procedure, using cetyltrimethylammonium bromide (CTAB) as a surfactant, which acts as the structure directing agent, and 2,2′,2″-nitriletriethanol (TEA), which controls the hydrolysis and co-condensation reaction rates of Ti, Ge and Si and allows the self-assembling processes between the inorganic precursors and the surfactant micelles to occur, as described previously.[14] Two Ti-Ge-MCM-41 catalysts were prepared (GeTiSi10 and GeTiSi15) using TEOS, $Ti(OC_4H_9)_4$, and $GeCl_4$ as the silicon, titanium and germanium sources, respectively. The gel composition ratios used were 2 : 0.046 : 0.023 : 7 : 0.52 : 180 : 0.5 for GeTiSi10 and 2 : 0.050 : 0.032 : 7 : 0.52 : 180 : 0.5 for GeTiSi15 (Si : Ti : Ge : TEA : CTAB : H_2O : NaOH). After adding water slowly under vigorous stirring, the reaction mixture was aged at 25 °C for 24 h. The resulting mesostructured powder was then collected by filtration, washed with water and ethanol, and air-dried. To obtain the final mesoporous material, the as-synthesized solid was calcined at 500 °C for 5 h under a static air atmosphere.

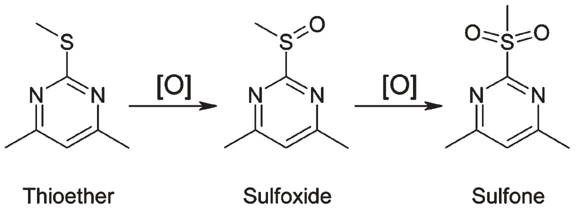


Fig. 1 Schematic showing the oxidation of 4,6-dimethyl-2-methylthiopyrimidine to the corresponding sulfoxide and then to the sulfone.

The Ti-SBA-15 catalysts were prepared *via* an analogous sol-gel route using Pluronic P-123, a non-ionic polyethoxylated-polypropoxylated surfactant, and low pH solution for hydrolysis.[15] In each case, tetraethyl orthosilicate, tetraethylgermanate and tetrapropyl orthotitanate were employed as sources of silicon, germanium and titanium, respectively. The full details have been described previously.[13]

Table 1 summarises the main characteristics of the catalysts used in this study. In each case, the titanium is well dispersed in these samples, as indicated from the comparison of the chemical and XPS analysis.

1-Ethyl-3-methylimidazolium tetrafluoroborate ([emim][BF_4]) and triflate ([emim][OTf]) ionic liquids were prepared from 1-ethyl-3-methylimidazolium chloride by a metathesis reaction using $NaBF_4$ and HOTf, respectively.[16] Each ionic liquid was purified by dissolving the ionic liquid in dichloromethane and washing this solution extensively with water before drying at 80 °C at 0.2 mmHg vacuum. The purity of ILs was confirmed by ^1H, ^{19}F and ^{13}C-NMR spectroscopy. The water content for both ionic liquids was found to be less than 0.2 wt% by Karl–Fisher titration. The chloride content, measured by ionic chromatography,[17] was below 20 ppm for both ionic liquids. The substrate, 4,6-dimethyl-2-methylthiopyrimidine, was synthesized as described by Hunt *et al.*,[18] and its purity was checked by HPLC analysis and ^1H and ^{13}C-NMR spectroscopy. Spectroscopic grade dioxane and ethanol were obtained from Aldrich and used as received without further purification.

The experiments were performed using the following procedure. To 1 g of IL and 5 mg catalyst, 0.3 mmol H_2O_2 (as a 2 M solution in dioxane) and 0.2 mmol substrate were added and the reaction mixture stirred at 40 °C. Aliquots of reaction mixture of 20 mg were taken, diluted with 1 cm^3

Table 1 Chemical composition, determined by ICP-AES, and textural and XPS parameters of the catalysts used

		Chemical composition		Textural parameters		XPS parameters		
						Binding energies		
Catalyst	Form of sample	Ti/Si × 100	Ge/Si × 100	BET surface/m^2	Pore diameter/nm	$Ti(2p_{3/2})$	Si(2p)	Ti/Si atomic ratio × 100
GeTiSi10	MCM-41	2.25	1.14	954	2.98	459.6	104.2	2.11
GeTiSi15		2.34	1.55	998	3.04	459.6	104.3	2.24
Ti1	SBA-15	1.50	—	610	3.50	459.5	104.3	0.67
Ti2		1.50	—	920	5.60	459.5	104.2	0.54

HPLC-grade acetonitrile, filtered and analyzed by HPLC. HPLC analysis was performed on an Agilent 1200 liquid chromatograph, using a C8 (Eclipse-XDC8) column with an eluent containing acetonitrile : water (1 : 1), at 1 cm^3 min^{-1} and 254 nm detector wavelength.

In order to examine the extent of titanium leaching, a higher quantity of catalyst was used (10 mg), in order to minimize the losses due to physical manipulations. After the end of each reaction, the mixture was centrifuged for 5 min at 2500 rpm using a BTL bench centrifuge. The liquid phase was then decanted, and the catalyst washed with 3 × 5 cm^3 HPLC grade acetone. After drying the catalyst at 120 °C for 12 h, the reaction was repeated with fresh ionic liquid and substrate. The titanium content of the separated ionic liquid was analyzed by ICP-AES.

All turnover frequencies (TOF) are expressed as g of oxidized thioether per g of catalyst per h, after 30 min of reaction.

Results and discussion

Catalytic activity

Table 2 compares the results from the catalytic sulfoxidation of 4,6-dimethyl-2-methylthiopyrimidine using each catalyst, in dioxane, ethanol, [emim][BF_4] and [emim][OTf]. The turnover frequency, TOF, was measured over the first 30 min of reaction, where the maximum conversion was 25%. Within each form of catalyst, *i.e.* MCM-41 or SBA-15, the order of reactivity for the solvents was the same; for the MCM-41 catalysts ethanol > [emim][BF_4] > dioxane ≫ [emim][OTf] whereas for the SBA-15 catalysts [emim][BF_4] > [emim][OTf] ≫ dioxane > ethanol. The differences between the activity in the molecular solvents and [emim][BF_4] was small using the MCM-41 catalysts. It is also clear that the rate of reaction was much higher for the MCM-41 catalysts compared with the SBA-15 systems.

The reactions in the ionic liquids also showed significantly higher selectivities with respect to formation of sulfoxide *versus* over oxidation to the sulfone, compared with either ethanol or dioxane for all the catalysts. Fig. 2 shows a comparison of the time variation for GeTiSi15 in ethanol and [emim][OTf]. In ethanol, even at low conversions, the sulfoxide selectivity is poor, for example at 50% conversion the selectivity is only 90.0% and at 100% conversion this has decreased further to 73.9%. In comparison in [emim][OTf], the sulfoxide selectivity at all conversions is >91%. Similar trends are found with all the catalysts for both organic and ionic liquid solvents, with the highest selectivity found using GeTiSi15 in [emim][BF_4].

Titanium leaching

As is clear from Table 2, there is a considerable difference in the amount of titanium leaching for each catalyst and solvent system examined. Figs. 3 and 4 show the variation of TOF and amount of titanium leaching as a function of the recycle number for GeTiSi15 and Ti1 catalysts, respectively. For all the MCM-41 catalysts, there is a sharp decrease in the TOF after the first reaction before the activity stabilizes at a similar level for all the solvents used. Although there is also a decrease in activity with successive reactions for the SBA-15 catalysts, this loss is more gradual. This change in the behavior between

Table 2 Turnover frequencies and the percentage titanium leached (compared with the fresh catalyst) measured over the first 30 min of reaction and sulfoxide selectivity (at 100% conversion) as a function of catalyst and solvent used for the selective sulfoxidation of 4,6-dimethyl-2-methylthiopyrimidine using hydrogen peroxide at 40 °C

Catalyst	Solvent	TOF/h^{-1}	Selectivity (%)[a]	Leached Ti (%)
GeTiSi10	Dioxane	0.94	69.5	23.3
	Ethanol	1.22	75.3	24.5
	[emim][BF_4]	1.06	89.2	16.5
	[emim][OTf]	0.38	87.3	11.5
GeTiSi15	Dioxane	2.56	67.4	38.6
	Ethanol	3.06	73.9	41.2
	[emim][BF_4]	2.89	93.4	18.4
	[emim][OTf]	0.95	91.8	12.0
Ti1	Dioxane	0.08	78.5	2.0
	Ethanol	0.01	58.6	2.6
	[emim][BF_4]	0.21	90.2	0.9
	[emim][OTf]	0.14	85.7	1.1
Ti2	Dioxane	0.05	75.6	1.9
	Ethanol	0.01	65.2	2.5
	[emim][BF_4]	0.15	87.3	1.0
	[emim][OTf]	0.12	83.1	1.1

[a] At 100% conversion.

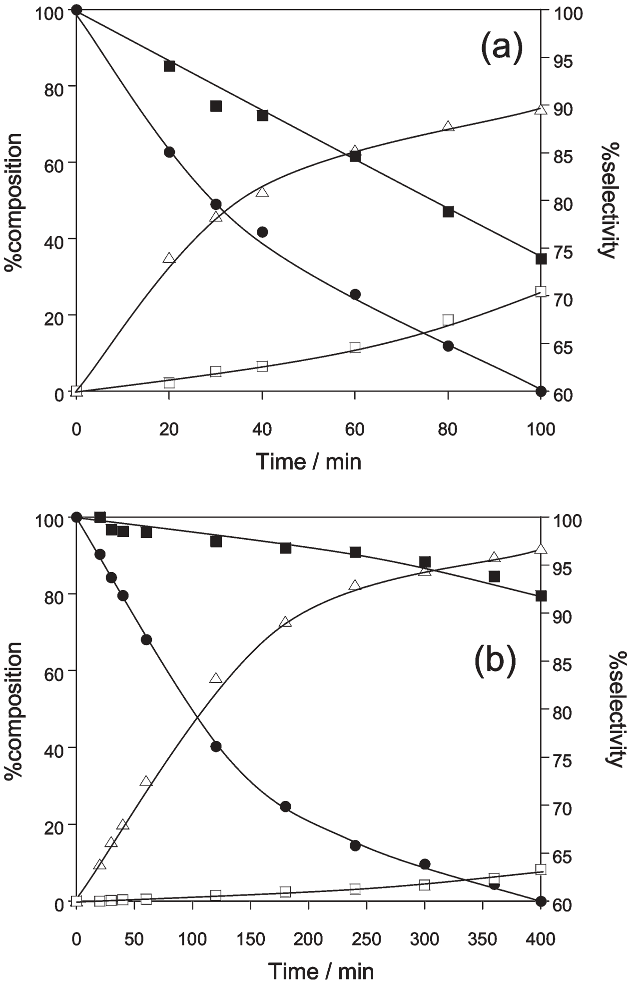


Fig. 2 Variation of percentage composition with respect to 4,6-dimethyl-2-methylthiopyrimidine (●), sulfoxide (△) and sulfone (□) and sulfoxide selectivity (■) as a function of time using GeTiSi15 and hydrogen peroxide in (a) ethanol and (b) [emim][OTf] at 40 °C.

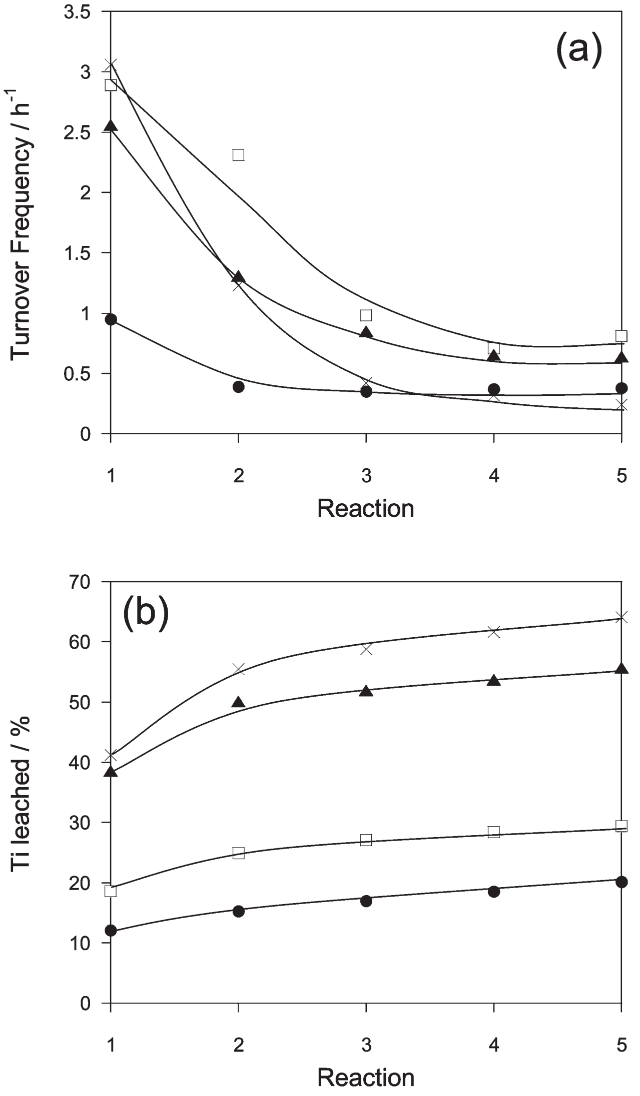


Fig. 3 (a) Turnover frequency (taken over the first 30 min of reaction) and (b) cumulative %Ti leaching with respect to the original catalyst as a function of catalyst recycle for the selective sulfoxidation of 4,6-dimethyl-2-methylthiopyrimidine using GeTiSi15 and hydrogen peroxide in ethanol (×), dioxane (▲), [emim][BF$_4$] (□) and [emim][OTf] (●).

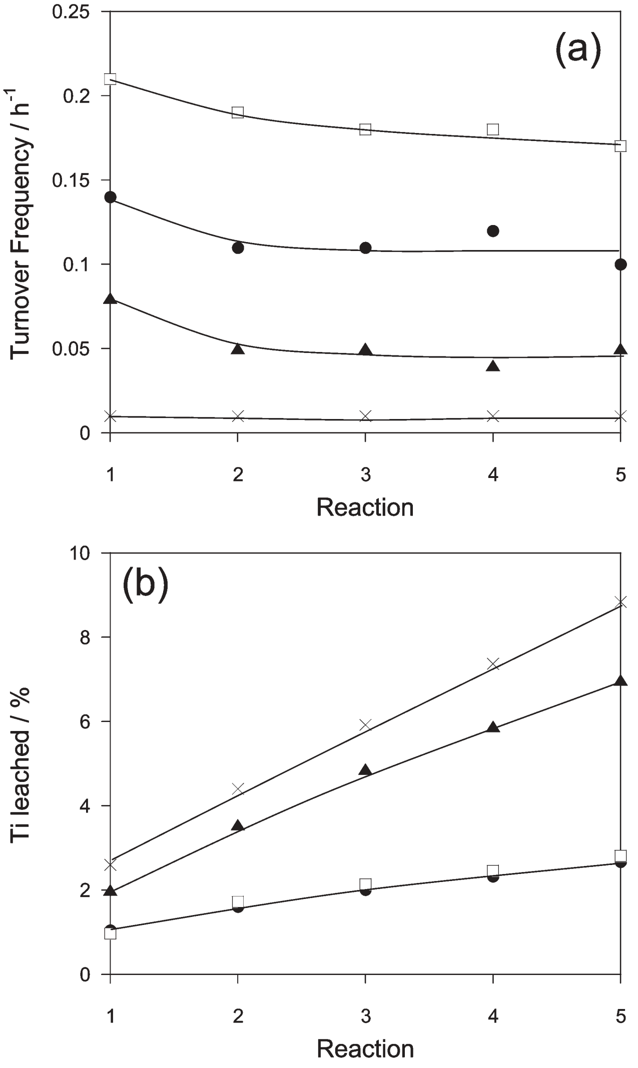


Fig. 4 (a) Turnover frequency (taken over the first 30 min of reaction) and (b) cumulative %Ti leaching with respect to the original catalyst as a function of catalyst recycle for the selective sulfoxidation of 4,6-dimethyl-2-methylthiopyrimidine using Ti1 and hydrogen peroxide in ethanol (×), dioxane (▲), [emim][BF$_4$] (□) and [emim][OTf] (●).

the two catalysts is reflected in the amount of titanium leaching. For both catalysts, the leaching is much less in the ionic liquids than found in the molecular solvents. For example, in ethanol, almost 40% of titanium is leached from the catalyst during the first reaction using GeTiSi15 catalysts and more than 50% of the total amount of titanium present in the original catalyst is lost after two reactions. In [emim][BF$_4$], although the leaching is also significant, only 25% of the titanium in the catalyst is leached after two reactions. Furthermore, if the MCM-41 catalyst is compared with the SBA-15 material, the leaching is much lower in all solvents in the latter. Even in ethanol, less than 9% of the titanium content of the catalyst is leached over five reactions.

The IR spectra of the GeTiSi15 catalyst before and after reaction in [emim][BF$_4$] and ethanol are in agreement with the leaching results, Fig. 5. In both solvents, the band located at 960 cm^{-1} decreases progressively with the number of recycles but drops more significantly in ethanol than [emim][BF$_4$]. This absorption corresponds to the stretching vibrations of a SiO$_4$ tetrahedron perturbed by the presence of a (SiO$_3$)Si–O–Ti group.[19] With increased leaching of titanium, the band intensity falls.

Although three types of bonds can be present in titanosilicates, *i.e.* Ti–O–Ti, Si–O–Si, and Si–O–Ti, due to the low titanium content, around 2%, few Ti–O–Ti bonds are likely. Furthermore, the bond Si–O–Si is very resistant to hydrolysis in acidic or weak basic solutions and therefore the solubility of the catalyst is dependent on the breaking of the Ti–O–Si bonds. The comparative stability of the SBA-15 and MCM-41 catalysts was unexpected. It was thought that the atrane synthesis route[14] used to prepare the MCM-41 catalysts would result in more intimately substituted Ti and Ge in the silica matrix and, consequently more stable catalysts. However, as

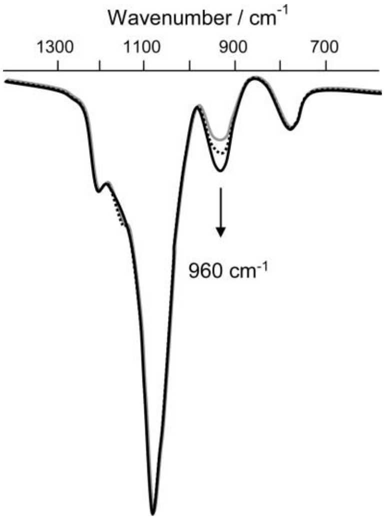


Fig. 5 Infra-red spectra of dried GeTiSi15 catalyst before (black), and after the selective sulfoxidation of 4,6-dimethyl-2-methylthiopyrimidine reaction in ethanol (grey) and [emim][BF_4] (dashed).

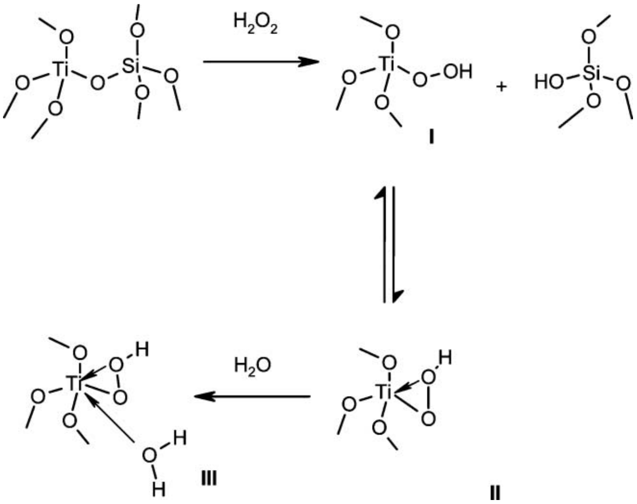


Fig. 6 Proposed mechanism for hydrogen peroxide catalysed solvolysis of titanosilicate catalysts.

observed, these catalysts showed much lower stability than the SBA-15 materials. The increased leaching of the MCM-41 catalysts compared with the SBA-15 catalysts is in agreement with the increased amount of surface titanium in the former materials from the surface analysis results shown in Table 1. As the stability of the catalysts is due to the adsorption of the hydrogen peroxide on the titanium active centre, with greater accessibility to the titanium, more adsorption occurs and the probability of dissolution increases.

The adsorption of peroxide and, therefore the stability of the catalyst, is also strongly dependent on the solvent–peroxide interaction.[20] It is already known that framework titanium ions can reversibly change their coordination geometry easily depending on the solvent environment. For example, XAFS studies of TS-1 have indicated that Ti–O distances increase when the material is exposed to water (1.94 Å), and return to their initial value (1.82 Å) when dehydrating conditions are applied.[21] The coordination of water also leads to a bathochromic shift in the UV-vis spectra from 208 nm to 238 nm, in accordance with calculated peak values for tetrahedrally and octahedrally oxygen-coordinated Ti^{4+}.[22] Fig. 6 shows the postulated mechanism associated with the interaction of H_2O_2–H_2O with the titanosilicate structure. Initially, hydroperoxides (**I**) are generated through hydrolysis of Ti–O–Si bonds, which rearrange into a pentacoordinated Ti complex (**II**) due to the ability of the hydroperoxide ion to act as a bidentate ligand. The complex **II** may add a molecule of water, leading to a hexacoordinated Ti complex **III**, evidenced both by experimental results[23] and DFT calculations.[24] Furthermore, if complex **II** is formed in *tert*-butanol, it reacts with the solvent, and *tert*-butylhydroperoxide (TBHP) is produced by a ligand-exchange reaction, showing the reversibility of Ti coordination by hydroperoxide anion.[22] The Ti–O–Si link may be reformed *via* a condensation reaction of the –Ti–OH and –Si–OH species eliminating water.[25] It has been postulated that the titanium leaching from TS-1 is related to further reactions at the titanium centre following the initial hydrolysis of the Si–O–Ti bonds.[26] Interesting, the same experiments show that catalytic activity is also associated with titanium tetracoordinated by O–Si groups, and not only to Ti–OH groups.

The reversible stability of TS-1 has been compared with Ti-Beta zeolite, for example. In this case irreversible degradation of catalytic properties associated with high titanium leaching following reaction in the presence of hydrogen peroxide has been reported.[27] Exposure to the oxidant produces a high amount of defects on the catalyst surface, cleaving more than one Si–O–Ti link per Ti ion. Finally, these ions are removed from the material, and agglomerate as extra framework crystalline, octahedral coordinated TiO_2. Similarly, Ti-MCM-41 materials, employed in epoxidation of cyclohexene with hydrogen peroxide were less stable compared with TS-1.[28]

The large differences observed between the leaching in each of the solvents in this study indicate that solvents can significantly stabilise the structure of the materials with respect to solvolysis. This may be associated with the deactivating effect that the ionic liquid has on strongly hydrogen bonded molecules. For example, both spectroscopic studies[29,30] and molecular dynamics[31] calculations have shown that at low concentrations water binds strongly to the ionic liquid and in turn the water–water interactions are significantly reduced. The water is highly dispersed throughout the ionic liquid and this in turn reduces the chemical activity of the water. This has been demonstrated by the observation that water sensitive reagents, such as platinum-diphosphine complexes, are highly stable in the ionic liquid, even in the presence of water.[32] In comparison, water in organic solvents, even strong hydrogen bonding solvents such as alcohols, forms micelles and the water maintains its activity and coordinating ability.[33] Similar interactions are likely to occur with hydrogen peroxide in the ionic liquids compared with the molecular solvents. Obviously, there is a need to strike a balance between no activity and so much coordination that extensive dissolution occurs. In the case of water, the interaction is found with the anion[29,31] and, therefore, it is probable that the hydrogen peroxide activity will be strongly dependent on the anion as well. This is in agreement with the results in this study; the triflate is a stronger hydrogen bonding acceptor than tetrafluoroborate and consequently the catalytic activity of the hydrogen peroxide is lower in the triflate ionic liquid. Furthermore, it is interesting to note that for the MCM-41 catalysts, which showed high degrees of leaching, the triflate ionic liquid had significantly smaller amounts of titanium in solution following reaction than the tetrafluoroborate ionic liquid.

As shown by Trukhan *et al*., the SBA-15 catalysts show good recyclability and the activity is mainly due to a surface process.[34] It is therefore possible to examine the effect of the ionic liquid compared with the molecular solvents on the inherent activity of the heterogeneous catalyst–hydrogen peroxide system. Although the ionic liquid–hydrogen peroxide interaction is stronger than in the case of dioxane or ethanol, the activity of both ionic liquids was higher. This indicates that the ionic liquid interaction with the catalyst promotes the sulfoxidation reaction. Cimpeanu *et al*. have shown that the activation may be related to the interaction of the acidic proton at the C(2) position on the imidazolium cation with the titanium active site.[13] The higher activity in the ionic liquid is observed, despite the fact that they are much more viscous than the molecular organic solvents studied, for example the viscosity of ethanol is 1.2 cP at 20 °C compared with 32 cP at 25 °C for [emim][BF_4].[35] Mass transfer limitations are important to consider for reactions in ionic liquids and these reduce the rate of heterogeneously catalysed processes, in general.[6] Although there is clearly an interaction of the ionic liquid with the catalyst,[36] the catalyst does not undergo solvolysis and the titanium is not leached from the framework.

In comparison, given the large degree of leaching found in the MCM-41 catalysts, it is not as simple to distinguish the effect of the solvent on the catalytic activity for these catalysts. In the present study, the used solvent was replaced with fresh solvent on recycling and, therefore, the amount of titanium leached within each recycle, *i.e.* not the cumulative amount leached, reflects the concentration in solution present during reaction. As the homogeneous reaction rate will only be determined by the amount of titanium in solution, if the TOFs are calculated as a function of the amount of titanium in solution, for a given solvent these should be constant if the reaction is solely associated with the homogeneous reaction. Whilst similar values are obtained for ethanol, for all the other solvents this TOF increases significantly with the reaction number. For ethanol it may be the case that the surface reaction rate is small, in agreement with the very low activity for the SBA-15 catalytic activity results. However, for the other solvents used, although a major component of the reactivity is associated with the homogeneous process, the surface reaction also contributes significantly. This is in agreement with the observation that on comparing the reaction in the absence of catalyst, after stirring the GeTiSi15 catalyst for 1 h in the presence of the oxidant and solvent, with that in the presence of catalyst just over half the rate could be accounted for by the homogeneous reaction.[7] The effect of the solvent is complex as it will affect both the homogeneous and heterogeneous rates. As described above the ionic liquid does appear to promote the surface process but the effect on the homogeneous reaction is still not understood and is the subject of further study.

Although the large increase in TOF between the two catalyst types may be attributed in part to the increase in leaching, the heterogeneous activity of the catalysts is also different. This cannot be attributed to a difference in the porosity/structure of the catalyst as both the catalyst types used in this study are mesoporous and, therefore, the mass transport of the substrate is similar in each case for a given solvent. It is possible that the increase in TOF is due to the presence of germanium; however, due to the complex relationship between the homogeneous and heterogeneous reaction rates it is difficult to ascertain the role of the germanium in the fresh MCM-41 catalysts. An examination of the TOF for each catalyst for the 4th recycle, *i.e* the 5th reaction, does indicate that the germanium is not simply a spectator species. In these reactions, the concentrations of titanium in solution are similar for a given solvent and, therefore, any contribution to the homogeneous reaction rate will be the same for both catalyst systems. It is clear that, even though the titanium content has been reduced significantly in the MCM-41 materials compared with the SBA-15 due to leaching, the TOF, based on total mass of catalyst, is still much higher for the MCM-41 materials. If the TOF is calculated with respect to the amount of titanium the difference in the TOF is over an order of magnitude indicating that the germanium acts as a promoter for the reaction.

Conclusions

Ti-containing molecular sieves catalysed sulfoxidations occur with comparable rate in both molecular solvents and ionic liquids. The use of ILs as solvents results in a superior stability of the tested catalysts compared with either protic or aprotic molecular solvents. This fact is thought to be due to the solvation properties of ILs with respect to water and hydrogen peroxide which lowers the proton-donating character of these molecules.

Acknowledgements

This work was supported by an EU Marie Curie Early Stage Training Site Fellowship, contract number HPMT-GH-00-00147-03, QUILL and the EPSRC under grant GR/R68757.

Valentin Cimpeanu,[a] Christopher Hardacre,*[b] Vasile I. Pârvulescu*[c] and Jillian M. Thompson[b]
[a]*"C. D. Nenitzescu" Institute of Organic Chemistry, Splaiul Independentei 202B, Bucharest 060023, Romania*
[b]*The QUILL Centre and School of Chemistry, Queen's University Belfast, Belfast, Northern Ireland, UK BT9 5AG*
[c]*University of Bucharest, Department of Chemical Technology and Catalysis, B-dul Regina Elisabeta 4-12, Bucharest 030016, Romania*

References

1 For example, D. E. De Vos, M. Dams, B. F. Sels and P. A. Jacobs, *Chem. Rev.*, 2002, **102**, 3615; T. Mallat and A. Baiker, *Chem. Rev.*, 2004, **104**, 3037.
2 *Fine Chemical through Heterogeneous Catalysis*, ed. R. A. Sheldon and H. van Bekkum, Wiley-VCH, Weinheim, 2001.
3 *Ionic Liquids in Synthesis*, ed. T. Welton and P. Wasserscheid, Wiley-VCH, Weinheim, 2003.
4 K. R. Seddon, *Nat. Mater.*, 2003, **2**, 363.

5 R. T. Carlin and J. Fuller, *Chem. Commun.*, 1997, 1345.
6 K. Anderson, P. Goodrich, C. Hardacre and D. W. Rooney, *Green Chem.*, 2003, **5**, 448.
7 V. Cimpeanu, V. I. Pârvulescu, P. Amorós, D. Beltrán, J. M. Thompson and C. Hardacre, *Chem. Eur. J.*, 2004, **10**, 4640.
8 X. G. Xie, J. P. Lu, B. Chen, J. J. Han, X. G. She and X. F. Pan, *Tetrahedron Lett.*, 2004, **45**, 809; K. Okubo, M. Shirai and C. Yokoyama, *Tetrahedron Lett.*, 2002, **43**, 7115; H. Hagiwara, Y. Shimizu, T. Hoshi, T. Suzuki, M. Ando, K. Ohkubo and C. Yokoyama, *Tetrahedron Lett.*, 2001, **42**, 4349; S. A. Forsyth, H. Q. N. Gunaratne, C. Hardacre, A. McKeown, D. W. Rooney and K. R. Seddon, *J. Mol. Catal. A*, 2005, **231**, 61.
9 C. Hardacre, D. W. Rooney, J. M. Thompson and S. P. Katdare, *World Patent*, WO03028882, 2003; C. Hardacre, S. P. Katdare, D. Milroy, P. Nancarrow, D. W. Rooney and J. M. Thompson, *J. Catal.*, 2004, **227**, 44; H.-Y. Shen, Z. M. A. Judeh, C. B. Chiang and Q.-H. Xia, *J. Mol. Catal. A*, 2004, **212**, 301.
10 J. S. Yadav, B. V. S. Reddy, M. S. Reddy and N. Niranjan, *J. Mol. Catal. A*, 2004, **210**, 99.
11 R. A. Sheldon, M. Wallau, I. W. C. E. Arends and U. Schuchardt, *Acc. Chem. Res.*, 1998, **31**, 485.
12 Y. Deng, C. Lettman and W. F. Maier, *Appl. Catal., A*, 2001, **214**, 31.
13 V. Cimpeanu, A. N. Pârvulescu, V. I. Pârvulescu, D. T. On, S. Kaliaguine, J. M. Thompson and C. Hardacre, *J. Catal.*, in press.
14 S. Cabrera, J. El Haskouri, C. Guillem, J. Latorre, A. Beltrán, D. Beltrán, M. D. Marcos and P. Amorós, *Solid State Sci.*, 2000, **2**, 405–420; J. El Haskouri, S. Cabrera, M. Gutierrez, A. Beltrán-Porter, D. Beltrán-Porter, M. D. Marcos and P. Amorós, *Chem. Commun.*, 2001, 309.
15 D. T. On, D. Lutic and S. Kaliaguine, *Micropor. Mesopor. Mater.*, 2001, **435**, 44; A. Ungureanu, D. T. On, E. Dumitriu and S. Kaliaguine, *Appl. Catal., A*, 2003, **254**, 203.
16 J. D. Holbrey and K. R. Seddon, *J. Chem. Soc., Dalton Trans.*, 1999, 2133; L. Crowhurst, P. R. Mawdsley, J. M. Perez-Arlandis, P. A. Salter and T. Welton, *Phys. Chem. Chem. Phys.*, 2003, **5**, 2790.
17 C. Villagrán, M. Deetlefs, W. Pitner and C. Hardacre, *Anal. Chem.*, 2004, **76**, 2118.
18 R. R. Hunt, E. R. Sayer and J. F. W. McOmie, *J. Chem. Soc.*, 1959, 525.
19 L. Y. Chen, G. K. Chuah and S. Jaenicke, *J. Mol. Catal. A*, 1998, **132**, 281.
20 M. Ziolek, *Catal. Today*, 2004, **90**, 145.
21 Z. Liu and R. J. Davis, *J. Phys. Chem.*, 1994, **98**, 1253.
22 B. Notari, *Adv. Catal.*, 1996, **41**, 271.
23 G. Bellussi, A. Carati, M. G. Clerici, G. Maddinelli and R. Millini, *J. Catal.*, 1992, **133**, 220.
24 D. H. Wells, W. N. Delgass and K. T. Thomson, *J. Am. Chem. Soc.*, 2004, **126**, 2956.
25 W. Lin and H. Frei, *J. Am. Chem. Soc.*, 2002, **124**, 9292.
26 L. Davies, P. McMorn, D. Bethell, P. C. B. Page, F. King, F. E. Hancock and G. J. Hutchings, *Chem. Commun.*, 2000, 1807.
27 A. Carati, C. Flego, E. P. Massara, R. Millini, L. Carluccio, Jr., W. O. Parker and G. Bellusi, *Micropor. Mesopor. Mater.*, 1999, **30**, 137.
28 L. Y. Chen, G. K. Chuah and S. Jeanicke, *Catal. Lett.*, 1998, **50**, 107.
29 L. Cammarata, S. G. Kazarian, P. A. Salter and T. Welton, *Phys. Chem. Chem. Phys.*, 2001, **3**, 5192.
30 A. Mele, C. D. Tran and S. H. D. Lacerda, *Angew. Chem., Int. Ed.*, 2003, **42**, 4364.
31 C. G. Hanke and R. M. Lynden-Bell, *J. Phys. Chem. B*, 2003, **107**, 10873.
32 V. Farmer and T. Welton, *Green Chem.*, 2002, **4**, 97; S. Doherty, P. Goodrich, C. Hardacre, H. K. Luo, D. W. Rooney, K. R. Seddon and P. Styring, *Green Chem.*, 2004, **6**, 63.
33 L. Dougan, S. P. Bates, R. Hargreaves, J. P. Fox, J. Crain, J. L. Finney, V. Reat and A. K. Soper, *J. Chem. Phys.*, 2004, **121**, 6456 and references therein.
34 N. N. Trukhan, V. N. Romannikov, A. N. Shmakov, M. P. Vanina, E. A. Paukshtis, V. I. Bukhtiyarov, V. V. Kriventsov, I. Y. Danilov and O. A. Kholdeeva, *Micropor. Mesopor. Mater.*, 2003, **59**, 73.
35 A. Noda, K. Hayamizu and M. Watanabe, *J. Phys. Chem. B*, 2001, **105**, 4603.
36 D. J. Gorman-Lewis and J. B. Fein, *Environ. Sci. Technol.*, 2004, **38**, 2491.

A design-of-experiments approach to modeling activity coefficients in solvent mixtures: a case study using platinum(II) acetylacetonate in mixtures of acetone, cyclohexanol, 1,2,3,4-tetrahydronaphthalene and propylene carbonate†

Scott Flanagan,*[a] Eric Hall,[a] Wade Bowie,[a] James W. Fuhs,[b] Robbie Logan,[a] Farzaneh Maniei[c] and Andrew Hunt[a]

Received 3rd December 2004, Accepted 31st March 2005
First published as an Advance Article on the web 14th April 2005
DOI: 10.1039/b418130a

The solubility of platinum(II) acetylacetonate ($Pt(acac)_2$) in various solvent mixtures of acetone, cyclohexanol, propylene carbonate and 1,2,3,4-tetrahydronaphthalene (THN) have been determined at 25 °C and 1 atm, using thermogravimetric analysis (TGA) and inductively coupled plasma mass spectrometry (ICP-MS). The densities of the saturated solutions were determined by pycnometry. The entropy of fusion and melting point of $Pt(acac)_2$ were determined by differential scanning calorimetry (DSC) to be 41.4 J mol^{-1} K^{-1} and 512.5 K, respectively. From this data, the ideal mole fraction at saturation (x_{ideal}) of $Pt(acac)_2$ was calculated to be 0.0278, which is more than twice the highest reported solubility of that compound. In this effort, mixtures of acetone, propylene carbonate and THN exhibit cosolvency for $Pt(acac)_2$, with the greatest measured molar solubility of $C_{\text{sat}} = 0.0675$ mol L^{-1} occurring at the 1 : 1 : 1 v : v : v ratio of these three solvents. A new equation was developed for activity coefficients in solvent mixtures and used to predict $\ln \gamma$ for $Pt(acac)_2$ to within 3.6% of the measured values. The concept of Intercomponent Mixture Parameters (IMPs) is introduced in relation to Scheffé mixture polynomials as applied to the prediction of activity coefficients in solvent mixtures.

Scott Flanagan

Scott Flanagan was born in 1966. He earned a PhD in inorganic chemistry at Rice University in 1995, studying synthetic models for the reactivity of blue copper proteins with Professor Lon J. Wilson. While at Rice, Dr. Flanagan also published several papers in the area of fullerene electrochemistry, including the first paper to describe the electrochemical behavior of C_{60}. In 1996, he became a postdoctoral fellow at the Georgia Institute of Technology where he worked in the laboratory of Professor William S. Rees, Jr. investigating the chemistry of alkylphosphorus-sulfur clusters, binuclear silver compounds and magnesium CVD precursors. Currently, he is a Senior Project Scientist with nGimat, working to develop precursors for metal and metal oxide coatings using the combustion chemical vapor deposition (CCVD) process and to develop environmentally friendly organic solvent mixtures for industrial use.

Introduction

Industry is under ever increasing pressure to replace organic solvents that have been in use for decades with more benign alternatives that have lower toxicity and pose less threat to the environment. Many solvents have been banned from use by various governments due to environmental concerns. Of the solvents that remain, many companies have begun to ban the use of solvents that were once mainstays of formulation chemistry in order to reduce the costs of regulatory compliance. Faced with a reduced list of solvent choices, an alternative is to make greater use of mixtures of solvents that are still accepted as safe. Mixed organic solvents have the advantage that the properties of the mixture can be adjusted by varying the relative amount of each component in the mixture. Not only can solvent mixtures be found to replace undesirable pure solvents, but in most cases, the mixture composition can be optimized to exceed the performance of the undesirable pure solvent. In this way, formulation chemists still retain access to an entire spectrum of solvent properties, even though the choice to use green solvents is more limiting.

By careful selection of a set of relatively benign organic solvents chosen to cover a wide range of solvent properties, large numbers of undesired solvents can be replaced with mixtures of this smaller set of benign solvents. For such an approach to be generally useful in industry, a method is needed to optimize the composition of solvent mixtures with minimal experimentation. The statistical design of experiments (DOE) approach has previously been adapted for use with the

---

† This work was presented at the Green Solvents for Synthesis Meeting, held in Bruchsal, Germany, 3–6 October 2004.
*sflanagan@ngimat.com

properties of mixtures, and Scheffé developed a series of polynomial equations tailored to model multi-component mixtures.[1,2] The drawback to using these mixture polynomials is that they are not based upon knowledge of the underlying solution thermodynamics. Here we demonstrate how a mixture design polynomial can be incorporated into a model based on solution thermodynamics in such a way that the experimental efficiency of the DOE approach is retained, without having to abandon a sound physical model. Several other models are in wide use for predicting solute activity coefficients from tabulated parameters of the pure components (Extended Hansen, MOSCED),[3–5] from binary interaction parameters (NRTL, UNIQUAC),[6,7] or from tabulated functional group contributions (UNIFAC).[8] While UNIQUAC and NRTL provide excellent predictions for multicomponent systems, they require many parameters that may or may not be available for all solutes and solvents of interest, and they require considerable expertise to implement properly. Our model differs from these approaches in that experimental data is required. This does not present a disadvantage for most industrial applications, since the application of DOE methodology minimizes the amount of data that must be collected, and such methods are already familiar to many in industry and can be implemented by non-specialists. During the development of new products, tabulated parameters are frequently unavailable for components that are being introduced for the first time, so some degree of experimental measurement would be required even when using the models mentioned above. The simplex centroid design has been shown to efficiently describe a q component mixture using as few as $2^{(q-1)}$ data points.[2]

Here we present the solubility, density and activity coefficients of platinum(II) acetylacetonate ($Pt(acac)_2$) solutions at 25 °C in various mixtures of up to four solvents. The solvents were chosen to cover a wide range of solvent properties while maintaining co-miscibility: acetone is a moderately polar organic solvent, 1,2,3,4-tetrahydronaphthalene (THN) is a non-polar aromatic, cyclohexanol is a moderately good hydrogen bond donor, and propylene carbonate is a highly polar, non-hydrogen bonding solvent. Each of the solvents is inexpensive and available in bulk quantities from major chemical manufacturers, making them suitable for industrial applications. In addition, the solvents were chosen to avoid any that are regulated as hazardous air pollutants (HAPs) under Section 112(b)(1) of the United States Clean Air Act.[9] In principle, other sets of solvents could have been chosen to meet other requirements. One can envision choosing a set for minimal human toxicity, minimal flammability, or other requirements, followed by optimization of the mixture composition for the desired solute. The solute chosen for this study, $Pt(acac)_2$, is one of the most widely available and least expensive organoplatinum compounds, and as such finds wide use as a precursor for platinum-containing materials and catalysts.[10,11]

Results and discussion

The results of the solubility measurements are summarized in Table 1. All solubility measurements were made using thermogravimetric analysis (TGA), with the exception of pure cyclohexanol. The concentration of $Pt(acac)_2$ in cyclohexanol was below the limit of quantitation (LOQ) for TGA, so that solution was analyzed using inductively coupled plasma mass spectrometry (ICP-MS). Experimental errors in the TGA and ICP-MS methods were estimated to be less than ±2% by measuring the solubility of chromium(III) acetylacetonate in benzene and comparing the results to three different literature sources.[12–14] In addition, the solubility of palladium(II) acetylacetonate in benzene was measured by TGA and ICP-MS and found to differ from the one available literature value[14] by only 1%. The solution density data (Table 1) were used to convert the measured molar concentrations to mole fraction. The melting point, T_m, and the entropy of fusion, ΔS_{fus}, of $Pt(acac)_2$ were determined by DSC to be 512.5 K and 41.4 J (mol K)$^{-1}$, respectively. $Pt(acac)_2$ shows signs of decomposition after melting, observable in the DSC as an endotherm occurring at 248 °C. The fusion endotherm observed at 239 °C was compared to another Pt complex, dimethylplatinum cyclooctadiene (Me_2PtCOD), that does not exhibit signs of decomposition, and the enthalpy of fusion values are of similar magnitude (41.4 J (mol K)$^{-1}$ for $Pt(acac)_2$ *vs.* 47.0 J g^{-1} for Me_2PtCOD). We therefore conclude that the enthalpy of fusion measurement was not compromised by the subsequent decomposition. The ideal mole fraction solubility of $Pt(acac)_2$ can be calculated using the equation:

$$\ln x_{ideal} = \frac{\Delta S_{fus}}{R}(1 - \frac{T_m}{T}) \tag{1}$$

where T is the temperature of the solution and R is the molar gas constant. This calculation yields a value for x_{ideal} of 0.0280, which is more than four times the highest observed mole fraction concentration. The activity coefficients of the saturated solutions (γ_{sat}) were calculated using eqn. (2) and are summarized in Table 1.

$$\ln \gamma_{sat} = \frac{\Delta S_{fus}}{R}(1 - \frac{T_m}{T}) - \ln x_{sat} \tag{2}$$

Table 1 The molar solubilities ($C_{sat}/10^{-3}$ mol L^{-1}), mole fraction solubilities (x_{sat}), solution densities (ρ_{sat}/g mL^{-1}) and activity coefficients (γ_{sat}) of $Pt(acac)_2$ in mixtures of acetone (ϕ_1), cyclohexanol, (ϕ_2) propylene carbonate (ϕ_3) and THN (ϕ_4) (ϕ = volume fraction)

#	ϕ_1	ϕ_2	ϕ_3	ϕ_4	$C_{sat}/10^{-3}$ mol L^{-1}	x_{sat}	ρ_{sat}/g mL^{-1}	γ_{sat}
1	1	0	0	0	47.1	0.00350	0.799	2.08
2	0	1	0	0	10.1	0.00107	0.955	3.27
3	0	1/2	1/2	0	43.5	0.00418	1.066	1.90
4	0	1/2	0	1/2	20.3	0.00244	0.957	2.44
5	0	1/3	1/3	1/3	54.3	0.00576	1.044	1.58
6	1/2	1/2	0	0	36.9	0.00279	1.011	2.31
7	1/3	1/3	0	1/3	41.3	0.00410	0.910	1.92
8	1/3	1/3	1/3	0	50.0	0.00432	0.992	1.87
9	1/4	1/4	1/4	1/4	58.0	0.00556	0.984	1.62
10	1/3	0	1/3	1/3	67.5	0.00622	1.003	1.50
11	1/2	0	0	1/2	66.5	0.00642	0.892	1.47
12	1/2	0	1/2	0	43.7	0.00344	1.010	2.10
13	0	0	1/2	1/2	63.1	0.00665	1.097	1.44
14	0	0	1	0	33.4	0.00285	1.207	2.29
15	0	0	0	1	24.2	0.00332	0.969	2.13
16	1/4	0	1/2	1/4	58.4	0.00527	1.053	1.67
17	1/4	0	1/4	1/2	66.2	0.00665	0.996	1.44
18	1/2	0	1/4	1/4	65.3	0.00563	0.959	1.60

The values for γ_{sat} range from 1.44 to 3.27, with the highest value observed in 100% cyclohexanol. The source of the nonideality is not certain at this time, but may derive from an inability for Pt(acac)$_2$ to act as a hydrogen bond acceptor coupled with its rather moderate dipole moment. Thus, cyclohexanol, a hydrogen bond donor of weak polarity is not a good solvent.

The activity coefficient data for solutions 1–15 were initially fit using a Scheffé mixture design of the form:

$$\begin{gathered}\ln \gamma_{\text{sat}} = b_1\boldsymbol{\phi}_1 + b_2\boldsymbol{\phi}_2 + b_3\boldsymbol{\phi}_3 + b_4\boldsymbol{\phi}_4 + b_{12}\boldsymbol{\phi}_1\boldsymbol{\phi}_2 + b_{13}\boldsymbol{\phi}_1\boldsymbol{\phi}_3 + \\ b_{14}\boldsymbol{\phi}_1\boldsymbol{\phi}_4 + b_{23}\boldsymbol{\phi}_2\boldsymbol{\phi}_3 + b_{24}\boldsymbol{\phi}_2\boldsymbol{\phi}_4 + b_{34}\boldsymbol{\phi}_3\boldsymbol{\phi}_4 + b_{123}\boldsymbol{\phi}_1\boldsymbol{\phi}_2\boldsymbol{\phi}_3 + \\ b_{124}\boldsymbol{\phi}_1\boldsymbol{\phi}_2\boldsymbol{\phi}_4 + b_{134}\boldsymbol{\phi}_1\boldsymbol{\phi}_3\boldsymbol{\phi}_4 + b_{234}\boldsymbol{\phi}_2\boldsymbol{\phi}_3\boldsymbol{\phi}_4 + b_{1234}\boldsymbol{\phi}_1\boldsymbol{\phi}_2\boldsymbol{\phi}_3\boldsymbol{\phi}_4\end{gathered} \tag{3}$$

where γ_{sat} is the mole fraction solubility, $\boldsymbol{\phi}_1$, $\boldsymbol{\phi}_2$, $\boldsymbol{\phi}_3$ and $\boldsymbol{\phi}_4$ are the volume fractions of acetone, cyclohexanol, propylene carbonate and THN, respectively, and b_k are adjustable fitting parameters. The values for b_k were found to be: $b_1 = 2.08$, $b_2 = 3.27$, $b_3 = 2.29$, $b_4 = 2.13$, $b_{12} = -1.47$, $b_{13} = -0.346$, $b_{14} = -2.53$, $b_{23} = -3.51$, $b_{24} = -1.03$, $b_{34} = -3.09$, $b_{123} = -2.31$, $b_{124} = -0.356$, $b_{134} = 0.0294$, $b_{234} = -3.62$, $b_{1234} = 5.36$. This procedure gives an exact fit to the data since the number of fitted parameters is equal to the number of data points in a simplex centroid design. The fitted equation was then used to predict $\ln \gamma_{\text{sat}}$ for solutions 16–18, giving predicted values of $\ln \gamma_{16} = 1.61$, $\ln \gamma_{17} = 1.43$ and $\ln \gamma_{18} = 1.59$. These values differ from the experimentally obtained values by 3.6%, 0.2% and 0.7%, respectively. On average, these differences are of the same magnitude as the estimate of experimental error.

While the Scheffé mixture design gives accurate values for $\ln \gamma$, it is an entirely empirical approach; the form of the equation does not have any underlying physical meaning. One commonly used predictive equation for estimating activity coefficients where Hildebrand parameters are available for all of the solvents and the solute takes the form:[15]

$$\ln \gamma_i = \left(\frac{V_i}{RT}\right)(\delta_i - \bar{\delta})^2 + \ln\left(\frac{V_i}{\bar{V}}\right) + 1 - \left(\frac{V_i}{\bar{V}}\right) \tag{4}$$

where γ_i is the activity coefficient of component i, V_i is the molar volume of component i, δ_i is the Hildebrand parameter of component i, R is the molar gas constant, T is the temperature, $\boldsymbol{\phi}_i$ is the volume fraction of component i, n is the number of components and $\bar{\delta}$ and $\bar{V}$ are given by the following equations:

$$\bar{\delta} = \sum_{k=1}^{n} \phi_k \delta_k \tag{5}$$

$$\bar{V} = \sum_{k=1}^{n} x_k V_k \tag{6}$$

For a system with three solvents and one solute, eqn. (5) becomes:

$$\bar{\delta} = \boldsymbol{\phi}_1\delta_1 + \boldsymbol{\phi}_2\delta_2 + \boldsymbol{\phi}_3\delta_3 + \boldsymbol{\phi}_4\delta_4 \tag{7}$$

Substituting the resulting expression for $\bar{\delta}$ into the term $(\delta_i - \bar{\delta})^2$ from eqn. (4) and expanding the polynomial yields:

$$\begin{gathered}(\delta_4{}^2) + (-2\delta_4\delta_1)\boldsymbol{\phi}_1 + (-2\delta_4\delta_2)\boldsymbol{\phi}_2 + (-2\delta_4\delta_3)\boldsymbol{\phi}_3 + \\ (2\delta_1\delta_2)\boldsymbol{\phi}_1\boldsymbol{\phi}_2 + (2\delta_1\delta_3)\boldsymbol{\phi}_1\boldsymbol{\phi}_3 + (2\delta_2\delta_3)\boldsymbol{\phi}_2\boldsymbol{\phi}_3 + (2\delta_1\delta_4)\boldsymbol{\phi}_1\boldsymbol{\phi}_4 + \\ (2\delta_2\delta_4)\boldsymbol{\phi}_2\boldsymbol{\phi}_4 + (2\delta_3\delta_4)\boldsymbol{\phi}_3\boldsymbol{\phi}_4 + (\delta_1{}^2)\boldsymbol{\phi}_1{}^2 + (\delta_2{}^2)\boldsymbol{\phi}_2{}^2 + \\ (\delta_3{}^2)\boldsymbol{\phi}_3{}^2 + (\delta_4{}^2)\boldsymbol{\phi}_4{}^2 + (-2\delta_4{}^2)\boldsymbol{\phi}_4\end{gathered} \tag{8}$$

For dilute solutions, the volume fraction of the solute, $\boldsymbol{\phi}_4$, is near zero, so terms containing this value can be dropped without materially affecting the calculation. The remaining expression is identical to a standard full quadratic with three factors ($\boldsymbol{\phi}_1$, $\boldsymbol{\phi}_2$ and $\boldsymbol{\phi}_3$), with coefficients equal to the terms in parentheses. The full quadratic polynomial has certain drawbacks for use in modeling mixture data. Scheffé developed a series of polynomials that are very well suited for use in mixture designs that differ from the full quadratic in that there are no constant terms and there are no "pure" second order terms (*i.e.*, terms containing $\boldsymbol{\phi}_n{}^2$ are omitted). Furthermore, the Scheffé polynomial incorporates higher order interaction terms not present in the standard full quadratic.

Applying this logic to eqn. (8) by eliminating the leading constant, the terms containing $\boldsymbol{\phi}_n{}^2$, the terms containing $\boldsymbol{\phi}_4$, and adding a third order interaction term, $\boldsymbol{\phi}_1\boldsymbol{\phi}_2\boldsymbol{\phi}_3$, gives a new expression, represented by D:

$$\begin{gathered}D = d_1\boldsymbol{\phi}_1 + d_2\boldsymbol{\phi}_2 + d_3\boldsymbol{\phi}_3 + d_{12}\boldsymbol{\phi}_1\boldsymbol{\phi}_2 + d_{13}\boldsymbol{\phi}_1\boldsymbol{\phi}_3 + \\ d_{23}\boldsymbol{\phi}_2\boldsymbol{\phi}_3 + d_{123}\boldsymbol{\phi}_1\boldsymbol{\phi}_2\boldsymbol{\phi}_3\end{gathered} \tag{9}$$

where it was necessary to replace the coefficients in eqn. (8) with a new set of constants d_k. For example, the term d_1 will contain information about the interaction between the solute and solvent 1, while d_{12} contains information about the interaction of the solute with mixtures of solvents 1 and 2, *etc*. For solutions in which the solute is more concentrated, $\boldsymbol{\phi}_4$ is no longer approximately zero. However, the elimination of terms containing $\boldsymbol{\phi}_4$ and δ_4 is still warranted, since the model is intended to characterize the behavior of the solute in each pure solvent, and in each possible permutation of solvent mixtures. For a four solvent mixture, D has a form analogous to eqn. (3), with extra terms for the additional combinations of solvents that are possible with a fourth solvent:

$$\begin{gathered}D = d_1\boldsymbol{\phi}_1 + d_2\boldsymbol{\phi}_2 + d_3\boldsymbol{\phi}_3 + d_4\boldsymbol{\phi}_4 + d_{12}\boldsymbol{\phi}_1\boldsymbol{\phi}_2 + d_{13}\boldsymbol{\phi}_1\boldsymbol{\phi}_3 + \\ d_{14}\boldsymbol{\phi}_1\boldsymbol{\phi}_4 + d_{23}\boldsymbol{\phi}_2\boldsymbol{\phi}_3 + d_{24}\boldsymbol{\phi}_2\boldsymbol{\phi}_4 + d_{34}\boldsymbol{\phi}_3\boldsymbol{\phi}_4 + d_{123}\boldsymbol{\phi}_1\boldsymbol{\phi}_2\boldsymbol{\phi}_3 + \\ d_{124}\boldsymbol{\phi}_1\boldsymbol{\phi}_2\boldsymbol{\phi}_4 + d_{134}\boldsymbol{\phi}_1\boldsymbol{\phi}_3\boldsymbol{\phi}_4 + d_{234}\boldsymbol{\phi}_2\boldsymbol{\phi}_3\boldsymbol{\phi}_4 + d_{1234}\boldsymbol{\phi}_1\boldsymbol{\phi}_2\boldsymbol{\phi}_3\boldsymbol{\phi}_4\end{gathered} \tag{10}$$

Thus, the application of mixture design methodology to eqn. (4) suggests the modified form:

$$\ln \gamma_i = \left(\frac{V_i}{RT}\right)D + \ln\left(\frac{V_i}{\bar{V}}\right) + 1 - \left(\frac{V_i}{\bar{V}}\right) \tag{11}$$

where D is the Scheffé mixture polynomial analogous to eqn. (9) and (10) having the same number of factors as there are solvents in the mixture. Scheffé gives a general form for this type of polynomial for an arbitrary number of components.[2] Eqn. (11) was used to model the data from Table 1, using the values of d_k as variable parameters for a nonlinear regression, while the other terms in eqn. (11) were supplied from the experimental data.

The d_k parameters were varied using an evolutionary algorithm[16] until the residuals for ln γ_i were minimized, giving the following values of d_k (J cm^{-3}) for Pt(acac)$_2$ in the solvents listed in Table 1: $d_1 = 37.2$, $d_2 = 49.7$, $d_3 = 37.7$, $d_4 = 31.5$, $d_{12} = -22.4$, $d_{13} = -5.2$, $d_{14} = -39.8$, $d_{23} = -51.6$, $d_{24} = -15.6$, $d_{34} = -46.7$, $d_{123} = -34.1$, $d_{124} = -5.4$, $d_{134} = 0.7$, $d_{234} = -53.0$, $d_{1234} = 78.5$. This model was used to predict ln γ_i for solutions 16–18 of ln $\gamma_{16} = 1.61$, ln $\gamma_{17} = 1.43$ and ln $\gamma_{18} = 1.59$, thus the physically informed model represented by eqn. (11) predicts values for the activity coefficients identical to the naïve model of eqn. (3). Unlike the b_k parameters in eqn. (3), the parameters of eqn. (11) offer some insight into the solution thermodynamics. The result of the fit is plotted in Fig. 1 to give a quaternary contour plot of the solubility of Pt(acac)$_2$ as a function of solvent composition.

It is interesting to note that the magnitude of d_{1234} is greater than for any of the other d_k parameters. We speculate that the importance of this higher-order term relates to the ability of a transition metal complex to coordinate solvent in solution. Pt(acac)$_2$ is coordinated equatorially by four oxygen atoms from the acac ligand, but there are two unoccupied axial sites that may undergo weak solvent coordination, so it is reasonable to believe that interaction parameters as high as 3 may be significant if axial coordination is involved. Furthermore, additional solvent interactions may take place in the outer solvation sphere, leading to the possibility of supramolecular assemblies involving all of the solvents present in the mixture. Thus, the quaternary interaction parameters can be expected to have significance in the system under study.

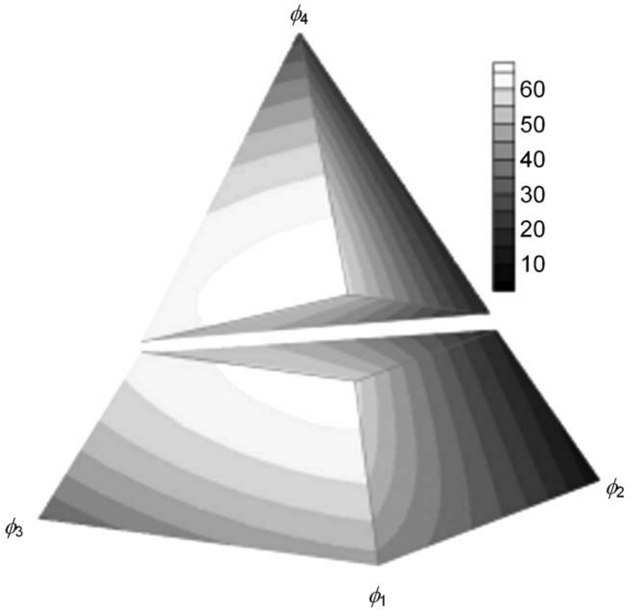


Fig. 1 Quaternary contour plot[21] of the concentration of saturated solutions of Pt(acac)$_2$ at 25 °C in mixtures of acetone (ϕ_1), cyclohexanol (ϕ_2), propylene carbonate (ϕ_3) and THN (ϕ_4) *vs.* solvent volume fraction. The legend indicates the concentration in units of 10^{-3} mol L^{-1}. The plot is cut across the midsection ($\phi_4 = 0.3$) to reveal the interior contours. The maximum molar concentration is calculated to be 68.9×10^{-3} mol L^{-1} at $\phi_1 = 0.406$, $\phi_2 = 0$, $\phi_3 = 0.187$ and $\phi_4 = 0.407$.

From eqn. (8), it can be seen that the parameters d_k are analogous to the product of two Hildebrand parameters, $\delta_i\delta_j$ (the squared terms having been discarded), and thus have units of energy divided by volume. Recalling that the Hildebrand parameter δ is defined as the square root of the cohesive energy density:

$$\delta = \sqrt{\frac{\Delta E_{\mathrm{vap}}}{V}} = \sqrt{\frac{\Delta H_{\mathrm{vap}} - RT}{V}} \qquad (12)$$

it becomes apparent that the terms d_k possess information relating to the cohesive energy density of the mixture of the solute and each of the components indicated by the subscript k. We speculate that the relative sign of each d_k parameter offers an indication of whether the particular interaction represented by each parameter leads to an increase or a decrease in the overall cohesive energy density of the solution. For this reason, we refer to the constants d_k as Intercomponent Mixture Parameters (IMPs). Unlike the Hildebrand parameter, which can only have values greater than or equal to zero due to the square root, the non-linear fit used to derive values for d_k permits positive or negative values. While it is reasonable to expect the cohesive energy density for a pure liquid in equilibrium with its vapor to always be greater than or equal to zero, when dealing with mixtures, there is always the possibility of either positive or negative heats of mixing. Hence, having a parameter such as d_k that can take on both positive and negative values should reflect the properties of a mixture more accurately. It is noteworthy that the IMP values obtained for Pt(acac)$_2$ are positive for the four terms representing interactions with pure solvents, namely, d_1, d_2, d_3 and d_4, even though no constraints were placed on those values during the data fit. The negative IMP values occur only for solvent mixtures, and our view is that these negative values indicate that the particular solvent–solvent interaction represented by the negative IMP makes a negative contribution to the overall cohesive energy density.

Conclusions

Fig. 1 demonstrates that mixtures of solvents can have properties that exceed those accessible using pure solvents. In this instance, mixtures of acetone, THN and propylene carbonate having v : v : v compositions of 1 : 1 : 1 have a greater ability to dissolve Pt(acac)$_2$ than any of the pure solvents alone. In addition, this mixture was specifically chosen to avoid the use of solvents that are regulated as hazardous air pollutants (HAPs) under Section 112(b)(1) of the United States Clean Air Act.[9] The use of a "universal set" of a small number of benign solvents chosen to encompass a broad range of solvent properties will enable the rapid design of solvent mixtures to replace environmentally harmful and toxic solvents. Application of Scheffé mixture designs to the prediction of activity coefficients shows promise as a means to predict solubilities in organic solvent mixtures, and we expect it to become a useful design tool in this area. In parallel with this effort, *n*Gimat has developed a software package, The Green Solvent Wizard™, to help industrial solvent users design solvent mixtures that are tailored to the users' end applications. The Green Solvent Wizardⓜ software is scheduled for commercial release in 2006.

Experimental

Solution preparation

All materials were used as received from the vendor: acetone (EM Science, OmniSolv, 99.5%), cyclohexanol (EM Science, 98% min.), 1,2,3,4-tetrahydronaphthalene (Aldrich, 99%), propylene carbonate (Lancaster, 99%), platinum (II) acetylacetonate (Strem, 98%). Mixtures of acetone, cyclohexanol, 1,2,3,4-tetrahydronaphthalene and propylene carbonate were prepared using the volume fraction for each solvent given in Table 1. Each solvent mixture was then equilibrated with an excess of $Pt(acac)_2$ in a constant temperature shaker bath at 25.0 °C for a minimum of 24 hours. Aliquots were withdrawn from the solutions using a glass syringe with a Teflon plunger and filtered through glass fiber syringe filters before analysis.

TGA

A TA Instruments Q500 TGA was used for solubility measurements. The temperature was calibrated using a Curie point measurement of nickel metal. The microbalance was calibrated with a 100 mg class M standard. Platinum pans with a maximum volume of 100 μL were loaded with either 25 or 50 μL of solution using a TD glass capillary micropipette (Drummond Scientific Co.). Nitrogen was used as the purge gas after passing through an O_2–H_2O trap. The samples were heated to 10–50 °C below the boiling point of the solvent or the lowest boiling component of the solvent mixture to avoid ejecting sample from the pan due to boiling. The samples were held at the initial temperature until the rate of weight loss became less than 0.05 wt.% per minute, at which point the temperature was increased at a rate of 10 °C min^{-1} to test for complete solvent removal and to decompose the residual solute. The amount of dissolved solute was determined from the mass recorded after the solvents had completely evaporated. The mass of platinum obtained after decomposition was crosschecked with the mass of solute to ensure that the observed mass was consistent with the expected stoichiometry of decomposition.

DSC

A TA Instruments Q1000 DSC was used for melting point (T_m) and heat of fusion (ΔH_{fus}) measurements. The cell and temperature were calibrated with sapphire over the same temperature range for which measurements were to be performed and also with the melting transition of an indium metal standard. Crimped aluminium pans were filled with 1–10 mg of sample. Nitrogen was used as the purge gas. The samples were rapidly equilibrated to a temperature selected to be 30–50 °C below their melting point, and then the temperature was increased at a rate of 10 °C min^{-1} through the end of the melt. T_m was determined by the onset point of the endothermic peak. ΔH_{fus} was determined by the area under the endothermic peak using a linear baseline. ΔS_{fus} was calculated as $\Delta H_{fus}/T_m$.

Density

A specific gravity bottle (Ace Glass) was used in conjunction with an analytical balance (Ohaus AP250D) for density measurements. Calibrations of the specific gravity bottle's volume were performed using the known densities of deionized water and acetone.[17] To measure the solution densities, the clean, dry, tared specific gravity bottle was filled with the sample, equilibrated to 25 °C in a controlled temperature bath, wiped dry, and the filled bottle's weight was recorded. The recorded weight was corrected for buoyancy according to published methods.[18,19]

ICP-MS

Sample preparation. Samples were digested in order to destroy the organic components and to ensure a matrix match with the standards prior to analysis in the ICP-MS using a standard microwave digestion with nitric acid: 2.5 mL of doubly distilled HNO_3 (GFS Chemicals, Inc.) was placed in each of three 23 mL Parr microwave acid digestion bombs. To each of these, 50 μL of the saturated solution to be analyzed was added using a glass capillary micropipette. The vessels were sealed and the samples were individually digested in a 700 W microwave oven at 30% of full power for 5 minutes. The vessels were allowed to cool for approximately 30 minutes, at which time the contents of each were quantitatively transferred to 25 mL volumetric flasks and diluted to volume with 1% HNO_3.

Instrumental analysis. Platinum concentrations in the digested samples were determined using a Thermo Elemental PQ Excell ICP-MS spectrometer. The instrument response and stability were optimized for a 1 ppb standard solution containing 14 elements over a wide range of masses (Li to U). The instrument was then calibrated for platinum in the range of 1 to 50 ppb using a NIST traceable platinum standard (High Purity Standards, Inc.). Unknown samples were then analyzed after being diluted to bring the observed platinum concentration for each solution to within the calibrated range of the instrument.

Error analysis

Uncertainties in the volume of the 10 mL pycnometer, analytical balance and density of the high purity water standard are estimated to be 2×10^{-4} mL, 2×10^{-5} g, and 1×10^{-6} g mL^{-1}, respectively. Using standard equations for propagation of error[20] gives an uncertainty of 3×10^{-6} g mL^{-1} for the density determinations, which far exceeds the precision required to calculate the mole fractions, thus we only report 3 decimal places for the densities in Table 1. The uncertainty in the TGA balance, the micropipettes and the molecular weight of $Pt(acac)_2$ are 5×10^{-6} g, 1.3×10^{-7} L, and 0.008 g mol^{-1}, respectively, which translates to an uncertainty in the measured molar concentrations of 3×10^{-4} mol L^{-1}, or approximately ±3% of the lowest concentration reported. This value is comparable to the differences observed between our measurements and the literature values for $Cr(acac)_3$ and $Pd(acac)_2$. Propagation of the uncertainties in the density and the molarity through the mole fraction calculation gives an uncertainty of 2 × 10^{-5} mole fraction.

Acknowledgements

This material is based upon work supported by the National Science Foundation under SBIR Grants DMI-0128268 and DMI-0238674.

Scott Flanagan,*[a] Eric Hall,[a] Wade Bowie,[a] James W. Fuhs,[b] Robbie Logan,[a] Farzaneh Maniei[c] and Andrew Hunt[a]
[a]*nGimat Co., nanoEngineered Materials, 5315 Peachtree Industrial Blvd., Atlanta, GA, 30341, USA. E-mail: sflanagan@ngimat.com*
[b]*Northrop Grumman Laser Systems, 2787 South Orange Blossom Trail, Apopka, FL, 32703, USA*
[c]*Metametrix Clinical Laboratory, 4855 Peachtree Industrial Blvd., Suite 201, Norcross, GA, 30092, USA*

References

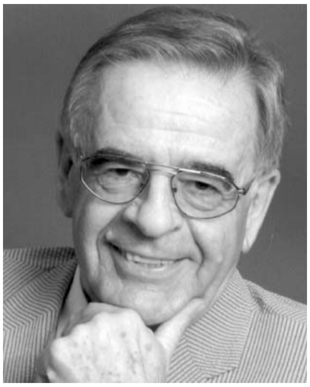
1 H. Scheffé, *J. R. Stat. Soc. B*, 1958, **20**, 344–360.
2 H. Scheffé, *J. R. Stat. Soc. B*, 1963, **25**, 235–263.
3 T. C. Frank, J. R. Downey and S. K. Gupta, *Chem. Eng. Prog.*, 1999, **95**, 41–61.
4 E. R. Thomas and C. A. Eckert, *Ind. Eng. Chem. Proc. Des. Dev.*, 1984, **23**, 194–209.
5 M. J. Lazzaroni, D. Bush, C. A. Eckert, T. C. Frank, S. K. Gupta and J. D. Olsen, *Ind. Eng. Chem. Res.*, 2005, in press.
6 H. Renon and J. M. Prausnitz, *AIChE J.*, 1968, **14**, 135.
7 D. S. Abrams and J. M. Prausnitz, *AIChE J.*, 1975, **21**, 62.
8 J. G. Gmehling, T. F. Anderson and J. M. Prausnitz, *Ind. Eng. Chem. Fundam.*, 1978, **17**, 269–273.
9 Office of Air Quality Planning and Standards, U.A.T.W., *Section 112 Hazardous Air Pollutants*, 2001, United States Environmental Protection Agency, Research Triangle Park, NC, USA (http://www.epa.gov/ttn/atw/orig189.html).
10 S. Sun, C. B. Murray, D. Weller, L. Folks and A. Moser, *Science*, 2000, **287**, 1989–1992.
11 R. Gomez, T. Lopez, V. Bertin, R. Silva, P. Salas and I. Schifter, *J. Sol-Gel Sci. Technol.*, 1997, **8**, 847–849.
12 M. M. Jones, J. L. Wood and W. R. May, *J. Inorg. Nucl. Chem.*, 1961, **23**, 305–309.
13 M. Yamamoto and Y. Yamamoto, *Anal. Chim. Acta*, 1976, **87**, 375–386.
14 W. C. Fernelius, *Inorg. Synth.*, 1958, **5**, 111.
15 T. C. Frank, J. R. Downey and S. K. Gupta, *Chem. Eng. Prog.*, 1999, **95**, 41–61.
16 *Premium Solver Platform™ for use with Microsoft Excel®*, Frontline Systems, Inc., Incline Village, NV, 2002.
17 *NIST Chemistry WebBook, NIST Standard Reference Database Number 69*, ed. P. J. Linstrom and W. G. Mallard, March 2003, National Institute of Standards and Technology, Gaithersburg, MD, 20899 (http://webbook.nist.gov).
18 R. M. Schoonover and F. E. Jones, *Anal. Chem.*, 1981, **53**, 6, 900–902.
19 D. P. Shoemaker, C. W. Garland and J. I. Steinfeld, *Experiments in Physical Chemistry*, 3rd edn., McGraw Hill, Inc., New York, 1974.
20 P. R. Bevington and D. K. Robinson, *Data Reduction and Error Analysis for the Physical Sciences*, 2nd edn., McGraw Hill, Inc., New York, 1992.
21 *Tecplot® 9.2*, Tecplot, Inc., Bellevue, WA, 2002.

Polarity of ionic liquids determined empirically by means of solvatochromic pyridinium *N*-phenolate betaine dyes†‡

Christian Reichardt

Received 4th January 2005, Accepted 18th March 2005
First published as an Advance Article on the web 18th April 2005
DOI: 10.1039/b500106b

Solutions of the zwitterionic betaine dye 2,6-diphenyl-4-(2,4,6-triphenylpyridinium-1-yl)phenolate are solvatochromic, thermochromic, piezochromic, and halochromic. That is, the position of the longest-wavelength intramolecular CT absorption band depends on the solvent polarity, solution temperature, external pressure, and the nature and concentration of added salts. The outstanding large negative solvatochromism of this standard betaine dye has been used to introduce spectroscopically an empirical scale of solvent polarity, called the $E_T(30)$ or E_T^N scale, which includes meanwhile a large number of molecular solvents and solvent mixtures. In this review, efforts to determine empirically the polarity of room-temperature ionic liquids by means of this betaine dye are summarized and discussed , because ionic liquids have gained importance as environmentally more benign new reaction media in the framework of Green Chemistry.



Christian Reichardt

Christian Reichardt was born in 1934 in Ebersbach, Saxony, Germany. After one year (1953–1954) at the "Fachschule für Energie" in Zittau, former GDR, as a teaching assistant, he studied chemistry at the "Carl Schorlemmer" Technical University in Leuna-Merseburg, GDR, and, after moving illegally to West Germany (FRG), at the Philipps University in Marburg, where he obtained his PhD in 1962 under the tutelage of Prof. K. Dimroth, and completed his Habilitation in 1967. From 1971 until his retirement in 1999 he was Professor for Organic Chemistry in Marburg. He was visiting professor at the Universities of Barcelona, Spain (1988), Bratislava, Slovak Republic (1998), and Oita, Japan (2000). He has authored and co-authored more than 160 paper and patents and a book, Solvents and Solvent Effects in Organic Chemistry, which was translated into French, Chinese, and Russian. He received in 1989 the literary prize of the Fonds der Chemischen Industrie, Frankfurt am Main, for this book, and the Marie-Skłodowska-Curie-Medal of the Polish Chemical Society in 2000. His research interests are in synthetic organic chemistry (chemistry of aliphatic dialdehydes and polymethine dyes) and in physical organic chemistry (solvatochromism of organic dyes, solvent effects in organic chemistry, empirical parameters of solvent polarity).

Introduction

Most chemical reactions carried out in the laboratory or in industry take place in solution. That means, the selection of a proper solvent, appropriate for the reaction under study, is, amongst other reaction parameters, of paramount importance for the success of a chemical process carried out in solution. Nowadays it is well known, that solvents can have a strong influence on the position of chemical equilibria, on reaction rates, as well as on the position and intensity of spectral absorption bands (*e.g.* UV/Vis, IR, EPR, NMR). A compilation of all kinds of solvent effects can be found in refs. 2 and 3.

However, these mainly organic solvents, belonging to the group of volatile organic compounds (VOC's), account for a great proportion of environmental pollution and waste material; their use is often problematic owing to their toxicity, volatility, flammability, and environmental hazards.[4] Therefore, the development of environmentally more friendly solvents[5,6] or even solvent-free reactions[7] continues to be of great interest as an important step in the direction of "Green Chemistry".[8]

Among the alternative reaction media studied as substitutes for classical organic solvents are plain water,[9] fluorous media (*e.g.* highly fluorinated alkanes, ethers, and tertiary amines),[10] supercritical fluids (*e.g.* scf-CO_2),[11] and particularly ionic liquids.[12]

Water, fluorous media, and supercritical fluids belong to the well-known class of molecular liquids. In addition to atomic liquids, ionic liquids represent a quite different group of solvents, consisting in the crystalline state entirely of ions and as molten salts at room temperature (Fig. 1).

A recent representative example of a room temperature ionic liquid is 1-(1-butyl)-3-methylimidazolium hexafluorophosphate (mp 12 °C), commonly abbreviated as $[bmim]^+[PF_6]^-$. Atomic liquids are liquid sodium or mercury. Valuable reaction media are also binary mixtures at the borderline between molecular and ionic liquids such as, for example, a 5 M solution of lithium perchlorate in diethyl ether (LPDE).[13]

---

† This work was presented at the Green Solvents for Synthesis Meeting, held in Bruchsal, Germany, 3–6 October 2004.

‡ Part XXIX in the series "Pyridinium *N*-phenoxide betaine dyes and their application to the determination of solvent polarities". For Part XXVIII, see ref. 1

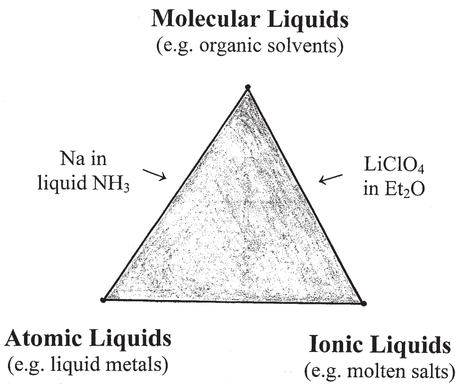


Fig. 1 Classification of solvents according to their characteristic chemical bonds.[2]

Such concentrated LiClO$_4$ solutions can be considered as diluted ionic liquids because they contain only about one to two ether molecules per lithium cation, which is therefore not fully coordinated.

Molecular solvents such as water can undergo autoprotolysis according to eqn. (1), with $c(H_3O^+) = c(HO^-) = 10^{-7}$ mol L^{-1} at 25 °C, that is with a very low but nevertheless not negligible ion concentration.

$$\underset{\text{an ionogen}}{2(H_2O)_l} \xrightleftharpoons{25\ ^\circ C} (H_3O^+)_{aq} + (HO^-)_{aq} \qquad (1)$$

In contrast, in ionic liquids such as [bmim]$^+$[PF$_6$]$^-$ the ion concentration is with $c(\text{bmim}^+) = c(PF_6^-) \approx 4.8$ mol L^{-1} (calculated with $\rho = 1.37$ g cm^{-3}) more than 10^7 times larger, according to eqn. (2):

$$\underset{\text{an ionophore}}{(\text{bmim}^+PF_6^-)_s} \xrightleftharpoons{>12\ ^\circ C} (\text{bmim}^+)_l + (PF_6^-)_l \qquad (2)$$

Compounds which are already fully ionic in the crystalline state are called ionophores, whereas compounds with molecular crystal lattices which form ions only in solution by reaction with the solvent or with itself (autoprotolysis) are described as ionogens.[14]

Therefore, the group of solvents located at the corner bottom-right of the solvent triangle of Fig. 1 should be called non-aqueous, at room temperature liquid, (fully) ionic solvents (NARTLIS).

NARTLIS are not a more recent discovery, they are already known since 1914 as Paul Walden published his seminal paper "*Über die Molekulargröße und elektrische Leitfähigkeit einiger geschmolzener Salze*",[15] in which he described the properties of ethylammonium nitrate (EtNH$_3^+$NO$_3^-$, EAN; mp 13–14 °C), purposely prepared for electric conductivity measurements. He wrote in 1914: "*Das Studium der geschmolzenen Salze, Leitfähigkeit, Dichte, Zähigkeit, usw. betreffend, ist in den letzten Jahren sehr eingehend gepflegt worden.... Gewählt wurden wasserfreie Salze, welche bei niedrigen Temperaturen, etwa bis zu 100 °C schmelzen*" ("The study of molten salts concerning conductivity, density, viscosity, *etc.*, has been thoroughly studied during the last years... Water-free salts were selected, which melt at relatively low temperatures, about up to 100 °C").[15] The latter definition for NARTLIS is still used today: ionic liquids are defined as materials that are composed entirely of cations and anions and that melt at or below 100 °C.[12] Other room-temperature liquid salts such as ethyl-, dimethyl-, and trimethylammonium nitrite, already obtained by Ray and Rakshit in 1911, are not stable and decompose spontaneously on standing.[16]

These first NARTLIS seem to have been forgotten for decades. Meanwhile, the chemistry of high-melting inorganic molten salts and salt mixtures (eutectics) as reaction media has been developed; see refs. 17 and 18 for reviews. However, the application of these purely inorganic ionic liquids as reaction media suffers from the necessary high working temperatures (*ca.* 100–1000 °C), incompatible with organic reaction partners, and their often highly corrosive properties with respect to the reaction vessels. The lowest-melting purely inorganic salt eutectics melt at *ca.* 150 °C.

The use of ionic liquids as reaction media has experienced a renaissance over the last decades with the introduction of highly asymmetric, diffusely charged organic cations and water-stable, non-coordinating, bulky inorganic anions, leading to frustrating molecular packing in the crystal lattice. Amongst them are mono-, di-, tri-, and tetraalkylammonium salts, tetraalkylphosphonium salts, 1,3-di- and 1,2,3-trialkylimidazolium salts, 1-alkyl- as well as 1,3- and 1,4-dialkylpyridinium salts, and 1,1-dialkylpyrrolidinium salts.[12] A recent extensive compilation of all kinds of NARTLIS, together with their physical properties, can be found in ref. 19.

Swain *et al.* introduced already in 1967 tetra-*n*-hexylammonium benzoate (THAB; mp −50 °C) as ionic solvent for kinetic and electrochemical studies,[20] but the breakthrough was made by the introduction of the first 1-alkylpyridinium[21] and 1-methyl-3-alkylimidazolium salts[22] with anions such as [AlCl$_4$]$^-$,[22a] [AlBr$_4$]$^-$,[22b] and [BF$_4$]$^-$.[22c] A more detailed history of the recent development of NARTLIS can be found in refs. 12 and 23.

The current interest in NARTLIS is stimulated for three reasons: (i) they are considered as environmentally benign solvents, mainly because of the very low vapor pressure under ambient conditions; (ii) Because of the wide range of employable cations and anions, new ionic solvents with specific, desired properties can be easily prepared; and (iii) they can improve the reactivities of dissolved reactants in a variety of chemical processes (see ref. 24 for some recent examples). The latter property is strongly connected with the solvation capability of NARTLIS for solutes, that is with the question, whether ionic liquids are superpolar, polar, or less polar solvents in comparison with the commonly used molecular solvents.

Intermolecular solute–solvent interactions and solvent polarity

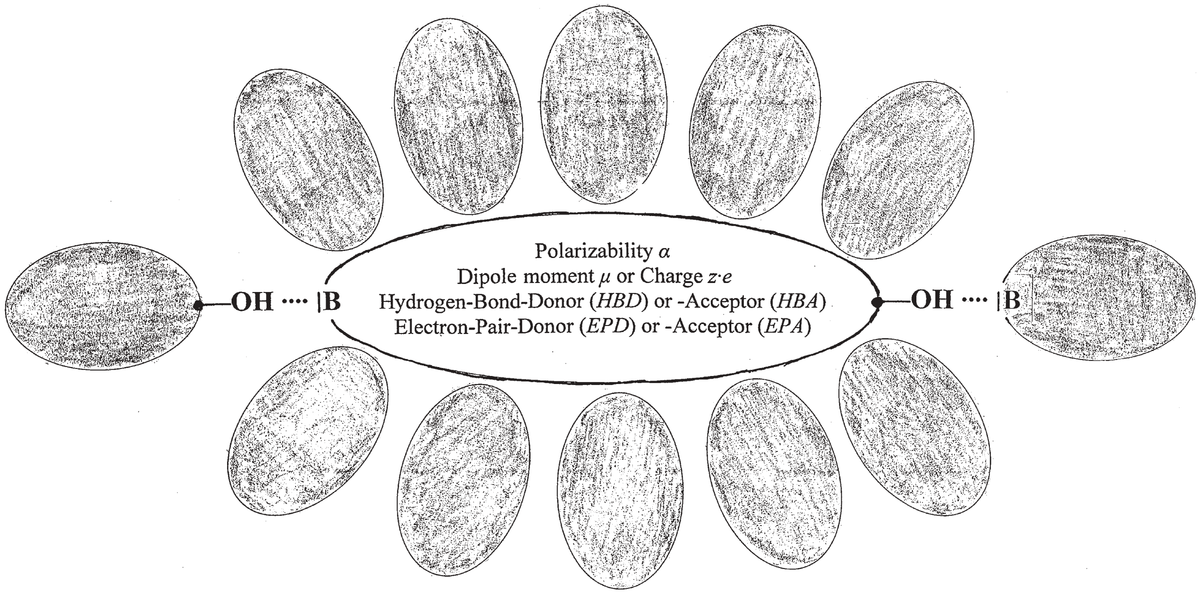
Chemists usually attempt to understand solvent effects on chemical processes in terms of the solvent polarity. The expression solvent polarity can be found in every chemistry textbook, however, mostly with a rather vague definition. What does solvent polarity really mean?

Attempted by the simplicity of electrostatic models for intermolecular solute–solvent interactions, considering solvents as non-structured homogeneous continuum, physical chemists have often used relative permittivities ε_r ("dielectric constants"), dipole moments μ, and refractive indices n_D (or functions thereof) as macroscopic physical solvent polarity parameters. However, solute–solvent interactions take place on a molecular–microscopic level, with individual, mutually interacting solvent molecules surrounding the ions or molecules of the solute, leading to loose or tight solvation shells, as shown in Fig. 2.

The solute species in Fig. 2 can have a polarizability α, a dipole moment μ, or a charge ze, responsible for nonspecific interaction forces, but it can also act as hydrogen-bond donor (HBD; right-hand side) and/or hydrogen-bond acceptor (HBA; left-hand side) and as electron-pair donor (EPD; Lewis base) and electron-pair acceptor (HBA; Lewis acid), responsible for specific interaction forces. In highly structured solvents such as water, solvophobic (hydrophobic) interactions are additionally possible. Because of this multitude of solute–solvent interactions, macroscopic physical solvent parameters have often failed in correlating solvents effects qualitatively and quantitatively.

Therefore, solvent polarity should be defined in another way. As early as 1965, the author proposed a rather simple, pragmatic definition of solvent polarity,[25] which was accepted in 1994 by the IUPAC committee responsible for the edition of *Glossary of Terms Used in Physical Organic Chemistry*,[26] and has also found its way in some textbooks.[2,3,27] Accordingly, solvent polarity is simply defined as the "overall solvation capability (or solvation power) for (i) educts and products, which influences chemical equilibria; (ii) reactants and activated complexes ("transition states"), which determines reaction rates; and (iii) ions or molecules in their ground and first excited state, which is responsible for light absorptions in the various wavelength regions. This overall solvation capability depends on the action of *all*, nonspecific and specific, intermolecular solute–solvent interactions, excluding such interactions leading to definite chemical alterations of the ions or molecules of the solute".[25,26]

Obviously, solvent polarity defined in this way cannot be measured by single macroscopic physical solvent parameters such as relative permittivity, dipole moment, and refractive index (or functions thereof). Solvent polarity, so defined, is much better described empirically by molecular–microscopic solvent-dependent reference processes. Carefully selected, well-understood, sufficiently solvent-sensitive reference processes, and the empirical parameters derived therefrom, reflect the multitude of possible solute–solvent interactions much better than single physical constants of the solvent. In this approach, solvents are considered as a discontinuous, more or less structured medium, consisting of individual, mutually interacting solvent molecules. The use of model processes to describe quantitatively the influence of internal parameters on chemical processes is not new: the correlation of substituent effects on chemical processes by means of the famous Hammett equation, derived empirically from the ionisation of substituted benzoic acids in water at 25 °C as reference reaction, is well known to all chemists.[28]



Nonspecific Interaction Forces:

- → Instantaneous Dipole/Induced Dipole Forces (Dispersion or London Forces)
- → Dipole/Induced Dipole Forces (Induction or Debye Forces)
- → Dipole/Dipole Forces (Orientation or Keesom Forces)
- → Ion/Dipole Forces (Coulomb Forces)

Specific Interaction Forces:

- → *HBD* or/and *HBA* Interactions
- → *EPD*/*EPA* or Charge–Transfer Interactions
- → Solvophobic Interactions (only in highly structured solvents such as water)

Fig. 2 Schematic two-dimensional illustration of nonspecific and specific intermolecular interaction forces between a solute species (neutral molecule or ion) and twelve solvent molecules in the first solvation shell.

By virtue of its exceptionally large negative solvatochromism (*i.e.* hypsochromic band shift with increasing solvent polarity), the pyridinium *N*-phenolate betaine dye shown in Fig. 3 was particularly suitable as a UV/Vis spectroscopic indicator of solvent polarity, using its long-wavelength intramolecular charge-transfer (CT) absorption as solvent-dependent reference process for the empirical determination of solvent polarity.[29,30]

According to its inherent molecular structure, the betaine dye in Fig. 3 (i) exhibits a large permanent dipole moment ($\mu_G \approx 15$ D[31]), suitable for the registration of dipole/dipole and dipole/induced dipole interactions; (ii) it possesses a large polarizable π-electron system with altogether 44 π-electrons, suitable for the registration of dispersion interactions; and (iii) the phenolate oxygen atom exhibits a highly basic EPD centre, suitable for the interaction with hydrogen-bond donors (H-bonding interaction) and Lewis acids (EPD/EPA interaction). Because the positive charge is delocalised and sterically somewhat shielded, interactions with EPD solvents (Lewis bases) are small and practically not registered. In acidic solvents, the betaine dye is (reversibly) protonated and the long-wavelength solvatochromic visible absorption band disappears. In that case, other less basic solvatochromic dyes should be used for the determination of solvent polarities.[30*b*] The X-ray structure determination of a 4-bromo-substituted derivative shows that the betaine dye is far from being planar; the interplanar angle between the pyridinium and the phenolate moiety amounts to 65°.[32]

The extraordinarily large negative solvatochromism of this betaine dye stems from the differential solvation of its highly dipolar electronic ground state ($\mu_G \approx 15$ D[31]) and its considerably less dipolar first excited state ($\mu_E \approx 6$ D[33]), as illustrated in Fig. 4. With increasing solvent polarity, the dipolar ground-state is more stabilized by solvation than the less dipolar Franck–Condon excited state, which may be even somewhat destabilized because its solvation shell is still equal to that of the ground state according to the Franck–Condon principle. As result, the long-wavelength solvatochromic, intramolecular CT absorption band is hypsochromically shifted from $\lambda_{max} = 810$ nm in diphenyl ether (the least polar solvent in which the betaine dye is sufficiently soluble) to $\lambda_{max} = 453$ nm in water (the most polar solvent in which the betaine dye is scarcely soluble), which corresponds to a solvent-induced band shift of $\Delta\lambda = -357$ nm (or $\Delta\nu = 9730$ cm^{-1} resp. $\Delta E_T = 28$ kcal mol^{-1} = 117 kJ mol^{-1} = 1.2 eV). Recent measurements have shown that the excited-state dipole moment of the betaine dye is antiparallel to that of the ground state, which means that the dipole flip on photoexcitation amounts up to $\Delta\mu \approx 15$ D $-$ (-6) D ≈ 21 D.[34]

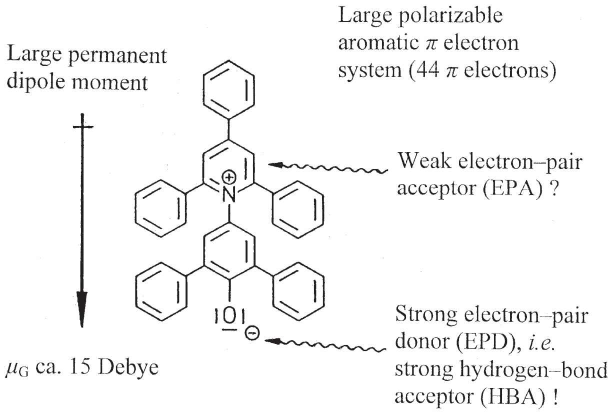


Fig. 3 Molecular structure and ground-state properties of the negatively solvatochromic standard betaine dye no. 30,[29,30] used for the determination of $E_T(30)$ values: 2,6-diphenyl-4-(2,4,6-triphenylpyridinium-1-yl)phenolate.

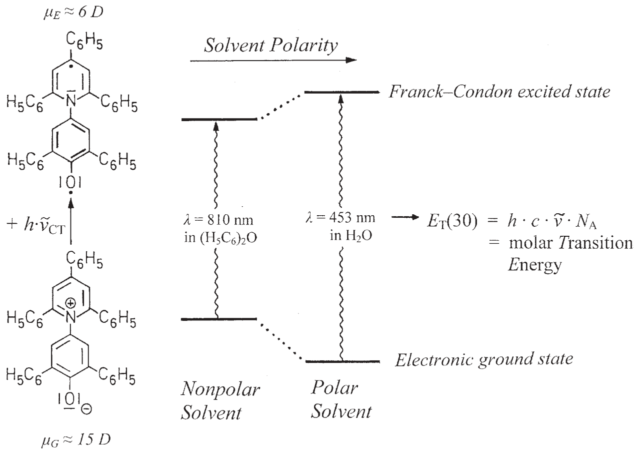


Fig. 4 Qualitative illustration of the solvent influence on the intramolecular charge-transfer visible absorption of the standard betaine dye no. 30[29,30] ($\mu_G > \mu_E$) and definition of the $E_T(30)$ values as its molar electronic transition energies; *cf.* also eqn. (3).

Since the solvatochromic absorption band of this betaine dye lies within the visible region of the spectrum, even a visual estimate of solvent polarity can often be made: for example, its solution colour is red in methanol, violet in ethanol, blue in 2-propanol, green in acetone, and yellowish-green in methoxybenzene.[30*a*] With binary mixtures of solvents with different polarity, nearly every colour of the visible spectrum can be produced. On the other hand, this behaviour can be used for the quantitative determination of the composition of binary solvent mixtures.[35] Many convenient and versatile experiments to demonstrate visually the different polarities of organic solvents by means of betaine dye no. 30 (which is commercially available), using test tubes or overhead projectors, have been recently described in the *Journal of Chemical Education*.[36–40]

$E_T(30)$ and E_T^N solvent polarity scales

The solvatochromic visible absorption of betaine dye no. 30 (Fig. 3) has been used as a solvent-dependent reference process to define empirically a solvent polarity scale, called $E_T(30)$ scale.[29,30] These $E_T(30)$ values are simply defined as the molar *t*ransition *e*nergies (in kcal mol^{-1}; 1 kcal = 4.184 kJ) of the standard betaine dye no. 30, measured in solvents of different polarity at room temperature (25 °C) and normal pressure (1 bar), according to eqn. (3),

$$E_T(30)/\text{kcal mol}^{-1} = hc\tilde{\nu}_{max}N_A = (2.8591 \times 10^{-3})\tilde{\nu}_{max}/\text{cm}^{-1} = 28591/(\lambda_{max}/\text{nm}) \tag{3}$$

where $\tilde{\nu}_{max}$ is the wavenumber and λ_{max} the wavelength of the maximum of the long-wavelength, solvatochromic, intramolecular CT absorption band of the standard betaine dye, and h, c, and N_A are Planck's constant, the speed of light, and Avogadro's constant, respectively. According to Fig. 4, high $E_T(30)$ values correspond to high solvent polarity.

The indicator dye no. 30 is not soluble in nonpolar solvents such as aliphatic hydrocarbons, perfluorohydrocarbons, and tetramethylsilane (TMS); it is therefore not possible to determine their $E_T(30)$ values directly. For this reason, a more lipophilic betaine dye with five *t*-butyl groups in the 4-positions of the five peripheral phenyl groups of the standard betaine dye was synthesized und used as a secondary solvatochromic probe dye.[41] The excellent linear correlation between the E_T values of the two betaine dyes for those solvents, in which both dyes are soluble, allows the calculation of $E_T(30)$ values for such nonpolar solvents in which the primary probe dye no. 30 is not soluble enough for UV/Vis spectroscopic measurements.[41]

The $E_T(30)$ scale ranges from 63.1 kcal mol^{-1} for water, the most polar solvent, to 30.7 kcal mol^{-1} for TMS, the least polar solvent, for which $E_T(30)$ values are experimentally available. In order to avoid the non-SI unit "kcal mol^{-1}" and the recalculation of all $E_T(30)$ values into the SI unit "kJ mol^{-1}", in 1983 the dimensionless normalized E_T^N scale was introduced, using water (E_T^N = 1.00) and TMS (E_T^N = 0.00) as reference solvents to fix the scale, according to eqn. (4).[41]

$$E_T^N = [E_T(\text{solvent}) - E_T(\text{TMS})]/[E_T(\text{water}) - E_T(\text{TMS})] = [E_T(\text{solvent}) - 30.7]/32.4 \qquad (4)$$

$E_T(30)$ and E_T^N values are known for more than 360 solvents and for many binary and even ternary solvent mixtures; for compilations see refs. 2,3,30,42. These and other empirical parameters of solvent polarity have been successfully applied in the correlation analysis of solvent influences on chemical equilibria, reaction rates, and spectral absorptions within the framework of so-called linear free-energy relationships.[2,3,30,42] For a review on other, more recent applications of this solvatochromic probe dye, *e.g.* the determination of the polarity of polymer films, of silica and alumina surfaces, of microheterogeneous solutions (*e.g.* micellar solutions), and the use of E_T values in multiparameter correlation equations, see refs. 1 and 2. According to desirable specific applications of the solvatochromic indicator dye of Fig. 3, its molecular structure can be easily chemically modified by the introduction of various lipophilic or hydrophilic substituents or its direct connection to a polymer matrix; for examples see refs. 1 and 43.

A graphical representation of the E_T^N solvent polarity scale is given in Fig. 5, with a selection of fourteen common molecular solvents above the line and eight groups of ionic liquids below the line.

In going from left to right above the line, with increasing solvent polarity, one first finds the group of apolar non-HBD ("aprotic") solvents (*e.g.* cyclohexene, benzene, THF, dichloromethane), followed by the dipolar non-HBD ("aprotic") solvents (*e.g.* acetone, DMF, DMSO), and eventually the group of dipolar HBD ("protic") solvents (*e.g.* cyclohexanol, 1-propanol, ethanol, phenol, methanol, ethane-1,2-diol, and 2,2,2-trifluoroethanol). This quantitative classification of organic molecular solvents within three main groups is in good agreement with the qualitative solvent classification of Parker,[44] which has been adopted by most textbooks of organic chemistry.[27] In going from left to right below the line, the range of $E_T(30)$ values obtained for eight groups of NARTLIS can be found, determined directly or indirectly by means of the standard betaine dye no. 30 by many research groups all over the world.[45–60] Surprisingly, the range of $E_T(30)$ (*ca.* 42–63 kcal mol^{-1}) found, corresponding to E_T^N

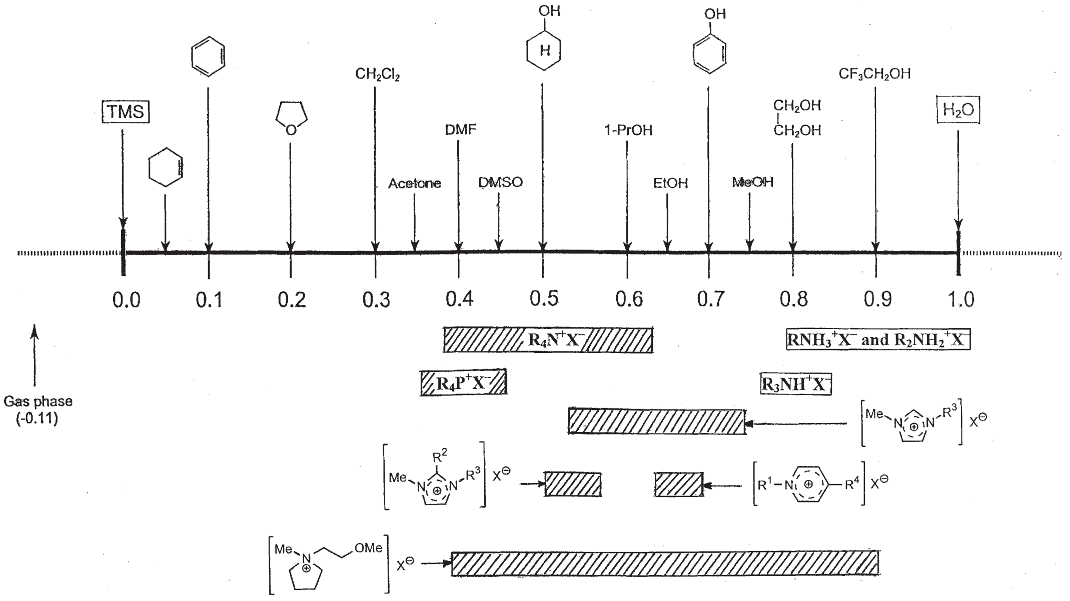


Fig. 5 Normalized solvent polarity scale E_T^N [*cf.* eqn. (4) for its definition] with E_T^N = 0.00 for tetramethylsilane (TMS) and E_T^N = 1.00 for water as arbitrarily fixed points, with ordering of fourteen selected solvents and the inclusion of eight groups of ionic liquids on this scale. The gas-phase E_T^N value is an extrapolated value and not directly measurable.[41]

values of *ca.* 0.35–1.00, is comparable to that of *dipolar non-HBD* and *dipolar HBD solvents*, depending on the inherent molecular structure of the ionic liquids studied.

Polarity of ionic liquids

The polarity of ionic liquids has been empirically determined by means of a variety of solvatochromic probe dyes, using their long-wavelength solvent-dependent absorptions or emissions.[45–62] In particular, the negative solvatochromism of the pyridinium *N*-phenolate betaine dye no. 30 (Fig. 3) has been used directly or indirectly to characterize ionic liquids by the solvent polarity parameter $E_T(30)$ resp. E_T^N.[45–60] Tables 1–5 collect the available $E_T(30)$ and the corresponding E_T^N values for thirty liquid ammonium salts (Table 1), nine tetraalkylphosponium salts (Table 2), thirty-three 1-methyl-3-alkyl- and 1-methyl-2,3-dialkylimidazolium salts (Table 3), five 1-alkyl- and 1,4-dialkylpyridinium salts (Table 4), and, amongst others, five 1,1-dialkylpyrrolidinium salts (Table 5), taken from the references given in the Tables.[45–60] Not all of them are room-temperature liquid salts; some $E_T(30)$ values were measured at higher temperatures (*e.g.* nos. **2**, **12**, **13**, **25–30** in Table 1).

Because of the strong thermochromism of solutions of the standard betaine dye,[30a] they are not directly comparable to those values measured at ambient temperatures. $E_T(30)$ values measured at higher temperatures are always lower than those determined at lower temperatures because solvent polarity decreases with increasing solution temperature.[30a]

An inspection of Tables 1–5 shows that $E_T(30)$ values determined for the same ionic liquid by various research groups differ sometimes considerably. Reasons for these

Table 1 $E_T(30)$ values (in kcal mol^{-1}) and the corresponding dimensionless E_T^N values of various liquid ammonium salts, $[R^1R^2R^3R^4N]^+\ X^-$, measured at the temperatures given. E_T values in parentheses are indirectly determined secondary values

No.	R^1	R^2	R^3	R^4	X^-	$t/°C^a$	$E_T(30)$	E_T^N	Ref.
1	H	H	H	H	$F_3C–CO_2^-$	130	43.6	0.398	47
Primary alkylammonium salts									
2	Et	H	H	H	Cl^-	120–150	62.3	0.975	47
3	Et	H	H	H	NO_3^-	rt	61.6	0.954	46*a*,*b*
						25	60.0^b	0.904^b	48
4	1-Pr	H	H	H	NO_3^-	rt	60.6	0.923	46*a*,*b*
5	1-Bu	H	H	H	SCN^-	rt	61.4	0.948	46*a*,*b*
6	2-Bu	H	H	H	SCN^-	rt	61.6	0.954	46*a*,*b*
Secondary dialkylammonium salts									
7	Me	Me	H	H	Cl^-	130	60.3	0.914	47
8	Me	Me	H	H	$Me_2N–CO_2^-$	r. t.^{c}	57.2	0.818	45
9	Et	Et	H	H	NO_3^-	rt	65.5	1.074	47
10	1-Pr	1-Pr	H	H	SCN^-	rt	63.3	1.006	46*a*,*b*
Tertiary trialkylammonium salts									
11	1-Bu	1-Bu	1-Bu	H	NO_3^-	rt	56.7	0.803	46*a*,*b*
Quaternary tetraalkylammonium salts^d									
12	Et	Et	Et	Et	$H_3C–CO_2^-$	45–90	48.6	0.553	47
						100–110	47.7	0.525	47
13	1-Bu	1-Bu	1-Bu	1-Bu	Br^-	105–130	43.3	0.389	47
14	1-Hex	1-Hex	1-Hex	1-Hex	$H_5C_6–CO_2^-$	25	43.9	0.407	47
						25	44.3	0.420	41
15	1-Oct	1-Oct	1-Oct	Me	Cl^-	125	44.1	0.414	47
16	1-Pr	1-Pr	1-Pr	1-Pr	$CHES^{-e}$	rt	50.9	0.624	46*a*,*b*
17	1-Bu	1-Bu	1-Bu	1-Bu	$CHES^{-e}$	rt	50.7	0.617	46*a*,*b*
18	1-Pe	1-Pe	1-Pe	1-Pe	$CHES^{-e}$	rt	49.5	0.580	46*a*,*b*
19	1-Pr	1-Pr	1-Pr	1-Pr	$MOPSO^{-f}$	rt	45.5	0.457	46*a*,*b*
20	1-Bu	1-Bu	1-Bu	1-Bu	$MOPSO^{-f}$	rt	46.5	0.488	46*a*,*b*
21	1-Pe	1-Pe	1-Pe	1-Pe	$MOPSO^{-f}$	rt	47.3	0.512	46*a*,*b*
22	1-Pr	1-Pr	1-Pr	1-Pr	BES^{-g}	rt	49.0	0.565	46*a*,*b*
23	1-Bu	1-Bu	1-Bu	1-Bu	BES^{-g}	rt	47.8	0.528	46*a*,*b*
24	1-Pe	1-Pe	1-Pe	1-Pe	BES^{-g}	rt	49.0	0.565	46*a*,*b*
25	1-Pr	1-Pr	1-Pr	1-Pr	HSO_4^-	160^h	(60)^i	(0.93)^i	49
26	1-Bu	1-Bu	1-Bu	1-Bu	HSO_4^-	170^h	(58)^i	(0.84)^i	49
27	1-Hex	1-Hex	1-Hex	1-Hex	ClO_4^-	105^h	(49)^i	(0.56)^i	49
28	1-Oct	1-Oct	1-Oct	1-Oct	ClO_4^-	136^h	(46)^i	(0.47)^i	49
29	1-Dec	1-Dec	1-Dec	1-Dec	ClO_4^-	124^h	(39)^i	(0.26)^i	49
30	1-Dod	1-Dod	1-Dod	1-Dod	ClO_4^-	120^h	(38)^i	(0.22)^i	49

[a] Temperatures or temperature ranges at which the salts are liquid and the UV/Vis absorption measurements have been made; rt means that the ammonium salt is liquid at room temperature and the measurements have been made at that temperature. [b] Averaged value from five independent measurements of different batches of the salt preparation. Ref. 48 also includes $E_T(30)$ values for binary mixtures of ethylammonium nitrate (EAN) with 1,2-dimethoxyethane, *t*-butanol, methanol, water, and dimethyl sulfoxide, as well as mixtures of dimethyl sulfoxide with ethylammonium chloride, tetraethylammonium chloride, and tetraethylammonium nitrate. [c] Dimethylammonium *N*,*N*-dimethylcarbamate (Dimcarb) is an ionic liquid with a network of intermolecular hydrogen bonds and decomposes at its boiling point (60–61 °C) into dimethylamine and carbon dioxide; see ref. 45 [d] 1-Pe = 1-Pentyl; 1-Hex = 1-Hexyl; 1-Oct = 1-Octyl; 1-Dec = 1-Decyl; 1-Dod = 1-Dodecyl. [e] $CHES^-$ = 2-(cyclohexylamino)-ethanesulfonate. [f] $MOPSO^-$ = 2-hydroxy-3-(4-morpholino)propanesulfonate. [g] BES^- = 2-[*N*,*N*-bis(2-hydroxyethyl)amino]ethanesulfonate. [h] These UV/Vis absorption measurements have been made *ca.* 3–5 °C above the given melting points of the ammonium salts. [i] Indirectly determined secondary values, obtained by means of the solvent-dependent fluorescence band shifts of coumarin 153 {=2,3,6,7-tetrahydro-9-(trifluoromethyl)-1*H*,5*H*,*11*H-[1]benzopyrano[6,7,8-*ij*]quinolizin-11-one} and their linear correlation with the E_T^N values; see ref. 49

Table 2 $E_T(30)$ values (in kcal mol^{-1}) and the corresponding dimensionless E_T^N values of various liquid quaternary tetraalkylphosphonium salts, $[R^1R^2R^3R^4P]^+$ X^-, measured at the temperatures given. Me = Methyl; 1-Bu = 1-Butyl; 1-Oct = 1-Octyl; 1-Dod = 1-Dodecyl

No.	R^1	R^2	R^3	R^4	X^-	t/°C[a]	$E_T(30)$	E_T^N	Ref.
1	1-Bu	1-Bu	1-Bu	1-Bu	Cl^-	125–135	43.0	0.380	47
2	1-Oct	1-Bu	1-Bu	1-Bu	Cl^-	75–95	43.8	0.404	47
3	1-Dod	1-Bu	1-Bu	1-Bu	Cl^-	90–130	42.6	0.367	47
4	1-Bu	1-Bu	1-Bu	1-Bu	Br^-	110–130	43.5	0.395	47
5	1-Oct	1-Bu	1-Bu	1-Bu	Br^-	85–100	42.9	0.377	47
6	1-Dod	1-Bu	1-Bu	1-Bu	Br^-	100–130	44.5	0.426	47
7	1-Oct	1-Bu	1-Bu	1-Bu	I^-	40–85	43.5	0.395	47
8	1-Dod	1-Bu	1-Bu	1-Bu	I^-	50–75	42.3	0.358	47
9	1-Oct	1-Oct	1-Oct	Me	$Me_2PO_4^-$	25	43.8	0.404	47

[a] Temperatures or temperature ranges at which the salts are liquid and the UV/Vis absorption measurements have been made.

deviations are probably as follows: (i) many $E_T(30)$ values have not been directly determined with the solvatochromic standard betaine dye, but with other solvatochromic indicator dyes more suitable for experimental reasons. From the absorption or emission maxima of these secondary probe dyes, the $E_T(30)$ values have been recalculated by correlation equations. Obviously, these indirectly obtained $E_T(30)$ values are not so accurate as the directly measured values and, therefore, they are put in parentheses; (ii) it is often difficult to prepare ionic liquids with sufficient purity. Traces of polar impurities can sometimes alter the $E_T(30)$ values. In particular, small amounts of remaining water can change the polarity of an ionic liquid considerably. Usually, the water content of most NARTLIS mentioned in Tables 1–5 is consistent with atmospheric-moisture saturation of the ionic liquids through contact with air.

Table 3 $E_T(30)$ values (in kcal mol^{-1}) and the corresponding dimensionless E_T^N values of various liquid 1-methyl-3-alkyl(R^3)-imidazolium salts, $[R^3mim]^+$ X^-, and 1-methyl-2-alkyl(R^2)-3-alkyl(R^3)-imidazolium salts, $[R^2,R^3mim]^+$ X^-, measured at the temperatures given; E_T values in parentheses are indirectly determined secondary values

No.	R^2	R^3	X^-	t/°C[a]	$E_T(30)$	E_T^N	Ref.
1-Methyl-3-alkyl(R^3)-imidazolium salts (R^2 = H)							
1	H	Et	BF_4^-	rt	53.7	0.710	53
				rt	(47.5–49.1)[b]	(0.519–0.568)[b]	52*e*
2	H	Et	Tf_2N^-[c]	25	52.6	0.676	51*e*,51*f*
				rt	53.1	0.690	60
				rt	(47.6)[b]	(0.522)[b]	52*c*
3	H	Et	$(NC)_2N^-$	rt	51.7	0.648	60
4	H	1-Pr	BF_4^-	rt	53.1	0.691	53
5	H	1-Pr	Tf_2N^-[c]	25	51.9	0.654	55*a*
6	H	1-Bu	Cl^-	25	50.6[d]	0.614[d]	54
7	H	1-Bu	NO_3^-	rt	51.8	0.651	56
				rt	(52.1)[e]	(0.661)[e]	52*a*
8	H	1-Bu	$H_3C–CO_2^-$	rt	49.2	0.571	56
9	H	1-Bu	$F_3C–CO_2^-$	rt	51.1	0.630	56
10	H	1-Bu	BF_4^-	25	52.5	0.673	50*b*,55*c*
				rt	52.7	0.680	53
				25	54.6[d]	0.738[d]	54
				rt	(48.9)[f]	(0.562)[f]	52*b*
				rt	(47.1–48.9)[b]	(0.506–0.562)[b]	52*e*
				25	(52.5)[n]	(0.673)[n]	52*f*
11	H	1-Bu	ClO_4^-	rt	52.9	0.684	59*a*
12	H	1-Bu	PF_6^-	25	52.3	0.667	50*a*,50*b*,51*c*[g],51*e*[g],51*f*[h]55*c*
				25/30	52.4	0.670	51*b*[i],51*d*,51*g*[j],56
				25	52.5	0.673	51*a*, 59*b*
				rt	52.6	0.676	60
				30	(52.6)[k]	(0.676)[k]	51*d*[k]
				rt	52.7	0.679	53
				25	53.2[d]	0.694[d]	54
				rt	(52.4)[e,l]	(0.670)[e,l]	52*a*
				rt	(49.0)[e,m]	(0.565)[e,m]	52*a*
				rt	49.0	0.565	52*d*
				25	(53.1)[n]	(0.691)[n]	52*f*
13	H	1-Bu	SbF_6^-	25	52.5	0.673	59*b*
14	H	1-Bu	Tf_2N^-[c]	25	50.0	0.596	51*e*,51*f*
				25	51.5	0.642	50*b*,55*c*
				rt	51.6	0.645	60
				rt	(47.1)[b]	(0.506)[b]	52*c*
				25	(52.5)[n]	(0.673)[n]	52*f*
15	H	1-Bu	TfO^-[o]	25	52.3	0.667	50*b*,55*c*
				25	(52.1)[n]	(0.661)[n]	52*f*
16	H	2-Bu	BF_4^-	rt	52.7	0.679	53
17	H	1-Hex	Cl^-	25	48.9[d]	0.562[d]	54
18	H	1-Hex	BF_4^-	25	53.6[d]	0.707[d]	54
19	H	1-Hex	PF_6^-	25	52.0[d]	0.657[d]	54
20	H	1-Hex	Tf_2N^-[c]	rt	51.9	0.654	60
21	H	1-Oct	Cl^-	25	48.5[d]	0.549[d]	54
22	H	1-Oct	BF_4^-	25	52.4[d]	0.670[d]	54

Table 3 (*Continued*)

No.	R^2	R^3	X^-	$t/°C^a$	$E_T(30)$	E_T^N	Ref.
23	H	1-Oct	PF_6^-	25	50.0^d	0.596^d	54
				25	51.2	0.633	50*b*,55*c*
				rt	51.3	0.636	50*a*
				rt	$(46.8)^e$	$(0.497)^e$	52*a*
24	H	1-Oct	Tf_2N^{-c}	25	51.1	0.630	50*b*,55*c*
25	H	1-Dec	TF_2N^{-c}	25	51.0	0.627	55*a*
26^p	H	2-Methoxyethyl	BF_4^-	rt	53.3	0.698	53
27^p	H	2-Methoxyethyl	Tf_2N^{-c}	25	54.1	0.722	55*a*
28^p	H	2-Hydroxyethyl	Tf_2N^{-c}	25	60.8	0.929	55*a*
29	H	Benzyl	Tf_2N^{-c}	25	52.4	0.670	55*a*
1-Methyl-2-alkyl(R^2)-3-alkyl(R^3)-imidazolium salts ($R^3 \neq H$)							
30	CH_3	1-Bu	BF_4^-	25	49.4	0.576	59*b*
31	CH_3	1-Bu	Tf_2N^{-c}	rt	48.4	0.546	60
				25	48.6	0.552	50*b*
32	CH_3	1-Oct	BF_4^-	25	48.3	0.543	50*b*
33	CH_3	1-Oct	Tf_2N^{-c}	25	47.7	0.525	50*b*

[a] Temperatures at which the salts are liquid and the UV/Vis measurements have been made; rt means room or ambient temperature. [b] Indirectly determined secondary E_T values, obtained by means of the solvent-dependent steady-state fluorescence behaviour of three EDA dyes: coumarin-153 (C 153), 2-(dimethylamino)-6-propanoylnaphthalene (PRODAN), and 4-aminophthalimide (AP). The E_T values given depend somewhat on the fluorescent probe used; see ref. 52*c*. [c] Tf_2N^- = bis(trifluoromethanesulfonyl)imide, $(F_3C–SO_2)_2N^-$. [d] Indirect E_T values recalculated from Kamlet and Taft's α and π^* values according to Table 1 and eqn. (4) in ref. 54. [e] Indirectly determined secondary E_T values, obtained by means of the static solvent-dependent fluorescence band shifts of 4-(dimethylamino)phthalimide (DAP) and their linear correlation with the $E_T(30)$ values; see ref. 52*a*. [f] Indirectly determined secondary E_T values, obtained by means of the static solvent-dependent fluorescence band shifts of coumarin-153 (C 153); see ref. 52*b*. [g] Refs. 51*c* and 51*e* also include E_T values for binary mixtures of **11** with water and with ethanol. [h] Ref. 51*f* also includes E_T values of binary mixtures of **11** with other ionic liquids. [i] Ref. 51*b* also includes E_T values of binary mixtures of **11** with water. [j] Ref. 51*g* also includes E_T values of ternary mixtures of **11** with ethanol and water. [k] Indirectly determined E_T values, obtained by means of the solvatochromic visible absorption band of 2,6-dichloro-4-(2,4,6-triphenylpyridinium-1-yl)phenolate [$E_T(33)$]. Ref. 51*d* also includes E_T values of dry and wet **11** at temperatures of 10–70 °C. [l] Determined after drying *in vacuo* at room temperature for 48 h (water content *ca.* 0.324 mol L^{-1}); see ref. 52*a*. [m] Determined after drying under more stringent conditions, *i.e.* in vacuo at 75 °C for 24 h (water content *ca.* 0.015 mol L^{-1}); see ref. 52*a*. [n] Indirect E_T values recalculated from Kamlet and Taft's α and π^* values according to Table 2 and eqn. (4) in ref. 52*f*. The $E_T(30)$ values used in ref. 52*f* were derived from the analogous $E_T(33)$ values, obtained by means of the solvatochromic visible absorption band of 2,6-dichloro-4-(2,4,6-triphenylpyridinium-1-yl)phenolate. [o] TfO^- = trifluoromethanesulfonate, $F_3C–SO_3^-$. [p] Such 3-methoxyethyl- or 3-hydroxyethyl-substituted 1-methylimidazolium salts belong to a subclass of ionic liquids with incorporated functional groups for additional specific solvent–solute interactions. For a recent review on such task-specific ionic liquids see J. H. Davies jr., *Chem. Lett. (Tokyo)*, 2004, **33**, 1072–1077.

For example, the $E_T(30)$ value of $[bmim]^+[PF_6]^-$ not dried (no. **12** in Table 3) with $c(H_2O) \approx 0.15$ mol L^{-1} is 52.9 kcal mol^{-1} ($E_T^N = 0.685$), after drying *in vacuo* at 70 °C for several hours with $c(H_2O) \approx 0.006$ mol L^{-1} (determined by Karl–Fischer titration) it changes to $E_T(30) = 52.3$ kcal mol^{-1} ($E_T^N = 0.667$).[50a] The influence of added water (and ethanol) on the $E_T(30)$ values of $[bmim]^+[PF_6]^-$ has been systematically studied: in going from mole fraction $x(H_2O) = 0.00$ to 1.00 in water/$[bmim]^+[PF_6]^-$ solutions, the solvatochromic absorption band of the standard betaine dye is hypsochromically shifted by $\Delta\lambda = -93$ nm from $\lambda_{max} = 546$ nm [$E_T(30) = 52.4$] to $\lambda_{max} = 453$ nm [$E_T(30) = 63.1$].[51e] On the other hand, the water content of ionic liquids can be determined with visible-range spectroscopy using the betaine dye and corresponding calibration curves.[51b,51d]

Table 4 $E_T(30)$ values (in kcal mol^{-1}) and the corresponding dimensionless E_T^N values of various liquid 1-alkyl(R^1)-pyridinium and 1-alkyl(R^1)-4-alkyl(R^4)-pyridinium salts, measured at room temperature. E_T values in parentheses are indirectly determined secondary values

No.	R^1	R^4	X^-	$t/°C^a$	$E_T(30)$	E_T^N	Ref.
1	1-Pr	H	BF_4^-	rt	52.1	0.661	53
2	1-Bu	H	BF_4^-	rt	51.4	0.639	53
				rt	$(44.9)^b$	$(0.438)^b$	52*a*
3	1-Bu	H	Tf_2N^{-c}	rt	51.7	0.648	60
4	1-Pr	CH_3	BF_4^-	rt	52.4	0.670	53
5	1-Bu	CH_3	BF_4^-	rt	51.1	0.630	53

[a] Temperatures at which the salts are liquid and the UV/Vis measurements have been made; rt = room temperature. [b] Indirectly determined secondary E_T value, obtained by means of the static solvent-dependent fluorescence band shifts of 4-(dimethylamino)phthalimide (DAP) and their linear correlation with the $E_T(30)$ values; see ref. 52*a*. [c] Tf_2N^- = bis(trifluoromethanesulfonyl)imide, $(F_3C–SO_2)_2N^-$.

In addition to the pure ionic liquids compiled in Tables 1–5, the polarity of a number of binary and even ternary mixtures of NARTLIS with other molecular[48,51c,51e,51g,52f] and ionic liquids[51f] have been studied.

It should be mentioned that concentration effects of the betaine dye when dissolved in $[bmim]^+[PF_6]^-$ were investigated in the concentration range c(betaine dye) = 50 to 500 µmol L^{-1}: the positions of the solvatochromic absorption band were within $\Delta\lambda_{max} = \pm 1$ nm of each other, demonstrating that the Beer–Lambert law is obeyed within this concentration range.[51a] This suggests the lack of any aggregation or mutual interaction among the betaine dye molecules, at least at concentrations of c(betaine dye) $\leqslant 500$ µmol L^{-1} ($\leqslant 5 \times 10^{-4}$ mol L^{-1}), which are usually sufficient for the solvatochromic UV/Vis spectroscopic measurements.[51a]

The simple model of an ionic liquid given in Fig. 6 illustrates nicely, that a zwitterionic molecule such as our solvatochromic betaine dye fits quite well into the framework of a liquid consisting entirely of ions. The zwitterionic solute seems to be

Table 5 $E_T(30)$ values (in kcal mol^{-1}) and the corresponding dimensionless E_T^N values of miscellaneous liquid salts, measured at the temperatures given

No.	Salt	X$^-$	t/°C^a	$E_T(30)$	E_T^N	Ref.
1	Eutectic mixture of lithium acetate (31%)/sodium acetate (25%)/potassium acetate (44%)	$H_3C–CO_2^-$	50–120	64.7	1.049	47
2	1-(2-Methoxyethyl)-1-methyl-pyrrolidinium salts **2a**	$F_3C–CO_2^-$	rt	42.7	0.370	56
	2b	$H_3C–CO_2^-$	rt	47.5	0.519	56
	2c	$H_3C–SO_3^-$	rt	56.0	0.781	56
	2d	NO_3^-	rt	57.9	0.840	56
	2e	$F_3C–SO_3^-$	rt	60.2	0.911	56
3	1-(1-Butyl)-1-methylpyrrolidinium-bis(trifluoromethanesulfonyl)imide	Tf_2N^-	25	48.3	0.544	59*b*

^{a} Temperatures or temperature range at which the salts are liquid and the UV/Vis absorption measurements have been made; rt = room temperature.

solvated by a microscopic environment like the bulk molten salt and experiences normal nonspecific intermolecular (or better interionic) electrostatic interactions. At low solute concentrations, there is no driving force for an association of the solute betaine molecules discernible. For a more detailed discussion of the model given in Fig. 6 see ref. 47. A somewhat modified picture arises from recent molecular dynamics simulations of the nonspecific and specific solute–solvent as well as solvent–solvent interactions for solutions of betaine dye no. 30 (Fig. 3) in $[bmim]^+[PF_6]^-$ (mp 12 °C) at room temperature;[63] see also ref. 64.

The individual $E_T(30)$ values of altogether *ca.* 80 ionic liquids, collected in Tables 1–5, have been summarized in Table 6, which contains the $E_T(30)$ and E_T^N polarity ranges and the corresponding averaged mean values for eight groups of ionic liquids for which $E_T(30)$ values were available, together with the corresponding molecular liquids having similar $E_T(30)$ values. The polarity ranges given in Table 6 are also graphically included in Fig. 5 for comparison with molecular liquids.

An inspection of Table 6 and Fig. 5 reveals that the polarity of ionic liquids with a range of $E_T(30) \approx 42–63$ kcal mol^{-1} ($E_T^N \approx 0.35–1.00$) fits quite well into the existing empirical solvent polarity scale for molecular solvents. Their polarity is comparable to that of molecular *dipolar non-HBD* and *dipolar HBD* solvents. That is, they behave not as superpolar but as quite normal polar solvents. This is not surprising if one compares the continuous intramolecular charge separation on going from neutral apolar solvents *via* dipolar and zwitterionic molecular solvents to the ion pairs of molten salts, as illustrated in Fig. 7. Ionic liquids seem to be the logical end of this sequence of solvent groups.

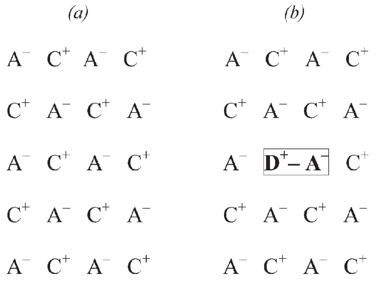


Fig. 6 Schematic two-dimensional representation of a simple model for ionic liquids consisting of cations (C^+) and anions (A^-) with (*a*) no solute, and (*b*) a zwitterionic donor-acceptor compound $D^+–A^-$ as solute, which corresponds to the betaine dye of Fig. 1, according to Pienta *et al.*[47]

Amongst the ionic liquids collected in Table 6 and shown in the lower part of Fig. 5, the primary, secondary, and tertiary alkylammonium salts ($E_T^N \approx 0.81–1.1$) are found in the polarity range of *dipolar HBD ("protic") solvents*, corresponding to that of the alcohols. Typical examples are ethylammonium nitrate (EAN; no. **3** in Table 1; E_T^N = 0.904[48]), dimethylammonium dimethylcarbamate (Dimcarb; no. **8** in Table 1; E_T^N = 0.818[45]), and tri-*n*-butylammonium nitrate (no. **11** in Table 1; E_T^N = 0.803[46a,b]). All three types of ionic liquids behave as HBD solvents because of the presence of ammonium ions with three, two, or one acidic N–H hydrogen atom(s), which can specifically interact with the phenolate part of the solvatochromic betaine dye. In contrast, fully alkylated quaternary ammonium salts such as tetra-*n*-hexylammonium benzoate (no. **14** in Table 1; E_T^N = 0.407[47]) exhibit as non-HBD solvents a solvent polarity similar to that of *dipolar non-HBD ("aprotic") solvents* like DMF (E_T^N = 0.386[30b]). Tetraalkylphosphonium salts (Table 2; $E_T^N \approx 0.35–0.44$) belong also to this group of dipolar non-HBD solvents.

Ionic liquids of the imidazolium type (Table 3) can be divided into those with a 1-methyl-3-alkyl-substitution pattern ($E_T^N \approx 0.53–0.75$) and those with an additional methyl substituent in C(2) position ($E_T^N \approx 0.50–0.56$). It is known that 1-methyl-3-alkylimidazolium cations can act as weak hydrogen-bond donors because of the weak acidic C(2)–H hydrogen atom at the heterocyclic ring.[65] Recent molecular dynamics simulations are consistent with the formation of weak specific hydrogen bonds between the cation of $[bmim]^+[PF_6]^-$ and the phenolate oxygen of the standard betaine no. 30 (Fig. 3).[63]

The importance of hydrogen bonding for the overall solvation polarity can easily be seen if one compares in Table 3 the E_T^N values of the HBD solvent no. **28** [with a 3-(2-hydroxyethyl) substituent] with that of the non-HBD solvent no. **27** [with a 3-(2-methoxyethyl) substituent].[55a] As expected, the E_T^N value of the more polar solvent **28** is by *ca.* 0.2 units (=0.929 − 0.722) larger than that of **27**.

Even under mild basic conditions, the C(2)–H atom of imidazolium ions can be removed to yield resonance-stabilized, nucleophilic singlet-diaminocarbenes;[66] these imidazolium-based ionic liquids are therefore chemically not inert.[67] Replacement of this C(2)–H atom by an alkyl group shifts the 1,2,3-trialkylsubstituted imidazolium salts to the less polar class of non-HBD solvents and make them also chemically more inert.[67b]

Table 6 Polarity of ionic liquids (NARTLIS) according to their $E_T(30)$ (bold-faced) and E_T^N values (in parentheses); see also Fig. 5

Ionic Liquids	Range[a]	Mean value[a]	Molecular liquids with corresponding $E_T(30)$ values
Primary and secondary alkylammonium salts, $[RNH_3]^+X^-$ and $[R_2NH_2]^+X^-$	**57–66** (0.81–1.1)	**61** (0.94)	H_2O, 63 $F_3C–CH_2OH$, 60
Tertiary trialkylammonium salt, $[R_3NH]^+X^-$	**57** (0.81)	**57** (0.81)	$HOCH_2–CH_2OH$, 56 $H–CONH_2$, 56
Quarternary tetraalkylammonium salts, $[R_4N]^+X^-$	**43–51** (0.38–0.63)	**47** (0.50)	2-Butanol, 47 $H_3C–CN$, 46 $H_3C–SO–CH_3$, 45
Quarternary tetraalkylphosphonium salts, $[R_4P]^+X^-$	**42–45** (0.35–0.44)	**43** (0.38)	$H_3C–CO–CH_3$, 42 $H–CON(CH_3)_2$, 43
1-Methyl-3-alkylimidazolium salts, $[R^3mim]^+X^-$	**48–55** (0.53–0.75)	**52** (0.66)	$H_3C–CH_2–OH$, 52 $H_3C–CONHCH_3$, 52
1-Methyl-2,3-dialkylimidazolium salts, $[R^2,R^3mim]^+X^-$	**47–49** (0.50–0.56)	**48** (0.53)	2-Propanol, 48 1-Heptanol, 48.5
1-Alkyl- and 1,4-dialkylpyridinium salts	**51–53** (0.63–0.69)	**52** (0.66)	$H_3C–CH_2OH$, 52 $H_3C–CONHCH_3$, 52
1-Methyl-1-(2-methoxyethyl)pyrrolidinium salts	**43–60** (0.38–0.90)	**53** (0.69)	$H_3C–CH_2OH$, 52 $H_3C–CONHCH_3$, 52

[a] Only directly measured primary $E_T(30)$ and E_T^N values, taken from Tables 1–5, have been used for the determination of the ranges and mean values.

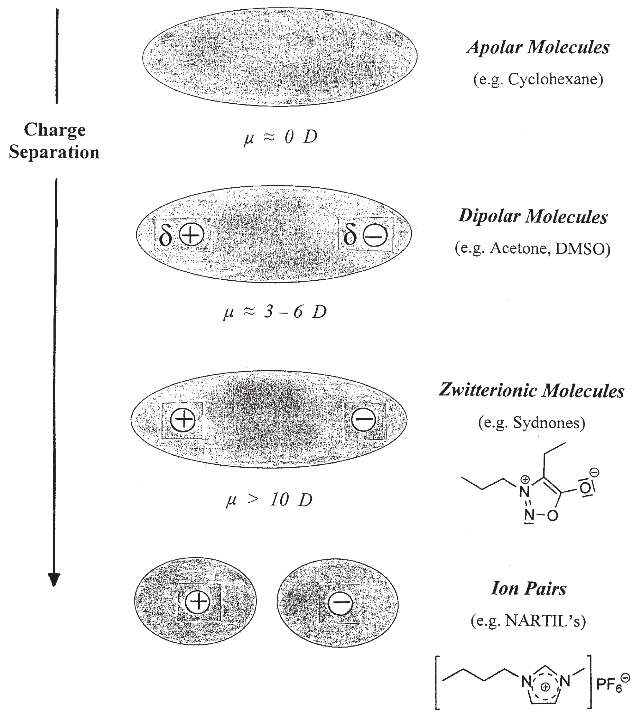


Fig. 7 Continuously increasing charge separation on going from neutral molecular solvents to the ion pairs of molten salts.

Depending on the length of the 1,3-alkyl substituents in the cation and the nature of the anion of the imidazolium-based ionic liquids **1–29** (Table 3), these NARTLIS exhibit E_T^N values between *ca.* 0.5 and 0.7 (Table 6). The increase of the length of one of the 1,3-alkyl substituents causes a small decrease in E_T^N values; alternation of the anion has only little influence on the E_T^N value. In comparison with conventional molecular organic solvents, it can generally be said that the polarity of these 1,3-dialkyl-imidazolium-based ionic liquids corresponds to that of short-chain primary and secondary alcohols and secondary amides such as *N*-methylformamide. The polarity of the 1-alkyl- and 1,4-dialkylpyridinium salts **1–5** in Table 4 behaves quite similarly.

In Fig. 8, the manifold of possible intermolecular solute–solvent interactions with 1,3-dialkylimidazolium-based ionic liquids as solvent is schematically given. Most of these intermolecular interactions can be registered by the solvatochromic betaine as solute, but not all of them: the betaine dye is neither a hydrogen-bond donor (HBD solute) nor an electron-pair acceptor (EPA solute). This demonstrates the limits of a single-parameter approach for the empirical determination of solvent polarity and the necessity for an extension of this approach by multiparameter treatments of solvent effects (see later).[59b,68]

Surprisingly, the polarity of the 1-(2-methoxyethyl)-1-methylpyrrolidinium salts **2a–2e** in Table 5 covers a rather wide range of E_T^N = 0.37–0.91, depending strongly on the nature of the anion.[56]

The only inorganic molten salt for which a reliable E_T^N value is available is the ternary eutectic mixture no. **1** in Table 5.[47] Its E_T^N value of 1.049 corresponds to that of water (E_T^N = 1.000).

It should be mentioned that in addition to betaine no. 30, a variety of other solvatochromic probe molecules were used to determine analogously empirical measures of solvent polarity, for example the visible absorption of the positively solvatochromic phenoxazone dye Nile Red[51a,52d,61] and the fluorescence emission of pyrene and pyrenecarboxaldehyde.[51a,51e,51f,51g,62] The sequence of solvent polarities obtained by other solvatochromic indicator dyes is in most cases analogous to that obtained with our pyridinium *N*-phenolate betaine dye no. 30, which gives some confidence in this purely empirical method.

Using the solvent-dependent $a(^{14}N)$ hyperfine splitting constants of the nitroxide radical 4-amino-2,2,6,6-tetramethylpiperidine-1-oxyl (ATEMPO), which correlate satisfactorily with the $E_T(30)$ values of molecular solvents, $E_T(30)$ values of a variety of ionic liquids were indirectly determined recently by EPR spectroscopy.[77] These polarity values judged from EPR measurements in ionic liquids agree surprisingly well with

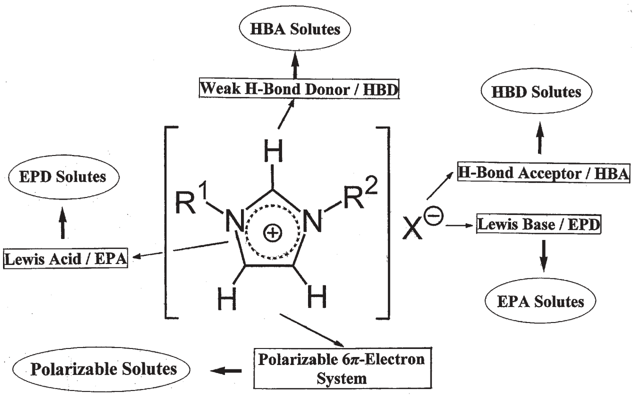


Fig. 8 Possible intermolecular solute–solvent interactions with 1,3-dialkylimidazolium-based ionic liquids as solvents. Solvent properties in rectangles; solute properties in ellipses.

those obtained directly by means of solvatochromic betaine dyes.[77]

In summary, the polarity of NARTLIS does not show any spectacular behaviour; they behave as normal liquids, with some desirable new physical properties, *e.g.* negligible vapour pressure. Each solvent ion is surrounded by a sphere of oppositely charged other solvent ions with complete dissociation, because an imaginary ion pair lacks stability as the electrostatic attractive force between the ions of the ion pair is nullified by the equal interactions of each ion with all its surrounding ions.

The strong electrostatic interactions between the solvent ions of ionic liquids lead to high values of their cohesive pressure c, defined as $c = \Delta U_V/V_m$ (with ΔU_V and V_m equal to energy of vaporization and molar volume, respectively[2]), and of the related Hildebrand's solubility parameter δ ($\delta = c^{0.5}$).[64b,69] A recent experiment-based estimate of the internal energies of vapourization for some $[bmim]^+X^-$ salts has led to ΔU_V values of *ca.* 200 kJ mol^{-1}, which are significantly greater than those of conventional molecular solvents with $\Delta U_V \approx$ 20–40 kJ mol^{-1}.[69] This explains the extreme small vapour pressures of NARTLIS, which have been recently calculated to be of the order of $P_{sat} \approx 10^{-10}$ Pa for $[bmim]^+[PF_6]^-$ at 25 °C; that is smaller than the lower detection limit of the usual vapour pressure measurements.[70]

Multiparameter correlation equations

In applying $E_T(30)$ and E_T^N solvent polarity parameters, it is tacitly assumed that the intermolecular solute–solvent interactions of the reference betaine dye no. 30 (Fig. 3) are similar to those in the system under investigation the prediction of whose solvent effects is being studied. This is obviously true only for closely related solvent-dependent processes. Nevertheless, the particular combination of intermolecular solute–solvent interactions registered by the zwitterionic indicator dye can be met very often, as their successful application to countless other solvent-dependent processes demonstrates.[1–3]

According to its intrinsic molecular structure (Fig. 3), this betaine dye is not prone to register the Lewis basicity resp. electron-pair donor (EPD) and hydrogen-bond acceptor (HBA) properties of solvents. This drawback can be overcome by using the two-parameter eqn. (5), including the donor number DN of Gutmann *et al.*[71] as a second parameter for the registration of the EPD properties of the surrounding medium:[72]

$$\mathrm{XYZ} = (\mathrm{XYZ})_0 + \alpha E_T(30) + \beta \mathrm{DN} \qquad (5)$$

XYZ and $(XYZ)_0$ stand for the solute property under study (*e.g.* log K, log k, $\tilde{\nu}_{max}$, *etc.*), determined in solvents of different polarity and in a reference medium (inert solvent or gas phase), respectively. This equation has been successfully applied for many further solvent-dependent processes for which $\beta \neq 0$;[72] for good one-parameter $E_T(30)$ correlations β has to be zero.

A more rigorous approach for the treatment of multiple interacting solvent effects has been proposed by Kamlet, Abboud, and Taft (KAT)[73,74,76] with the three-parameter eqn. (6), also called *linear solvation energy relationship*,

$$\mathrm{XYZ} = (\mathrm{XYZ})_0 + s\pi^* + a\alpha + b\beta \qquad (6)$$

in which π^* represents the solvent's dipolarity/polarizability, and α and β are measures of the solvent's HBD acidity and HBA basicity, respectively. All three solvent parameters were determined UV/Vis spectroscopically by means of carefully selected solvatochromic reference compounds: the π^* values from the $\pi \rightarrow \pi^*$ absorption of some nitroaromatics (*e.g.* 4-nitroanisole and *N*,*N*-dimethyl-4-nitroaniline[74]), the α and β values from pairs of homomorphic compounds such as 4-nitroanisole and the betaine dye no. 30 as well as 4-nitroaniline and *N*,*N*-diethyl-4-nitroaniline, respectively. The π^* scale ranges from $\pi^* = 0.00$ for cyclohexane to $\pi^* = 1.00$ for dimethyl sulfoxide; the α scale from $\alpha = 0.00$ for cyclohexane to $\alpha = 1.96$ for hexafluoro-2-propanol, and the β scale from $\beta = 0.00$ for cyclohexane to $\beta = 1.00$ for hexamethylphosphoric acid triamide (HMPT). In order to establish eqn. (6) for a certain solvent-dependent process, this process should be studied in a variety of solvents differing in their π^*, α, and β values. The regression coefficients s, a, and b are solvent-independent characteristics of the process under study and indicative of its susceptibility to the solvent properties described by π^*, α, and β. Altogether, eqn. (6) allows to describe nonspecific and specific solute–solvent interactions simultaneously by means of three orthogonal, *i.e.* mutually independent, empirically determined solvent parameters.[73,74]

A correlation analysis of the $E_T(30)$ resp. E_T^N values by means of the KAT eqn. (6) has been done by Marcus[75,76a] for 166 organic molecular solvents, leading to eqns. (7a) and (7b) ($n = 166$; $r = 0.979$), respectively:

$$E_T(30)/\mathrm{kcal\ mol^{-1}} = 31.2 + 11.5\pi^* + 15.2\alpha \qquad (7a)$$

$$E_T^N = 0.01 + 0.36\pi^* + 0.47\alpha \qquad (7b)$$

These multiparameter correlations clearly demonstrate that the $E_T(30)$ resp. E_T^N values measure preferably the solvent's dipolarity/polarizability (given by π^*) and HBD acidity (given by α). In HBD solvents, the HBD acidity can even be the dominant solvent property: the quotient a/s of the corresponding regression coefficients [see eqn. (6)] is 1.3 for eqns. (7a) and (7b). For non-HBD solvents with α equal to zero, the $E_T(30)$

resp. E_T^N values essentially reflect only a blend of the solvents' dipolarity (→dipole–dipole, dipole–induced dipole interactions) and polarizability (→dispersion interactions), in good agreement with the intrinsic molecular structure of the betaine dye no. 30 (Fig. 3).

For many ionic liquids the KAT parameters have been determined: see refs. 46,47,50*b*,51*d*,51*e*,51*f*,52*f*,54,59*b*,68, in particular Table 6 in ref. 19 and Table 1 in ref. 59*b* For example, the KAT values for $[bmim]^+[PF_6]^-$ are $\pi^* = 1.03$, $\alpha = 0.63$, and $\beta = 0.21$,[59b] corresponding to $E_T(30)$ and E_T^N values of 52.3 kcal mol^{-1} and 0.667 kcal mol^{-1}, respectively (no. **12** in Table 3). A comparison of the KAT values obtained for ionic liquids with those of molecular liquids again shows that ionic liquids behave as quite normal liquids, the KAT values of which fit well into the existing framework of π^*, α, and β values for molecular liquids. For example, the KAT values of water are $\pi^* = 1.09$, $\alpha = 1.17$, and $\beta = 0.47$.[2,76] However, the interpretation of KAT values of ionic liquids in terms of their molecular structure is somewhat more complicated because they consist of cations and anions with different properties with respect to their dipolarity/polarizability, HBD acidity, and HBA basicity (see Fig. 8). A detailed discussion of the KAT values of NARTLIS is outside the scope of this review and the reader is referred to the references given above.

Acknowledgements

The work done in Marburg reviewed herein is the result of a gratifying collaboration with my former coworkers mentioned in the references and was financially supported by the *Deutsche Forschungsgemeinschaft*, Bonn, and the *Fonds der Chemischen Industrie*, Frankfurt am Main. For helpful advice I thank Prof. Cinzia Chiappe, Pisa, Italy, Prof. Siddharth Panday, Socorro, NM, Prof. Colin F. Poole, Detroit/USA, Prof. Anunay Samanta, Hyderabad, India, and Prof. Thomas Welton, London, UK.

Christian Reichardt
Department of Chemistry, Philipps University, Hans-Meerwein-Strasse, D-35032 Marburg, Germany. E-mail: Reichardt-Marburg@t-online.de

References

1 C. Reichardt, *Pure Appl. Chem.*, 2004, **76**, 1903–1919.
2 C. Reichardt, *Solvent Effects in Organic Chemistry*, Wiley-VCH, Weinheim, 3rd edn., 2003.
3 E. Buncel, R. Stairs and H. Wilson, *The Role of the Solvent in Chemical Reactions*. Oxford University Press, Oxford, 2003.
4 *Handbook of Solvents (+ Solvent Data Base on CD-ROM)*, ed. G. Wypych, ChemTec Publishing, Toronto, 2001, particularly chapters 17, pp. 1149–1200, 20, pp. 1315–1418, and 21, pp. 1419–1505.
5 *Modern Solvents in Organic Synthesis*, ed. P. Knochel, Springer, Berlin, 1999.
6 D. J. Adams, P. J. Dyson and S. J. Tavener, *Chemistry in Alternative Reaction Media*. Wiley, Chichester, 2004.
7 A. Loupy, in *Modern Solvents in Organic Synthesis,*, ed. P. Knochel, Springer, Berlin, 1999, pp. 153–207.
8 (*a*) P. T. Anastas and J. C. Warner, *Green Chemistry: Theory and Practice*. Oxford University Press, Oxford, 1998; (*b*) A. S. Matlack, *Introduction to Green Chemistry*. Marcel Dekker, New York, 2001; (*c*) W. M. Nelson, *Green Solvents for Chemistry – Perspectives and Practice*, Oxford University Press, Oxford, 2003, particularly chapter 6.5.8, pp. 168–177.
9 (*a*) P. A. Grieco, *Organic Syntheses in Water*. Blackie Academic and Professional, London, 1998; (*b*) N. Akiya and P. E. Savage, *Chem. Rev.*, 2002, **102**, 2725–2750.
10 (*a*) *Handbook of Fluorous Chemistry*, ed. J. A. Gladysz, D. P. Curran and I. T. Horváth, Wiley-VCH, Weinheim, 2004; (*b*) A. Endres and G. Maas, *Chem. Unserer Zeit*, 2000, **34**, 382–393.
11 (*a*) *Chemical Synthesis Using Supercritical Fluids*, ed. P. G. Jessop and W. Leitner, Wiley-VCH, Weinheim, 1999; (*b*) R. Noyori, *Chem. Rev.*, 1999, **99**, 353–634; (*c*) W. Leitner, *Acc. Chem. Res.*, 2002, **35**, 746–756; W. Leitner, *Chem. Unserer Zeit*, 2003, **37**, 32–38; (*d*) Y. Marcus, *J. Phys. Org. Chem.*, 2005, **18**, 373–384.
12 (*a*) D. W. Rooney and K. R. Seddon, in *Handbook of Solvents*, ed. G. Wypych, ChemTec Publishing, Toronto, and William Andrew Publishing, New York, 2001, chapter 21.2, p. 1459–1484; (*b*) *Ionic Liquids in Synthesis*, ed. P. Wasserscheid and T. Welton, Wiley-VCH, Weinheim, 2003; (*c*) P. Wasserscheid, *Chem. Unserer Zeit*, 2003, **37**, 52–63; (*d*) C. Chiappe and D. Pieraccini, *J. Phys. Org. Chem.*, 2005, **18**, 275–297.
13 S. Sankararaman and J. E. Nesakumar, *Eur. J. Org. Chem.*, 2000, 2003–2011.
14 R. Fuoss, *J. Chem. Educ.*, 1955, **32**, 527.
15 (*a*) P. Walden, *Bull. Acad. Imp. Sci. St.-Petersbourg*, 1914, **8**, 405–422, *Chem. Zentralbl.*, 1914, 1800; (*b*) See also: S. Sugden and H. Wilkins, *J. Chem. Soc.*, 1929, 1291–1298; (*c*) D. F. Evans, A. Yamauchi, R. Roman and E. Z. Casassa, *J. Colloid Interface Sci.*, 1982, **88**, 89–96; (*d*) D. Mirejowski and E. M. Arnett, *J. Am. Chem. Soc.*, 1983, **105**, 1112–1117; (*e*) D. A. Jaeger and C. E. Tucker, *Tetrahedron Lett.*, 1989, **30**, 1785–1788.
16 P. C. Ray and J. N. Rakshit, *J. Chem. Soc.*, 1911, 1470–1475.
17 (*a*) W. Sundermeyer, *Angew. Chem.*, 1965, **77**, 241–258, *Angew. Chem., Int. Ed. Engl.*, 1976, **4**, 222–238; (*b*) W. Sundermeyer, *Chem. Unserer Zeit*, 1967, **1**, 150–157.
18 *Ionic Liquids*, ed. D. Inman and D. G. Lovering, Plenum Press, New York, 1981.
19 C. F. Poole, *J. Chromatogr. A*, 2004, **1037**, 49–82.
20 C. G. Swain, A. Ohno, D. K. Roe, R. Brown and T. Maugh, *J. Am. Chem. Soc.*, 1967, **89**, 2648–2649.
21 (*a*) F. H. Hurley and T. P. Wier, *J. Electrochem. Soc.*, 1961, **98**, 203–206; (*b*) H. L. Chum, V. R. Koch, L. L. Miller and R. A. Osteryoung, *J. Am. Chem. Soc.*, 1975, **97**, 3264–3265.
22 (*a*) J. S. Wilkes, J. A. Levisky, R. A. Wilson and C. L. Hussey, *Inorg. Chem.*, 1982, **21**, 1263–1264; (*b*) J. R. Sanders, E. H. Ward and C. L. Hussey, *Proc. Electrochem. Soc.*, 1986, **86–1**, 307–316, *Chem. Abstr.*, 1986, **104**, 156804s, special issue on molten salts; (*c*) J. S. Wilkes and M. J. Zaworotko, *J. Chem. Soc., Chem. Commun.*, 1992, 965–967.
23 P. Wasserscheid and W. Keim, *Angew. Chem.*, 2000, **112**, 3926–3945, *Angew. Chem., Int. Ed.*, 2000, **39**, 3772–3789.
24 (*a*) N. L. Lancaster, T. Welton and G. B. Young, *J. Chem. Soc., Perkin Trans. 2*, 2001, 2267–2270; (*b*) N. L. Lancaster, P. A. Salter, T. Welton and G. B. Young, *J. Org. Chem.*, 2002, **67**, 8855–8861; (*c*) N. L. Lancaster and T. Welton, *J. Org. Chem.*, 2004, **69**, 5986–5992; (*d*) L. Crowhurst, N. L. Lancaster, J. M. Pérez Arlandis and T. Welton, *J. Am. Chem. Soc.*, 2004, **126**, 11549–11555; (*e*) C. Chiappe, D. Pieraccini and P. Saullo, *J. Org. Chem.*, 2003, **68**, 6710–6715.
25 C. Reichardt, *Angew. Chem.*, 1965, **77**, 30–40, *Angew. Chem., Int. Ed. Engl.*, 1965, **4**, 29–40.
26 P. Müller, *Pure Appl. Chem.*, 1994, **66**, 1077–1184, particularly p. 1151.
27 A. Streitwieser, C. H. Heathcock and E. M. Kosower, *Introduction to Organic Chemistry*, MacMillan Publishing Company, New York, 4th edn., 1992, p. 677 ff. and Essay 4.
28 (*a*) L. P. Hammett, *Physical Organic Chemistry*, McGraw-Hill, New York, 2nd edn., 1970; L. P. Hammett, *Physikalische Organische Chemie.*, Verlag Chemie, Weinheim, 1973, p. 352 ff; (*b*) J. Shorter, *Chem. Unserer Zeit*, 1985, **19**, 197–208.
29 K. Dimroth, C. Reichardt, T. Siepmann and F. Bohlmann, *Justus Liebigs Ann. Chem.*, 1963, **661**, 1–37. In this first publication, this betaine dye had by chance the formula number 30. Therefore, the number 30 was later on added to E_T to give $E_T(30)$ in order to avoid confusion with E_T used in photochemistry as abbreviation for triplet energy.
30 (*a*) C. Reichardt, *Chem. Soc. Rev.*, 1992, **21**, 147–153; (*b*) C. Reichardt, *Chem. Rev.*, 1994, **94**, 2319–2358.

31 A. Schweig and C. Reichardt, *Z. Naturforsch., Part A*, 1966, **21a**, 1373–1376, value for 2,6-di-*t*-butyl-4-(2,4,6-triphenylpyridinium-1-yl)phenolate for solubility reasons.

32 R. Allmann, *Z. Kristallogr.*, 1969, **128**, 115–132.

33 W. Liptay, *Z. Naturforsch., A*, 1965, **20**, 1441–1471; W. Liptay, *Z. Naturforsch., A*, 1966, **21**, 1605–1618.

34 (*a*) M. C. Beard, G. M. Turner and C. A. Schmuttenmaer, *J. Am. Chem. Soc.*, 2000, **122**, 11541–11542; (*b*) C. A. Schmuttenmaer, *Chem. Rev.*, 2004, **104**, 1759–1779, particularly p. 1769.

35 (*a*) H. Langhals, *Angew. Chem.*, 1982, **94**, 739–749; *Angew. Chem., Int. Ed. Engl.*, 1982, **21**, 724–733; (*b*) R. D. Skwierczynski and K. A. Connors, *J. Chem. Soc., Perkin Trans. 2*, 1994, 467–472; (*c*) M. Rosés, C. Ráfols, J. Ortega and E. Bosch, *J. Chem. Soc., Perkin Trans. 2*, 1995, 1607–1615; M. Rosés, C. Ráfols, J. Ortega and E. Bosch, *J. Chem. Soc., Perkin Trans. 2*, 1996, 1497–1503; E. Bosch, F. Rived and M. Rosés, *J. Chem. Soc., Perkin Trans. 2*, 1996, 2177–2184; C. Ráfols, M. Rosés and E. Bosch, *J. Chem. Soc., Perkin Trans. 2*, 1997, 243–248; M. Rosés, U. Buhvestov, C. Ráfols, F. Rived and E. Bosch, *J. Chem. Soc., Perkin Trans. 2*, 1997, 1341–1348.

36 D. A. Johnson, R. Shaw and E. F. Silversmith, *J. Chem. Educ.*, 1994, **71**, 517.

37 B. R. Osterby and R. D. McKelvey, *J. Chem. Educ.*, 1996, **73**, 260–261.

38 T. Deng and W. E. Acree, Jr., *J. Chem. Educ.*, 1999, **76**, 1555–1556.

39 M. F. Vitha, *J. Chem. Educ.*, 2001, **78**, 370–372.

40 C. Machado and V. G. Machado, *J. Chem. Educ.*, 2001, **78**, 649–651.

41 C. Reichardt and E. Harbusch-Görnert, *Liebigs Ann. Chem.*, 1983, 721–743.

42 (*a*) C. Reichardt, *Angew. Chem.*, 1979, **91**, 119–131; *Angew. Chem., Int. Ed. Engl.*, 1979, **18**, 98–110; (*b*) O. Exner, *Correlation Analysis of Chemical Data*. Plenum Press, New York, 1988.

43 (*a*) C. Reichardt, D. Che, G. Heckenkemper and G. Schäfer, *Eur. J. Org. Chem.*, 2001, 2343–2361; (*b*) C. Reichardt, M. Eschner and G. Schäfer, *J. Phys. Org. Chem.*, 2001, **14**, 737–751.

44 A. J. Parker, *Q. Rev. Chem. Soc.*, 1962, **16**, 163–187; A. J. Parker, *Adv. Org. Chem.*, 1965, **5**, 1–46; A. J. Parker, *Adv. Phys. Org. Chem.*, 1967, **5**, 173–235; A. J. Parker, *Chem. Rev.*, 1969, **69**, 1–32.

45 (*a*) W. Schroth, H.-D. Schädler and J. Andersch, *Z. Chem.*, 1989, **29**, 56–57; (*b*) W. Schroth, J. Andersch, H.-D. Schädler and R. Spitzner, *Chem.–Ztg.*, 1989, **113**, 261–271.

46 (*a*) S. K. Poole, P. H. Shetty and C. F. Poole, *Anal. Chim. Acta*, 1989, **218**, 241–264; (*b*) C. F. Poole, *J. Chromatogr., Part A*, 2004, **1037**, 49–82.

47 W. B. Harrod and N. J. Pienta, *J. Phys. Org. Chem.*, 1990, **3**, 534–544.

48 I.-M. Herfort and H. Schneider, *Liebigs Ann. Chem.*, 1991, 27–31.

49 E. Bart, A. Meltsin and D. Huppert, *J. Phys. Chem.*, 1994, **98**, 3295–3299.

50 (*a*) P. Wasserscheid, C. M. Gordon, C. Hilgers, M. J. Muldoon and I. R. Dunkin, *J. Chem. Soc., Chem. Commun.*, 2001, 1186–1187; (*b*) M. J. Muldoon, C. M. Gordon and I. R. Dunkin, *J. Chem. Soc., Perkin Trans. 2*, 2001, 433–435.

51 (*a*) K. A. Fletcher, I. A. Storey, A. E. Hendricks, Sh. Pandey and Si. Pandey, *Green Chem.*, 2001, **3**, 210–215; (*b*) K. A. Fletcher and S. Pandey, *Appl. Spectrosc.*, 2002, **56**, 266–271; (*c*) K. A. Fletcher and S. Pandey, *Appl. Spectrosc.*, 2002, **56**, 1498–1503; (*d*) S. N. Baker, G. A. Baker and F. V. Bright, *Green Chem.*, 2002, **4**, 165–169; (*e*) K. A. Fletcher and S. Pandey, *Proc. Electrochem. Soc.*, 2002, **19**, 244–256, *Chem. Abstr.*, 2003, **139**, 266433, special issue on molten salts; (*f*) K. A. Fletcher, S. N. Baker, G. A. Baker and S. Pandey, *New J. Chem.*, 2003, **27**, 1706–1712; (*g*) K. A. Fletcher and S. Pandey, *J. Phys. Chem. B*, 2003, **107**, 13532–13539.

52 (*a*) S. N. V. K. Aki, J. F. Brennecke and A. Samanta, *J. Chem. Soc., Chem. Commun.*, 2001, 413–414; (*b*) R. Karmakar and A. Samanta, *J. Phys. Chem. A*, 2002, **106**, 4447–4452; (*c*) R. Karmakar and A. Samanta, *J. Phys. Chem. A*, 2003, **107**, 7340–7346; (*d*) S. Saha, P. K. Mandal and A. Samanta, *Phys. Chem. Chem. Phys.*, 2004, **6**, 3106–3110; (*e*) A. Samanta, personal communication, University of Hyderabad, 2004; (*f*) C. P. Fredlake, M. J. Muldoon, S. N. V. K. Aki, T. Welton and J. F. Brennecke, *Phys. Chem. Chem. Phys.*, 2004, **6**, 3280–3285.

53 S. Park and R. J. Kazlauskas, *J. Org. Chem.*, 2001, **66**, 8395–8401.

54 J. G. Huddleston, G. Broker, H. Willauer and R. D. Rogers, in *Ionic Liquids – Industrial Applications for Green Chemistry*, ed. R. D. Rogers and K. Seddon, American Chemical Society, Washington, DC, 2002, pp. 270–288.

55 (*a*) S. V. Dzyuba and R. A. Bartsch, *Tetrahedron Lett.*, 2002, **43**, 4657–4659; (*b*) S. V. Dzyuba and R. A. Bartsch, *Chem. Phys. Chem.*, 2002, **3**, 161–166; (*c*) R. A. Bartsch and S. V. Dzyuba, in: *Ionic Liquids as Green Solvents – Progress and Prospects*, American Chemical Society, Washington, DC, 2003, p. 289–299; *Chem. Abstr.*, 2004, **140**, 253495.

56 J. L. Kaar, A. M. Jesionowski, J. A. Berberich, R. Moulton and A. J. Russel, *J. Am. Chem. Soc.*, 2003, **125**, 4125–4131.

57 J. A. Ingram, R. S. Moog, N. Ito, R. Biswas and M. Maroncelli, *J. Phys. Chem. B*, 2003, **107**, 5926–5932.

58 V. Znamenskiy and M. N. Kobrak, *J. Phys. Chem. B*, 2004, **108**, 1072–1079.

59 (*a*) T. Welton, in *Ionic Liquids in Synthesis*, ed. P. Wasserscheid and T. Welton, Wiley-VCH, Weinheim, 2003, p. 94–99, (particularly Table 3.5–1 on p. 97); (*b*) L. Crowhurst, P. R. Mawdsley, J. M. Perez-Arlandis, P. A. Salter and T. Welton, *Phys. Chem. Chem. Phys.*, 2003, **5**, 2790–2794.

60 (*a*) C. Chiappe, P. Piccioli, D. Pieraccini, P. De Maria and G. Siani, poster presented at *Green Solvents for Synthesis*, Bruchsal, Germany, October 3–6, 2004; (*b*) C. Chiappe, personal communication, Pisa, October 18, 2004.

61 (*a*) A. J. Carmichael and K. R. Seddon, *J. Phys. Org. Chem.*, 2000, **13**, 591–595; (*b*) W. Ogihara, T. Aoyama and H. Ohno, *Chem. Lett.*, 2004, **33**, 1414–1415.

62 P. Bonhote, A.-P. Dias, N. Papageorgiou, K. Kalyanasundaram and M. Grätzel, *Inorg. Chem.*, 1996, **35**, 1168–1178.

63 V. Znamenskiy and M. N. Kobrak, *J. Phys. Chem. B*, 2004, **108**, 1072–1079.

64 (*a*) M. G. Del Pópolo and G. A. Voth, *J. Phys. Chem. B*, 2004, **108**, 1744–1754; (*b*) W. Schröer and H. Weingärtner, *Pure Appl. Chem.*, 2004, **76**, 19–27.

65 (*a*) A. Elaiwi, P. B. Hitchcock, K. R. Seddon, N. Srinivasan, Y.-M. Tan, T. Welton and J. A. Zora, *J. Chem. Soc., Dalton Trans.*, 1995, 3467–3472; (*b*) J. Ross and J. Xiao, *Chem. Eur. J.*, 2003, **9**, 4900–4906; (*c*) J. Dupont, *J. Braz. Chem. Soc.*, 2004, **15**, 341–350, and references cited in these papers.

66 Recent review on stable singlet-diaminocarbenes: W. Kirmse, *Angew. Chem.*, 2004, **116**, 1799–1801, *Angew. Chem., Int. Ed.*., 2004, **43**, 1767–1769.

67 (*a*) V. K. Aggarwal, J. Emme and A. Mereu, *J. Chem. Soc., Chem. Commun.*, 2002, 1612–1613; (*b*) J.-C. Hsu, Y.-H. Yen and Y.-H. Chu, *Tetrahedron Lett.*, 2004, **45**, 4673–4767.

68 J. L. Anderson, J. Ding, T. Welton and D. W. Armstrong, *J. Am. Chem. Soc.*, 2002, **124**, 14247–14254.

69 K. Swiderski, A. McLean, C. M. Gordon and D. H. Vaughan, *J. Chem. Soc., Chem. Commun.*, 2004, 2178–2179.

70 Y. U. Paulechka, G. J. Kabo, A. V. Blokhin, O. A. Vydrov, J. W. Magee and M. Frenkel, *J. Chem. Eng. Data*, 2003, **48**, 457–462.

71 V. Gutmann, *The Donor–Acceptor Approach to Molecular Interactions*. Plenum, New York, 1978.

72 (*a*) T. M. Krygowski and W. R. Fawcett, *J. Am. Chem. Soc.*, 1975, **97**, 2143–2148; *Aust. J. Chem.*, 1975, **28**, 2115–2124; *Can. J. Chem.*, 1976, **54**, 3283–3292; (*b*) W. R. Fawcett, *J. Phys. Chem.*, 1993, **97**, 9540–9546; (*c*) W. R. Fawcett, *Liquids, Solutions, and Interfaces – From Classical Macroscopic Descriptions to Modern Microscopic Details*. Oxford University Press, Oxford, 2004, ch. 4.9, p. 191 ff.

73 (*a*) M. J. Kamlet, J.-L. M. Abboud and R. W. Taft, *J. Am. Chem. Soc.*, 1977, **99**, 6027–6038, 8325–8327; (*b*) J.-L. M. Abboud, M. J. Kamlet and R. W. Taft, *Prog. Phys. Org. Chem.*, 1981, **13**, 485–630; (*c*) M. J. Kamlet, J.-L. M. Abboud, M. H. Abraham and R. W. Taft, *J. Org. Chem.*, 1983, **48**, 2877–2887; (*d*) R. W. Taft, J.-L. M. Abboud, M. J. Kamlet and M. H. Abraham, *J. Solution Chem.*, 1985, **14**, 153–186.

74 C. Laurence, P. Nicolet, M. T. Dalati, J.-L. M. Abboud and R. Notario, *J. Chem. Phys.*, 1994, **98**, 5807–5816.

75 Y. Marcus, *Chem. Soc. Rev.*, 1993, **22**, 409–416.

76 (*a*) Y. Marcus, *The Properties of Solvents*. Wiley, Chichester, 1998, particularly Table 4.3 on p. 145 ff; (*b*) J.-L. M. Abboud and R. Notario, *Pure Appl. Chem.*, 1999, **71**, 645–718.

77 A. Kawai, T. Hidemori and K. Shibuya, *Chem. Lett.*, 2004, **33**, 1464–1465.

Green Chemistry in Ethiopia: the cleaner extraction of essential oils from *Artemisia afra*: a comparison of clean technology with conventional methodology†

Nigist Asfaw,*[a] Peter Licence,*[b] Alexander A. Novitskii[c] and Martyn Poliakoff[b]

Received 2nd December 2004, Accepted 4th April 2005
First published as an Advance Article on the web 18th April 2005
DOI: 10.1039/b417961g

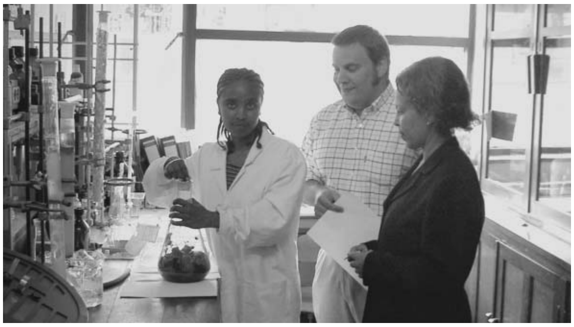
One of the principal aims of Green Chemistry is to bring the benefits of modern chemical manufacture to developing countries without imposing the environmental burden that has plagued the industrialised world. In this paper we present early results from a comparative study of greener extraction methods (microwaves, ultrasound, supercritical fluids) on *Artemisia afra*, a plant traditionally employed as a fragrance, insect repellent and as a treatment for heart troubles and coughs. We show that lower temperature extraction methods give a qualitatively larger range of extracts than traditional hydrodistillation and therefore may have some promise for use in developing countries.

Introduction

Over the past 15 years or so, Green Chemistry has matured from a series of Principles and aspirations into a more sustainable methodology that can be used in the development of new science. However, one of the key aims remains the dissemination and teaching of Green Chemistry to both developed and developing nations. This was a major goal of the IUPAC Working Party on Green Chemistry and was again highlighted in 2002 with the publication of "Green Chemistry in Africa".[1] Thus, it comes as quite a surprise to find that Green Chemistry is virtually unknown in many areas of the developing world. Although sustainable development is becoming an issue in some corporations, very few factories have tried to implement cleaner production, thus the concept of Green Chemistry is relatively new in Ethiopia. This paper describes one attempt to remedy this situation.

Ethiopia celebrates a huge diversity in natural resources, particularly endemic plants.[2,3] This richness offers tremendous opportunities for Ethiopia to pursue novel routes towards sustainability that are not possible elsewhere. The discovery of new biologically active compounds including pharmaceuticals and agrochemicals is a high priority in the modern chemicals industry. Extraction of biologically active components from plants is one of the more sustainable approaches that may be employed, since for many generations, innumerable plants have provided the raw materials for traditional remedies used in the treatment of a wide variety of ailments and medical conditions.

The extraction of essential oils and other neutraceutical components from plants is a major research focus in Ethiopia.[4] This research is often seen as a "local speciality" due to the fact that a large proportion of the flora are endemic to this region. Essential oils are complex mixtures of volatile substances obtained from aromatic plants and herbs. In general, the individual components of an oil are present in quite low concentrations and are widely dispersed throughout the bulk plant matrix. Consequently, concentrating and



Dr Nigist Asfaw was appointed Assistant Professor at Addis Ababa University in 2001 on completion of her PhD at the University of Oslo. Prior to this, she worked at the Ethiopian Spice Extraction Factory in Addis. Her research encompasses the extraction and structural elucidation of natural products and essential oils from plant species endemic to Ethiopia. Nigist is a Member of the Royal Society of Chemistry.

Dr Pete Licence is currently a CRYSTAL Faraday Research Fellow in The Clean Technology Group at the University of Nottingham, UK. He is an organic chemist and his main research interests concern the application of alternative solvents towards the development of sustainable and environmentally benign chemistries. Pete was recently invited to become Visiting Professor at Addis Ababa University, Ethiopia.

In December 2004, Pete and Nigist jointly led The First Green Chemistry Workshop in Ethiopia. The photo shows them together with a student in the lab at Addis.

---

† This work was presented at the Green Solvents for Synthesis Meeting, held in Bruchsal, Germany, 3–6 October 2004.

*nigista@chem.aau.edu.et (Nigist Asfaw)
peter.licence@nottingham.ac.uk (Peter Licence)

extracting these components is prerequisite to any assessment of potential biological activity.

Conventionally, a range of methods including solvent extraction, expression, adsorption, steam distillation and hydrodistillation are employed in the collection of essential oils. Unfortunately, most of these methods are expensive in terms of equipment and energy consumption. Furthermore, some of the components of essential oils mixtures are known to be thermally labile and prone to chemical changes during high-temperature extraction.[5] More sustainable, lower energy, and more targeted extraction methods would improve both the efficiency and indeed the economic impact of the process.

In this paper, we report a comparative study of low-energy extraction methods (microwave, ultrasound, supercritical/liquid CO_2),[6–8] with the intention of identifying alternative, potentially greener methods of isolating essential oils from plants. The subject of our study, *Artemisia afra* (*A. afra*), a member of the genus *Artemisia*, one of the largest and most widely distributed of the daisy family (*Anthemideae Asteraceae*)[9] was chosen for the following reasons: *i*) *A. afra* is a common species widely spread throughout Ethiopia, East, Central and South Africa; *ii*) for generations, the plant has traditionally been employed as both a fragrance and to treat ailments ranging from coughs to heart troubles; and *iii*) there have been extensive studies on the extraction of essential oils from *A. afra* and they are well characterised.[4,10–12] Here we compare the effectiveness of lower energy methods of extraction with conventional hydrodistillation methods and the qualitative composition of the essential oils obtained. Future work will address the environmental impact of the methods examined.

Experimental

Plant material, preparation and reagents

The samples of *A. afra* were collected from the Bale region in Southern Ethiopia in June 2004. A voucher specimen (no. 286) of the plant material has been authenticated and deposited at the National Herbarium, Addis Ababa University. The aerial parts of *A. afra* were dried in the shade and the plant material was sealed in an envelope before transportation to the UK. All chemical reagents (Aldrich) were used without further purification. Standard grade CO_2 (Cryoservices (UK) Ltd, 99.88% purity) was used as supplied.

Extraction methods

Hydrodistillation. Hydrodistillation of finely chopped plant material (20 g) was carried out for three hours using a Clevenger apparatus. The essential oil produced was collected from the apparatus as a fragrant yellow oil. The oil was dried over anhydrous sodium sulfate before being stored under an inert atmosphere at 4 °C prior to analysis.

Microwave assisted extraction. Rehydrated, finely chopped plant material (20 g) was extracted using a CEM Discover extraction apparatus (300 W power and atmospheric pressure); the essential oil extract was recovered using a Clevenger apparatus. The recovered oil was dried over anhydrous sodium sulfate and stored under an inert atmosphere at 4 °C prior to analysis.

Ultrasound assisted extraction. A glass round bottomed flask was charged with finely chopped plant material (10 g) and diethyl ether (to cover the plant material); the flask was fitted with a Liebig condenser (reflux) and was immersed in an ultrasonic cleaning bath (Ultrawave Ltd, 30 kHz). The contents of the flask were sonicated for 15, 30, 45, and 60 min intervals. Analysis of the extract solution by GC-FID revealed that 30 min was the optimum duration with minimal improvement after this time. Essential oils were recovered from solution after drying over anhydrous sodium sulfate, filtration and careful removal of solvent. The concentrated oil was stored under an inert atmosphere at 4 °C prior to analysis.

These experiments were repeated using water as the sonicating medium; however recovery of the essential oils from the tepid water was problematic.

CO_2 assisted extraction. This was conducted using a laboratory assembled extractor. Extractions of the dry plant material (20 g) were carried out dynamically using both liquid (lCO_2) and supercritical CO_2 ($scCO_2$); oils were recovered after a single stage decompression of the CO_2. Essential oils and volatile materials were carefully trapped in a cooled receiver before venting the expanded CO_2. Extracts were stored under an inert atmosphere at 4 °C prior to analysis.

Chromatographic analysis

All oil samples were analysed, by GC-FID and GC-MS. GC-FID was carried out using a Shimadzu GC-2010, fitted with a DB-5 (10 m × 0.1 mm, 0.1 μm film thickness) fused silica column. Oven temperature programming: 60 °C (5 min), 60–240 °C (5 °C min^{-1}), and 240 °C (10 min). Helium was used as carrier gas at a flow rate of 9.6 mL min^{-1}, sample injection (1.0 μL) was carried out with a split ratio of 50 : 1 at a temperature of 210 °C, the FID temperature was 260 °C. Retention indices (Kováts)[13] were determined for the major components by comparison of retention times, on a DB-5 column, with those of a homologous series of *n*-alkanes. GC-MS analyses were carried out using a Thermo Finnigan Polaris-Q GC-MS. A DB-5 column (30 m × 0.25 mm, 0.25 μm film thickness) fused silica column was used with oven temperature programming: 40 °C (1 min), 40–220 °C (10 °C min^{-1}), and 220 °C (6 min). Helium was used as carrier gas at a flow rate of 1 ml min^{-1}. Splitless sample injection (0.1 μL) was carried out at a temperature of 210 °C. Structural assignment was confirmed by computerized matching of the acquired mass spectra with library spectra.

Results

In general, the oils obtained from each experiment were very similar in appearance, pale coloured and fragranced. As expected, the composition of the extract was quite complicated with many components resolved using GC-FID, however, the profile was found to be very similar to that previously determined for a sample of the same genus.[4] A typical GC-FID trace of a hydrodistilled oil is shown in Fig. 1.

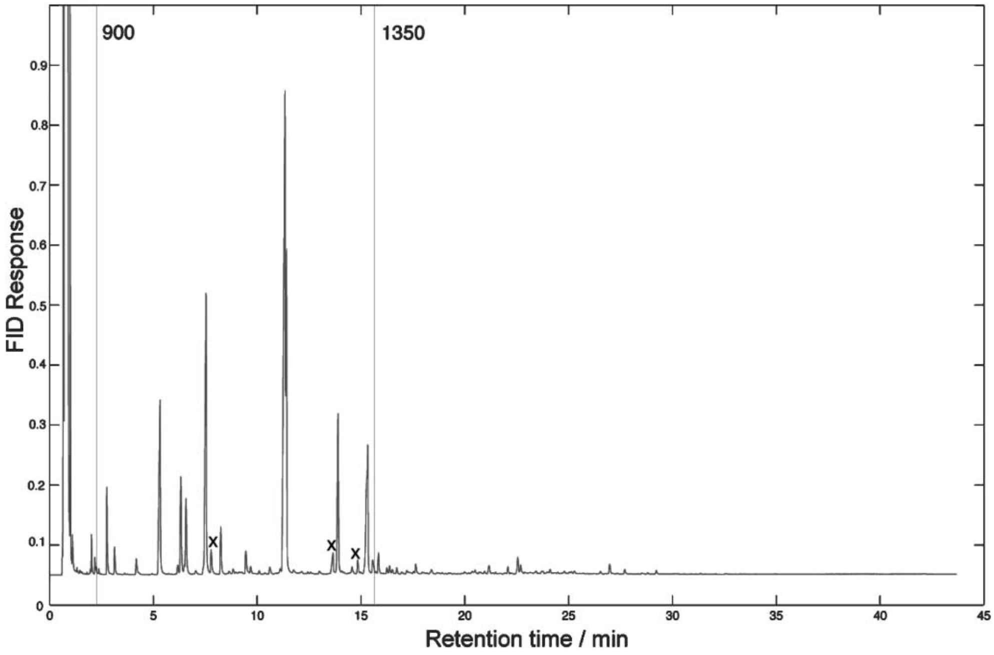


Fig. 1 Typical GC-FID trace of the essential oil of *A. afra* obtained by hydrodistillation. The components listed in Table 1 correspond to the peaks shown between the grey lines indicating the range of experimentally determined Kováts indices,[13] from 900 to 1350. The components giving rise to the peaks labelled X remain unidentified.

The profile of the materials observed in the sample is similar to many odoriferous essential oils that are generally composed of low molecular weight monoterpenes (see Fig. 2) and oxygenated derivatives including alcohols and esters including acetates, see also Fig. 3.

Microwave assisted extraction cannot be employed on dried plant materials because the evaporation of volatiles is promoted by water from within the substrate matrix. Thus rehydration was carried out by soaking the material in water for an hour followed by draining of excess water before extraction. Extracted essential oils were collected using a standard Clevenger apparatus; the extracts were carefully dried with a minimal amount of anhydrous sodium sulfate before analysis. The volume of oil extracted was measured at regular time periods throughout the extraction (10, 30, 60 min), but there was no significant increase in the volume of the oil after 10 min. The yield of oils obtained was determined as 1.3% (v/w), compared to 1.5% (v/w) after 3 hours traditional hydrodistillation. The advantage of the microwave method is rapidity; it took only 2 min to obtain the first droplet of essential oil, compared to 25 mins for hydrodistillation. The composition of the oil after 10 min was also found to be comparable to that of hydrodistilled oils, see Table 1.

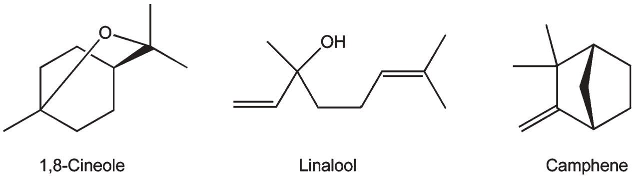


Fig. 2 Selected structures of some of the components positively identified in the essential oils extracted from *A. afra*, see also Fig. 3.

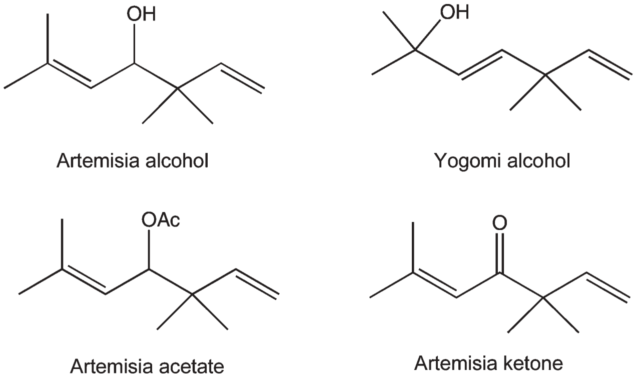


Fig. 3 Structures of key oxygenated components positively identified in the essential oils extracted from *A. afra*.

After 10 min of microwave extraction, the major oxygenated components of the oil, Artemisia acetate and Artemisia alcohol, were present in 25.6 and 14.7%, respectively. The relative amounts of these two components in the hydrodistilled oil were 26.8 and 9.9% respectively. Interestingly, the concentration of yogomi alcohol in the hydrodistilled oil is more than twice that found in the microwave extracted oil, 8.1 and 3.6% respectively, see Table 1. We tentatively attribute the decrease in relative concentration of Artemisia alcohol and apparent increase in that of yogomi alcohol to thermal rearrangement in hydrodistilled oils.

Thermal rearrangement is an ever-present factor in the extraction of thermally labile components; suppression of rearrangements of this class allows the true composition of the native oil to be determined. Hydrodistillation is generally carried out over prolonged periods of time; microwave extraction is a very rapid procedure that reduces the time that

Table 1 Components giving rise to the more obvious peaks in the GC-FID analysis, the structure of all entries was confirmed by GC-MS fragmentation and comparison with a mass spectral library (NIST)

		Relative peak areas (%)				
I_k[a]	Compound	$scCO_2$[b]	lCO_2[c]	Sonic[d]	µ-wave[e]	HD[f]
903	Santolina triene	0.6	0.6	1.7	2.3	2.1
917	α-Pinene	—	—	–	0.4	0.8
956	Camphene	0.6	0.6	0.5	0.9	0.6
999	Yogomi alcohol	0.4	0.4	0.1	3.6	8.1
1027	Limonene	2.6	4.1	2.5	4.8	3.6
1033	1,8-Cineole	2.2	1.4	1.6	3.0	2.9
1061	Artemisia ketone	6.8	9.9	7.1	13.3	12.4
1080	Linalool	0.3	0.3	0.2	0.8	1.7
1116	*p*-Menthatriene	2.4	2.5	1.8	1.4	1.0
1172	Artemisia acetate	22.4	17.4	12.7	25.6	26.8
1174	Artemisia alcohol	11.3	14.5	11.4	14.7	9.9
1255	Geraniol	4.5	5.5	2.9	6.2	6.2
1305	Bornyl acetate	3.6	2.2	2.5	4.1	8.2
	8 Sesquiterpenes	13	16	29	—	—

[a] Experimentally determined Kováts indices on the DB-5 column.[13] [b] $scCO_2$: extraction carried out for 20 min at 50 °C, 100 bar. Liquid CO_2 (at −10 °C) was delivered to the extractor vessel at a constant flow rate of 5 mL min^{-1}. [c] lCO_2: extraction carried out for 20 min at 30 °C, 100 bar; liquid CO_2 (at −10 °C) was delivered to the extractor vessel at a constant flow rate of 5 mL min^{-1}. [d] Ultrasonic irradiation for 30 min, in diethyl ether at ambient temperature and pressure. [e] Microwave irradiation for 10 min, at ambient pressure. [f] Hydrodistillation for 180 min.

the distillates are at high temperature thereby reducing the amount of rearranged product collected. This is supported by the data obtained from other lower-temperature extraction methods that were investigated. In the case of essential oils that were recovered after ultrasound or CO_2 assisted extraction, the composition of yogomi alcohol was determined to be 0.1 and 0.4% respectively, see Table 1.

In the cases of ultrasound assisted extractions, plant material was sonicated in ether at ambient temperature for 15, 30, 45, and 60 min intervals. Minimal qualitative improvement was observed in the extracts recovered after 30 min, Fig. 4. The yield of oils was notably lower, 0.7% (v/w), this could be attributed to inefficient washing of the sample after irradiation or indeed incomplete cellular lysis. Analysis of the composition of the essential oil by GC indicated the presence of 8 additional sesquiterpenes amounting to 29% of the total extract (by relative % peak areas). These sesquiterpenes were not detected in the essential oils obtained by either hydrodistillation or microwave assisted extraction.

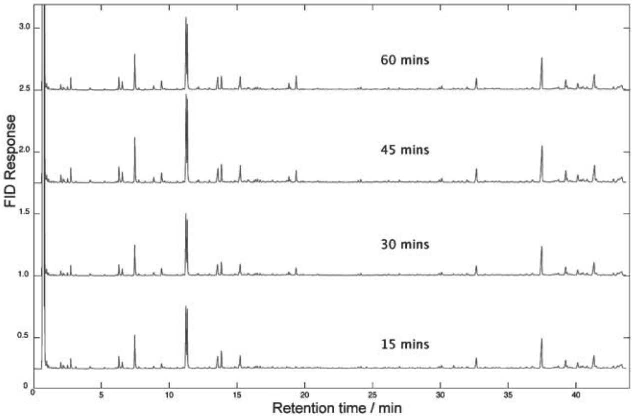


Fig. 4 Comparative GC-FID traces of ultrasound assisted extraction of *A. afra*, each trace was recorded after the annotated time period, minimal qualitative improvement is observed after 30 min. Note that all analytical samples were prepared identically (in total organic content) and the traces have been normalised with respect to the large solvent peak on the extreme left of the chromatograms.

The application of ultrasound irradiation facilitated the low-temperature rupturing of plant cell membranes, thereby liberating the volatile components from the cellular structures. Once liberated, these components were readily extracted using solvents. Attempts to replace organic solvents with water are on-going. Initial attempts although promising, were problematic simply because the volatiles are not particularly soluble in tepid water.

Utilisation of compressed CO_2 is quite widespread in the extraction of many types of plant materials including coffee beans on a bulk scale. To complete our study, we carried out a series of extractions of *A. afra* using both liquid and supercritical CO_2. The GC profile of the oils obtained by these methods was similar to that obtained by ultrasound assisted extractions, *i.e.* higher molecular weight sesquiterpenes were also observed. The differences between extractions carried out under either liquid or supercritical conditions were minimal with all components being efficiently extracted with liquid CO_2. Recovery of oils was very good when compared to the other methods investigated, 3.2% (v/w); however efficient trapping of volatile components was required to prevent "blow out" and subsequent yield reduction.

Conclusions

Fig. 5 shows comparative GC-FID traces for the 3 methods investigated compared to conventional hydrodistillation.

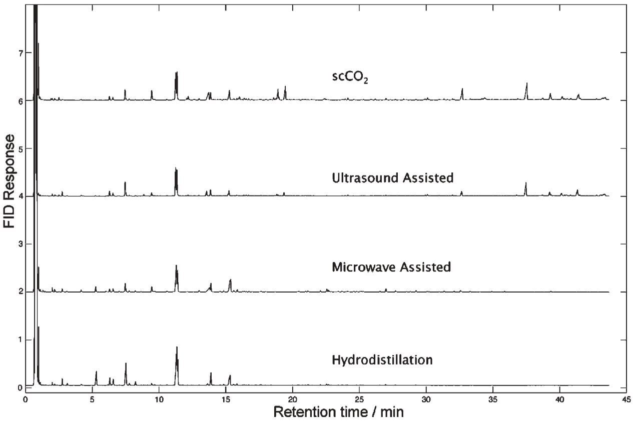


Fig. 5 Comparative GC-FID analyses for extracts recovered using different techniques, traces have been normalised as in Fig. 4. Note that unlike the chromatograms in Fig. 4, there are significant qualitative differences between these traces. In particular the additional peaks at longer retention time in both the CO_2 and ultrasound assisted extractions. These peaks correspond to higher molecular weight sesquiterpenes that are not obtained in oils from either microwave assisted extraction or hydrodistillation.

Although extraction methods have previously been compared for other plant materials,[6,7] this is the first time that such a comparison has been made for *A. afra*. It is clear that both ultrasound and CO_2 assisted methods extracted extra components that are not volatile enough to be extracted by the other techniques. This observation could turn out to be extremely important since some biologically interesting materials may be identified in this higher molecular weight fraction.

It is, of course too early to make a definite recommendation of which method will be "greenest". However, our work indicates that microwave assisted extraction is by far the most rapid and is ideally suited to solvent-free screening of plant materials. As a result, microwave apparatus is to be set up in Addis Ababa University in the near future. Careful examination of Fig. 5 also raises the interesting possibility of combining extraction methods to achieve a modest separation of the components. For instance, microwave methods do not lead to the removal of higher molecular weight sesquiterpenes that are readily extracted by either supercritical or liquid CO_2. Combination of these two methodologies in tandem should, in principle, achieve a rapid and useful fractionation of the oil. Work is in progress to establish whether this would be a feasible strategy in practice.‡

Acknowledgements

We thank our colleagues in the Clean Technology Group at The University of Nottingham, in particular Messrs M. Guyler, M. Dellar, P. Fields. R. Wilson and D. Litchfield of the Chemistry Workshops for their invaluable technical assistance. We are grateful to Ermias Lulekal and Haile Yineger for collecting the samples of *A. afra* and to Professor Sebsebe Demissew for identification and authentication of the plant material. We are grateful to Dr C. J. Hayes for the loan of microwave apparatus and to Drs J. R. Hyde, S. L. Y. Tang and Miss E. Roberts for helpful discussions. We thank The Royal Society, The CRYSTAL Faraday Partnership and the EPSRC (Grant Nos. GR/R06205 and GR/S25227) for financial support.

Nigist Asfaw,*[a] Peter Licence,*[b] Alexander A. Novitskii[c] and Martyn Poliakoff[b]
[a]*Chemistry Department, Science Faculty, Addis Ababa University, P. O. Box 1176, Addis Ababa, Ethiopia.*
E-mail: nigista@chem.aau.edu.et; Fax: + 251 155 0655;
Tel: + 251 155 0844
[b]*School of Chemistry, The University of Nottingham, University Park, Nottingham, UK NG7 2RD. E-mail: peter.licence@nottingham.ac.uk;*
Fax: +44 115 951 3058; Tel: +44 115 951 3386
[c]*Chemistry Department, Moscow State University, Vorobjovy Gory, Moscow, 119899, Russia. Fax: +7 095 939 0067; Tel: +7 095 939 3571*

References

1 *Green Chemistry In Africa*, ed. P. Tundo and L. Mammino, INCA, Venice, Italy, 2002.
2 I. Friis, S. Edwards, E. Kelbessa and S. Demissew, *Diversity and Endemism in the Flora of Ethiopia and Eritrea—What do the published Flora volumes tell us*, in *Biodiversity Research in the Horn of Africa Region*, ed. I. Friis and O. Ryding, C.A. Reitzes Forlag, Copenhagen, 2001, 173–193.
3 S. Demissew, I. Nordal and O. E. Stabbetorp, *Flowers of Ethiopia and Eritrea, Aloes and other Lillies*, Shama Books, Addis Ababa, Ethiopia, 2004.
4 http://www.ics.trieste.it/essentialoils/EssentialOils.aspx, September 2004.
5 N. Asfaw, H. J. Storesund, L. Skattebøl and A. J. Aasen, *Phytochemistry*, 2001, **58**, 489–492.
6 E. E. Stashenko, B. E. Jaramillo and J. R. Martinez, *J. Chromatogr., A*, 2004, **1025**, 93–103.
7 C. D. Kanakis, D. J. Daferera, P. A. Tarantilis and M. G. Polissiou, *J. Agric. Food Chem.*, 2004, **52**, 4515–4521.
8 F. Gaspar, *Ind. Eng. Chem. Res.*, 2002, **41**, 2497–2503.
9 M. D. Esteban, I. G. Collado, F. A. Macias, G. M. Massanet and F. R. Luis, *Phytochemistry*, 1986, **25**, 1502–1504.
10 E. H. Graven, L. Webber, M. Venter and J. B. Gardner, *J. Essent. Oil Res.*, 1990, **2**, 215–220.
11 B. M. Lawrence, Artemisia afra oil, in Progress in Essential Oils, *Perfum. Flavor.*, 1984, **9**, 56.
12 Tadele Worku and P. Rubiolo, *J. Essent. Oil Res.*, 1996, **7**, 355–357.
13 E. Kováts, *Helv. Chim. Acta*, 1958, **41**, 1915–1932.

---

‡ **Safety note**: *some of the experiments described in this paper involve the use of relatively high pressures and require equipment with the appropriate pressure rating. It is the responsibility of individual researchers to verify that their particular apparatus meets the necessary safety requirements.*

Continuous hydrogenation reactions in supercritical CO_2 "without gases"†

Jason R. Hyde,*[a] Ben Walsh,[a] Jasbir Singh[b] and Martyn Poliakoff*[a]

Received 24th December 2004, Accepted 30th March 2005
First published as an Advance Article on the web 18th April 2005
DOI: 10.1039/b419276a

Continuous fixed-bed hydrogenation reactions are one of the most promising reactions studied under supercritical conditions. A reactor and supporting equipment has been developed in a collaboration between the University of Nottingham and HEL Ltd. to provide the means for small-scale experimental research. The high pressure gases required to achieve the supercritical state are not supplied by bottled or liquefied gases, but by the *in situ* decomposition of formic acid, HCO_2H, which can be selectively decomposed to produce CO_2 and H_2. These gases can be used directly as both the supercritical solvent and reagent gases. Further control of the H_2 concentration can be achieved by the parallel decomposition of other liquid precursors, namely ethyl formate HCO_2Et, which can produce $C_2H_6 + CO_2$. We report the hydrogenation of several organic substrates to demonstrate this approach, its application in research and its potential as a development tool.

Introduction

Supercritical carbon dioxide, $scCO_2$, has been shown to be a viable alternative to conventional organic solvents in many reactions.[1–3] The demonstration of several areas of important chemistry in $scCO_2$ has led to significant interest from both academia and industry.[4] An issue in developing this technology is the use of the specialist high pressure equipment, which is usually unavailable to the non-specialist chemist. Indeed the lack of bench-scale equipment has been identified as a generic barrier to the implementation of new Green Chemistry technologies.[5] At Nottingham, we have developed a new approach, which decomposes liquid reagents, namely HCO_2H and HCO_2Et, to form a supercritical fluid mixture without the requirement for specialist compressors and high pressure gas cylinders.[6] This technology could encourage the use of $scCO_2$ in hydrogenation reactions usually performed in ordinary organic solvents by synthetic laboratories.

Hydrogenation reactions have been extensively studied in $scCO_2$. The total miscibility of supercritical media with permanent gases and a wide range of organic molecules reduces the mass transport limitations which are encountered when hydrogenations are performed using conventional organic solvents.[7,8] Hydrogenation reactions do not necessarily require a solvent; however the SCF acts as a solvent under these conditions, removing any generated heat and transporting both the substrate and H_2 to the catalyst. There is also significant interest in a combination of micro-reactor technology[9] and SCFs; our gasless method of gas dosing may allow this to be realised, as the mass flow of H_2 can be accurately controlled.

The purpose of this paper is to show that SCF hydrogenation can be carried out on a very small-scale by incorporation of a 'gasless' H_2 generator into our recently described automated reactor.[10] We use the hydrogenation of several alkenes, ketones and aldehydes to illustrate the use of this hybrid reactor rather than to convey the ultimate possibilities of SCF hydrogenation.

Results and discussion

Decomposition of HCO_2H

The decomposition of HCO_2H has previously been shown to be viable as the source of molecular H_2 for supercritical hydrogenation reactions.[6] HCO_2H can decompose by two different mechanisms, thermal which produces a mixture of $CO + H_2O$, and catalytic decomposition[11] which produces $CO_2 + H_2$. It is essential to minimise the thermal decomposition as to avoid the formation of CO, which can poison noble metal

Jason Hyde gained his degree in Chemistry in 1996 from the University of Wales, Bangor, after which he studied for his PhD in Electrocatalysis, under the supervision of Maher Kalaji and Peter Holiman. Jason moved to the School of Chemistry's Clean Technology Group at the University of Nottingham in November 1999, as a post-doctoral involved in the development of both the "Gasless Technology" in collaboration with HEL Ltd. and the "Automated" apparatus, as well as projects related to the fine chemical producer, Thomas Swan & Co. Ltd. His current research interests include, reactions in supercritical fluids and novel chromatographic techniques, most recently, the application of the generalised correlation function to GC data.

---

† This work was presented at the Green Solvents for Synthesis Meeting, held in Bruchsal, Germany, 3–6 October 2004.

*Martyn.poliakoff@Nottingham.ac.uk (Martyn Poliakoff)

catalysts. We achieve this by utilising a combination of two techniques. Firstly, HCO_2H is delivered cold to the decomposition catalyst; this reduces the probability of HCO_2H decomposing thermally prior to meeting the catalytic bed. Secondly, the catalytic bed is heated to a high temperature; this increases the rate of decomposition, and also leads preferentially to $H_2 + CO_2$. The addition of small amounts of H_2O to the HCO_2H also holds an advantage in that any CO produced by the thermal decomposition is removed by the reverse water gas shift reaction. The levels of CO can be minimised by manipulation of the temperatures, pressures and residence time, by changing the appropriate flow rates of HCO_2H. To demonstrate this, HCO_2H was decomposed and the product gases were injected into a μ-GC (Varian 4900), capable of detecting CO, CO_2 and H_2.

The decomposition of HCO_2H was monitored for a continuous period of 72 hours. Fig. 1 shows the composition of gases which does not change markedly during this time. Initially, a small quantity of CH_4 (<2% not shown), was generated by the hydrogenation of CO; this, however, decreases over time, showing that the activity of the decomposition catalyst does decrease slightly but the levels of CO_2, and hence H_2, were unaffected. This example does show that the "without gases" reactor is capable of performing for nine continuous 8-hour working days without changing catalyst. In fact, we have run many of the examples presented in this paper with the same sample of decomposition catalyst that was used for over 2 weeks.

Hydrogenation of alkene/alkyne moieties

We have previously reported briefly the hydrogenation of several simple alkenes.[6] The hydrogenation of 1-octene and cyclohexene are striking, both are hydrogenated quantitatively at 80 °C and 100 bar, using HCO_2H as the source of both H_2 and CO_2. These hydrogenation reactions are highly exothermic; in fact, we have found that the hydrogenation of cyclohexene can be used to preheat the catalyst bed to temperatures sufficient to initiate other hydrogenation reactions. If left uncontrolled, the reactions can often lead to hotspots within the reactor. Nevertheless, even using the "without gases" approach, conversions and selectivities are comparable to those found in conventional supercritical reactors.[12,13]

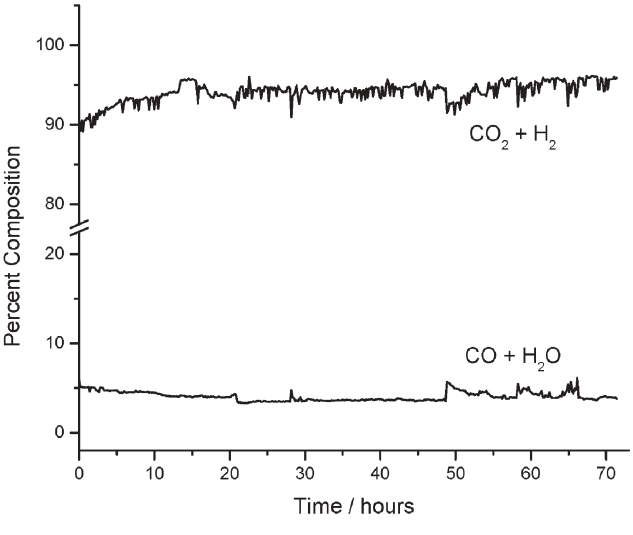


Fig. 1 Graph illustrating the make-up of gases from a single decomposition catalyst bed, 2% Pd/SiO_2, over a period of 72 hours. μ-GC samples were taken every minute. CH_4 was detected during the first 5 hours at levels approaching 1–2%. As it can be seen, there is little change in activity over the entire time frame.

The control of the H_2 concentration is the key to hydrogenation reactions in $scCO_2$.[12,14] We have adopted a similar methodology for the "without gases" equipment to provide this control. The decomposition of ethyl formate, HCO_2Et, leads to the decomposition products, C_2H_6 and CO_2; the critical temperature of C_2H_6 is similar to CO_2, thus by decomposing the two liquid precursors in parallel, a mixture of $C_2H_6 + CO_2$ can be produced, with a controllable amount of H_2, Fig. 2.

The key advantage of this method is that both precursors are liquid, and so control over concentrations and volumetric flow rates of gases is achieved by controlling the volumetric flow rates of liquids prior to decomposition. To demonstrate the tunable nature of HCO_2H/HCO_2Et mixtures, we have reported previously the hydrogenation of 1-octyne.[6] By varying the ratio of precursor feed flow rates, it is possible to dilute the H_2 in the SCF solvent, and alter the conversion of the reduction of 1-octyne to octane. Of course, because this reduction is facile, there was no partial reduction to 1-octene, which could be achieved with a suitable choice of catalyst, *e.g.* Lindlar.[15]

In this paper we concentrate on systematic studies of HCO_2H as a source of H_2 in conjunction with a highly automated reactor.[10] As far as we are aware, this is the first time that SCF hydrogenation reactors have been automated on such a small-scale. This has been possible because of the "without gases" approach to dosage of H_2. In order to remove potential complications of phase separation, these reactions were carried out with pure CO_2 rather than CO_2/C_2H_6. As CO_2 is liquefiable, a HPLC pump can be used for this application and can still deliver the slow flow rates required. However, HCO_2H is still required for the source of molecular H_2, since H_2 is a permanent gas and cannot be delivered at such slow rates under pressure.

There have been previous reports[16] of the hydrogenation of styrene in $scCO_2$ and indeed we have investigated this reaction several times, utilising different catalysts. Here, the reaction is performed using a polymer supported Pd catalyst, Deloxan®.

Fig. 3 shows the effect of raising the catalyst bed temperature whilst the concentration of H_2 remains at a constant 2 : 1 (*i.e.* 2-fold excess of H_2). Nearly complete reduction of styrene to ethyl benzene was observed at temperatures approaching 350 °C. Unlike auto-thermal hydrogenation reactions, where the yield of the hydrogenated product changes from 0 to approximately 90%

Fig. 2 The key principle of the "without gases" approach to SCF hydrogenation. Changing the flow ratio of HCO_2H and HCO_2Et changes the concentration of H_2 in the SCF.

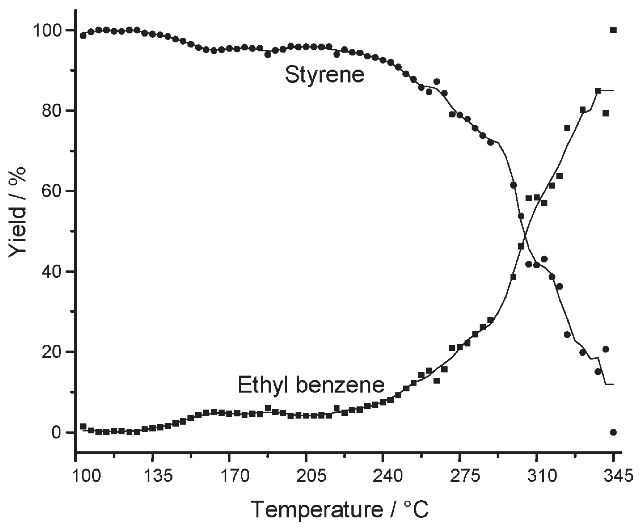


Fig. 3 A plot of yield of ethyl benzene from the hydrogenation of styrene at 100 bar increasing the temperature from 100 to 350 °C over Deloxan II 5% Rh. Reactor: 12 mm × 7 cm; flow rates: CO_2 = 1 mL min^{-1}, HCO_2H = 0.5 mL min^{-1}, substrate = 0.1 mL min^{-1}.

within an interval of a few degrees Celsius, the yield of ethyl benzene increased steadily from 0 to 90% over a range of 70 °C. This is consistent with the hydrogenation of styrene being *less* exothermic than say hydrogenation of 1,4-vinyl-cyclohexene.[17] There was no evidence of total hydrogenation producing ethyl cyclohexane.

Hydrogenation of carbonyl moieties

Selective hydrogenation of aliphatic aldehydes and ketones to alcohols has been the subject of several studies at Nottingham. In general, the yields are much lower than those of the alkene analogues. To probe the ability of Ru metal to catalyse this reduction, the hydrogenation of nonaldehyde was attempted over 5% Ru on Deloxan, Fig. 4; the temperature of the catalyst bed was ramped from 150 to 250 °C over a period of 10 hours at 100 bar. Above 200 °C the major reaction was hydrogenolysis with only 10 to 15% of the hydrogenated product, nonane, and 5 to 10% partially hydrogenated nonanol. There were <10% lower alkanes present, probably formed from the cracking of nonaldehyde.

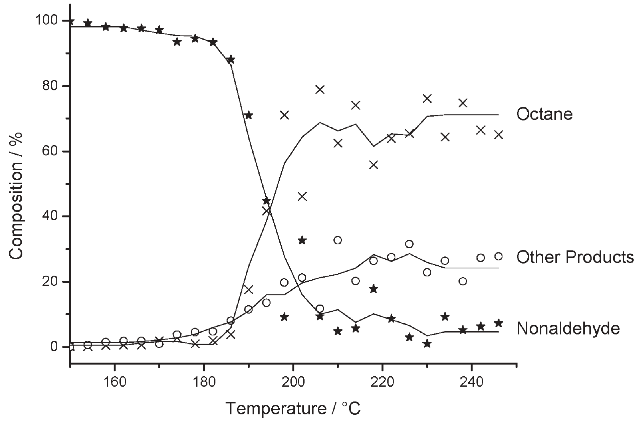


Fig. 4 Plot of the hydrogenation of nonaldehyde over 5% Ru on Deloxan at 150 bar increasing the temperature of the catalyst bed from 150 to 250 °C. Reactor: 12 mm × 7 cm; flow rates: CO_2 = 1 mL min^{-1}, HCO_2H = 0.5 mL min^{-1}, substrate = 0.1 mL min^{-1}.

The selectivity did not change at higher temperatures. This is similar to the pioneering work of Suen and Fan for the hydrogenation of heptaldehyde over a Ni catalyst,[18] where the reaction yielded hexane and heptanol; however heptane was not detected in their experiments. The result in Fig. 4 is typical of aldehyde reductions in SCFs; the loss of CO dominates the formation of the alcohol. For example Hitzler *et al.* performed several exploratory reactions, which only produced alcohols in small yields.[14]

The hydrogenation of cyclohexanone to cyclohexanol was somewhat more selective, with up to 18% yield; however the dehydrogenated product, phenol, was also detected in the "without gases" reactor. Conventionally, Cu catalysts have been used in this reaction.[19] Unfortunately, residual H_2O in the H_2/SCF mixture generated "without gases" causes leaching of Cu under these conditions. In principle, the gas mixture could be dried if such catalysts were to be used.

Hydrogenation of *trans*-cinnamaldehyde

trans-Cinnamaldehyde is commonly used as an activity/selectivity indicator due to the wide range of functional groups that can be reduced by H_2. Recently, Arai and coworkers[20] hydrogenated cinnamaldehyde in $scCO_2$ over a Pt catalyst at 50 °C. They showed that 3-phenylpropan-1-ol was formed from cinnamaldehyde *via* hydrocinnamaldehyde. At low temperatures, their hydrogenation was 80% selective for cinnamyl alcohol; however, the reaction took over 4 days to reach completion. The same group also hydrogenated cinnamaldehyde in $scCO_2$ as a batch process over Pt catalysts.[21] At 50 °C, selectivities to cinnamyl alcohol generally exceeded 90% although the total conversion was usually below 50%. The hydrogenation of cinnamaldehyde has also been performed by Chatterjee *et al.*[22] in $scCO_2$ over Ru–Pt and Pt catalysts, who achieved 100% selectivity to cinnamyl alcohol at 50 °C.

Arai's selectivity towards cinnamyl alcohol is unusual and is normally difficult to achieve when employing a Pd or Pt catalyst. We have performed the continuous hydrogenation of cinnamaldehyde with a 10 : 1 cinnamaldehyde : H_2 ratio, at 100 bar, whilst increasing the catalyst bed temperature from 180 to 280 °C, Fig. 5. We failed to observe high selectivity for the alcohol. The maximum yield obtained for hydrocinnamaldehyde was 80%. At higher temperatures, the selectivity for propyl benzene increases, with increased competition from the formation of hydrocinnamaldehyde. The yield of hydrocinnamaldehyde reached a maximum at 195 °C. Over-hydrogenation to produce propyl benzene has been observed previously in our conventional CO_2 reactors. Propyl benzene is formed by the elimination of H_2O from cinnamaldehyde under the high temperatures and over-pressure of H_2 used in this reaction. The optimum temperature for the reduction of cinnamaldehyde is 220 °C, a result which is consistent with previous findings.[23]

Quite a different selectivity profile was obtained when the catalyst bed was held at 200 °C and the *flow rate of HCO_2H*

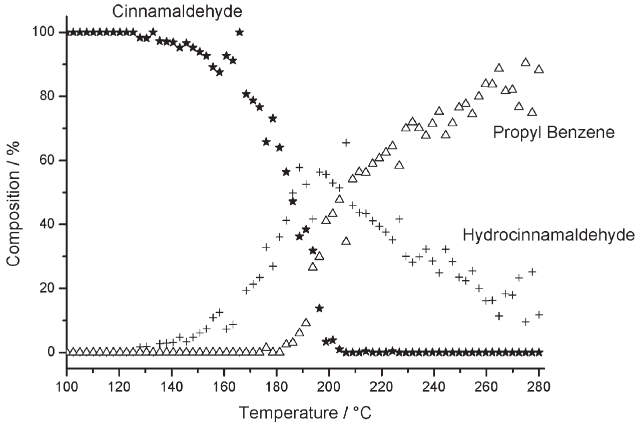


Fig. 5 Illustrating the effect of catalyst bed temperature on the hydrogenation of cinnamaldehyde over 2% Pd/SiO_2 at 100 bar, varying the temperature of the catalyst bed from 180 to 280 °C. Reactor: 12 mm × 7 cm; flow rates: $CO_2 = 1$ mL min^{-1}, $HCO_2H = 1$ mL min^{-1}, substrate = 0.1 mL min^{-1}.

was varied. Fig. 6 shows the results from the hydrogenation of cinnamaldehyde over 2% Pd/SiO_2 at 225 °C and 100 bar whilst varying the flow of HCO_2H from 0.01 to 0.5 mL min^{-1}; this equates to varying the H_2 : cinnamaldehyde ratio from 0.1 : 1 to 5 : 1.

As can be seen in Fig. 6, ethyl benzene was detected at low H_2 concentrations (or slow HCO_2H flow rates). Increasing the H_2 concentration reduced conversion to ethyl benzene, favouring instead conversion to the desired product, hydrocinnamaldehyde. As the flow of HCO_2H was further increased, the yield of hydrocinnamaldehyde reached a maximum with near quantitative conversion at 0.25 mL min^{-1} of HCO_2H. Increasing the H_2 concentration in the system further, suddenly switched the product from hydrocinnamaldehyde to propyl benzene.

It is clear that the sudden change in product from hydrocinnamaldehyde at low H_2 concentrations, to propyl benzene at higher H_2 concentrations, occurs at 0.3 mL min^{-1} of HCO_2H; this is equivalent to a 3 : 1 molar excess of H_2. Three molar equivalents of H_2 are required to hydrogenate cinnamaldehyde to propyl benzene. Therefore, this sudden switch in selectivity appears to be related to the molar ratio of H_2 available for the reaction to proceed. At the highest H_2 concentrations, only propyl benzene and cinnamaldehyde were detected. This suggests that the hydrogenation reaction, to form propyl benzene, may be starving the system of H_2, thus increasing the quantity of starting material in the output stream. The hydrogenation reaction is also likely to be highly exothermic, and this starvation effect may be caused by the formation of catalyst hot-spots. These hot-spots may be responsible for driving the over-hydrogenation.

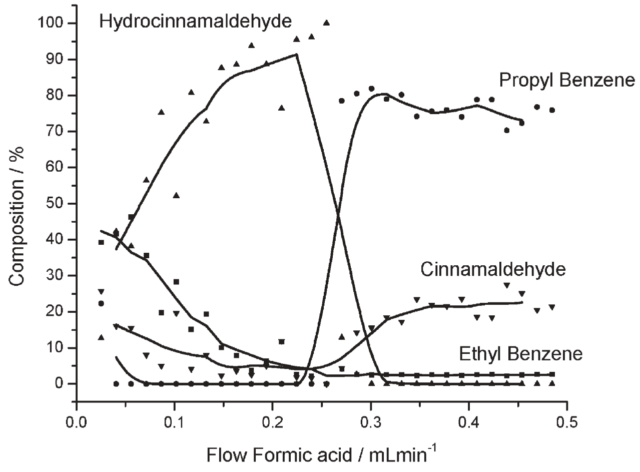


Fig. 6 The effect of HCO_2H flow rate, and hence concentration of H_2 on the hydrogenation of cinnamaldehyde over 2% Pd/SiO_2 at 225 °C and 100 bar. Reactor: 12 mm × 7 cm. Flow rates: $CO_2 = 1$ mL min^{-1}, substrate = 0.1 mL min^{-1}.

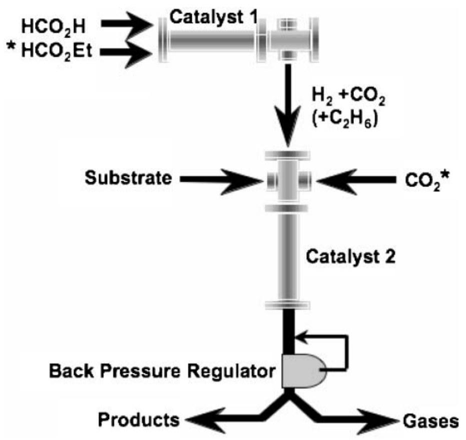
Conclusions

We have demonstrated that the "without gases" approach to SCF chemistry is versatile and provides a convenient methodology to anyone who wishes to experiment with SCFs. The hydrogenation reactions described here can be controlled by either modifying the flow rates of materials, by addition of ethyl formate or other decomposable substrates, or by direct addition of $H_2 + CO_2$ into a more conventional SCF reactor. The results have proved to be both reproducible and consistent with literature values, which validates the methodology. The formation of small quantities of CO in the effluent gases does not appear to affect the activity of the catalyst markedly; uncontrolled, however, the concentration of CO could rise to levels that may be detrimental to the catalytic performance. Most of the reactions here involve only CO_2. We believe that the use of C_2H_6/CO_2 mixtures from decomposition of HCO_2Et will make relatively little difference in most cases. This is because, although scC_2H_6 is a poorer solvent than $scCO_2$, most hydrogenation mixtures are biphasic and therefore solvent power is not an overriding factor.

As described at the Bruchsal conference, HEL Ltd. is engineering a commercial version of the "without gases" reactor, which incorporates the technology described above in a self-contained reactor module with 3 high-pressure pumps, for delivering HCO_2H, HCO_2Et and organic substrate respectively, pressure control and an integral computer. This apparatus probably represents the smallest automated continuous supercritical reaction system currently on the market.

Experimental

All equipment was constructed from 318-SS (SwageLok®) with HPLC pumps (Gilson 802) and a back pressure regulator (Jasco 880), assembled as outlined in Scheme 1. HCO_2H (90%, Aldrich) and HCO_2Et (99.9%, Aldrich) and organic substrates were used as supplied. Pt 5% (7–10 g, reactor 1) was heated to 450 °C. The flow of HCO_2H and HCO_2Et was then started until system pressure was reached. Organic substrates were introduced *ca.* 30 min after the system pressure had stabilised. Samples were collected directly and injected into a GLC (DB5, 30 m, 0.25 μm, various oven temperature profiles). In some cases, where outlined in the text, a separate CO_2 (Jasco PU-1580-CO_2) HPLC pump was used to dilute the H_2 and



Scheme 1 Schematic diagram of the experimental set-up. Ethyl formate, HCO_2Et and formic acid, HCO_2H, are pumped into the same catalyst bed *via* separate HPLC pumps. Fluid feeds marked with an asterisk, *, are interchangeable and are not used at the same time. Substrates are introduced to the reactor stream *via* a HPLC pump. Products were collected directly downstream from the back pressure regulator.

maintain a constant flow rate. Full experimental details of the automated apparatus can be found elsewhere.[10]

Acknowledgements

We thank HEL Ltd., Thomas Swan & Co. Ltd. and the EPSRC (GR/R41644) for funding and support. We also thank Messers M. Guyler, P. Fields, and R. Wilson and Drs S. K. Ross, F. R. Smail and P. Licence for their help and advice.

Jason R. Hyde,*[a] Ben Walsh,[a] Jasbir Singh[b] and Martyn Poliakoff*[a]
[a]*School of Chemistry, University of Nottingham, University Park, Nottingham, UK NG7 2RD.*
E-mail: Martyn.poliakoff@Nottingham.ac.uk
[b]*HEL Ltd., 50 Moxon Street, Barnet, Herts, UK EN5 5TS*

References

1 A. Baiker, *Chem. Rev.*, 1999, **99**, 453.
2 J. R. Hyde, P. Licence, D. N. Carter and M. Poliakoff, *Appl. Catal., A: Gen.*, 2001, **222**, 119–131.
3 E. J. Beckman, *J. Supercrit. Fluids*, 2004, **28**, 121–191.
4 P. Licence, J. Ke, M. Sokolova, S. K. Ross and M. Poliakoff, *Green Chem.*, 2003, **5**, 99–104.
5 *Facilitating the uptake of Green Chemical Technologies*, The Crystal Faraday Partnership, CookPrior Ltd., London, 2004.
6 J. R. Hyde and M. Poliakoff, *Chem. Commun.*, 2004, 1482–1483.
7 *Chemical Synthesis Using Supercritical Fluids*, ed. P. G. Jessop and W. Leitner, Wiley-VCH, Weinheim, 1999.
8 S. van den Hark and M. Härröd, *Appl. Catal., A: Gen.*, 2001, **210**, 207–215.
9 W. Ehrfeld, V. Hessel and H. Loewe, *Microreactors: New Technology for Modern Chemistry*, Wiley-VCH, Weinheim, 2000.
10 B. Walsh, J. R. Hyde, P. Licence and M. Poliakoff, *Green Chem.*, 2005, **7**, DOI: 10.1039/b413890b.
11 J. S. Francisco, *J. Chem. Phys.*, 1992, **96**, 1167–1175.
12 M. G. Hitzler and M. Poliakoff, *Chem. Commun.*, 1997, 1667–1668.
13 V. Arunajatesan, B. Subramaniam, K. W. Hutchenson and F. E. Herkes, *Chem. Eng. Sci.*, 2001, **56**, 1363–1369.
14 M. G. Hitzler, F. R. Smail, S. K. Ross and M. Poliakoff, *Org. Process Res. Dev.*, 1998, **2**, 137–146.
15 G. C. Bond, *Catalysis by Metals*, Academic Press, London, 1962.
16 H. S. Phiong, F. P. Lucien and A. A. Adesina, *J. Supercrit. Fluids*, 2003, **25**, 155–164.
17 J. R. Hyde, B. Walsh and M. Poliakoff, in preparation, 2005.
18 T. J. Suen and S. Fan, *J. Am. Chem. Soc.*, 1942, **64**, 1460–1462.
19 N. Ravasio, R. Psaro and F. Zaccheria, *Tetrahedron Lett.*, 2002, **43**, 3943–3945.
20 M. Shirai, T. Tanaka and M. Arai, *J. Mol. Catal. A: Chem.*, 2001, **168**, 99–103.
21 B. M. Bhanage, Y. Ikushima, M. Shirai and M. Arai, *Catal. Lett.*, 1999, **62**, 175–177.
22 M. Chatterjee, Y. Ikushima and F. Y. Zhao, *Catal. Lett.*, 2002, **82**, 141–144.
23 D. N. Carter, PhD Thesis, University of Nottingham, 2003.

Progress in evaluation of risk potential of ionic liquids—basis for an eco-design of sustainable products†

Bernd Jastorff,[a] Kerstin Mölter,[a] Peter Behrend,[a] Ulrike Bottin-Weber,[a] Juliane Filser,[a] Anna Heimers,[a] Bernd Ondruschka,[c] Johannes Ranke,*[a] Maike Schaefer,[a] Heike Schröder,[a] Annegret Stark,[c] Piotr Stepnowski,[b] Frauke Stock,[a] Reinhold Störmann,[a] Stefan Stolte,[a] Urs Welz-Biermann,[d] Susanne Ziegert[a] and Jorg Thöming[a]

Received 9th December 2004, Accepted 12th April 2005
First published as an Advance Article on the web 19th April 2005
DOI: 10.1039/b418518h

Motivated by the prevailing need for a sustainable development and taking the principles of Green Chemistry as a starting point, the present paper describes new and updated findings regarding a sustainable product design for ionic liquids. The focus is on environmental risk. Nevertheless, cytotoxicity testing and first indicative results from a genotoxicity study extend present knowledge also with regard to possible effects on humans. The structural variability of commercially available ionic liquids as well as the abundance of theoretically accessible ionic liquids is illustrated and the consequences for an integrated risk assessment accompanying the development process are discussed. The side chain effect on toxicity for imidazolium type ionic liquids was confounded by more complex biological testing. Also, an influence of an anion on cytotoxicity is shown for the first time. Testing of presumed metabolites of the imidazolium type cations showed a significantly lower biological activity in cytotoxicity studies than their parent compounds. The importance of a purity assessment for ionic liquids is pointed out and a collection of methods that is believed to be adequate is presented. In addition to risk analysis, the use of life cycle analysis for the multi-objective problem of designing ionic liquids is sketched and an eco-design scheme for ionic liquids is proposed. In conclusion, the paper illustrates the complex nature of the development processes ionic liquids are currently undergoing and provides guidance on which aspects have to be kept in mind.

Introduction

Chemistry plays a very important role in Sustainable Development as has been pointed out in chapter 19 of Agenda 21.[1] For today's chemists, designing benign industrial chemicals, products and processes is both a vision and a mission.

The principles of Green Chemistry as proposed by Anastas and Warner[2] in 1998 offer guidelines as to how chemists can direct their efforts towards more sustainability in research and development of new chemical entities and products. Principle *4* and *10* direct their design strategy.

Chemical products should be designed to preserve efficacy of function while reducing toxicity.

(4th Principle of Green Chemistry[2])

Chemical products should be designed so that at the end of their function they do not persist in the environment, and break down into innocuous degradation products.

The interdisciplinary "Project Team Ionic Liquids" at the Centre for Environmental Research and Technology (UFT) in Bremen is coordinated by Prof. Bernd Jastorff and was founded in May 2002. In several projects, technicians, PhD students, post-docs and professors from different departments (Bioorganic Chemistry, Process Integrated Waste Minimisation, General and Theoretical Ecology, Epidemiology) are working together combining the specialised knowledge of their different disciplines. Important national and international network partners are the Pomeranian Centre for Environmental Research and Technology (POMCERT) in Gdańsk (Poland) and the Merck KGaA in Darmstadt (Germany).

Project Team Ionic Liquids

---

† This work was presented at the Green Solvents for Synthesis Meeting, held in Bruchsal, Germany, 3–6 October 2004.
*jranke@uni-bremen.de

(10th Principle of Green Chemistry[2])

To fulfil these missions, chemists have to network their synthetic efforts with other disciplines, because designing safer chemicals is an inter-/transdisciplinary challenge. In development of new drugs or pesticides this collaboration is the state of the art in industry. Due to economic and traditional reasons this is currently not standard practice in the development of new industrial chemicals. Is it possible to make economic use of the design strategy and the tremendous experience gained in risk assessment of chemicals and their degradation products in pharmaceutical and pesticide development without concurrently raising the development costs to the same dimensions as in pharmaceutical industry? We are far from being able to provide an adequate answer to this question at this moment, but our transdisciplinary team is evaluating the chances offered by a work-sharing cooperation between academia, industry and small and medium enterprises (SMEs).

Ionic liquids—a model for a sustainable design of new chemical entities and products

Our model case for the development of sustainable industrial chemicals is the fascinating class of new organic solvents called "ionic liquids" (ILs). As has been pointed out by Seddon,[3] Wasserscheid and Welton,[4] Rogers and Seddon[5] and others, ILs have the potential to improve existing processes and new developments in a multitude of fields in chemistry and chemical technology.[3–5] Beside their advantages in chemical synthesis, catalysis, extraction, biotechnology, electrochemistry and other applications, they offer one very important advantage compared to classical volatile organic solvents: They possess no detectable vapour pressure and thus—provided that they are both pure and stable—do not emit volatile organic compounds. Occupational health in and technical safety of new processes are strongly improved. But does this already make them "green" or even "sustainable" chemicals?

In 2003 we discussed this question and offered a transdisciplinary strategy to assess potential risks of ionic liquid entities and design sustainable products.[6] In short, we proposed the following tools:

- interdisciplinary theoretical and work-sharing experimental collaboration
- selection of lead chemicals according to the "testkit concept"
- (eco)toxicological test battery on different levels of complexity
- assessment of the molecular interaction potential, shape and conformational flexibility, chemical and biochemical reactivity of a chemical entity from a systematic algorithm
- evaluation of qualitative and quantitative structure–activity relations (T-SAR[7,8]/QSAR)
- theoretical assessment of presumable transformation products due to metabolic reactions based on T-SAR
- multidimensional risk analysis (release, spatiotemporal range, bioaccumulation, biological activity and uncertainty)[9]

This strategy is directed at the design of products with high process efficiency, acceptable costs and low toxic potential for man and the environment.

We are aware that these objectives are idealistic ones, which will often produce dilemmas and conflicts of objectives. But one should keep in mind that the main paradigm change in thinking and acting introduced by Agenda 21 is indeed not to fight for either economical, social or ecological needs, but to commonly search for an acceptable compromise. Successful pursuance of this aim requires the development of close partnerships between different R&D institutions and industrial stakeholders within the areas of production and application to allow for a fruitful discussion about design parameters and product profiles.

Fig. 1 shows the interrelations between the objectives of sustainable product design and the aspects of structural elements of chemicals to be optimised within a design process.[6]

Collaboration between academia and industry

Green chemicals may be designed in academia alone, but development of sustainable industrial products and processes need the experience and input of chemical industry. Therefore our academic team and Merck KGaA, New Business Chemicals, Darmstadt, Germany, joined into a strategic partnership. The work-shared objectives are i) assessing (eco)toxicological hazards of ionic liquid entities, ii) developing a toolbox of structural elements of ionic liquids which can be used in order to reduce the hazard potential for man and the environment, (iii) fine tuning of chemical structures of ionic liquids tailormade for defined technological applications at an acceptable cost–benefit ratio. Lead chemicals to assess the (eco)toxicological data as defined according to the T-SAR guided testkit concept[6] will be synthesized by the industrial partner, risk relevant data will be measured by the UFT team and the industrial partner depending on the special expertise existing in either institution. While technological needs will be defined by customers of Merck KGaA, technical solutions will be developed in a joint effort.

Compared to the suggestions published earlier[6] by the UFT team this paper presents an improved strategy to consider the whole life cycle of a new chemical at the earliest level of development. The algorithm for a sustainable product design is orientated to the needs of special applications. It includes the assessment of the purity of ionic liquids used in technical applications ("technical grade") and in biological testing

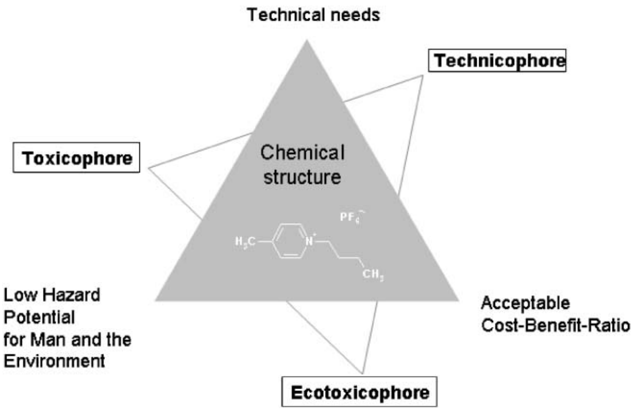


Fig. 1 Aspects of sustainable product design.

("analytical grade"). Therefore we will briefly present a set of analytical methods necessary to discuss the question of purity of ionic liquid entities.

We will also present new (eco)toxicological data demonstrating whether and how structural elements influence toxicity at different levels of biological complexity. The biological data given here are only representative and exemplary to support our conclusions with respect to design criteria. Experimental details of biological testing and the full range of data obtained will be published elsewhere.

The pool of ionic liquid entities—dilemma or chance?

Ionic liquids are a class of new chemical compounds that are the target of rapidly growing scientific and technological interest, indicated by a continuously growing number of publications and new chemical entities. The first successful implementation of an industrial process has been recently reported.[10]

Simply claiming that ionic liquids are the solvents of the future would mean hiding a dilemma. In fact, the term ionic liquids comprises an indefinite number of diverse chemical entities, so far 10^{12} accessible compounds have been estimated.[11] Also indefinite is the number of possible technological applications and usage patterns of ionic liquids, their individual life cycles (including recycling and waste treatment) and, last but not least, the targets for biological effects on man and the environment at all levels of biological complexity.

This dilemma excludes a screening process or the "let's try" approach to find a specific ionic liquid for a specific technology or use that fulfils the criteria to be a sustainable chemical product or process.

On the other hand the huge number of designable chemical entities opens up the chance of tuning the structural elements of an ionic liquid in a way that the principles of Green Chemistry and sustainable development can be fulfilled in an acceptable manner. As pointed out already this includes the discussion and solution of conflicts between technological needs, (eco)toxicological acceptance and economical chances. It is the chemist's opportunity to guide such development processes by designing and synthesising tailored ionic liquid entities within a multidisciplinary network. This process has already started, in a somehow systematic manner.

To define the structural elements of a toolbox aimed at supporting the design of sustainable ionic liquids, we analysed the structures of existing ionic liquids according to T-SAR. We defined three types of substructures: the positively charged moiety we call "headgroup", the one, two or more side chains R_1, R_2 *etc.* which represent substituents on this headgroup and the type of anion. Figs. 2 and 3 give a selection of those substructures already for sale. Through collaboration, our network has access to more than 140 different ionic liquid entities at the moment.

With increasing knowledge of the biological effects that different structural elements have on the (eco)toxicity of ionic liquids ("toxicophore" and "ecotoxicophore", *cf.* Fig. 1) as well as their intrinsic influence on physical and chemical properties which determine the usage pattern of ionic liquids ("technicophore") the design process will overcome the synthesis of new ionic liquids merely directed by chemical interest. Thus the pool of theoretically existing ionic liquid chemical entities will be used rationally and not by chance.

A flexible (eco)toxicological test battery

The classical hazard assessment of new industrial chemicals is directed by regulations, standardised procedures and is thus inflexible. The number and complexity of biological test systems and thus the costs of the evaluation increase with the proposed production volume of a chemical.

From an economical point of view it is impossible to perform such expensive procedures for all chemicals and processes in the development process, especially as many chemical entities are only potential candidates.

Therefore we advocate the concept of a flexible test strategy for ionic liquids and other industrial chemicals (*e.g.* antifouling biocides)[12,13] during their design and development phase. For the selection of test systems, considerations about the information value and the cost–benefit ratio of test results are taken into account. The number of chemical entities ("lead chemicals") tested in a distinct biological system is matched to the input of money and time needed for a specific test.

While test systems at higher levels of complexity allow for a better understanding of the effects of ionic liquids on a complex environment, molecular and cellular test systems are useful to improve our knowledge about the impact of specific structural elements and the way they should be modified in order to reduce their hazardous potential.

The (eco)toxicological tests of ionic liquid entities aim for the identification of the individual effects of different headgroups (with identical side chains and anions), anions (with identical cations) and systematic variations of R_1, R_2 *etc.* at identical head groups and with identical anions. In the following section novel results from different levels of complexity with respect to these questions will be summarised.

Substructures of ionic liquids influence their biological effects

To understand the impact the change of a structural element of an ionic liquid entity has on its (eco)toxicological effects, we asked the following questions:

i) How does an increase of the length of a side chain R_1, R_2 *etc.* affect biological activity, if we keep anion and headgroup constant?

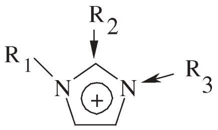
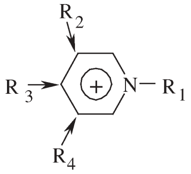
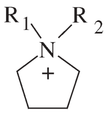
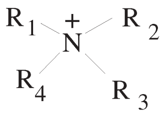
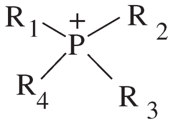
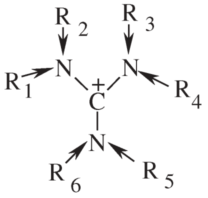
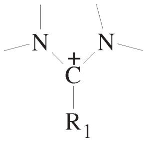
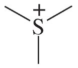
ii) Does the exchange of an anion effect biological activity?

iii) Does the type of headgroup influence the biological activity?

iv) Is a detoxification of ionic liquids by metabolic processes possible?

Side chain length effects

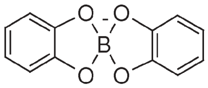
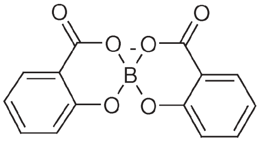
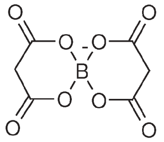
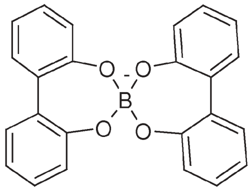
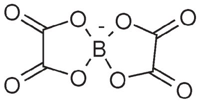
In 2003 we published our first systematic investigations of the influence of an increasing chain length of R_1 or R_2 of the imidazolium cation moiety on the cytotoxicity in marine bacteria and two types of mammalian cell cultures.[14] This

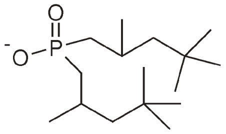
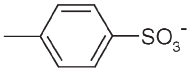
Headgroup	Side chain
	$R_{1/3}$= -H^{1,3}, -CH$_3^{1\text{-},6}$, -C$_2$H$_5^{1\text{-}6}$,-C$_3$H$_7^{4,6}$ -C$_4$H$_9^{1\text{-}6}$, -C$_5$H$_{11}^{3}$, -C$_6$H$_{13}^{1,3\text{-}6}$, -C$_8$H$_{17}^{3,4,6}$, -C$_{10}$H$_{21}^{3}$, -C$_{12}$H$_{25}^{3}$, -C$_{14}$H$_{29}^{3}$, -C$_{16}$H$_{33}^{3}$, -C$_{18}$H$_{37}^{3}$, -Allyl^{2}, - -Benzyl^{3,6}, -Phenylpropyl^{3}, -1*H*,1*H*,2*H*,2*H*-Perfluorooctyl^{4} R_2= -H$^{1\text{-}6}$, -CH$_3^{1\text{-}6}$, Nortallow^{5}
	R_1= -C$_2$H$_5^{3}$,-C$_3$H$_7^{4,6}$, -C$_4$H$_9^{3,5,6}$ -C$_6$H$_{13}^{3}$, -C$_8$H$_{17}^{3}$ $R_{2/4}$= -H$^{3\text{-}6}$, -CH$_3^{3,4,6}$, -C$_2$H$_5^{3}$ R_3= -H^{3,4,5}, -CH$_3^{3,4,5}$
	$R_{1/2}$= -CH$_3^{3}$, -C$_2$H$_5^{3}$, -C$_3$H$_7^{3}$, -C$_4$H$_9^{3}$, -C$_6$H$_{13}^{3}$, -C$_8$H$_{17}^{3}$
	$R_{1\text{-}4}$= -CH$_3^{1,3,5}$, -C$_2$H$_5^{3,5}$, -C$_2$H$_5$-OH^{5}, -C$_4$H$_9^{3,4}$, -C$_5$H$_{11}^{4}$, -Cyclohexyl^{5}, -C$_8$H$_{17}^{3,5}$, -C$_{13}$H$_{27}^{5}$, -Cocos^{5}, -Tallow^{5}, -Polyethylenglycolether^{5},-Stearyl^{5}
	$R_{1\text{-}4}$= -CH$_3^{3}$, -C$_2$H$_5^{3}$, -C$_4$H$_9^{3,4}$, -iC$_4$H$_9^{3,4}$, -C$_6$H$_{13}^{3,4,6}$, -C$_8$H$_{17}^{3}$, -C$_{14}$H$_{29}^{3,4,6}$, -C$_{16}$H$_{33}^{3}$, -Phenyl^{3}
	$R_{1\text{-}6}$= -H^{3}, -CH$_3^{3}$, -C$_2$H$_5^{3}$, -C$_3$H$_7^{3}$, -iC$_3$H$_7^{3}$
	R_1= -O-CH$_3^{3}$, -O-C$_2$H$_5^{3}$, -S-C$_2$H$_5^{3}$
 2	

Sources:
1. BASF: BASIONIC Produkt Range, brochure. 2. IoLiTec: http://www.iolitec.de/.
3. Merck KGaA: http://www.ionicliquids-merck.de/. 4. Sigma-Aldrich/Fluka: http://www.sigmaaldrich.com/.
5. Solvent Innovation: http://www.solvent-innovation.com/. 6. Strem: Catalog NO.20., 2004-2006.

Fig. 2 Selection of headgroups and side chains used in commercially available ionic liquids. This list is not meant to be complete.

effect was also evident in other blood cell lines (U937 and NB4, unpublished results) and in HeLa cells.[15] We have checked this "side chain length effect" in the meantime with a multitude of different combinations of cations and anions. It always became evident: the shorter the chain length(s) of side chain(s), the lower the cytotoxicity.

Main-group	Structure	Name
3		
B	$[BF_4]^-$	Tetrafluoroborate$^{2-6}$
	$[B(CN)_4]^-$	Tetracyanoborate^3
		Bis-[1,2-benzenediolato(2-)] borate^3
		Bis-[salicylato(2-)]-borate^3
		Bis-[malonato(2-)]-borate^3
		Bis-[2,2'biphenyl-diolato-(2-)-O,O']-borate^3
		Bis-[oxalato(2-)]-borate^3
Al	$[AlCl_4]^-$	Tetrachloroaluminate^1
4		
C	$[HC(SO_2CF_3)_2]^-$	Bis(trifluoromethanesulfonyl)methide^3
	$[C(SO_2CF_3)_3]^-$	Tris(trifluoromethylsulfonyl)methide^{3,4}
	$[CH_3COO]^-$	Acetate^1
	$[CF_3COO]^-$	Trifluoroacetate^3
	$[H_3C\text{-}(CH_2)_8\text{-}COO]^-$	Decanoate^{3,4,6}
5		
N	$[NO_3]^-$	Nitrate^{2,4}
	$[(CN)_2N]^-$	Dicyanamide$^{2-6}$
	$[N(CF_3)_2]^-$	Bis(trifluoromethyl)imide^3
	$[N(SO_2CF_3)_2]^-$	Bis(trifluoromethylsulfonyl)imide$^{2-6}$
	$[N(SO_2CF_2CF_3)_2]^-$	Bis(pentafluoroethylsulfonyl)imide^{4,6}

Main-group	Structure	Name
P	$[PO4]^{3-}$	Phosphate^{5,6}
	$[(H_3CO)_2PO_2]^-$	Dimethyl phosphate^{,5}
	$[(H_5C_2O)_2PO_2]^-$	Diethyl phosphate^3
	$[PF_6]^-$	Hexafluoro phosphate$^{2-6}$
	$[(C_2F_5)_3PF_3]^-$	Tris(pentafluoroethyl)-trifluorophosphate^3
	$[(C_3F_7)_3PF_3]^-$	Tris(heptafluoropropyl)-trifluorophosphate^3
	$[(C_4F_9)_3PF_3]^-$	Tris(nonafluorobutyl)-trifluorophosphate^3
		Bis(2,4,4-trimethylpentyl)-phosphinate^{3,4,6}
	$[(C_2F_5)_2P(O)O]^-$	Bis(pentafluoroethyl)-phosphinate^3
Sb	$[SbF_6]^-$	Hexafluoroantimonate^3
6		
S	$[SCN]^-$	Thiocyanate^{1,2,4}
	$[HSO_4]^-$	Hydrogen sulfate^1
	$[CH_3OSO_3]^-$	Methyl sulfate$^{1,3-6}$
	$[C_2H_5OSO_3]^-$	Ethyl sulfate^{1,3,5}
	$[C_4H_9OSO_3]^-$	Butyl sulfate^{3,5}
	$[C_6H_{13}OSO_3]^-$	Hexyl sulfate^{3,5}
	$[C_8H_{17}OSO_3]^-$	Octyl sulfate$^{3-6}$
	$[C_8F_{17}SO_3]^-$	Heptadecafluorooctanesulfonate^4
	$[H_3CO(CH_2)_2O(CH_2)_2OSO_3]^-$	2-(2-methoxyethoxy)-ethylsulfate^{4,5,6}
	$[CH_3SO_3]^-$	Methanesulfonate^{2,4}
	$[CF_3SO_3]^-$	Trifluoromethanesulfonate^{2,3,4}
	$[C_4F_9SO_3]^-$	Nonafluorobutanesulfonate^4
		Tosylate$^{2-6}$
7		
	$[Cl^-]$	Chloride$^{1-6}$
	$[Br]^-$	Bromide$^{2-6}$
	$[I]^-$	Iodide^3

Subgroup	Structure	Name
Subgroup	$[Co(CO)_4]^-$	Cobalttetracarbonyl^3

Sources:
1. BASF: BASIONIC Produkt Range, brochure. 2. IoLiTec: http://www.iolitec.de/.
3. Merck KgaA: http://www.ionicliquids-merck.de/. 4. Sigma-Aldrich/Fluka: http://www.sigmaaldrich.com/.
5. Solvent Innovation: http://www.solvent-innovation.com/. 6. Strem: Catalog NO.20., 2004-2006.

Fig. 3 Selection of anions currently used in commercially available ionic liquids. This list is not meant to be complete.

Following our concept of a flexible test battery we also investigated the "side chain length effect" at the molecular level, selecting acetylcholine esterase as a model enzyme. This enzyme was chosen because of the similarity of the chemical structure of many ionic liquid cations and acetylcholine. Both are cationic and the positive charge is masked by lipophilic residues. In addition the amino acid side chains forming the wall of the channel-like cleft, in which the acetylcholine molecule is bound are hydrophobic in nature, thus offering potential for hydrophobic interaction with the side chains of an ionic liquid, in case it is recognized and consequently bound to the active site of the enzyme.[16] Results for a large set of ionic liquids have been published[17] which also show a pronounced "side chain length effect". The inhibitory potential of an ionic liquid increases with an increase in chain length of the alkyl substituent. The results obtained confirm our T-SAR based choice of the acetylcholine esterase as a test system for ionic liquid toxicity.

Following our concept, as the next level of biological complexity we chose two higher plants which are well established as test organisms to assess ecotoxicological hazards of industrial chemicals: lesser duckweed (*Lemna minor*), a floating aquatic organism and garden cress (*Lepidium sativum*), a fast growing terrestrial plant.

Both assays[18,19] are much more time consuming than cell culture and enzyme tests. Therefore we chose only two ionic liquids to evaluate the effect of the alkyl chain length: 3-butyl-1-methylimidazolium and 1-octyl-3-methylimidazolium tetrafluoroborates ([bmim][BF_4] and [omim][BF_4], respectively).

Fig. 4 shows some results obtained with these two ionic liquid entities on the aquatic organism *Lemna minor*. Compared to the control, the growth (observed as number of foliaceous fronds) in the variant with [omim][BF_4] was significantly decreased (87% reduction) at a concentration of 10 mg L^{-1}. No significant decrease (~4%) was observed at the same concentration of [bmim][BF_4]. A significant decrease in number of fronds (60%) was observed with [bmim][BF_4] at a concentration of 100 mg L^{-1}.

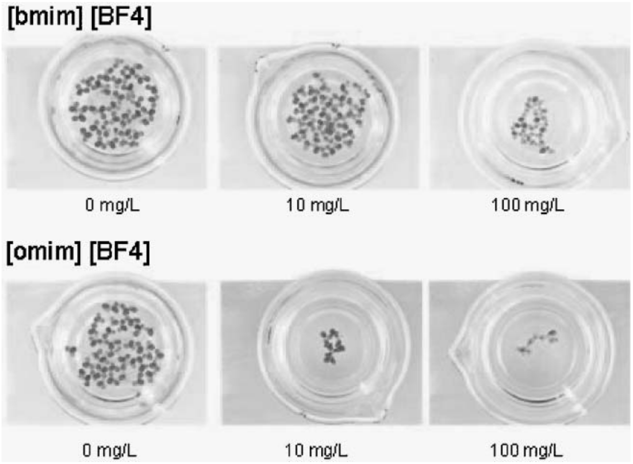


Fig. 4 Beakers with *Lemna minor* after 7 days (end of test). Nutrient solution (Steinberg medium) contained [bmim][BF_4] (above) and [omim][BF_4] (below) in concentrations ranging between 0–100 mg L^{-1}.

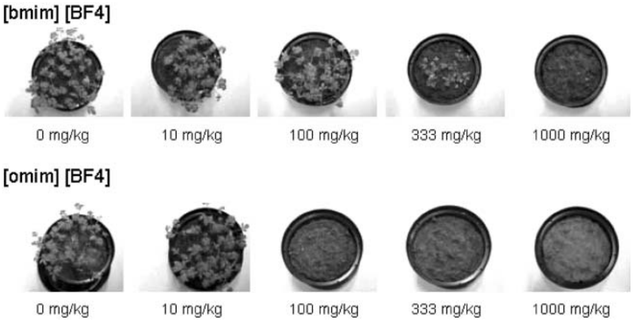


Fig. 5 Pots with garden cress (*Lepidium sativum*) after 21 days (end of test). Soil (Lufa 2.2) was spiked with [bmim][BF_4] (above) and [omim][BF_4] (below) in concentrations ranging between 0–1000 mg kg^{-1}.

Fig. 5 demonstrates the influence of the side chain length of both lead chemicals on the terrestrial plant *Lepidium sativum*. The number of seedlings was significantly decreased in samples with [omim][BF_4] at a concentration of 100 mg kg^{-1} (0% germination), whereas significant effects in samples with [bmim][BF_4] were only observed at the highest concentration of 1000 mg kg^{-1}. The average germination in all controls was 95%. Details will be published elsewhere.

Both tests with higher plants confirm again the results of the other tests: the longer the side chain of the ionic liquid, the higher the (eco)toxicity.

We additionally tested the genotoxicity of two ionic liquids using a standard test with mammalian blood cells. The Sister Chromatid Exchange (SCE)[20] assay shows the same trend with respect to the alkyl chain length. Again [bmim][BF_4] was chosen as lead chemical. This time it was compared to the decyl substituted entity ([dmim][BF_4]). In detail, [bmim][BF_4] caused no genotoxic effects (for the endpoint SCE aberrations and replication index) within a concentration range from 0 up to 20 μmol L^{-1}. In contrast, [dmim][BF_4] showed a dose dependent trend within a concentration range from 0 up to 10 μmol L^{-1}. Increasing doses of [dmim][BF_4] caused slightly increasing frequencies of SCE and decreasing fidelity of the target cells as observed *via* the replication index, although the parameters were not statistically different from the controls (unpublished results).

All results obtained at all biological levels tested so far revealed increasing toxicity (lower EC_{50} values, EC_{50} is the effective concentration, where 50% of the cells have died) due to elongated n-alkyl chain length. These results are consistent with published data.[14,15,21,22]

Anion effects on toxicity of ionic liquid entities

We have recently started a systematic investigation to answer the question of whether exchanging the anion in a given ionic liquid with another will positively or negatively influence the (eco)toxicity of the new ionic liquid entity. Taking into account the number of anions already used in ionic liquids (see Fig. 3), it is necessary to understand the relation between structure and biological effect of the type of anion in an ionic liquid, while starting to use anions as a tool to tune their physical, chemical and technological properties. We started to

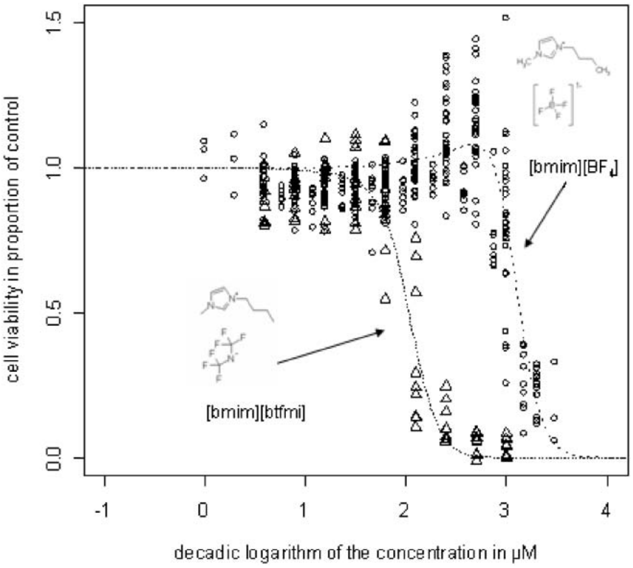


Fig. 6 Influence of different anions ($[BF_4]$ and [btfmi]) of ionic liquids on the viability of promyelocytic leukemia rat cells (WST-assay).

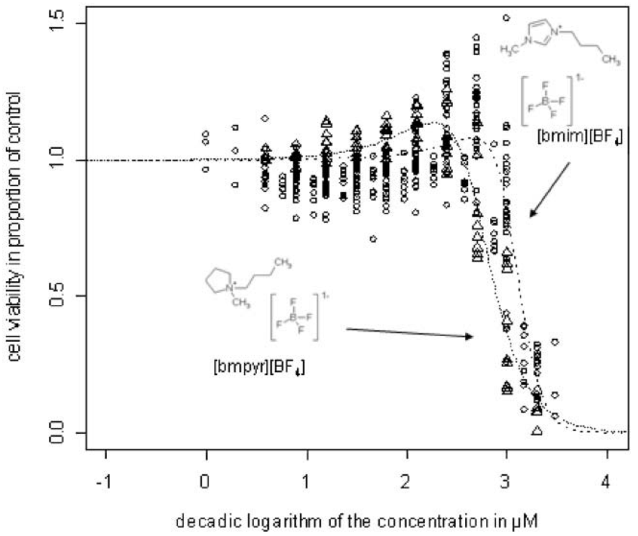


Fig. 7 Influence of different headgroups ([bmim] and [bmpyr]) of ionic liquids on the viability of promyelocytic leukemia rat cells (WST-assay).

screen testkits of ionic liquids where the cation structure is kept constant and the anion is varied with the standard WST-cell viability assay. Here we report the first conclusion which can be drawn from these studies.

Fig. 6 clearly shows an anion effect on cytotoxicity. We selected those anions which yielded the strongest difference in biological activity. As discussed in a former publication,[14] there are several anions which exhibit no significant difference. A publication describing in detail the cytotoxicological results obtained with more than 20 anions and a T-SAR based discussion of possible molecular mechanisms for the observed anion effects is in preparation.

Effects of the cation "headgroup" on the toxicity of ionic liquids

As shown in Fig. 2 several different chemical structures can form the positively charged "headgroup" in ionic liquid entities. With the WST-cell viability assay and the acetylcholine esterase inhibition assay we have screened a range of different substructures. Summarising these data it becomes evident that the chemical nature of a "headgroup" also influences the biological activity, although this influence varies and is in some cases only marginal. Fig. 7 and Fig. 8 demonstrate this observation exemplarily.

Chemical transformation of the side chains of ionic liquids may reduce toxicity

In 2003 we published a scheme for a theoretically predicted metabolism of the 1-butyl-3-methylimidazolium [bmim] cation formulated according to an algorithm published by Jastorff and coworkers.[8,23] Since investigations in model systems have just started, this working hypothesis has not been experimentally confirmed.

We have continued the theoretical formulation of further presumable metabolites of the [bmim] cation and additionally those of the 1-octyl-3-methylimidazolium ([omim]) cation and

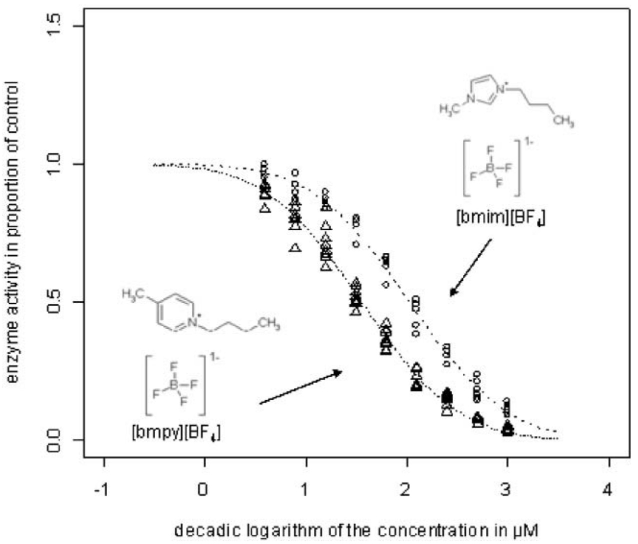


Fig. 8 Influence of different headgroups ([bmim] and [bmpy]) of ionic liquids on the activity of acetylcholine esterase (WST-assay).

thus predicted more than 50 chemical entities as candidates for inclusion in the pathways to their complete mineralisation.[24]

We decided to synthesise some of the most probable predicted metabolites using published standard procedures and determined their cytotoxicity as compared to the parent ionic liquids using the WST-cell viability assay.[24] Other "metabolites" like methyl-, butyl- and octylimidazole were purchased commercially. It should be mentioned that some of the metabolites can also be understood as functionalised ionic liquids. The functional groups introduced were a primary alcoholic hydroxyl function, a carbonyl function and the carboxyl group. Indeed some of these intermediate compounds are liquid at room temperature.[24]

Figs. 9 and 10 show the structures of the potential metabolites selected from the theoretical metabolic

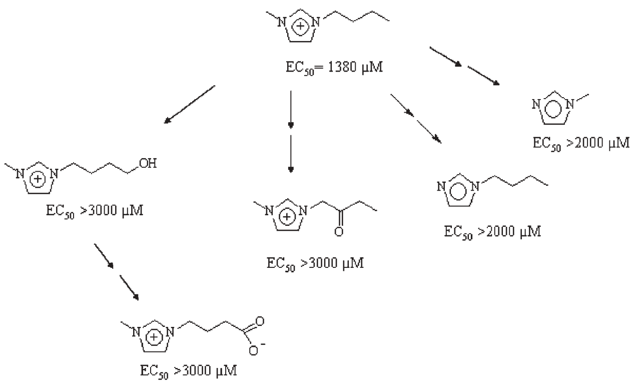


Fig. 9 Cytotoxicity of [bmim] cation in comparison to some of its hypothetical metabolites.

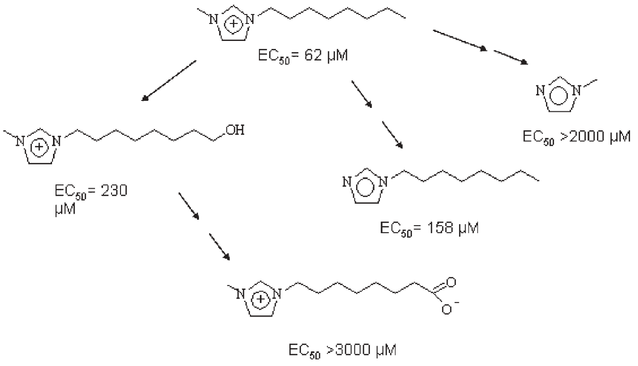


Fig. 10 Cytotoxicity of [omim] cation in comparison to some of its hypothetical metabolites.

schemes.[6,24] The corresponding cytotoxicity data (EC_{50} values) are given under the structural formulae. These data have been obtained with our standard cytotoxicity test and evaluation procedure.[14]

The biological data clearly indicate that the presumable transformation products ("metabolites") of both ionic liquid entities are less toxic compared to their parent chemicals. Since we have decided not to test cytotoxicity at concentrations higher than 3 mmol L^{-1}, the data given are either below (then exactly) or above that threshold.

Again, a side chain length effect is found for both the alkyl imidazoles (methyl- and butyl- >3000 µM, octyl- = 200 µM) and some of the functionalised cations, *e.g.* those compounds carrying a terminal hydroxyl function at the butyl ($EC_{50} >$ 3000 µM) or the octyl moiety (EC_{50} = 250 µM), respectively. Metabolic transformation to the carboxyl function yields no side chain length effect up to 3000 µM. In conclusion the introduction of polar functional groups into an alkyl chain yields a reduction in cytotoxicity. These results confirm the relation between lipophilicity and cell viability as discussed in a recent publication.[14]

The need for a purity assessment of ionic liquids

An analytical grade purity of an ionic liquid is necessary, if reliable physical, chemical and biological data are to be determined. However, for technical uses demanding analytical quality is not always feasible. Due to economic reasons only a technical grade may be sustainable. To accept such a "technical grade" quality as sustainable, the nature and the amounts of impurities have to be analysed prior to use and their potential risks for man and the environment have to be assessed. The easiest way to do this is to also use the technical grade ionic liquid as the test chemical for (eco)toxicological testing, and to compare the data obtained with those measured with the analytical grade quality. Discrepancies only have to be evaluated and eliminated by further purification if the technical grade exhibits a higher toxicity.

Properties and chemical nature of impurities may also be of importance if the whole life cycle of a chemical product or production process is taken into account, since the impurities may have an impact on the design of waste treatment processes. In summary, the problem of purity as part of the criteria for a sustainable ionic liquid—arising due to multiple usage patterns as products or within processes (synthesis, catalysis, extraction, thermal fluids, new batteries *etc.*)—in our opinion can most rationally and adequately be solved if a purity check as shown in Fig. 11 is used as the standard of analysis of an ionic liquid. Otherwise side effects of impurities cannot be excluded.[21,25]

To check the purity of the ionic liquids for diverse usage patterns, we propose a combination of several methods. Impurities that are volatile at temperatures up to the decomposition of the ionic liquids should be monitored by gas chromatography. Highly volatile compounds can be measured with headspace-GC and less volatile impurities can be detected using liquid injection of sample solutions in lower alcohols. Halide impurities, most frequently stemming from the alkylation of amines or phosphines with alkyl halides in the synthesis of ionic liquids, can be titrated by the Volhard method, lower concentrations in the ppm range can be determined using Nessler cylinders. Due to the influence of traces of water on the physical and chemical properties of ionic liquids, Karl–Fischer titration or GC analysis of water content should be routinely applied. For the quantification of cations and anions, *i.e.* the main components of structurally similar ionic impurities, reversed-phase or ion exchange HPLC coupled with a suitable detector like UV (in the case of *e.g.* imidazolium or pyridinium cations)[26,27] or conductivity as a more general method can be applied. Recently, a capillary

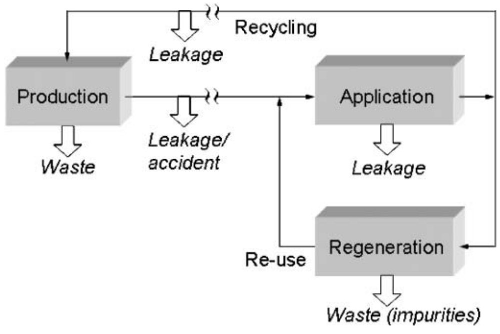


Fig. 11 Life cycle of an industrial chemical that satisfies sustainability criteria. The extent of leakage and (unavoidable) waste streams depends highly on the type of product and process.

electrophoretic method for resolving selected imidazolium ionic liquid cations has also been presented.[28]

The combination of all these methods will lead to a reasonably complete picture of impurities of the applied ionic liquid. Furthermore, for studies on bioaccumulation, transformation or persistence, the determination of even low concentrations of an ionic liquid and its metabolites in different media (*e.g.* water, soil, cell extracts), a tailored sample preparation and chromatographic analysis coupled to structure elucidation methods are a prerequisite. Recently methods for the analysis of imidazolium ionic liquids in aqueous environmental samples have been developed.[29]

Eco-design of ionic liquids

In 2003 we proposed a first draft for a sustainable product design.[6] Here we present a refinement of our approach for discussion within an interested scientific community in academia and industry.

The design procedure for "green" ionic liquids currently applied is the following: synthesise a set of ionic liquids, test their biodegradability and (eco)toxicological properties, choose those that show an environmentally benign character, and subsequently try to find a technical application for them. As an alternative concept, we propose an application specific eco-design. This includes the strategy outlined in this publication of defining a toolbox of structural elements valuable for the sustainable design and tuning of ionic liquids in technological applications.

For improving the sustainability of a product the cradle-to-grave impacts of this product on man, environment and profit are to be optimised. Among these impacts are (eco)toxicological hazards as discussed in the sections above and depletion of resources during the whole life-cycle. Depending on the application of the chemical compound and re-use and recycle options, material losses due to leakages and waste streams occur (Fig. 11). These losses, as well as the energy demand of regeneration determine the life cycle inventory (LCI). The results obtained for the environmental categories considered frequently yield conflicting objectives. With economical goals included into consideration the dilemma becomes even worse. If the resulting multi-objective optimization problem can be described mathematically an eco–eco trade-off can solve it.[30] In the other case a sequential-iterative procedure, as proposed here, appears to be the best choice.

The general objective in the design of chemicals is to obtain technicophore properties which promise an economical usage of novel compounds. In eco-design there is the environmentally benign character of the substance that has to be considered as an accessory objective. Instead of searching for an eco-solution that satisfies such a second objective, the ecotoxicophore properties as well as the regenerability can be taken as design-constraints. The resulting eco-design scheme is illustrated in Fig. 12.

In a first loop of the iterative scheme the (eco)toxicity of the proposed compound is evaluated by the screening tests described above. We suppose that for each ionic liquid with a high toxicity another chemical structure with comparable technicophore properties but with a lower toxicity can be found. This means that if a chemical compound is found for example to have a low EC_{50} value, we will again apply the structure–activity relationships to propose and synthesise a new chemical structure with similar technicophore properties.

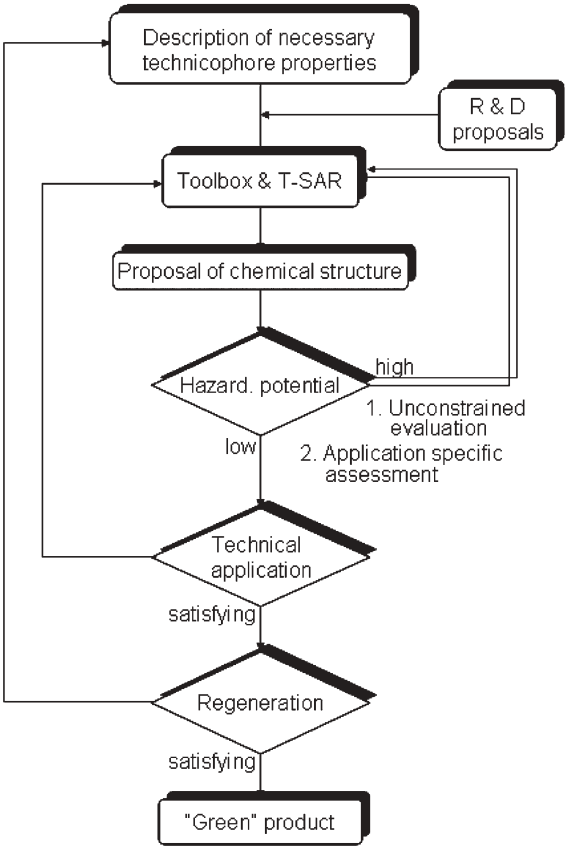


Fig. 12 Algorithm for the iterative eco-design procedure of ionic liquids.

However, the risk potential is not determined alone by the toxic character of the compound but by the three issues of environmental relevance, the waste streams of production and regeneration, and the leakage during production, usage and recycling. Obviously the leakage, differs quantitatively with application. During local usage of ionic liquids that serve as thermofluids, for example, leakages might cause soil and groundwater contamination. Used as solvents in two-phase aqueous systems, *e.g.* in biochemical production processes, ionic liquids are lost with discharged wastewater. On the other hand, if ionic liquids are used on closed chemical production sites, environmental issues are less likely.

To take this application-specific risk potential into account in the risk assessment we propose a second iteration in the eco-design algorithm. Here, the (eco)toxicological hazard potential of the new structural element or compound is assessed for a specific application on the basis of mass balances and indicator values. For the latter the absolute (eco)toxicological characteristics determined in the first iteration are used. The results are compared with constraints, *i.e.* defined values calculated with respect to no-effect-concentrations. Again, these data are taken from the screening tests.

Finally, if the ionic liquid passed an application test, it is to be tested whether the compound can be recovered after usage *e.g.* by regeneration, liquid–liquid extraction or nanofiltration. If so, the compound is considered a "green" product.

Conclusions and further research needs

It has been shown that considerable progress has been achieved concerning the assessment of the general biological activity of ionic liquids. This progress has so far focused on screening methods for larger sets of compounds, and on the class of imidazolium based ionic liquids. Some of these have been tested in more complex and resource consuming chronic single-species tests, forming the second level of a flexible biological test battery. The last step would consist of multi-species tests for those chemicals which are of high interest with respect to technological, economical and (eco)toxicological aspects.

To obtain more information about the influence of ionic liquids on human health for example after skin contact or during handling of powdered solids additional toxicological data are required. Almost no information about carcinogenicity, genotoxicity or teratological effects is available. First preliminary results with respect to genotoxic effects (SCE-assay) for [bmim][BF4] and [dmim][BF4] were presented here.

More information about the transformation pathways and kinetics of ionic liquids under different environmental conditions and within organisms is necessary. Theoretical metabolism considerations have been presented[8,24] and biodegradability studies using the OECD "Closed Bottle Test" were performed for several imidazolium based ionic liquids.[31] Further, recent studies investigating the degradation of imidazolium ionic liquids using different oxidation processes showed that degradation efficiency depends on the n-alkyl substituents[32] and first sorption results have been published.[33] Environmental exposure estimations are severely complicated by the fact that the ionic constituents of ionic liquids tend to be surface active, so conventional bulk phase oriented exposure models are of limited validity.

For further risk assessment studies, more (eco)toxicological data and data on the exposure pathways (for selected technical applications), (bio)transformation and sorption processes as well as bioaccumulation studies are necessary.

In general, more attention has to be drawn to suitable regeneration and/or recycling methods, taking into account the whole life cycle of ionic liquids. The adequate combination of the above elements and a lively communication and discussion of the results provides the opportunity for a truly sustainable development of this fascinating group of chemical substances.

Acknowledgements

The work of this paper is part of the project "Designing Molecular Test Systems for Toxicological and Ecotoxicological Risk Assessment" which is financially supported by the NATO collaborative linkage grant EST.CLG.979251 and of the project "Establishment and Development of the Test Set Ecotoxicity/Toxicity" which is financially supported by the senator for Women, Health, Youth, Social Affairs and Environmental Protection of the Freie Hansestadt Bremen. Support of the Polish Ministry of Scientific Research and Information Technology under grants DS 8000-4-0141-5 and BW 8000-5-0141-5 is also acknowledged. Further we want to thank Christian Jungnickel for improving the English. Special thanks go to Iris Burfeindt and Ute Uebers for carrying out ecotoxicity assays as well as to Anja Müller for checking substance identities with ESI-MS. Dr. N. Ignatiev kindly provided some ionic liquids not commercially available that were synthesised in the lab of Merck KGaA. Contributions of Tanja Juffernholz and Wojciech Mrozik that are not presented in this report are gratefully acknowledged.

**Bernd Jastorff,[a] Kerstin Mölter,[a] Peter Behrend,[a] Ulrike Bottin-Weber,[a] Juliane Filser,[a] Anna Heimers,[a] Bernd Ondruschka,[c] Johannes Ranke,*[a] Maike Schaefer,[a] Heike Schröder,[a] Annegret Stark,[c] Piotr Stepnowski,[b] Frauke Stock,[a] Reinhold Störmann,[a] Stefan Stolte,[a]
Urs Welz-Biermann,[d] Susanne Ziegert[a] and Jorg Thöming[a]**
[a]*UFT - Centre for Environmental Research and Technology, University of Bremen, Leobener Straße, D-28359 Bremen, Germany.*
E-mail: jranke@uni-bremen.de
[b]*Faculty of Chemistry, University of Gdansk, Ul. Sobieskiego 18/19, PL-80-952 Gdańsk, Poland*
[c]*Institute for Technical and Environmental Chemistry, Friedrich-Schiller-University Jena, Lessingstraße 12, D-07743 Jena, Germany*
[d]*Merck KGaA, New Ventures Materials, Frankfurter Straße 250, D-64293 Darmstadt, Germany*

References

1 http://www.un.org/esa/sustdev/documents/agenda21/english/agenda21toc.htm.
2 P. T. Anastas and J. C. Warner, *Green Chemistry Theory and Practice*, Oxford University Press, New York, 1998.
3 K. R. Seddon, *Green Chem.*, 2002, **4**, G35–G36.
4 P. Wasserscheid and T. Welton, *Ionic Liquids in Synthesis*, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany, 2002.
5 R. D. Rogers and K. Seddon, *Ionic Liquids: Industrial Applications for Green Chemistry*, American Chemical Society, ACS Symp. Ser. 818, Oxford University Press, Washington (DC), 2002.
6 B. Jastorff, R. Störmann, J. Ranke, K. Mölter, F. Stock, B. Oberheitmann, W. Hoffmann, J. Hoffmann, M. Nüchter, B. Ondruschka and J. Filser, *Green Chem.*, 2003, **5**, 136–142.
7 C. A. Doose, J. Ranke, F. Stock, U. Bottin-Weber and B. Jastorff, *Green Chem.*, 2004, **6**, 259–266.
8 B. Jastorff, R. Störmann and U. Wölke, *Struktur-Wirkungs-Denken in der Chemie—eine Chance für mehr Nachhaltigkeit*, Universitätsverlag, Aschenbeck und Isensee, Oldenburg, Germany, 2003.
9 J. Ranke and B. Jastorff, *Environ. Sci. Pollut. Res.*, 2000, **7**, 105–114.
10 J. Baker, Ionic Liquids set ideas flowing, *Eur. Chem. News*, 27.09.–03.10.2004.
11 J. D. Holbrey and K. R. Seddon, *Clean Prod. Proc.*, 1990, **1**, 223–226.
12 F. Stock, *Zelluläre und subzelluäre Testsysteme zur Beurteilung des biologischen Gefährdungspotenzials von Chemikalien im nachhaltigen Chemikaliendesign. Konzept einer Teststrategie und ihre Anwendung in zwei Fallbeispielen*, PhD Thesis, University of Bremen, 2004.
13 F. Stock and B. Jastorff, in preparation, 2004.
14 J. Ranke, K. Mölter, F. Stock, U. Bottin-Weber, J. Poczobutt, J. Hoffmann, B. Ondruschka, J. Filser and B. Jastorff, *Ecotoxicol. Environ. Saf.*, 2004, **58**, 396–404.
15 P. Stepnowski, A. C. Składanowski, A. Ludwiczak and E. Łączyńska, *Hum. Exp. Toxicol.*, 2004, **23**, 11, 513–517.
16 M. L. Raves, M. Harel, Y. P. Pang, I. Silman, A. P. Kozikowski and J. L. Sussman, *Nat. Struct. Biol.*, 1997, **4**, 57.

17 F. Stock, J. Hoffmann, J. Ranke, R. Störmann, B. Ondruschka and B. Jastorff, *Green Chem.*, 2004, **6**, 286–290.

18 DIN EN ISO 5667-16: Water quality—Sampling—Part 16: Guidance on biotesting of samples, International Organization for Standardization, Geneva, 1998.

19 ISO 11269-2: Soil Quality—Determination of the effects of pollutants on soil flora—Part 2: Effects of chemicals on the mergence and growth of higher plants, International Organization for Standardization, Geneva, 1995.

20 Genetic Toxicology: *in vitro* Sister Chromatid Exchange Assay in Mammalian Cells, OECD Guideline for testing chemicals 479, Organisation for Economic Co-operation and Development, Paris, 1986.

21 R. P. Swatloski, J. D. Holbrey, S. B. Memon, G. A. Caldwell, K. A. Caldwell and R. D. Rogers, *Chem. Commun.*, 2004, 668–669.

22 J. Pernak, K. Sobaszkiewicz and I. Mirksa, *Green Chem.*, 2003, **5**, 52–56.

23 R. Störmann and B. Jastorff, *Sci. Total Environ.*, 1993, Suppl., 1657–1667.

24 S. Stolte, *Untersuchungen zum Metabolismus von Ionischen Flüssigkeiten am Beispiel der Imidazol-Derivate*, Diploma Thesis, University of Bremen, 2004.

25 K. R. Seddon, A. Stark and M.-J. Torres, *Pure Appl. Chem.*, 2000, **72**, 2275–2287.

26 P. Stepnowski, A. Müller, P. Behrend, J. Ranke, J. Hoffmann and B. Jastorff, *J. Chromatogr., A*, 2003, **993**, 173–178.

27 P. Stepnowski and W. Mrozik, *J. Sep. Sci.*, 2005, **28**, 2, 149–154.

28 M. Markuszewski, P. Stepnowski and M. Marszałł, *Electrophoresis*, 2004, **25**, 3450–3454.

29 P. Stepnowski, *Anal. Bioanal. Chem.*, 2005, **381**, 1, 189–193.

30 P. Erol and J. Thöming, *J. Cleaner Prod.*, 2005 (in press).

31 N. Gathergood, M. T. Garcia and P. J. Scammells, *Green Chem.*, 2004, **6**, 166–175.

32 P. Stepnowski and A. Zaleska, *J. Photochem. Photobiol., A: Chem.*, 2004, **170**, 45–50.

33 P. Stepnowski, Preliminary assessment of the sorption of some alkyl imidazolium cations as used in ionic liquids to soils and sediments, *Aust. J. Chem.*, **58**, 170–173.

Continuous flow homogeneous hydroformylation of alkenes using supercritical fluids†

Paul B. Webb, Thulani E. Kunene and David J. Cole-Hamilton*

Received 1st November 2004, Accepted 31st March 2005
First published as an Advance Article on the web 20th April 2005
DOI: 10.1039/b416713a

The hydroformylation of long chain alkenes, carried out as a continuous flow process by using a catalyst made *in situ* from [Rh(CO)$_2$(2,4-pentanedioate)] and [1-propyl-3-methylimidazolium][Ph$_2$P(3-C$_6$H$_4$SO$_3$)] dissolved in 1-octyl-3-methylimidazolium bis(trifluoromethylsulfonamide), is reviewed. The substrates are introduced into and the products are removed from the reactor dissolved in continuously flowing supercritical carbon dioxide. Optimisation studies allow long term operation with rates up to 500 catalyst turnovers h^{-1} and rhodium leaching into the product as low as 0.012 ppm. Using a different ligand based on the xantphos skeleton, linear : branched ratios in the product aldehydes can be as high as 40 : 1, but the rate is somewhat lower (272 h^{-1}) and the rhodium retention is slightly less efficient. By removing the ionic liquid and dissolving the catalyst in the mixture of products and substrates that develops during the reaction, it is possible to carry out the reaction at much lower pressures (125 bar). 1-alkyl-3-methylimidazolium salts of [Ph$_2$P(3-C$_6$H$_4$SO$_3$)] are used as ligands and the success of the reaction depends crucially on the alkyl chain employed in the imidazolium cation. Too long a chain causes large amounts of rhodium leaching, whilst too small a chain causes the solubility of the ligand to be too low so that the reaction is very poor and unliganded rhodium is rapidly extracted from the system. The best results are obtained using a pentyl chain, which gives a rate of 162 h^{-1} and rhodium leaching of 0.1–0.5 ppm. Comparisons of these systems with current commercial systems are made and consideration is given to the design of a plant suitable for operating these reactions in a totally emissionless fashion.

Introduction

The greenest of chemical processes would involve the production of a single desired product with 100% chemo, regio and stereoselectivity and with all the atoms of the starting material ending up in the product (100% atom economy). No volatile organic solvents would be used and any other solvent would be totally recycled. There would be little energy input and ideally the starting materials should all be available from renewable sources, with the products being biodegradable or recyclable.

One of the ways in which to promote cleaner chemistry is to use catalytic rather than stoichiometric reactions. Soluble or homogeneous catalysts based on transition metal complexes have the ability to act under very mild conditions and their selectivity can be tuned by careful choice of the ligands attached to the metal.[1] There is a problem, however, in that the products often cannot easily be separated from the solvent and especially the catalyst, because the temperature required for *e.g.* distillation is often above the decomposition temperature of the catalyst and the solvent.[1,2] In addition, most homogeneous catalytic reactions are carried out in batch or semi-continuous mode.‡ This means that less use is made in industry of these attractive catalysts than would be desirable as a result of their environmentally acceptable properties. In this paper, we

David Cole-Hamilton completed his undergraduate and postgraduate (supervisor Dr Tony Stephenson) studies at the University of Edinburgh before spending 4 years with Sir Geoffrey Wilkinson at Imperial College. Lectureship and Senior Lectureships at Liverpool University were followed by appointment to his current position of Irvine Professor of Chemistry at the University of St. Andrews in 1985. His main research interests are in the applications of organometallic chemistry in homogeneous catalysis and in materials chemistry.

---

† This work was presented at the Green Solvents for Synthesis Meeting, held in Bruchsal, Germany, 3–6 October 2004.

*djc@st-and.ac.uk

‡ Batch reactions are associated with considerable down-time for reactor cleaning and recharging, as well as for product separation. In semi-continuous mode, the reaction is run continuously, but some of the catalyst–product solution is removed continuously to a separator (usually a distillation column at atmospheric or reduced pressure). Some of the catalyst is always in an inactive state and under conditions for which it has not been optimized. This may lead to decomposition, precipitation or the formation of inactive species.

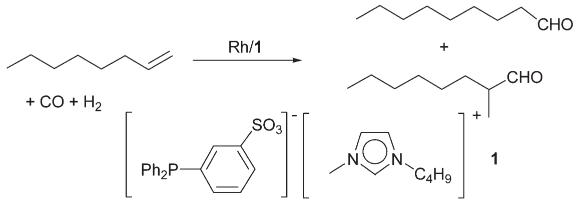
describe an approach towards achieving the ideal type of reaction described above, which overcomes the problems of homogeneous catalysis by having the catalyst immobilised within the reactor, whilst the substrate and product streams flow continuously. The product–catalyst separation is integral to the process. Some aspects of this work have been described before and are reviewed in the first part of the paper.[3–5]

Pioneering work by Brennecke, Beckman and co-workers[6–9] showed that ionic liquids, salts which are essentially involatile but are liquid at room temperature, are insoluble in supercritical carbon dioxide. Surprisingly, however, $scCO_2$ dissolves very readily in ionic liquids (up to 0.6 mole fraction). They also showed that organic compounds can be extracted from ionic liquids using supercritical carbon dioxide.[10,11] These results prompted us to investigate whether a system, in which an ionic complex is dissolved in an ionic liquid, might be used as a catalyst for a reaction with $scCO_2$ being employed as the transport vector for the substrates and products. We concentrated on the hydroformylation of long chain alkenes (Scheme 1), since this reaction is commercially important for the manufacture of plasticizer, soap and detergent range alcohols; it involves liquid and gaseous substrates and there is an issue of selectivity, the linear aldehyde product generally being much more desirable than the branched.[12,13] In addition, problems with the separation of the product when using rhodium catalysts, which operate under mild conditions and give better selectivity to the desired linear alcohol than cobalt based catalysts, have hampered the commercialisation of this highly attractive process.[2]

Experimental

Elemental analyses were performed by the University of St. Andrews Microanalysis service on a Carlo Erba 1110 CHNS analyser. NMR spectra were recorded on a Varian 300 spectrometer using protio impurities of the deuterated solvent as references for ^1H and ^{13}C chemical shifts, with tetramethylsilane at 0 ppm. ^{31}P chemical shifts are reported to high frequency of external 85% H_3PO_4. All reagents were used as received (Aldrich) without further purification, with the exception of liquid substrates for catalytic experiments which were dried and degassed according to literature methods. 1-Dodecene was purified further by distillation through a high efficiency column.

Gas chromatographic analyses of the product mixtures were carried out on a Hewlett-Packard 5890 series gas chromatograph equipped with both a flame ionisation detector (GC-FID for quantitative analyses) and a mass selective detector (GC-MS for qualitative analyses). The gas chromatograph was interfaced with a Hewlett-Packard Chemstation for the determination of peak areas by electronic integration. The GC-MS and GC-FID methods employed a Supelco™ Meridian MDN-35 low polarity, cross-linked phase comprised of a (35% phenyl)-methylpolysiloxane fused silica capillary column (30 m × 0.25 mm × 0.25 μm).



Scheme 1 Hydroformylation of 1-octene catalysed by a rhodium complex designed to be compatible with an ionic liquid.

Rhodium analyses of recovered fractions were measured by inductively coupled plasma mass spectrometry (ICP-MS) on an Agilent 7500a instrument. The instrument was modified for direct analyses of the organic fractions by using O_2 as a make-up gas to prevent carbon deposition on the sample and skimmer cones. Platinum cones were used together with a self-aspirating nebuliser held at −5 °C. Samples were diluted by 10% in a mixture of xylene and toluene (50 : 50) and ion counts were referenced against calibration curves obtained from standard solutions of $[Rh(acac)(CO)_2]$ (acacH is 2,4-dimethylpentanedione) in xylene–toluene (50 : 50). Standard solutions were run intermittently between samples to ensure that there were no drifts in instrument response and that the rate of aspiration was constant.

Ligand 2

Nixantphos[14] (0.100 g, 0.181 mmol) was dissolved in THF (50 cm^3) and NaH (1.5 mole equivalent, 60% in mineral oil) was added at 0 °C with stirring. The solution was allowed to warm to room temperature and refluxed for 1 hour. The solution was then cooled to room temperature, 1-bromo-3-chloropropane (1.075 cm^3, 1.08 mmol) was added quickly and the solution was refluxed overnight. The solution was cooled and the solvent was removed *in vacuo*. The solid residue was dissolved in dichloromethane and filtered through a glass sinter funnel. The solvent was then removed *in vacuo* and the solid crystallized from CH_2Cl_2/MeOH. The resulting white product was then dissolved in toluene (50 cm^3) and refluxed with 1-methylimidazole (3.34 cm^3, 100 mole equivalent) overnight. The solution was allowed to cool with the stirrer switched off and the product crystallized. It was collected by filtration (yield = 75%). Found: C 67.7, H 5.4, N 5.9, $C_{43}H_{40}N_3O_2P_2Cl$ requires: C 70.9 H 5.5 N 5.78;. ^1H NMR (300 MHz, CD_3OD, 298 K): δ 8.81 (s, 1H, NCHN)), 7.57 (s, 1H, NCHC*H*NCH_3), 7.33 (m, 12H, Ph), 7.24 (s, 1H, NC*H*CHNCH_3), 7.20 (m, 8H, Ph), 6.76 (t, *J*(H,H) = 7.8 Hz, 2H, Ph_2PCCHC*H*), 6.73 (d, *J*(H,H) = 7.8 Hz, 2H Ph_2PCCH), 6.05 (d, *J*(H,H) = 7.2 Hz, 2H, $Ph_2PCCHCHC$*H*CN), 4.39 (t, *J*(H,H) = 6.6 Hz, 2H, $NCH_2CH_2CH_2NCN$ with NC*H*$_2$), 3.82 (t, *J*(H,H) = 6.6 Hz, 2H, $NCH_2CH_2CH_2NCN$), 3.70 (s, 3H, NCH_3), 2.35 (q, *J*(H,H) = 6.6 Hz, 2H, $NCH_2CH_2CH_2NCN$). ^{13}C $\{^1H\}$NMR (300 MHz, CD_3OD, 298 K): δ 147.17 (t, *J*(P,C) = 20.8 Hz, CO), 136.76 (t, *J*(P,C) = 12.4 Hz, Ph_2PC), 136.73 (NCN), 133.64 (t, *J*(P,C) = 21.1 Hz, Ph_2PCCH), 133.03 (CN), 128.32 (CH), 128.01 (t, *J*(P,C) = 6.9 Hz, $Ph_2PCCHCH$), 125.31 (CH), 123.81 (CH), 123.47 (NCHCHNCH_3), 122.025 (NCHCHNCH_3), 112.49 (CH), 40.67 ($NCH_2CH_2CH_2NCN$), 35.06 ($NCH_2CH_2CH_2NCN$), 29.29 (NCH_3), 25.14 ($NCH_2CH_2CH_2NCN$). ^{31}P NMR (300 MHz, CD_3OD, 298 K): δ −18.62 (s).

The full experimental details of the flow system have been reported elsewhere.[4]

Results and discussion

Hydroformylation of long chain alkenes in supercritical fluid–ionic liquid biphasic systems

Initial studies. Our initial studies[3] on supercritical fluid–ionic liquid biphasic systems were carried out in 1-butyl-3-methylimidazolium (BMIM) hexafluorophosphate using 1-octene as the substrate for hydroformylation and a catalyst prepared *in situ* from [Rh(CO)$_2$(2,4-pentanedioate)] and [PrMIM][Ph$_2$P(3-C$_6$H$_4$SO$_3$)] (Pr = propyl). These demonstrated the concept (shown schematically in Fig. 1) and allowed continuous flow operation for up to 72 h with negligible leaching of rhodium into the collected product fractions (<1 ppm). This represented the first demonstration of continuous flow homogeneous catalysis where the product was of relatively low volatility, although supercritical fluids had been used to flush products from other solvents[15] or from ionic liquids[16,17] as well as in batch[16] or repetitive batch[15,17] processes. They had also been used to transport substrates and products over metal complex catalysts supported on a polymer in repetitive batch mode[18] or on silica with continuous flow operation.[19] At about the same time as our original work, coupling of ethene with styrene in a continuous flow system consisting of an immobile ionic liquid phase and a mobile compressed CO$_2$ phase (below the critical temperature) was reported.[20] Subsequently many other examples of reactions in supercritical fluid–ionic liquid biphasic systems have been reported using either metal complex or enzyme based catalysts. These include Wacker[21] oxidation, the formation of dimethyl carbonate,[22] cyclic carbonates from epoxides and CO$_2$,[23] acrylate dimerisation,[24] transesterification reactions,[25] and kinetic resolutions catalysed by lipase enzymes.[26–29] Asymmetric,[16] alkene[17] and carbon dioxide[17] hydrogenation reactions have all been carried out in ionic liquids with the products being removed by scCO$_2$, but not in flow systems. These processes have been reviewed.[2,30–32]

Improving the system performance. Although the initial reactions[3] were of interest because they provide proof of concept, the reaction rates were very low (5–10 catalyst turnovers h^{-1}, compared with >500 h^{-1} in the commercial rhodium catalysed hydroformylation of propene).[13] The conversions were also very low with the yields of products recovered after decompression of the CO$_2$ being only about 6–7%, the remainder being unreacted 1-octene.

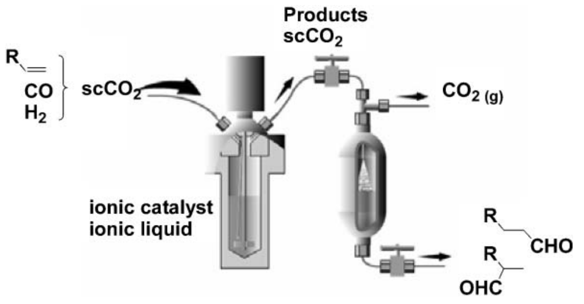


Fig. 1 Schematic of continuous flow homogeneous catalysis using a supercritical fluid–ionic liquid biphasic system.

We reasoned that the problem of low conversion was largely caused by poor mass transport of the substrate into the ionic liquid, where the catalyst resides, and we soon realised that the problem was intrinsic to the ionic liquid. With this in mind and being aware of work in which it had been reported[33] that the solubility of alkenes in alkylmethylimidazolium (alkMIM) based ionic liquids increases as the alkyl chain length is increased, we used a series of ionic liquids with different chain lengths. Both for 1-octene and for 1-dodecene, the results were dramatic and conversion efficiencies up to 86.5% in the continuous flow systems were obtained using [octMIM][NTf$_2$] or [decMIM][NTf$_2$] (oct = octyl, dec = decyl, NTf$_2$ = bis-trifluoromethyl sulfonamide).[4] We also showed that NTf$_2$ salts gave better rates than PF$_6$ salts when using the same imidazolium cation. This is advantageous because PF$_6^-$ is sensitive to water, giving HF and O$_2$PF$_2^-$,[3,34] whilst NTf$_2^-$ is stable towards water. We attribute these rate increases to the increased solubility of the alkene in the ionic liquid. Two examples of the increase in reaction rate on changing the ionic liquid are shown in Figs. 2 and 3.

We believe that 86.5% conversion is the maximum achievable in our one pass continuous flow system in which the stirring has not been optimised. Some substrate will inevitably remain in the scCO$_2$ and pass straight through the system without ever contacting a catalyst molecule. Subsequent optimisation reactions were all carried out in [octMIM][NTf$_2$].[4]

Further rate increases were obtained by changing the reaction parameters, the most important being the substrate flow and the partial pressure of the permanent gases. Fig. 4 shows the effect of CO/H$_2$ flow, with the turnover frequency increasing as the flow rate increases. We attribute this to an increased amount of substrate partitioning into the ionic liquid phase, where the catalyst resides, because the solubilising power of the supercritical phase is reduced by the increasing concentrations of permanent gases. There is a limit to how far this can be exploited as the solubilising power of the supercritical phase towards the product is also reduced and

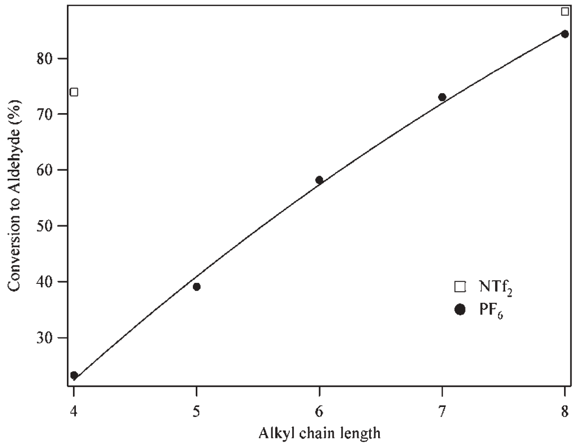


Fig. 2 Effect of anion and alkyl group in the 1-position of 1-alkyl-3-methylimidazolium salts on reaction rate (conversion in 1 h) for the hydroformylation of 1-dodecene in a batch reactor using Rh/[PrMIM][Ph$_2$P(3-C$_6$H$_4$SO$_3$)] and scCO$_2$. (Reproduced from ref 4; ©American Chemical Society.)

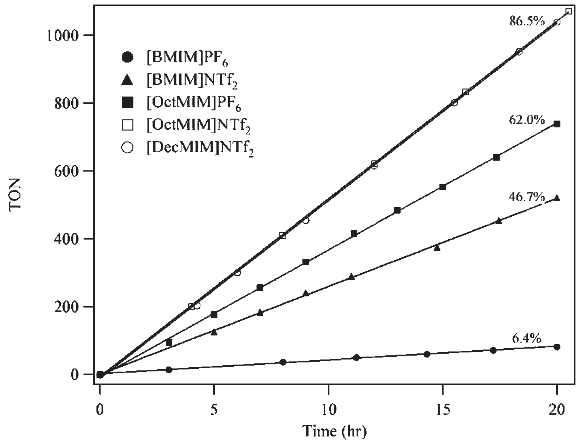


Fig. 3 Hydroformylation of 1-dodecene catalysed by Rh/[PrMIM][$Ph_2P(3\text{-}C_6H_4SO_3)$] in a variety of ionic liquids. The numbers are conversions of 1-dodecene in the isolated fractions. (Reproduced from ref. 4; ©American Chemical Society.)

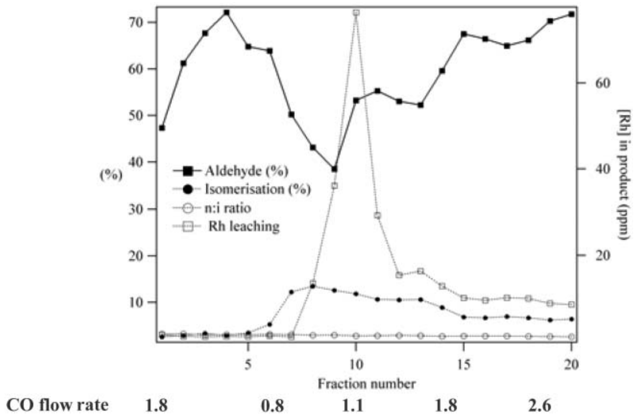


Fig. 5 Effect of changing the partial pressure of CO/H_2 during the continuous hydroformylation of 1-octene. The lines are provided to guide the eye. They do not imply trends between the points. The CO : H_2 ratio was kept constant at 1 : 1. (Reproduced from ref 4; ©American Chemical Society.)

there comes a point where not all of the product is extracted, mass balance is lost and product accumulates in the reactor until it and the catalyst solution are pushed out through the entire decompression system. Nevertheless, turnover frequencies up to 500, comparable to those for the commercial rhodium catalysed hydroformylation of propene,[12,13] have been observed under the optimum conditions (Fig. 4).[4] One other advantage of tuning the partition of the substrate and product between the two phases is that the less solubilising the supercritical phase, the less rhodium is extracted. Fig. 5 shows how the rate and rhodium extraction are affected by the partial pressure of CO and H_2. Decreasing the partial pressure of the permanent gases causes a decrease in rate and an increase in rhodium leaching because the supercritical phase is a better solvent for both the substrate and the catalyst. Under the optimum conditions of Fig. 4, the concentration of rhodium in the collected fractions is 0.012 ppm. This corresponds to 1 g in 40 tonnes of product aldehyde.[4] At the highest flow rates of Fig. 4, the leaching was higher, but it is difficult to be certain whether this is a genuine effect as these measurements were taken at the start of the series and we have found that high leaching is always observed in the early fractions of an experiment as a result of some entrainment during set-up. Several measurements were made with a CO flow rate of 4.33 mmol min^{-1} and the leaching decreased rapidly from an initial value of 1 ppm to 0.23 ppm. If these high values are genuine measurements of the leaching this could imply that at higher p_{CO}, unliganded rhodium complexes form and are removed because of their high solubility in $scCO_2$ or that some solution is aspirated from the system. In the later fractions (CO flow rates of 2.9–3.9 mmol min^{-1}), leaching was <0.06 ppm with the lowest value of 0.012 ppm being observed at a flow rate of 3.3 mmol min^{-1}.

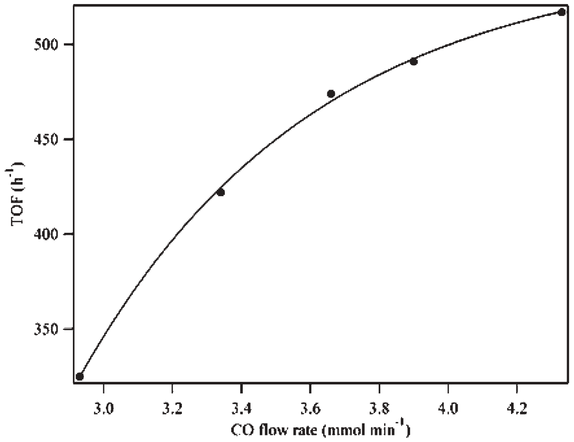
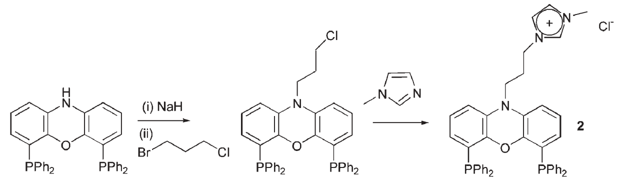


Fig. 4 Effect of CO flow rate on continuous flow hydroformylation of 1-octene catalysed by Rh/[PMIM][$Ph_2P(3\text{-}C_6H_4SO_3)$] in the [octMIM][$NTf_2$]/$CO_2$ biphasic system. (Reproduced from ref. 4; ©American Chemical Society.)

The question of long term stability of catalysts is also important for commercialisation. If the catalyst or ligand is decomposing, oxidising, or being extracted, the rate and selectivity change with time. We do not observe changes of this kind in any of our continuous reactions with reaction times of up to 72 h. In addition, we used one batch of catalyst solution over a period of 80 h (40 h on line). We then left the catalyst in the presence of the product at the reaction temperature and pressure for 4 weeks. On restarting the flows, the rate and selectivity were identical to those obtained in the run immediately prior to the 4 week break.[4]

Improving the reaction selectivity. In all of the reactions described above, we used [PrMIM][$Ph_2P(3\text{-}C_6H_4SO_3)$] as the ligand and linear selectivities were only modest (l : b ratio = 3–3.5).[4] In order to improve this selectivity, we designed and synthesised ligand **2** by the route shown in Scheme 2. Ligands based on the xanthene skeleton generally give very good linear selectivity in hydroformylation reactions[35] and the related ligand, **3**, has been shown to be an active hydroformylation catalyst in the ionic liquid, [1-butyl-3-methylimidazolium][PF_6] with excellent selectivity to the linear aldehyde and no detectable leaching of rhodium (<0.005 ppm) or phosphorus (<0.1 ppm) when the product was extracted with an organic solvent.[36]



Scheme 2 Synthesis of modified Xantphos ligand.

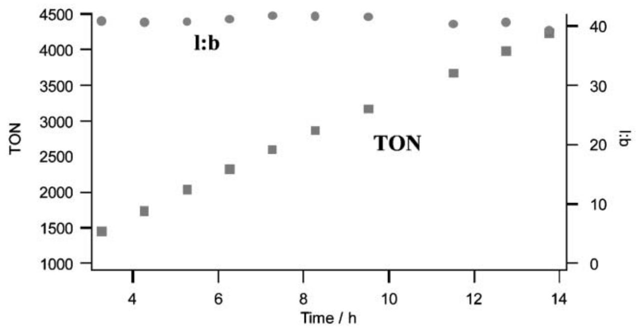
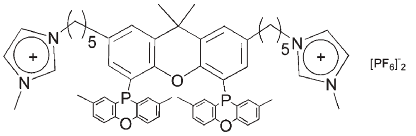


Fig. 6 Highly selective 1-octene hydroformylation using the modified Xantphos ligand shown in Scheme 2.



3

Fig. 6 shows that ligand **2** is no exception with a steady state rate of 272 catalyst turnovers h^{-1} and an l : b ratio of 40. Rhodium leaching is slightly higher than when using [PrMIM][Ph_2(3-$C_6H_4SO_3$)], at 0.2 ppm. The selectivity dropped dramatically after longer reaction times as a result of ligand oxidation (NMR evidence).

Reducing the operating pressure

Although the supercritical fluid–ionic liquid biphasic system described above works well with rates close to those that are required commercially, good l : b ratio using the right ligand, and low rhodium losses, the main disadvantage is the high overall operating pressure (200 bar). There are also some concerns over the long term use of ionic liquids. In particular, those with long alkyl chains on imidazolium cations are somewhat toxic[37] and behave as skin irritants[38] whilst PF_6^- salts are hydrolytically unstable producing HF and $[O_2PF_2]^-$.[34] It occurred to us that we might be able to overcome both of these problems by removing the ionic liquid and simply dissolving the catalyst in the steady state mixture of reactants and products that develops during the reaction. In reality, we start with the catalyst dissolved in the pure linear aldehyde product and carry out the hydroformylation reaction in the flow system. Fig. 7 shows the results of one such reaction and illustrates the success of the process. The choice of ligand is very important (see Table 1), since, if it is too lipophilic ([octMIM][Ph_2P(3-$C_6H_4SO_3$)]), significant extraction of rhodium occurs, but if it is too polar ([PrMIM][Ph_2P(3-$C_6H_4SO_3$)]), it is not sufficiently soluble in the product phase, unliganded rhodium complex is formed and the rhodium is rapidly lost from the system. Even with medium polarity ligands ([PentMIM][Ph_2P(3-$C_6H_4SO_3$)]), the flow rate must be controlled. Too high a flow rate leads to higher levels of 1-octene in the system. This causes some of the catalyst to precipitate and the conversion to drop. Further catalyst precipitates leading to a negative feedback loop and very poor catalysis. With only preliminary optimisation, we have been able to bring the operating pressure down from 200 to 125 bar.[5]

Comparison with commercial systems

When the project started, no systems had been commercialised for the rhodium catalysed hydroformylation of long chain

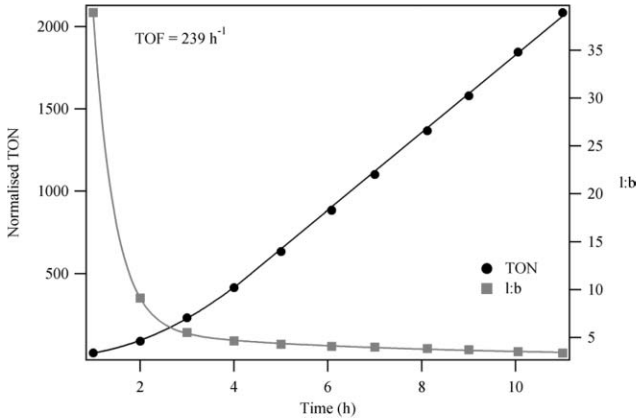


Fig. 7 Continuous flow hydroformylation of 1-octene in nonanal (initial solvent) with $scCO_2$ as the flowing phase. (Reproduced from ref. 5.)

Table 1 Hydroformylation of 1-octene at 100 °C catalysed by rhodium complexes of different phosphines, using $scCO_2$ to transport the substrate and gases into and the products out of the reactor[a]

Entry	Ligand R[b]	[Rh]/ mol dm^{-3}	[P]/ mol dm^{-3}	CO_2 flow/ nL min^{-1}	CO flow[c]/ mmol min^{-1}	Octene flow/ mmol min^{-1}	p^d/bar	TOF[e]/ h^{-1}	Conversion[f] (%)	[Rh] leaching[g] (ppm)
1	Pr	0.012	0.19	0.47	1.2[h]	0.042	140	22	25	35[i]
2	Pent	0.011	0.16	0.55	2.89	0.32	125	80	76	0.1–0.5
3	Pent	0.0057	0.043	0.55	2.78	0.32	125	162	77	0.1–0.5
4	Oct	0.015	0.22	0.65	1.59	1.27	140	208	50	5–10
5	Oct	0.015	0.22	0.65	2.34	1.27	140	239	57	5–10

[a] Starting solvent is 1-nonanal (16 cm^3), nL = normal litre. [b] In [RMIM][Ph_2P(3-$C_6H_4SO_3$)]. [c] CO : H_2 = 1 : 1. [d] Total pressure. [e] mol product (mol catalyst)$^{-1}$ h^{-1}. [f] % Aldehyde in recovered product. [g] [Rh] in recovered product. [h] CO : H_2 = 1 : 2. [i] High leaching early in the reaction.

Table 2 Comparisons of the systems reported in this paper with commercial hydroformylation systems

Process	BASF (Co)	Shell (Co/P)	SCF–IL[a] (**3**)	SCF[b]	UCC[c] (Rh/P)	Shell (Rh/P)
Substrate	1-octene	1-octene	1-octene	1-octene	*propene*	*propene*
[M]/mmol dm^{-3}	80	80	15	15	2.6	1.8
p/bar	*300*	80	*200*	125	**15**	**16**
T/°C	150	*200*	100	100	95	110
STY[d]/h^{-1}	0.5	0.3	**1.4 (0.74)**	**0.68**	0.2	0.1
Rate/mol dm^{-3} h^{-1}	2.8	1.8	**7.8 (4.1)**	**3.8**	2.1	1.0
TOF[e]/h^{-1}	*35*	*20*	**517** (272)	259	**770**	**556**
Linear%	*50*	80	75 (**92**)	75	**90**	83

Good aspects of reactions are highlighted in bold, problems are in italics.[a] Supercritical fluid–ionic liquid. [b] Supercritical fluid, catalyst dissolved in substrate–product mixture. [c] Union Carbide Corporation, data for commercial systems from ref. 13. [d] Space time yield (litres product (litre catalyst solution)$^{-1}$ h^{-1}. [e] Mol product (mol catalyst)$^{-1}$ h^{-1}.

alkenes, because the problem of separating the product from the catalyst had not been solved. Commercial processes use cobalt based catalysts with or without a modifying phosphine.[13] Rhodium catalysts are preferred for propene hydroformylation because of their higher reactivity, leading to milder operating conditions, and their better selectivity to the desired linear aldehyde product.[12,13]

Table 2 presents a comparison of the various different commercial systems in operation. It has been coded to highlight the major problems (*italic*) of the processes and the major advantages (**bold**). The supercritical fluid–ionic liquid biphasic process, especially when using the modified xantphos ligand, compares favourably with all the other processes, except that the overall pressure is very high. The process we have started to develop, which does not use the ionic liquid, but rather has the catalyst dissolved in the steady state mixture of substrates and products that develops during the reaction, looks to have extremely promising characteristics (no *italic* entries), although rhodium losses are still too high.

Scale-up and CO_2 recycling

We have considered the process synthesis that would be required for recycling CO_2 at the end of the reaction, hence making the process entirely emissionless. Although we envisaged using equipment we already have[39] for recompressing the CO_2 after decompression to collect the products, it became apparent that the problem is not so simple when the CO_2 contains permanent gases. In the case of CO_2 alone, it can be compressed or cooled to give liquid CO_2, which can then be pumped as a liquid. When CO and H_2 are present, however, they will accumulate in the gas phase, leading to a pressure build up. This phase consists of a mixture of CO, H_2 and CO_2, so that it must be warmed above its critical point (note T_c for CO_2 is 31.1 °C and this is lower when permanent gases are added) in order to compress it for passage back into the reactor along with fresh permanent gases. In a plant this could be achieved and, by IR monitoring the CO concentration in the reactor, the correct amount of top-up gas could be added. A conceptual plant design is shown in Fig. 8.

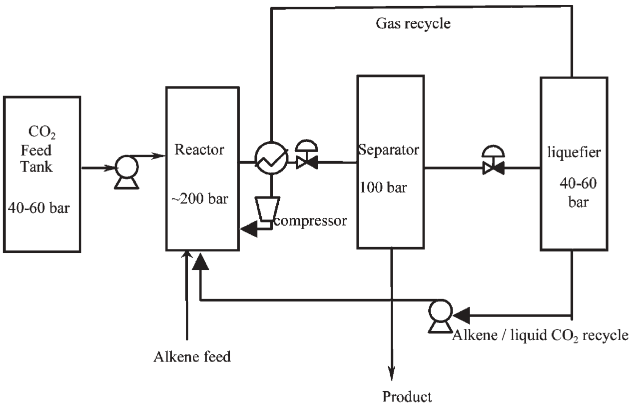


Fig. 8 Process design for continuous operation with full recycling.

Conclusion

We have developed the first continuous flow homogeneous catalytic process for products of relatively low volatility. It involves using $scCO_2$ as a transport vector whilst the catalyst is retained within the reactor dissolved in an ionic liquid. After optimisation, reaction rates for the hydroformylation of long chain alkenes are comparable with those required by industry. Very high linear selectivity at slightly reduced rates is possible using specially designed ligands and the retention of the catalyst within the reactor is very good (rhodium concentration within the product can be as low as 0.012 ppm). Another new process has been demonstrated in which the ionic liquid is omitted. This allows for operation at much lower overall pressure (125 bar as opposed to 200 bar). In principle this system is capable of operating without generating any waste or any emissions since the reaction studied, the hydroformylation of long chain alkenes, is 100% atom economic, the catalyst remains in the reactor at all times, the CO_2 could be recycled and no other solvents are required.

Paul B. Webb, Thulani E. Kunene and David J. Cole-Hamilton*
School of Chemistry, University of St. Andrews, St. Andrews, Fife, Scotland KY16 9ST. E-mail: djc@st-and.ac.uk; Fax: +44-1334-463808; Tel: +44-1334-463805

References

1 *Applied Homogeneous Catalysis with Organometallic Compounds*, ed. B. Cornils and W. A. Herrmann, VCH, Weinheim, 1996.
2 D. J. Cole-Hamilton, *Science*, 2003, **299**, 1702.
3 M. F. Sellin, P. B. Webb and D. J. Cole-Hamilton, *Chem. Commun.*, 2001, 781.
4 P. B. Webb, M. F. Sellin, T. E. Kunene, S. Williamson, A. M. Z. Slawin and D. J. Cole-Hamilton, *J. Am. Chem. Soc.*, 2003, **125**, 15577.
5 P. B. Webb and D. J. Cole-Hamilton, *Chem. Commun.*, 2004, 612.

6 L. A. Blanchard, D. Hancu, E. J. Beckman and J. F. Brennecke, *Nature*, 1999, **399**, 28.
7 L. A. Blanchard, Z. Y. Gu and J. F. Brennecke, *J. Phys. Chem. B*, 2001, **105**, 2437.
8 C. Cadena, J. L. Anthony, J. K. Shah, T. I. Morrow, J. F. Brennecke and E. J. Maginn, *J. Am. Chem. Soc.*, 2004, **126**, 5300.
9 J. L. Anthony, E. J. Maginn and J. F. Brennecke, *J. Phys. Chem. B*, 2002, **106**, 7315.
10 L. A. Blanchard and J. F. Brennecke, *Ind. Eng. Chem. Res.*, 2001, **40**, 287.
11 A. M. Scurto, S. Aki and J. F. Brennecke, *J. Am. Chem. Soc.*, 2002, **124**, 10276.
12 *Rhodium catalysed hydroformylation*, ed. P. N. W. M. Van Leeuwen and C. Claver, Kluwer, Dordrecht, 2000.
13 C. D. Frohling and C. W. Kohlpaintner, in *Applied Homogeneous Catalysis with Organometallic Compounds*, ed. B. Cornils and W. A. Herrmann, VCH, Weinheim, 1996.
14 L. A. van der Veen, P. H. Keeven, G. C. Schoemaker, J. N. H. Reek, P. C. J. Kamer, P. van Leeuwen, M. Lutz and A. L. Spek, *Organometallics*, 2000, **19**, 872.
15 M. F. Sellin and D. J. Cole-Hamilton, *J. Chem. Soc., Dalton Trans.*, 2000, **11**, 1681.
16 R. A. Brown, P. Pollet, E. McKoon, C. A. Eckert, C. L. Liotta and P. G. Jessop, *J. Am. Chem. Soc.*, 2001, **123**, 1254.
17 F. C. Liu, M. B. Abrams, R. T. Baker and W. Tumas, *Chem. Commun.*, 2001, 433.
18 R. J. Sowden, M. F. Sellin, N. De Blasio and D. J. Cole-Hamilton, *Chem. Commun.*, 1999, 2511.
19 N. J. Meehan, A. J. Sandee, J. N. H. Reek, P. C. J. Kamer, P. van Leeuwen and M. Poliakoff, *Chem. Commun.*, 2000, 1497.
20 A. Bosmann, G. Francio, E. Janssen, M. Solinas, W. Leitner and P. Wasserscheid, *Angew. Chem., Int. Ed.*, 2001, **40**, 2697.
21 Z. S. Hou, B. X. Han, L. Gao, T. Jiang, Z. M. Liu, Y. H. Chang, X. G. Zhang and J. He, *New J. Chem.*, 2002, **26**, 1246.
22 T. Jiang, B. X. Han, G. Y. Zhao, Y. H. Chang, L. Gao, J. M. Zhang and G. Y. Yang, *J. Chem. Res.*, 2003, (S)549.
23 H. Kawanami, A. Sasaki, K. Matsui and Y. Ikushima, *Chem. Commun.*, 2003, 896.
24 D. Ballivet-Tkatchenko, M. Picquet, M. Solinas, G. Francio, P. Wasserscheid and W. Leitner, *Green Chem.*, 2003, **5**, 232.
25 L. A. Gao, J. A. Tao, G. Y. Zhao, T. C. Mu, W. Z. Wu, Z. S. Hou and B. X. Han, *J. Supercrit. Fluids*, 2004, **29**, 107.
26 M. T. Reetz, W. Wiesenhofer, G. Francio and W. Leitner, *Chem. Commun.*, 2002, 992.
27 J. A. Laszlo and D. L. Compton, *ACS Symp. Ser.*, 2002, **818**, 387.
28 P. Lozano, T. de Diego, D. Carrie, M. Vaultier and J. L. Iborra, *Chem. Commun.*, 2002, 692.
29 M. T. Reetz, W. Wiesenhofer, G. Francio and W. Leitner, *Adv. Synth. Catal.*, 2003, **345**, 1221.
30 S. V. Dzyuba and R. A. Bartsch, *Angew. Chem., Int. Ed.*, 2003, **42**, 148.
31 C. C. Tzschucke, C. Markert, W. Bannwarth, S. Roller, A. Hebel and R. Haag, *Angew. Chem., Int. Ed.*, 2002, **41**, 3964.
32 *Supercritical fluid–ionic liquid biphasic systems*, D. J. Cole-Hamilton, T. E. Kunene, and P. B. Webb, in *Multiphase Homogeneous Catalysis*, ed. B. Cornils, Wiley, Weinheim, in the press.
33 P. Wasserscheid and W. Keim, *Angew. Chem., Int. Ed.*, 2000, **39**, 3773.
34 G. Smith, D. J. Cole-Hamilton, A. C. Gregory and N. G. Gooden, *Polyhedron*, 1982, **1**, 97.
35 M. Kranenburg, Y. E. M. Vanderburgt, P. C. J. Kamer, P. W. N. M. van Leeuwen, K. Goubitz and J. Fraanje, *Organometallics*, 1995, **14**, 3081.
36 R. P. J. Bronger, S. M. Silva, P. C. J. Kamer and P. van Leeuwen, *Chem. Commun.*, 2002, 3044.
37 R. P. Swatloski, J. D. Holbrey, S. B. Memon, G. A. Caldwell, K. A. Caldwell and R. D. Rogers, *Chem. Commun.*, 2004, 668.
38 B. Jastorff, R. Stormann, J. Ranke, K. Molter, F. Stock, B. Oberheitmann, W. Hoffmann, J. Hoffmann, M. Nuchter, B. Ondruschka and J. Filser, *Green Chem.*, 2003, **5**, 136.
39 B. Kaye, D. J. Cole-Hamilton and K. Morphet, *Stud. Conserv.*, 2000, **45**, 233.

Chemical recycling of polycarbonate in a semi-continuous lab-plant. A green route with methanol and methanol–water mixtures†

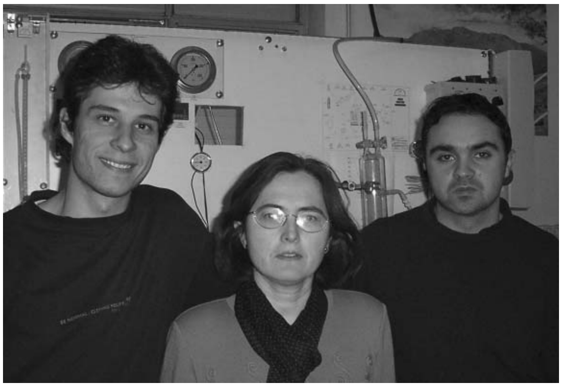
Raúl Piñero, Juan García* and María José Cocero

Received 11th January 2005, Accepted 14th April 2005
First published as an Advance Article on the web 22nd April 2005
DOI: 10.1039/b500461f

Alkali-catalysed depolymerization of polycarbonate (PC) wastes by alcoholysis in supercritical or near critical conditions has been studied in order to recover the essential monomer bisphenol A (BPA) and dimethyl carbonate (DMC) as a valuable by-product. This work aims to study the continuous process and possible scale-up for decomposition of both commercial PC and PC plastic wastes using methanol as solvent/reagent and NaOH as alkali catalyst. Total depolymerization of PC has been achieved working at a temperature range of 75–180 °C and pressures from 2 to 25 MPa. The influence of operation conditions on product yield, selectivity and reaction rate has been studied, including temperature, pressure, methanol/cosolvent ratio and catalyst concentration. BPA yields of 80–90% (kg product/kg PC) were achieved with a further crystallization and separation of the final product, resulting in BPA pure crystals (99.9%). DMC yield reached 35% (kg DMC/kg PC) and was proved to be strongly dependent on pressure and methanol/H_2O ratio. Non desired by-product yield was negligible when pure methanol was used as solvent and selectivity decreased with increasing methanol/H_2O ratio.

Introduction

Chemical recycling of polymer wastes has gained great importance during recent years. The increasing amount of polycarbonate wastes coming from CDs and plastic objects makes it necessary to develop a suitable process to recycle these materials. Several depolymerization processes have been reported in order to decompose PC into the form of its essential monomer, bisphenol A (BPA), which is the main raw material for polycarbonate (PC) manufacturing. Some organic solvent systems such as methylene chloride with ammonia or phenol in combination with an alkali catalyst were applied successfully for PC decomposition,[1,2] but they required a complicated product separation in addition to the environmental safety problems of using highly toxic organic solvents. On the other hand, several studies dealing with chemical recycling of poly(ethyleneterephthalate) (PET) reveal that alkali decomposition with non-aqueous solvents, such as ethylene glycol[3] at 150–180 °C and mixtures of ethanol or methanol with dioxane at lower temperatures[4] are also very effective. In addition, recent studies focused on the recycling of (PET) by methanolysis under supercritical or near critical conditions have shown excellent results. Complete depolymerization of PET was achieved providing dimethylterephthalate as the main product (90–100% yield) at 240–260 °C and 11 MPa with a reaction time of 30–50 min in a batch reactor,[5] and fine results with similar operation conditions have been obtained in a continuous lab-plant.[6] Some experiments on polycarbonate (PC) decomposition in a batch reactor have shown that alkali-catalysed methanolysis of PC at low temperature (40–60 °C) and atmospheric pressure hardly



Juan García, María José Cocero and Raúl Piñero

The High Pressure Processes Group, HPP, was set up by María José Cocero in 1998 to promote the use of supercritical fluids for the development of sustainable technological processes. The Green Engineering Group, GEG, was started by Juan García Serna as a new research line inside the HPP group to develop the Green Engineering philosophy. Currently, the GEG is formed of Juan García and Raúl Piñero working in collaboration with the HPP group. María José Cocero is a Chemical Engineering Professor, Juan García is an Assistant Lecturer and Raúl Piñero is a PhD student at the Department of Chemical Engineering and Environmental Technologies at the University of Valladolid (Spain).

---

† This work was presented at the Green Solvents for Synthesis Meeting, held in Bruchsal, Germany, 3–6 October 2004.

*jgserna@iq.uva.es

works since it provides very low yields (7% of bisphenol A) and requires a long reaction time (330 min),[7] thus a mixed solvent of methanol and toluene (1 : 1 v/v) is required to reach yields of 90–96% of BPA and improve reaction times. Another alternative based on catalysed hydrolysis has been performed with no presence of alcohols. In this case, decomposition of polycarbonate in subcritical and supercritical water using NaCl and Na_2CO_3 as catalysts offered quite disappointing results with yields of 67% at 300 °C for 6 h in a batch process.[8] This paper presents a quantitative study on depolymerization of both commercial polycarbonate and plastic wastes by alkali-catalysed alcoholysis in a continuous lab-plant within a large range of operation conditions: temperature, pressure, catalyst concentration (NaOH) and methanol/cosolvent ratio. The purpose of this work has been to try to minimise catalyst concentration and totally avoid the use of organic toxic cosolvents, *e.g.* toluene. Instead of that, water has been proposed as methanol cosolvent. The low reactivity of methanol at low pressure and temperature without additional organic solvents has been overcome by increasing both temperature and pressure and running the reaction in a continuous reactor. Bisphenol A (BPA) and dimethyl carbonate (DMC) have been obtained as the main products of PC plastic waste depolymerization. These compounds can be reused as raw materials for PC production in environmentally friendly processes where traditional phosgene has been replaced (melt-transesterification).[9]

Green tips

It should be stressed that the aim of this research is to study the recycling of optical disks giving a solution which considers the recovery of the starting monomers, *i.e.* BPA and DMC from either pure PC or CD wastes. That is the main reason why methanol has been used as the reagent. In general, when other different aliphatic alcohols, such as ethanol and n-propanol are used, dialkyl carbonates are obtained, *i.e.* diethyl carbonate and dipropyl carbonate respectively.[10] The use of ethanol and propanol is recommended to avoid VOC emissions whenever DMC is not required.

As regards the atom and mass economy one may observe that the depolymerization of PC with methanol is an addition reaction producing both BPA and DMC as desired products. Thus, the atom and mass efficiency is theoretically 100%.

From an exergetic point of view, the chemical recycling of PC into its starting monomers implies a considerable lost of exergy. There are other methods which lose less exergy. For instance, mechanical recycling, where the metal layer is separated by mechanical means, produces an excellent PC with almost the same optical properties.[11] However, this method can only be used with some specially prepared optical disks. In this way, the method proposed in this paper is a more general method which can be applied to all PC wastes.

Experimental

Materials and reagents

Pure poly[2,2-bis(4-hydroxyphenyl) propane carbonate] (PC) pellets with a particle size of 3 mm length × 2 mm diameter have been used as well as commercially available methanol (>99% purity) and sodium hydroxide (>99%). Standard samples of bisphenol A, phenol, 4-*p*-isopropylphenol, 4-*t*-butylphenol and dimethyl carbonate, all of them of 99.9% wt purity, were obtained from Aldrich and PC wastes coming from CDs and DVDs were collected for recycling tests. They were previously broken into pieces with 5 × 5 mm size, washed with hot deionized water (70 °C), and finally dried at 103 °C before being charged into the reactor.

Lab-plant

Depolymerization experiments have been performed in a semi-continuous plant whose flow diagram is represented in Fig. 1. The lab-plant has been designed to operate with a large range

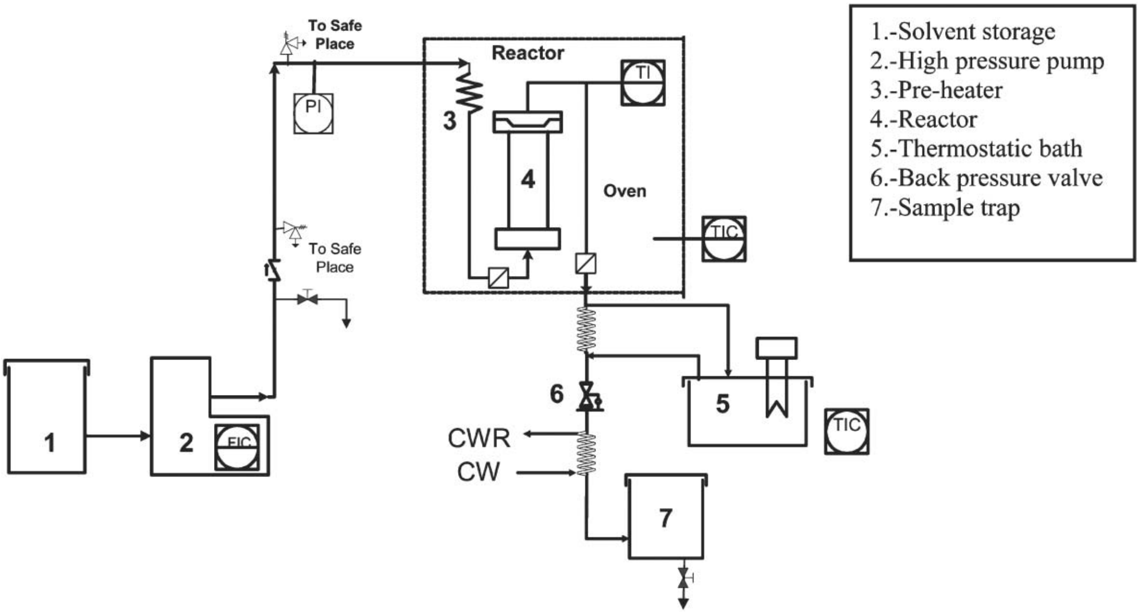


Fig. 1 Flow diagram of PC recycling lab-plant.

of operation conditions: temperatures from 20 to 400 °C and pressures from 0.1–30 MPa can be reached with a flow rate of 0.6 to 12 × 10^{-4} m^3 h^{-1}. PC pellets are charged into a high pressure vessel (10^{-4} m^3) confined inside an oven provided with a temperature control system. The liquid solvent (methanol + NaOH) is pumped and then preheated inside the oven before entering the reactor where reaction with the semi-melted polycarbonate takes place. The temperature of the reaction mixture is measured in the outlet of the reactor to know the real temperature of the process. Depending on the operation conditions, the outlet product can be quite viscous, especially at low temperature (10–15 °C). In order to facilitate the operation and avoid precipitation and blocking problems with the regulation valve, the reaction mixture is cooled with thermostatic water at 60–70 °C. The back pressure valve allows regulation of the pressure of the system and depressurisation of the outlet stream to atmospheric conditions. Cooling water is used to low the temperature of the product stream and condense it completely.

Quantitative/qualitative analysis of products

Reaction products were analyzed by high performance liquid chromatography (HPLC) and gas chromatography (GC) to identify and quantify bisphenol A (BPA) and dimethyl carbonate (DMC) respectively, as well as phenol and other aromatic by-products that could be formed, (see *Reaction pathway*, Scheme 1). The HPLC analyses were carried out on a Waters separation module equipped with an UV detector, (Waters 2487 Dual λ Absorbance) set at 254 nm, and a LC column Waters C-18 (5 μm particle size, 4.6 × 250 nm). The mobile phase, an acetonitrile–aqueous buffer solution (45 : 55, v/v), was employed with an isocratic flow rate of 0.6 × 10^{-4} m^3 h^{-1} at 40 °C. The reaction samples were diluted 25 times with methanol and 5 μL was injected. The Breeze Waters HPLC software was used for data acquisition and integration. The method provided a good separation of aromatic compounds, in particular phenols and bisphenols, showing high sensitivity for phenol and benzoic acid. Non-aromatic and volatile compounds such as DMC were not detected under these conditions. A gas chromatography (GC) method has been developed in order to identify and quantify DMC and other volatile compounds. Liquid samples were injected into HP 5890 GC equipment and reaction products were separated by a Teknokroma Hayesep P column (3 m × 1/8″, 60–80 μm). The components were detected by TCD using helium as carrier. The temperatures of the detector and injector port were 200 °C and 150 °C, setting a gradient temperature from 80 to 180 °C for the oven. Reaction samples of 2 μL were injected without dilution.

Final product purification. Crystallization of BPA

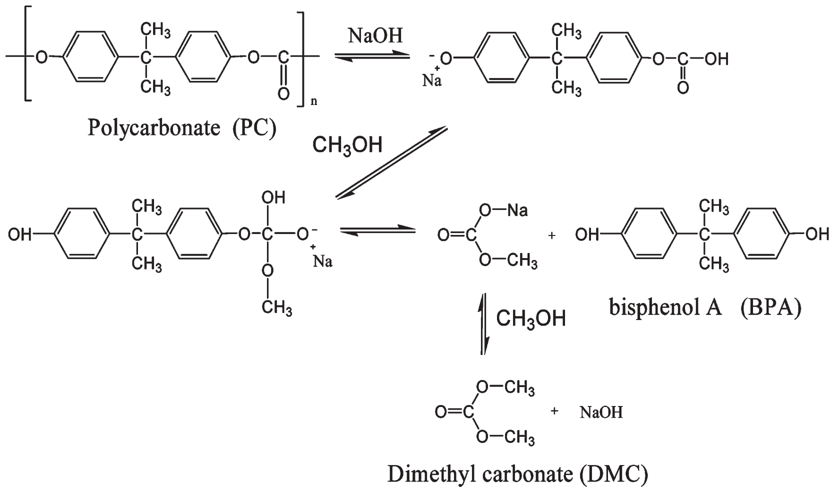
Separation and purification of bisphenol A were achieved by crystallization in water with further filtration and drying at 103 °C to get rid of water and volatile compounds. A 10^{-5} m^{-3} sample of the reaction mixture was quenched by pouring it into 2 × 10^{-4} m^3 of distilled water and letting the mixture stand at room temperature for 24 h. After filtrating and drying the crystals, the product purity was determined by HPLC and checked by FTIR spectroscopy. Instead of water, toluene was also used as anti-solvent (2 × 10^{-6} m^3 of sample in 10^{-5} m^3 toluene) in order to compare crystallization rate, yield and size of BPA crystals.

Results and discussion

Reaction pathway

Decomposition of polycarbonate in the presence of methanol and an alkali catalyst may be explained by different mechanisms of reaction which imply basically two possibilities: alkali-catalysed methanolysis and alkali reaction without methanol consumption. In the first one, methanol acts both as solvent and reagent, while the alkali (NaOH) improves the reaction rate as catalyst. The second one implies the consumption of NaOH as reagent with no reaction of methanol, which only acts as solvent.[9]

Scheme 1 shows the reaction mechanism for PC depolymerization by alkali-catalysed methanolysis where bisphenol A (BPA) is recovered and dimethyl carbonate (DMC) is obtained



Scheme 1 Mechanism of PC depolymerization by alkali-catalysed methanolysis with NaOH.

as a valuable by-product. The surface of PC particles is partially dissolved or swollen by the solvent effect, increasing the relative concentration of the functional group for attack by NaOH. The first step of this reaction route implies the attack of NaOH on the carbonate bond to break the polymer chain and produce half salt–half ester of carbonate; thus most of the alkali is reacted and its concentration decreases considerably. Due to the alkali consumption and lowering in concentration, the intermediate compound reacts with methanol, which breaks the double bond of the carbonate group and enables the methanol molecule to couple. Then, the second intermediate compound decomposes to give BPA and half salt of methyl carbonate, which finally reacts with methanol to produce DMC and regenerate NaOH for the catalytic cycle. The formation of DMC as a by-product implies that methanol acts as reagent and NaOH only as catalyst.

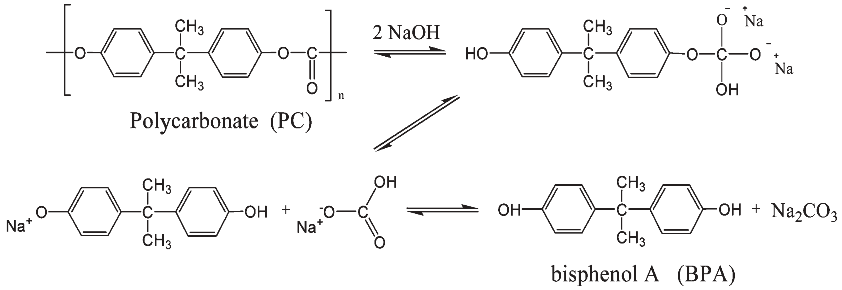
However, results so far indicate that DMC yield may be quite low at certain conditions of operation, which suggests that another mechanism without DMC formation controls the reaction pathway. Scheme 2 shows a possible reaction route in which methanol does not react and cannot enable the DMC production. In this case, NaOH acts as reagent and is consumed quantitatively instead of methanol. As a first step, the carbonate bond undergoes attack by NaOH and produces an equimolar mixture of half salt of carbonic acid and half salt of BPA. This mixture reacts and forms an equilibrium with another mixture system of sodium carbonate, which precipitates allowing BPA to stay in the phenolic form.

Some results have shown that depolymerization of PC may provide other compounds as a consequence of BPA degradation at high temperature, specially phenol and several by-products of bisphenol. In addition, it has been proved that depolymerization by hydrolysis or a combined mechanism of methanolysis–hydrolysis when using a mixed solvent of methanol–water, is less selective and generates different compounds (*e.g.* *p*-isopropylphenol, 4-*t*-butylphenol,*etc.*). Scheme 3 gives an overview of the reaction pathway when alcoholysis is carried out with methanol and NaOH as catalyst.

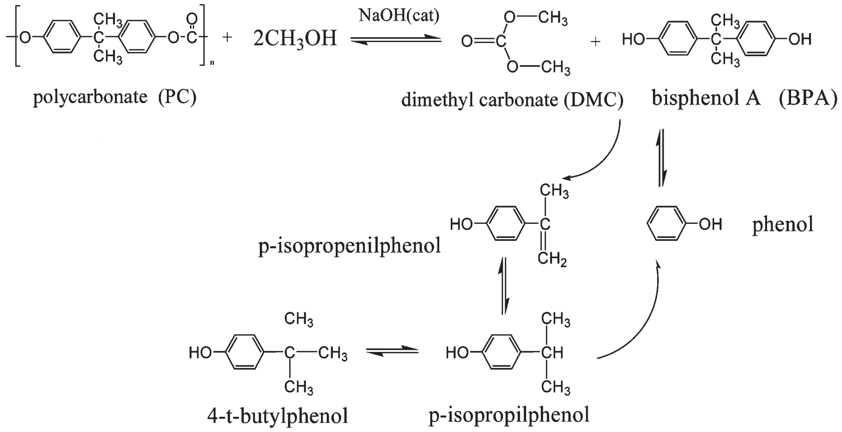
Anyway, the results obtained in the lab plant reveal that the reaction is extremely selective, specially when only methanol is used without water or any other solvent, giving the maximum yield of BPA and nearly negligible yields of by-products. The experimental results allow the two chemical pathways to be validated. Quantitative analyses of the reaction mixtures using HPLC and FTIR spectroscopy have been performed to prove that bisphenol A is nearly the only aromatic product formed in the reaction (Fig. 2). A suitable gas chromatography method has been also carried out to detect the presence in the reaction mixture of any other volatile compound which could be formed in the reaction, apart from DMC.

Effect of reaction conditions

The effect of the operation conditions on product yield and operation time for complete depolymerization of PC were studied in order to select the best conditions which allow optimal recovery of BPA and DMC reducing the amount of



Scheme 2 Mechanism of PC depolymerization by alkali reaction with no methanol reaction.



Scheme 3 Reaction pathway of PC decomposition with methanol and a catalytic amount of NaOH (assuming reaction mechanism 1).

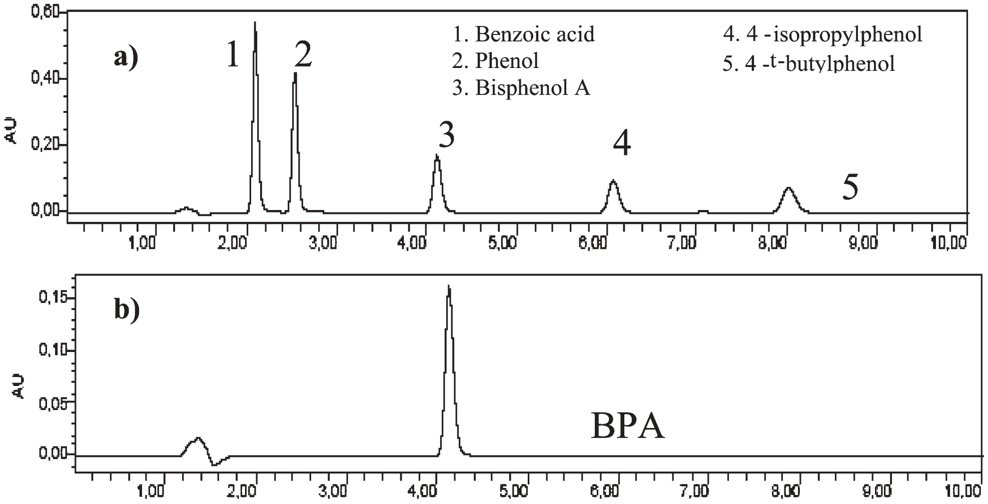


Fig. 2 (a) HPLC chromatogram of a standard solution used for HPLC calibration in the method described in the Experimental section (1200 ppm BPA). (b) HPLC chromatogram of a sample of the reaction mixture when methanol is used as solvent–reagent to depolymerize polycarbonate under the conditions described.

NaOH. Several reaction parameters have been studied including temperature, pressure, catalyst concentration and cosolvent effect. Reaction rate has been proved to be very dependent on temperature, catalyst concentration and H_2O/methanol ratio. However, no significant effects on reaction time were observed with pressure changes. On the other hand, DMC yield is strongly dependent on pressure, catalyst concentration and the presence of water, which inhibits DMC formation. All experiments have been performed at a flow rate of 3×10^{-4} m^3 h^{-1} using 0.020 kg of PC. The reaction parameters were varied one at a time, with all other conditions being fixed.

Effect of temperature

The effect of reaction temperature (75–180 °C) on product yield and rate of depolymerization was investigated at 10.0 MPa using a solution of methanol and NaOH (10 kg m^{-3}). Results are shown in Fig. 3. As the temperature was raised, the time for complete depolymerization decreased considerably, especially below 100 °C. The yield of BPA increases with temperature and keeps stable over 150 °C. It is particularly high (80–90%, kg BPA per kg PC) taking into account that the molar weight of the PC monomer is bigger than the BPA molar weight and the maximum yield of BPA (expressed in terms of kg BPA per kg PC) is approximately 90%. In the same way, the yield of DMC (which has an optimum of 35%, kg DMC per kg PC, assuming the reaction route given in Scheme 3) reached values of 8–20%, keeping more or less stable over 100 °C. Finally the production of non-desired by-products (such as phenol) is neglected giving a yield of approximately 1.5%. These results contrast with the poor yield (7% BPA) obtained when reaction is carried out at low temperature (40–60 °C) in a batch reactor, with a long reaction time (330 min),[7] and demonstrates that the reaction rate is considerably improved when the reaction is carried out under continuous flow conditions and the temperature is raised over 80–90 °C. In fact, both yield and time of operation are comparable with results obtained in a batch process (40–60 °C) in a mixed solvent of methanol and toluene (1 : 1 v/v) where a reaction time of 70 min was required to reach a 90–96% BP yield.[7]

Effect of pressure

As can be seen in Fig. 4, pressure has no influence on operation time and it is not a significant parameter for the kinetics of the reaction. The yield of BPA and phenol remains stable at 90% (kg BPA per kg PC) and 1.5% (kg phenol per kg PC). In this case, experiments have been carried out at 180 °C and an NaOH concentration of 2 kg m^{-3} which allow optimal recovery of BPA and DMC. The time required for complete decomposition is not affected significantly by changes in pressure. However, it is demonstrated

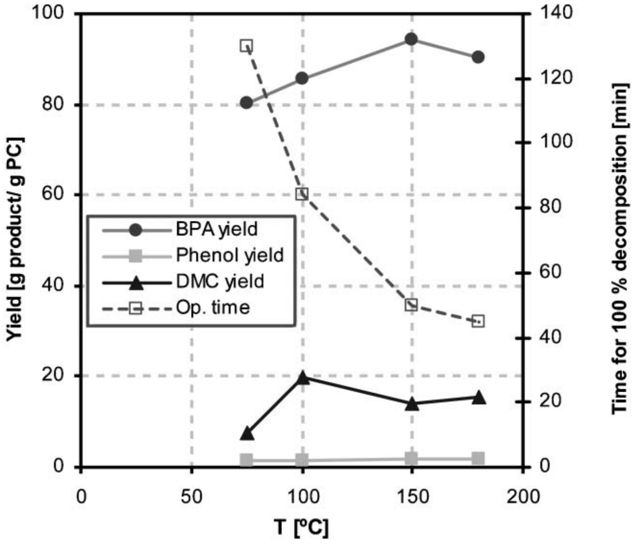


Fig. 3 Effect of temperature on PC (0.020 kg) decomposition in methanol at 10 MPa, [NaOH] 10 kg m^{-3} and flow rate 3×10^{-4} m^3 h^{-1}.

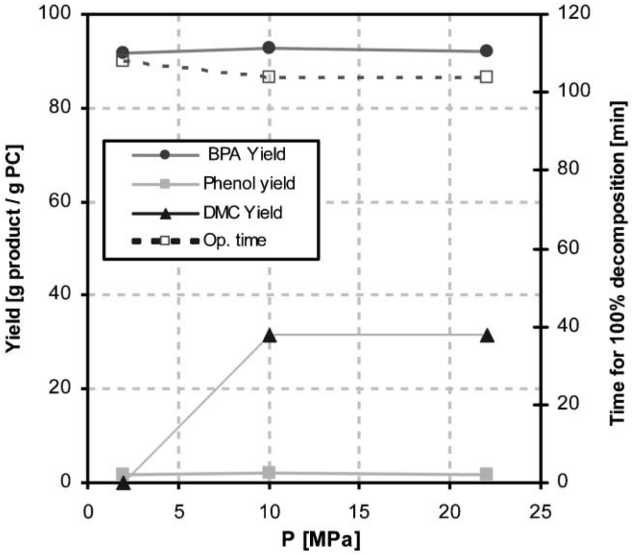


Fig. 4 Effect of pressure on PC (0.020 kg) decomposition in methanol at 180 °C, [NaOH] 2 kg m^{-3} and flow rate 3 × 10^{-4} m^3 h^{-1}.

that when the reaction is performed at low pressure (1.0 MPa), it inhibits the formation of DMC totally. Thus, pressure has little influence on the degree of depolymerization and the yield of products when reaction pressure surpasses the critical pressure of methanol, while the pressure has a great importance on DMC formation around the critical point. This is because the density of the solvent under supercritical conditions is high, nearly that of the normal liquid, enhancing the capacity for solvation.

Effect of catalyst concentration

To investigate the effect of NaOH concentration on the depolymerization behaviour of PC under near critical conditions, a series of experiments with different catalyst concentrations, varying from 0 to 10 kg m^{-3} NaOH, were performed at 180 °C, 10.0 MPa and a flow rate of 3 × 10^{-4} m^3 h^{-1}. Fig. 5 displays the influence of NaOH concentration up to 2 kg m^{-3} and then remains stable providing an optimal BPA recovery of 90% (kg BPA per kg PC). Catalyst concentration has no influence on phenol and other by-products whose yield can be considered negligible (1–2%). However, the yield of DMC is considerably affected by the amount of NaOH, initially increasing with increasing NaOH amount. However, from 2–3 kg m^{-3} increasing NaOH lowers the DMC formation. This suggests that a high catalyst concentration assists the mechanism of reaction where NaOH reacts quantitatively, (without methanol consumption, Scheme 2), but a catalytic amount of NaOH helps to initiate the reaction with a further reaction of methanol and recovery of NaOH in a catalytic circle, (Scheme 2). In addition, as the catalyst concentration was increased, the rate of depolymerization significantly decreased up to a concentration of 2–2.5 kg m^{-3}, and thereafter operation time decreased slowly.

Effect of cosolvent. H_2O/methanol ratio

The effect of a cosolvent such as water on both the rate of depolymerization and the yield of the reaction products was investigated in a mixed solvent of water and methanol at 180 °C and 10 MPa, by varying the ratio of H_2O/methanol (0, 0.5, 1, 1.5). As can be seen in Fig. 6, depolymerization of polycarbonate in the presence of water is less selective and the yield of BPA decreased (from 90 to 80%), although the yield of phenol does not increase since different by-products are formed instead. On the other hand, the presence of water inhibits the formation of DMC due to a lowering of the methanol concentration which prevents methanol from reacting (Scheme 2). Finally, time operation increased progressively with the ratio H_2O/methanol which represents another disadvantage for the use of water.

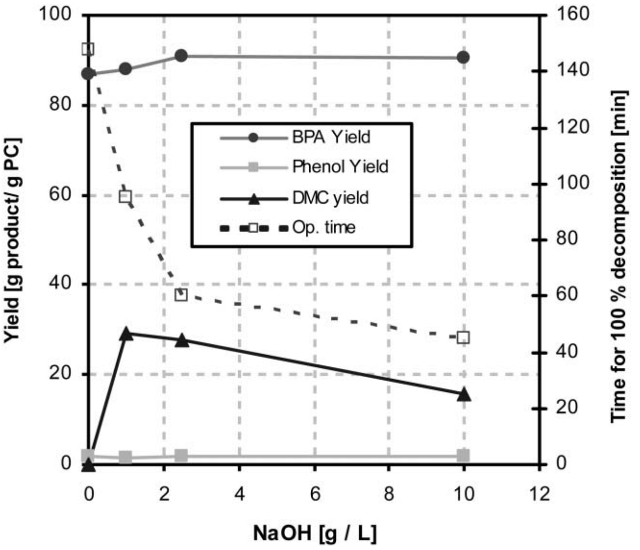


Fig. 5 Effect of catalyst concentration on PC (0.020 kg) decomposition in methanol at 10 MPa, 180 °C and flow rate 3 × 10^{-4} m^3 h^{-1}.

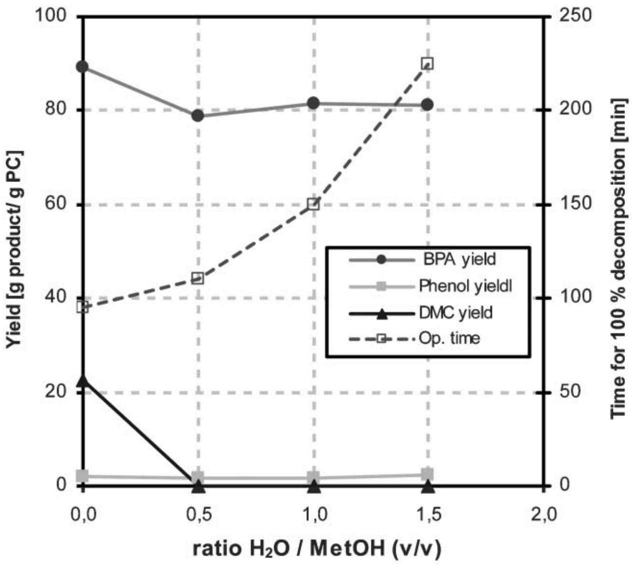


Fig. 6 Effect of cosolvent on PC (0.020 kg) decomposition at 180 °C, 10 MPa, [NaOH] 2 kg m^{-3} and flow rate 3 × 10^{-4} m^3 h^{-1}.

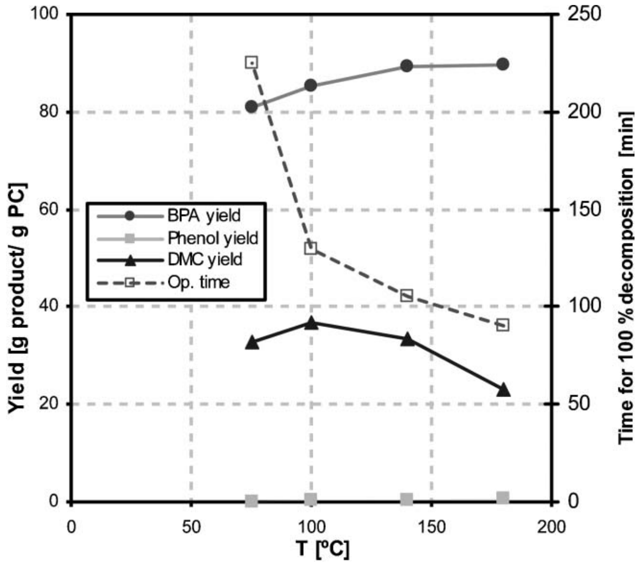


Fig. 7 Effect of temperature on chemical recycling of PC wastes (0.020 kg), at 10 MPa, 3 × 10^{-4} m^3 h^{-1} and [NaOH] = 2 kg m^{-3}.

Recycling of PC wastes

It is shown from the above-mentioned depolymerization results for pure PC that the optimal depolymerization conditions are at a temperature of 100–140 °C, a pressure of 9–10 MPa and an NaOH concentration of 1–2 kg m^{-3}. Under the optimal depolymerization conditions we have also studied the decomposition of waste polycarbonate (from CDs). The decomposition of the plastic wastes was performed at 10.0 MPa and 2 kg m^{-3} of NaOH, checking the effect of temperature on product yield and decomposition rate, and their behaviour was found to be completely analogous to the commercial PC. The results are shown in Fig. 7. The optimal temperature for PC recycling is around 120–140 °C, which allows maximum yields of both BPA and DMC to be obtained when the reaction in carried out at 10 MPa with a NaOH solution (2 kg m^{-3}) in pure methanol.

Crystallization of bisphenol A. Final product purity

Separation and purification of bisphenol A was achieved by crystallization in water, further filtration and drying. White BPA crystals were finally obtained with a purity of 99.9% wt. The purity of the final BPA crystals was analysed quantitatively by HPLC and the quality of the final product was also confirmed by FTIR spectroscopy analysis (Fig. 8). Fig. 9 shows the shape and size of the purified BPA crystals.

Conclusions

Polycarbonate depolymerization in methanol at near critical conditions is achieved providing bisphenol A and dimethyl carbonate. According to the results of the experiments, the optimal reaction conditions are 120–140 °C and 10 MPa with a catalytic reaction medium of 1.5–2 kg m^{-3} of NaOH in pure methanol. Under these conditions, an optimal yield of BPA and DMC is reached with negligible formation of non-desired by-products. The presence of water, as well as low pressure conditions, inhibits DMC formation. Reaction rate is considerably improved by temperature and NaOH

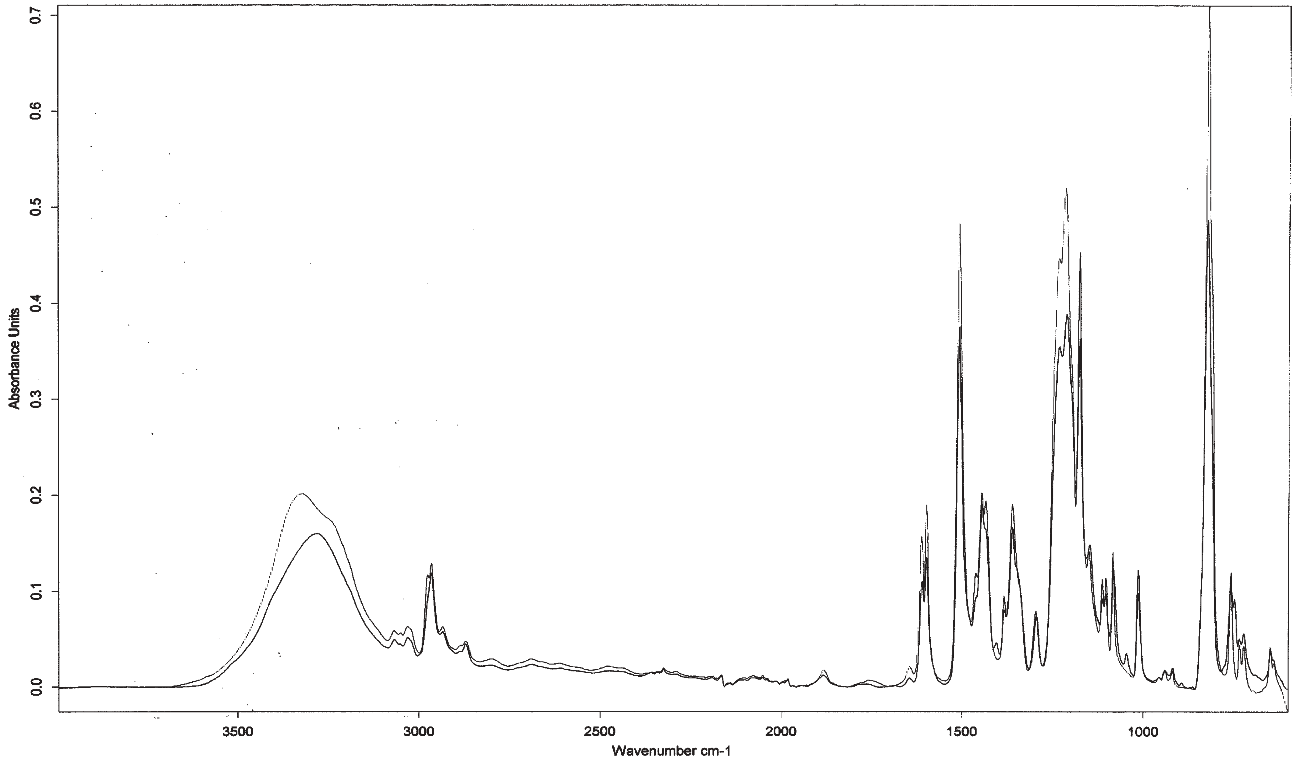


Fig. 8 FT plot showing the FTIR spectroscopy analyses of both commercial pure bisphenol A and the crystallized product obtained from the CDs recycling. As illustrated, both traces are nearly identical, which allows the final crystallized product to be identified as practically pure bisphenol A.

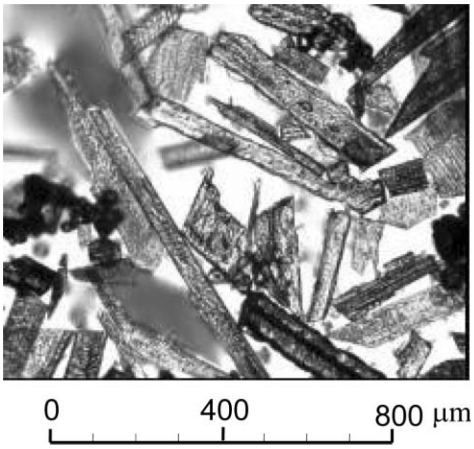


Fig. 9 Micrograph of the crystallized BPA final product obtained after the separation and purification process.

concentration, although a high catalyst concentration affects the mechanism of the reaction and makes DMC yield decrease. Reaction time increases with the ratio of H_2O/methanol, and selectivity is lower due to the formation of other aromatic products, while pressure has no significant influence on reaction rate. Experimental results in a continuous plant indicate that the alkali-catalysed methanolysis of PC at high pressure and temperature can be considered as a green process, not only because it allows the essential raw material to be recovered for the environmentally friendly manufacturing of PC, but it also employs less toxic solvents and minimises non-desired by-products by a greener more effective chemical route.

Acknowledgements

The authors wish to thank GEPESA (General Electric Plastics S.A.) for their scientific support and for the raw polycarbonate supplied for this work.

Raúl Piñero, Juan García* and María José Cocero
High Pressure Processes Group, Department of Chemical Engineering and Environmental Technology, University of Valladolid (Spain), c/Prado de la Magdalena s/n 47011, Valladolid, Spain.
E-mail: jgserna@iq.uva.es; Fax: +34 9834 23013; Tel: +34 983423174

References

1 D. Fox and E. N. Peters, US Patent No. 4.885.407, 1989.
2 S. J. Shafer, US Patent No. 5.336.814, 1994.
3 A. Oku, L.-C. Hu and E. J. Yamada, *Appl. Polym. Sci.*, 1997, **63**, 595.
4 L.-C. Hu, A. Oku, E. Yamada and K. Tomari, *Polym. J*, 1997, **29**, 708.
5 Y. Yang, Y. Lu, H. Xiang, Y. Xu and Y. Li, *Polym. Degrad. Stab.*, 2002, **75**, 185–191.
6 M. Goto, H. Koyamoto, A. Kodama, T. Hirose and S. Nagaoka, *J. Phys.: Condens. Matter*, 2002, **14**, 11427–11430.
7 L.-C. Hu, A. Oku and E. Yamada, *Polymer*, 1998, **39**, 3841–3845.
8 H. Tagaya, K. Katoh, J. Kadokawa and K. Chiba, *Polym. Degrad. Stab.*, 1999, **64**, 289–292.
9 W. B. Kim, A. Upendra and J. S. Lee, *Ind. Eng. Chem. Res.*, 2004, **43**, 1897–1914.
10 B. Tetsuo, Y. Eishin, M. Masaharu, O. Kenji and H. Masumi, *US Pat.*, 054238, 2004.
11 DaTARIUS, http://www.datarius.com, 2004.

View Online

Downloaded on 02 November 2010
Published on 03 May 2005 on http://pubs.rsc.org | doi:10.1039/B505148G

JOINT MEETING OF THE

2nd International Conference on Green and Sustainable Chemistry

AND THE

9th Annual Green Chemistry and Engineering Conference

June 20–24, 2005

HOTEL WASHINGTON ■ WASHINGTON, DC

Taking Measure of Green Progress: Opportunities to Meet Global Challenges

The program will include keynote addresses by leaders in the field, specialized workshops and numerous technical sessions in green chemistry and engineering. Leading international researchers from industry, academe, and government will discuss current status and key opportunities in the field. Attendees will:

- Learn the latest advances in green chemistry and engineering
- Hear what leading companies are doing to enhance competitiveness
- Discover how to build green chemistry and engineering into educational programs
- Assess future government actions and policies
- Network with participants from over 25 countries

KEYNOTE SPEAKERS

- **Prof. Ronald Breslow**, Columbia University
- **Dr. Linda Fisher**, Dupont
- **Prof. Ryoji Noyori**, RIKEN (The Institute of Physical and Chemical Research)
- **Prof. George Whitesides**, Harvard University

WORKSHOPS

- Green Chemistry and Engineering Education
- How to Write a Presidential Green Chemistry Challenge Nomination
- NSF Workshop on Biorenewable Resources
- Sustainability 101: Metrics and Best Practices

TECHNICAL SESSION TOPICS

- Alternative Synthesis and Solvents
- Biotech and Bio-based Materials
- Catalysis
- Electrochemistry
- Industrial Success Stories
- Metrics, Measures and Processes
- Nanotech and the Environment
- Green Chemistry and Engineering Awards
- Green Chemistry and Engineering Education
- Green Engineering
- Sustainable Energy
- Visions for the Future

Register online today to reserve your spot.

http://chemistry.org/meetings/greenchem2005.html

View Online

Downloaded on 02 November 2010
Published on 03 May 2005 on http://pubs.rsc.org | doi:10.1039/B505148G

Issues in Toxicology

New Series from the RSC

Series Editors

Professor Diana Anderson, *University of Bradford, UK*

Dr Michael D Waters, *National Institute of Environmental Health Science, N Carolina, USA*

Dr Timothy C Marrs, *Food Standards Agency, London, UK*

This series is devoted to coverage of modern toxicology and assessment of risk and is responding to the resurgence in interest in these areas of scientific investigation.

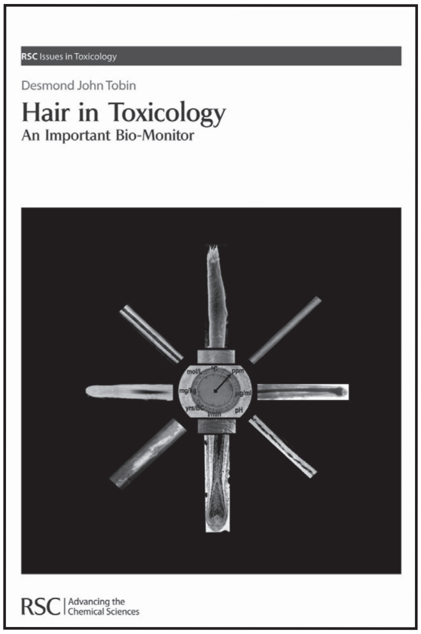
Topics covered include: hair in toxicology; toxicogenomics; reproductive (particularly male mediated) toxicology, biomarkers in toxicology, and possible chemical warfare

Ideal as a reference and guide to investigations in the biomedical, biochemical and pharmaceutical sciences at the graduate and post graduate level.

Readership academic researchers, graduate students, government institutions

Market toxicology, biomedicine, biochemistry, forensics and environmental/pollution sciences

Format hardcover



RSC Issues in Toxicology

Desmond John Tobin

Hair in Toxicology

An Important Bio-Monitor

RSC Advancing the Chemical Sciences

First title in the series

Hair in Toxicology: An Important Bio-Monitor

Edited by Desmond John Tobin, *University of Bradford*

This is the first book of its kind devoted exclusively to in-depth analysis of the hair shaft as an important tool for a diverse range of scientific investigations.

It covers:

- Information on the exposure of hair to chemicals and pollutants
- Toxicological issues relevant to the use of 'hair care' products
- The ability of hair to capture information on personal identity, chemical exposure, and environmental interactions
- How hair can provide an understanding of human life from archaeological and historical perspectives
- Future direction in the use of hair in toxicology

ISBN 0 85404 587 2 | approx 297 pages | approx £79.95 | Expected June 2005

www.rsc.org/books/5872

RSC | Advancing the Chemical Sciences

www.rsc.org/issuesintoxicology

01030502

Downloaded on 02 November 2010
Published on 03 May 2005 on http://pubs.rsc.org | doi:10.1039/B505148G

Conference on Knowledge-based Materials and Technologies for Sustainable Chemistry (MTSC)

1-5 June 2005 Tallinn, ESTONIA

Topics: new solvents and reaction media, catalysis and bio-catalysis, and development of new analytical techniques based on miniaturization and nanotechnology

COST Chemistry Action D29 workshop for workgroups is taking place during the conference.
One-day workshop for early stage scientists will be held in 1st June 2005.

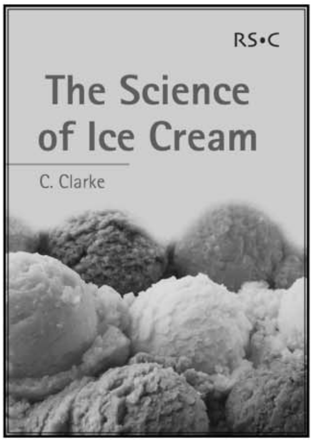
Deadline for abstract submission, advantageous registration and accommodation reservation is February 28, 2005.

Registration and submission of abstracts online
www.sustainchem.ttu.ee

Contacts: Mihkel Koel, project leader; vmihkel@chemnet.ee
Maria Borisova, organizer; mariab@chemnet.ee

1918 TALLINNA TEHNIKAÜLIKOOL TALLINN UNIVERSITY OF TECHNOLOGY · COST · The University of Nottingham · SIXTH FRAMEWORK PROGRAMME

The Science of Ice Cream



RSC Paperbacks
By C Clarke

This book is accessible to the general reader who has studied science to A level. It describes the link between the microscopic structure and the macroscopic properties of ice cream.

It describes:

- the physical chemistry underlying the manufacture of ice cream
- the ingredients and industrial production of ice cream and ice cream products
- a wide range of different physical and sensory techniques used to measure and assess ice cream
- the microstructure of ice cream and how this relates to the physical properties and ultimately the texture that you experience when you eat it

Softcover | 2004 | approx xvi + 182 | 0 85404 629 1 | £24.95 | RSC members' price £16.00

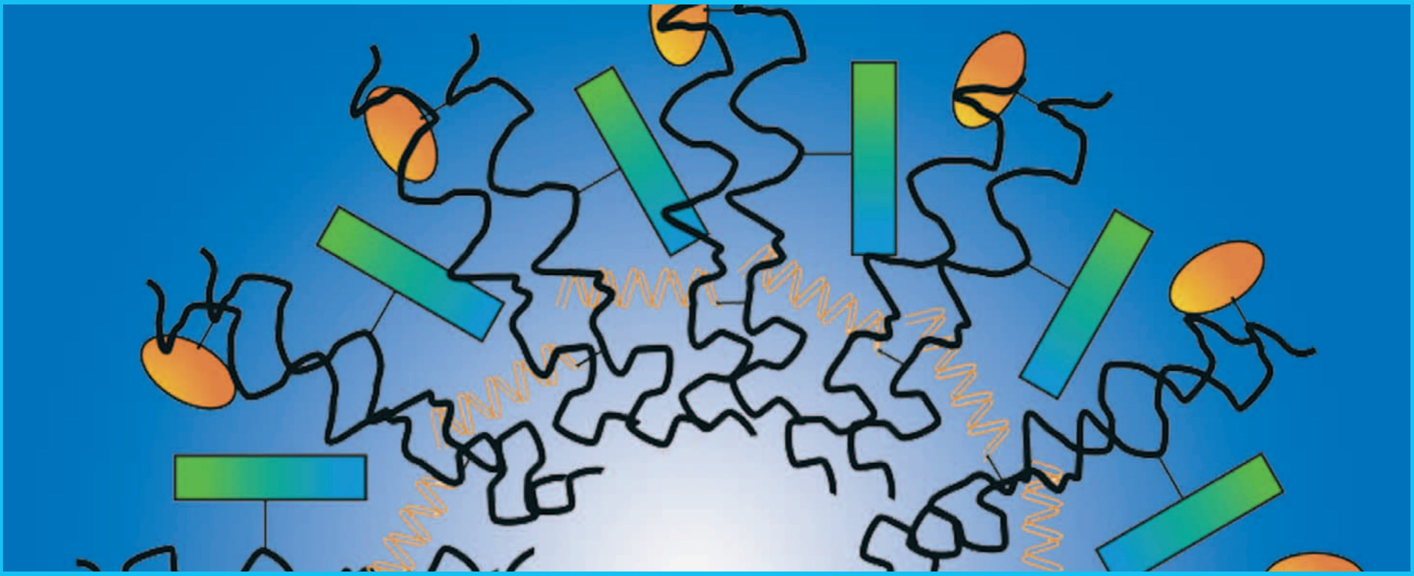
www.rsc.org/books/6291

RSCAD/3000422 MONO

Orders & further details **Sales & Customer Services**
Royal Society of Chemistry · Thomas Graham House
Science Park · Milton Road · Cambridge · CB4 0WF · UK

T +44(0)1223 432360 · F +44(0)1223 426017 · E sales@rsc.org
Or visit our websites: www.rsc.org and www.chemsoc.org
Registered Charity No. 207890

RS•C




CSR
Chemical Society Reviews
www.rsc.org/csr
RSC | Advancing the Chemical Sciences