My vision for *Green Chemistry*

Much has happened in the last twelve months in green chemistry. It continues to gain research prominence internationally, which is reflected in an ever-increasing number and quality of manuscripts received by the RSC for publication in the journal *Green Chemistry*. The journal is the premium journal for green chemistry, coming in with its first officially impact factor of 2.5—a great result for a journal which is now only in its fifth year. Many seminal papers have been published, and much progress has been made in bringing the journal to the fore. This is through the efforts of the contributing authors from many countries, the Editorial team, the Board, and the International Advisory Board. The enthusiasm for the journal in the wider context has been gratifying and I take this opportunity to thank all those involved in making it happen.

"*. . . Green Chemistry* has an impact factor of 2.5 . . ."

The journal is dedicated to green chemistry, with publications embracing the principles of green chemistry, which are found sprinkled in other journals, and as a multidisciplinary field there are a large number of such journals spanning the sciences and engineering. It is difficult to make a direct analysis of the percentage of overall publications which embrace the principles of green chemistry, but nevertheless it is rather small. Authors publishing in *Green Chemistry*, in addition to publishing in the premium journal for green chemistry, have their articles more exposed to the green chemistry community, beyond their own allied field. Such exposure must also be a significant benefit in advancing the field, and in this context, I encourage all potential authors to publish in *Green Chemistry*.

There has been some criticism that publications in the journal have been biased towards chemical synthesis and reaction media. This is in part a consequence of the link between green chemistry and the chemical and pharmaceutical industries. However, this is far from the full spectrum of green chemistry and we need to increase the scope of the journal. Publications are welcomed in ALL areas, including engineering, bio-catalysis, metrics, sustainable development, life cycle analysis, teaching, materials science, textile industry, bio-catalysis, and renewable resources, *etc*. These reflect the scope of material presented at conference dedicated to green chemistry.

Green Chemistry is a forum to facilitate the understanding of the value and importance of the field and to set standards and goals for the science. Quantifying the 'greenness' of a reaction or process (green chemistry metrics) need to further evolve. Toxicity is a key issue, and toxicity testing is important for green chemistry to move forward, as part of the march towards sustainable technologies. Toxicity will need to be considered in journal articles in the near future—watch out for details. Practicing researchers need to think about toxicity. It is no good saying 'we have done well with high yields, high atom efficiency *etc.*,' if there are serious toxicity issues.

Interest in green chemistry continues to increase in the academic, government and industrial sectors, and well as in the wider community where there is a realisation that green chemistry has the potential to ultimately develop sustainable technologies. With this increase and hopefully flow-on effect for the journal, we are looking for support of the journal in several ways, foremost submitting research papers. Then there are reviews, perspectives, and news articles, and the important refereeing of the papers to ensure we publish quality articles. For the latter, we would appreciate feedback on potential referees. Conferences dedicated to the green chemistry are more frequent, and beyond the journal there are books dedicated to the field, the most recent by Mike Lancaster, entitled 'Green Chemistry, An Introductory Text', also published by the RSC.

I embarked on research initiatives in green chemistry in the late nineties with university incentive seed funding for new research initiatives, while at Monash University. In the early days it was a case of discussing possible research in the field with colleagues, and once the research had been identified and started, I was amazed at the successes. In retrospect it became apparent that applying the principles of green chemistry increases innovation. There is a perception that research in green chemistry is too restrictive, particularly in the chemical sciences, but my experience is that it is more of a challenge, the innovation is up, and new chemistry is inevitable. It already has environmental and sustainable issues factored in, and therefore it is more likely to lead to down stream applications. This aside, there are winds of change for researchers, to encourage them to consider 'greening' their research. This is coming from postgraduate choice of research projects, pressures from industry and the community, and also pressures from government policy associated with targeting specific areas of research. Governments around the world are becoming increasingly aware of the importance of the field, which often comes under the umbrella of 'sustainability'. A rather provocative view, is that chemists have a moral obligation in taking on green chemistry as a contribution towards sustainable technologies.

Researchers should not feel that they need to make a quantum leap forward to advance green chemistry. Indeed, a quantum leap can be dangerous unless there is careful planning—'right the first time'. Incremental changes can result in big improvement in 'greenness', such as waste minimisation, resource utilisation *etc.*, perhaps while not entirely 'green'. Many researchers tend to stay in a loop—innovation leading to experiments leading to interpretation of results, refining the innovation, back to more experiments, and the cycle continues. Factoring in green chemistry is a paradigm shift, moving out of this circle, potentially with greater innovation, greater number of end users, greater chance of applications, greater appreciation of the community, and more, so why wouldn't you want to do green chemistry?

Green chemistry is complex, covering often disparate areas, and my vision for the journal is one of bringing all the areas of green chemistry to the journal, including metrics, life cycle analysis, and toxicity.

Professor Colin Raston is Chair of the Editorial Board of Green Chemistry, *and is the 2002 recipient of the Green Chemistry Award of the Royal Australian Chemical Institute.*

DOI: 10.1039/b302755b

The need for government funding for green chemistry in the USA

Green Chemistry and engineering refers to the design of chemical products and processes that reduce or eliminate the use and generation of hazardous substances, while keeping economic, as well as environmental, viability in mind. By virtue of more efficient use of raw materials and energy, products and processes that follow green chemistry principles are inherently more profitable and, thus, green chemistry and engineering are vital to the future of the U.S. chemical industry. An excellent example is the redesign of the sertraline process by Pfizer, an innovative technology that earned Pfizer a 2002 Presidential Green Chemistry Challenge Award. Sertraline is the active ingredient in the antidepressant drug Zoloft, which had global sales around $2.4 billion in 2001. Through fundamental process changes, Pfizer eliminated 440 metric tons of titanium dioxide wastes, 150 metric tons of 35% hydrochloric acid, and 100 metric tons of sodium hydroxide per year. Solvent usage was reduced from 60,000 gallons to 6,000 gallons per ton of sertraline produced. By implementing green chemistry principles, Pfizer has doubled overall yield, decreased raw material, energy, and water usage, and increased profitability.

The adoption of green chemistry and engineering technologies by industry is dependent upon advances in basic research. While some of this work is being performed in industry, significant contributions have been made by academia. Thus, government funding for green chemistry and engineering research is vital to the development of cleaner, safer and more profitable technologies. However, government funding for green chemistry and engineering research in the United States has been rather limited.

The primary mechanism for funding green chemistry and engineering research has been the NSF/EPA Technology for a Sustainable Environment (TSE) program. This program has awarded $45.8 million over six competitions since 1995. Projects have focused on a wide variety of research topics, such as less harmful solvents (*e.g.*, water, supercritical CO_2), biocatalysis, use of renewable feedstocks, process modeling and optimization, and life cycle assessment. The TSE program has been extremely successful in eliciting green chemistry and engineering proposals. As a result, funding success rates have been as low as 7%. This low success rate may well discourage good researchers from even applying to this program. The TSE program has been combined with the New Technologies for the Environment program into the new 2003 Environmental Technologies and Systems solicitation, which seeks proposals on fundamental and applied research in the physical and biological sciences and engineering that will lead to environmentally-benign methods for industrial processing/manufacturing; sustainable construction processes; and new science and technologies for pollution sensing and remediation. Since the overall program funding is just $9.5 million, and green chemistry and engineering is just one part of the solicitation, this cannot be considered a serious commitment to federal funding for green chemistry and engineering research.

Projects that could be classified as green chemistry and engineering are certainly funded by a number of other federal agencies, including DOE, DoD, and USDA. The DOE catalysis program, for example, promotes catalysis for green manufacturing technologies and the development of basic science for making new materials and processes for upgrading biobased feedstocks in terms of carbon management. The DoD sponsors a thin films coating program that supports research to eliminate VOCs and heavy metals from coatings. Through its Quality and Utilization of Agricultural Products program, the USDA seeks to promote new processes and new uses of bio-based materials, such as nutriceuticals, pharmaceuticals and biopesticides. Pockets of research funding within government agencies are important in engaging a broad constituency but are no substitute for a large-scale program focused on green chemistry and engineering research.

Anecdotal evidence suggests that government programs not specifically targeted at green chemistry and engineering or components thereof have, in some cases, actively discouraged proposals that identify themselves as green chemistry or green engineering. There appears to be a perception that the TSE program or programs from other agencies, such as those described above, that specifically solicit this type of research, should be sufficient to support all green chemistry or engineering research. Thus, it is difficult to identify any significant number of grants from, for instance, regular NSF programs, that might be considered green chemistry or green engineering research.

Because some green chemistry and engineering technologies are funded through several government programs, it is challenging to quantify the exact amount of funding that is given for this type of research. Nonetheless, it is clear that funding for green chemistry and engineering still remains a very small part of overall R&D funding. For instance, the TSE program has averaged only $5.7 million/year, in comparison to the overall NSF annual budget of $4.8 billion (fiscal year 2002), or the NSF Chemistry Division overall budget of about $150 million. Thus, NSF funding for green chemistry and engineering amounts to only 0.12% of the overall NSF budget and, by comparison, is just 3.8% of what is spent by the Chemistry Division. Even assuming that green chemistry and engineering funding through other agencies is ten times that of the TSE budget, this still pales in comparison with the overall federal spending on research and development of more than $100 billion annually. Considering the importance of green chemistry and engineering to the future of the U.S. chemical industry, the current government investment in this field can only be classified as appalling.

DOI: 10.1039/b302758a

It is imperative that government funding for green chemistry and engineering be transformed from its current pilot program status to true investment in the nation's future. A multifaceted approach is needed to implement a comprehensive program. All government funding agencies should work to incorporate programs and incentives for green chemistry and engineering in their portfolio. For some agencies, this will mean dramatically increased funding for programs specifically targeted for green chemistry and engineering. For others, this may mean designing new programs. NIH, for example, has a vested interest in the development of greener technologies that will minimize the use and production of toxic materials, thereby safeguarding human health. Green chemistry and engineering should also play an important role in the new U.S. Department of Homeland Security. By eliminating the use of hazardous materials in chemical plants, these facilities could then no longer be used as potential weapons by terrorists. Another mechanism to promote green chemistry and engineering would be to add new criteria to proposal evaluation that requires all researchers to be cognizant of the environmental impact of their work. At all agencies, incentives must be provided for program directors to fund green chemistry and engineering research in ways that do not negatively impact other programs. Furthermore, proposal reviewers with an understanding of green chemistry and engineering must be actively recruited to review proposals with a strong green chemistry and engineering emphasis.

In summary, there seems to be growing awareness in both academic and industrial scientific and engineering communities of the importance and benefits of green chemistry and engineering. In its 10-Year Outlook report on Complex Environmental Systems, NSF states that 'Chemical synthesis and manufacturing processes (must) *design in* rather than just *add on* environmentally sound technology.' However, the U.S. government investment in green chemistry and engineering does not seem to match the rhetoric. We call on all federal agencies to significantly increase their investment in green chemistry and engineering research in order to ensure a safe, sustainable, and secure future for our nation.

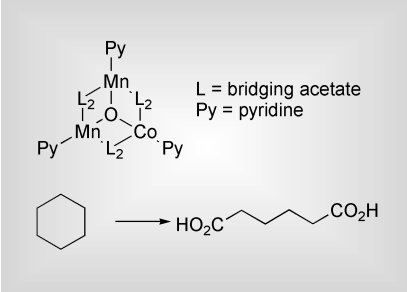
Joan F. Brennecke is Keating-Crawford Professor in the Department of Chemical Engineering at the University of Notre Dame. Mary M. Kirchhoff is Assistant Director at the Green Chemistry Institute (American Chemical Society).

Highlights

Duncan Macquarrie highlights some of the recent literature in green chemistry

Aerial oxidation

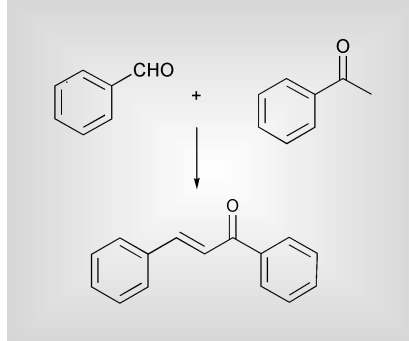
The aerial oxidation of hydrocarbons such as cyclohexane, and its mono-oxygenates to adipic acid is a key target to eliminate the use of nitric acid as stoichiometric oxidant. To this end, many researchers have developed routes (mostly metal-catalysed) involving the use of many terminal oxidants such as hydrogen peroxide, alkyl peroxides and hypervalent iodine compounds. Aerial oxidations have also been investigated with some success,



but always low conversions have been achieved. The group led by P. Ratnasamy from the National Chemical Laboratory in Pune, India, have now developed a trinuclear Co/Mn cluster system which gives almost complete conversion of cyclohexanone and cyclohexanol with very good selectivity towards adipic acid (*J. Catal.*, 2002, **212**, 39). Impressively, they also demonstrate that the oxidation of cyclohexane itself is possible with high conversions (up to 85.6%) although selectivity towards adipic acid is somewhat lower (up to 38%).

Basic catalysts

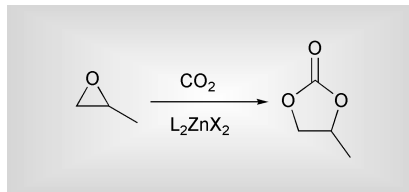
The development of novel strongly basic solids continues to produce new catalysts. Said Sebti of the University Hassan II in Casablanca, Morocco, and Jose Mayoral of the University of Zaragoza, Spain, have teamed up to develop an interesting strongly basic material (*J. Catal.*, 2003, **213**, 1) based on the thermal decomposition of sodium nitrate-modified natural phosphate (a mineral common in Morocco and broadly similar to hydroxyapatite). They have shown that the Claisen–Schmidt reaction is very smoothly catalysed by the material in the



presence of a small amount of methanol. The catalyst can be readily reused after filtration. Isolated yields are typically above 90%.

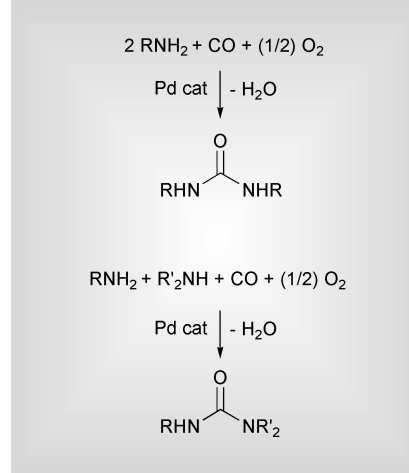
CO_x

The use of CO_2 as an alternative to phosgene is becoming more attainable via the formation of cyclic carbonates. The mechanism of action of one groups of catalysts has now been examined by workers at the CFC Alternatives Research Centre in Seoul, Korea University and Hanyang University, led by Hoon Sik Kim and Ho Gyeom Jang (*Chem. Eur. J.*, 2003, **9**, 3). They have shown that the choice of ligands around the central Zn



atom play a major role in the activity of the catalysts, with electron-donating ligands being more active. The nuclearity of the complex can also change – this is dependent on the epoxide formed, and not on the ligand environment; for example propylene oxide encourages the formation of dinuclear complexes, and ethylene oxide leads to trinuclear systems. The definition of some of the key features of the system will hopefully lead to more powerful and selective systems.

A similar area where CO_x has potential as a more benign building block than, for example, phosgene is the synthesis of ureas from amines. Bartolo Gabriele and his group at the University of Calabria and Mirco Costa at the University of Parma (both in Italy) have now shown that a simple PdI_2/KI system can catalyse the reaction of an amine with CO and oxygen (*Chem. Commun.*, 2003, 486). Substrate : Pd ratios of *ca.* 5000 were



found to give god rates of conversion and high yields. A pressure of CO_2 was found to be beneficial, thought to be due to the trapping of the amine as a carbamic acid. Excellent yields of symmetrical ureas were obtained very readily. More importantly, it was also found to be possible to form unsymmetrical amines, utilising the formation of an isocyanate intermediate. Thus the reaction of butylamine in the presence of dibutylamine led to a 71% yield of the tributyl urea, with only 17% of the dibutyl urea as a side product.

Ketones

Ammoximation

The ammoximation of ketones normally requires hydroxylamine, a reagent which is difficult to handle, and whose synthesis produces considerable waste. The ability of the TS-1 zeolite to achieve ammoximation using ammonia and hydrogen peroxide was a major advance, limited by the very small pore size of the material. Now a group led by Shinji Inagaki at the Toyota Central R+D lab in Nagakute-Aichi, Japan, has developed a larger pore material for this purpose

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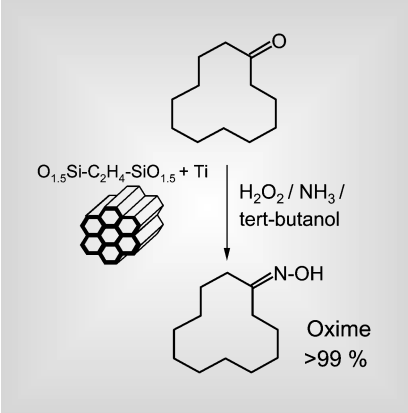
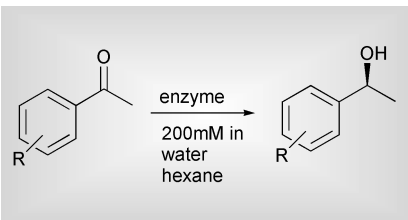


(*Chem. Commun*., 2003, 470). The material is a Ti substituted mesoporous silsesquioxane formed from tetraethoxyorthosilicate (a precursor to silica itself) and an ethylene-bridged disiloxane. Using this material, they have found that both cyclohexanone and cyclododecanone can both be very readily converted to the oxime under mild conditions. The role of the ethylene-bridged siloxane is considered to be critical in providing a hydrophobic environment for the reaction to proceed.

Reduction

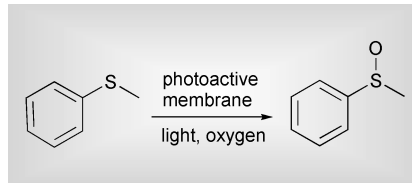
The reduction of ketones *via* enzymatic routes represents a potentially excellent and highly selective route to chiral alcohols. One major drawback is the low solubility of many ketones, which effectively limits the efficiency of the process by requiring very dilute solutions. Harald Gröger and colleagues at Degussa AG in Hanau have now come up with an efficient biphasic system which gets round this problem effectively (*Org. Lett*., 2003, **5**, 173). They used a hexane water



system for their reactions. The choice of hexane or heptane was critical to their success, as more polar solvent (including toluene) induced a rapid and extensive deactivation of the enzyme. With this system they achieved good conversions of acetophenones to the corresponding (S) isomers with ee's of 99%. The enzyme used was an alcohol dehydrogenase and NADH as cofactor. Conversion was independent of substrate concentration up to 200mM, significantly above what is possible with monophasic systems.

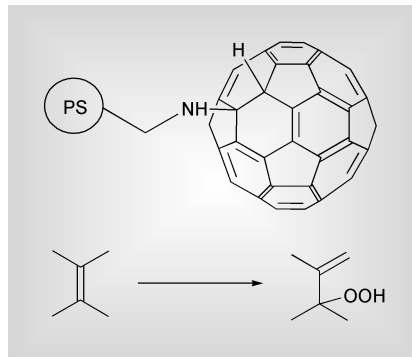
Photo-oxidations

Selective oxidation of sulfides to sulfoxides in a clean manner remains a challenge. An interesting approach based on photochemistry has been published by the groups led by Jyh-Myng Zen at the National Chung Hsing University in Taiwan (*Angew. Chem., Int. Ed.*, 2003, **42**, 577). Their setup involves a nafion



membrane encapsulating a $[Ru(bipy)_3]^{2+}$ cation. Irradiation of an aqueous acetonitrile solution of a sulfide in the presence of the membrane and oxygen led smoothly to high yields of the sulfoxide. Separation is easy, and the membrane can be reused easily.

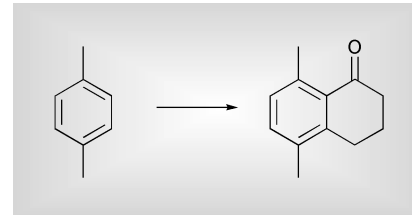
A further example of photo-oxidation is the use of supported fullerenes as singlet oxygen generators. The singlet oxygen can then be used in a series of addition reactions to form oxygenated compounds. The work, published by Anton Jensen and Coreen Daniels of Central Michigan



University, USA (*J. Org. Chem*., 2003, **68**, 207) involves the attachment of a fullerene onto aminomethylated polystyrene copolymers, and the subsequent generation of singlet oxygen from oxygen and light, which is then trapped by alkenes (*via* the ene reaction) or dienes (*via* the Diels–Alder reaction). α-Naphthol was also oxidised to the quinone. All the above reaction types are high-yielding.

Acylation of aromatics

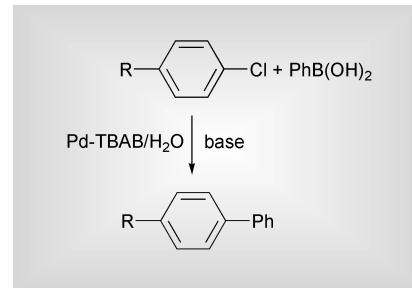
The clean acylation of aromatics is still an elusive goal, with the exception of highly



activated systems such as anisole. A communication from Hokkaido University, Japan, from the group of Toshio Okuhara contributes to this theme. (*Chem. Lett*., 2002, 1104). His group have used a silica-immobilised heteropolyacid to effect the acylation of alkylbenzenes with γ-butyrolactone, to give the bicyclic product. Using either $H_4SiW_{12}O_{40}$ or $H_3PW_{12}O_{40}$ on Aerosil, they achieved the alkylation of mesitylene with conversions as high as 91%, and selectivities up to 100%. This was in contrast to a range of other solid supports which were much less active. With *p*-xylene, the second step, acylation is also possible, and here a conversion of 75% and a selectivity of 78.7% were achieved.

Suzuki reaction

Advances continue to be made in the heavily investigated Suzuki reaction. The group led by Robin Bedford and Craig Butts at the University of Exeter, UK, have shown that aryl chlorides can be coupled under aqueous ligand-free conditions (*Chem. Commun*., 2003, 466) . They have found that the use of water as

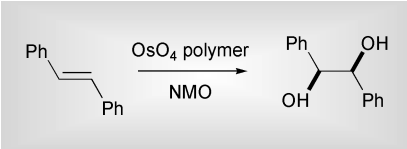


solvent along with tetrabutyl ammonium bromide (TBAB) allows the coupling of chloroanisole, chloroacetophenone and chlorotoluene with benzene boronic acid in reasonable times. The catalyst used in simply palladium acetate and potassium carbonate is used as the base. Yields up to 94.5% were achieved, and turnover numbers as high as 3200 were also possible.

Microencapsulation

Microencapsulation of reagents in polymers represents an interesting method of facilitating handling and separation of 'awkward' or expensive reagents and

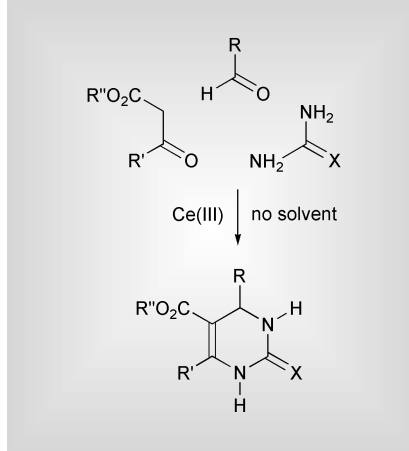
catalysts (see first review below). Here, the groups led by Steve Ley from Cambridge University, UK, has demonstrated the efficacy of an OsO_4 encapsulated in a polyurea polymer as a catalyst for dihydroxylation of alkenes (*Org. Lett*., 2003, **5**, 185). They formed



the reagent by polymerising a di-isocyanate with water in the presence of polyvinyl alcohol, osmium tetroxide and a polyether. The catalyst was then used to dihydroxylate a range of alkenes in excellent yields using *N*-methyl-morpholine oxide as co-oxidant. Five reuses were possible without loss in activity, and adsorption of product onto the polymer was not observed. The same catalyst could be used with sodium periodate for the cleavage of alkenes to ketones.

One-pot syntheses

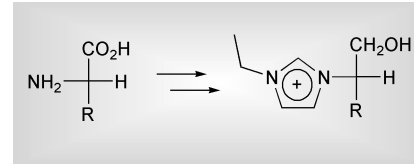
The telescoping of organic reactions by combination of steps into a single transformation has the potential advantage of minimising isolation procedures, and also may reduce the number of solvents used. The Biginelli reaction is one such



procedure where consecutive reactions are carried out in one pot. D. Subhas Bose and his colleagues from the Indian Institute of Chemical Technology have now shown that the Biginelli reaction can be performed under solvent free conditions with cerium (III) catalysis (*J. Org. Chem*., 2003, **68**, 587). This way, the reaction proceeds without solvent as well as it does in ethanol or water, and high yields are obtained. The presence of Ce as catalyst increases the yield obtained substantially compared to traditional Biginelli conditions.

Ionic liquids

Ionic liquids are a group of compounds which are generating considerable excitement. Very recently, chiral ionic liquids have been prepared, which may be useful in enantioselective reactions. Weiliang Bao and colleagues from Zhejiang University have published a route to chiral ionic liquids staring from



amino acids (*J. Org. Chem*., 2003, **68**, 591). Their route produces one chiral group attached to one of the ring N atoms. No applications were quoted, but the synthesis appears relatively widely applicable.

Reviews

Shu Kobayashi and Ryo Akiyama of the University of Tokyo have written a feature article on their polymer-microencapsulated catalytic systems. The overview looks at immobilised Sc, Os, Pd and Ru (*Chem. Commun*., 2003, 449).

Mark Ormerod reviews solid oxide fuel cells in *Chem. Soc. Rev.* (2003, **32**, 17) providing a fascinating overview of the current state of the art and discusses the challenges facing these alternative energy sources.

The Green Chemistry Institute

Dennis L. Hjeresen (GCI Director) and Mary Kirchhoff (GCI Assistant Director)

reflecting on two years in partnership with the American Chemical Society

January 2003 marked the second anniversary of the alliance between the Green Chemistry Institute (GCI) and the American Chemical Society (ACS). Two years ago, GCI was a few dedicated volunteers communicating the importance of green chemistry in cooperation with a worldwide network of like-minded scientists, engineers, and government and industry leaders. Because ACS is the world's largest scientific society, with over 163,000 members and a vast array of programs and services, the alliance between GCI and ACS was a little like merging a gnat with an elephant.

Since becoming part of ACS, our strategy has been to include green chemistry as a component of ACS activities rather than pursuing a distinctly separate green chemistry identity. For example, rather than scheduling a separate green chemistry technical track at national meetings we have promoted green chemistry within existing technical divisions. Thus, symposia have focused on applications in pharmaceuticals, agriculture, nuclear, energy, catalysis, ionic liquids, and education. The Fall 2003 ACS National Meeting will feature an ACS Presidential Event examining green chemistry applications for global environmental issues to kick off a week of programming on water, air, energy, and other issues of sustainability.

A very productive partnership has developed between GCI and the ACS Education and International Division. Joint work has occurred on a variety of new educational materials, from laboratory manuals to DVD's promoting green chemistry. GCI has worked with the Education Division to promote green chemistry through the existing Student Affiliates Program. Internationally, GCI has grown from 10 chapters to 24 in two years. In cooperation with the IUPAC CHEMRAWN program, GCI sponsored an educational training program in

Southeast Asia. National Science Foundation and Department of Energy support will sponsor the first Pan-American Advanced Studies Institute on Green Chemistry in July 2003.

GCI and ACS share strong support for education and research. In 2002, ACS dedicated a portion of the annual Petroleum Research Fund to be used for green chemistry. This is intended to provide catalytic support for green chemistry research and education initiatives. One of the first projects supported with these PRF funds was the new state-of-the-art green chemistry laboratory and instrumentation center at the University of Oregon, sponsored in cooperation with the Alice C. Tyler Perpetual Trust.

ACS has long demonstrated its support for green chemistry through extensive coverage of green chemistry research, programs, and activities in its publications, such as *Chemical and Engineering News* and *Environmental Science and Technology*. The ACS Award for Creative Advances in Environmental Science and Technology was recently named in memory of Joseph J. Breen, one of the co-founders of the Green Chemistry Institute. By forming an alliance with GCI, ACS has reinforced its reputation as a leader in green chemistry.

In short, the ACS has opened doors for the Green Chemistry Institute through its reputation for scientific excellence and its extensive network of members, programs, and ties to other professional organizations. These two years have brought significant organizational change but have only enhanced the enthusiasm of those involved. We look forward to a long, productive collaboration with ACS in promoting the adoption and implementation of green chemistry.

The Green Chemistry Institute (GCI) is a non-profit organization within the American Chemical Society (ACS) founded to promote green chemistry through research, education, information dissemination, conferences and symposia and international collaboration
GCI works across disciplines and academic, government, and industry sectors to promote the development and implementation of chemical products and processes that reduce or eliminate the use and generation of hazardous substances. Worldwide interest in green chemistry is reflected in over 20 international chapters currently affiliated with the Green Chemistry Institute.
See the GCI website: http://chemistry.org/greenchemistryinstitute

Green Chemistry in Africa

James Clark from the University of York reviews a recent addition to the green chemistry library which focuses on research and educational work in Africa

Introduction

'Green Chemistry in Africa' originates from a project of the IUPAC Interdivisional sub-committee on Green Chemistry with the specific aim of offering University lecturers a useful tool for their teaching activities. Another key objective of the book is to highlight the major roles of chemistry in the study of the problems that were discussed at the World Summit on Sustainable Development in South Africa last year.

The book is divided into six main sections—'General Aspects','Catalysis', 'Natural Products', 'Energy', 'Technologies' and 'Education'.

The moral basis of green chemistry

After an introductory short article on 'Green Chemistry in the International Context' the book starts with a chapter with the challenging title of 'The Moral Basis of Green Chemistry', the theme and substance of which is fundamental to the whole book. Here the author develops arguments around the 'Principle of Generic Consistency' which rather intriguingly has the same initials as the Principles of Green Chemistry! After discussion of underlying moral principles and the fundamentally important need to develop links between ethics and science, the author develops a case for green chemistry. He argues that it must be clear by now that green chemistry has a moral basis and goes on to consider how its application will impact on Africa. The vast reserves of raw materials in Africa gives the continent enormous potential for a major involvement in chemistry in the future. However, there has been very little, if any, action to arrest pollution in chemical manufacturing processes or to teach green chemistry. Indeed, the author argues, there has been little attempt to teach a relationship between technology and ethics (I must say at this point that in my experience this relationship is also largely ignored in many chemistry courses outside of Africa). Incorporating ethics into modern chemistry teaching and ensuring that decision-makers are aware of green chemistry are moral imperatives.

NGUMZO

The next chapter presents a conceptual framework for an effective green chemistry educational programme 'NGUMZO'. The proposal is the so-called 'Ham-tea-code' based on harmony, teamwork, consensus and decision which emphasises the role of each institution in paying more attention to the planning, management and development of its strategies, enhancement of student and staff performances, and regular evaluation of the technical education.

Catalysis

This section starts with a long chapter about 'Catalysis for Green Chemistry' which focuses on the use of catalysts based on palladium, iridium and rhodium. A very wide range of reactions are

considered with examples including hydrogenation, carbonylation and asymmetric synthesis. This is followed by a chapter on supported reagents and catalysis for green chemistry. The catalysts discussed are based on micelle templated silica or commercial silica gel. These are applied to various carbon–carbon bond forming reactions including Michael and Heck. The authors argue for a multi-disciplinary approach in pursuing the application of green chemistry. Biocatalysis is then described in the next chapter as a complementary approach in green chemistry. It describes how nature's catalysts can be used to generate many of the chemical products we need and using mild, low-polluting conditions. The chapter includes discussion on enzyme immobilisation and has a number of examples of biocatalytic processes.

Natural products

Natural Products is based on only one chapter on flavanoids—their structural features, biosynthesis, bioactivity and indigenous uses of plants containing flavanoids. This includes a consideration of the importance of flavanoids for medicinal purposes.

Energy

This section contains two chapters on anaerobic digestion and organic waste disposal and on renewable energies. The first of these shows that organic waste can be digested under anaerobic conditions to produce biogas and that the sludge left is rich in nitrogen and is a better fertiliser than the raw undigested waste. The chapter on renewable energy deals mostly (and appropriately for this book) on solar radiation, solar cells, photovoltaics and related ideas, though other renewable resources are also considered.

Technologies

This section has three chapters. The first of these considers the use of water as an environmentally benign solvent. Reactions considered include Diels–Alder, Michael additions and some transition metal catalysed reactions. Some industrial processes that run in water are described. The next chapter has a very different subject matter but one that is vital to the African economy—mining techniques and practices—and how the enforcement of environmental policies and guidelines by governments and public pressure have led to relatively safer mining practices in recent years. The final chapter in this section is from two Italians and deals with the relevance of green chemistry to sustainable industrial development.

Education

This final section contains only one chapter, which is unfortunate given the specific aim of the book. The chapter presents an overview of the challenges posed by green chemistry education and describes a number of pedagogical options. The last section of the chapter focuses on green chemistry education in Africa—needs and perspectives and ends with the statement that 'Sustainable chemistry becomes a pathway to sustainable development'.

Conclusion

This book contains a number of interesting articles on a diverse range of topics. The basic aim of the book—to support the teaching of green chemistry in Africa— is to be applauded and encouraged. The book nicely illustrates some of the aspects of green chemistry that are particularly relevant in an African context, including mining, the use of precious metal catalysts and the use of other natural products. Perhaps the most significant topics are at the beginning and end of the book—we must seek to exploit the rich resources of Africa with a clear awareness of ethics as well as technology and we must seek to introduce green chemistry into the African educational system.

Green Chemistry in Africa (ISBN 88 88214 07), co-editors Pietro Tundo and Liliana Mammino, is published by INCA and can be downloaded free of charge in pdf format from http://www.unive.it/pubblicazioni.htm

Recycling scrap tyres to valuable products

Paul Williams at the University of Leeds, UK, describes how a combination of pyrolysis and catalysis can be used to recycle tyres to produce high value products which make recycling not only environmentally effective but also commercially attractive.

The EU Landfill Directive

The recent EU Landfill Directive sets a deadline of July 2003 for the banning of whole tyres from waste landfill sites and shredded tyres by July 2006. This poses a major problem for the treatment and disposal of tyres throughout the European Union. It is estimated that 180 million scrap tyres are produced in the European Union each year of which about 35 million tyres are produced in the UK.

Landfill is the most common treatment and disposal option for tyres throughout Europe. However, this is clearly a waste of a resource and hence one of the main reasons for the banning of tyres from waste landfill sites. The EU has identified scrap tyres as a 'priority waste stream' requiring special treatment and disposal and has recommended that a target of 65% recovery of scrap tyres should be set by the member states.

The current recovery options for scrap tyres include, retreading the old tyre and material recovery for applications such as playgrounds, sports fields and road surfaces. Energy recovery through the

combustion of the tyre in cement kilns is a growing route for scrap tyres and a major cost saving to the high energy use cement industry. Tyres may still be used after 2006 at waste landfill sites but only for 'landfill engineering' for example in slope stabilisation. Although some of the alternative recovery routes can be further exploited, there still remains the problem of where most of the tyres that previously went to landfill will be diverted to after 2006. Consequently alternative, economic and environmentally acceptable treatment and disposal routes for scrap tyres are being urgently investigated.

Economic and environmentally acceptable treatment and disposal of tyres

One such alternative route is the novel application of pyrolysis to process scrap tyres. Pyrolysis involves the thermal degradation of the rubber of the tyre in the absence of oxygen to give an oil and gas leaving a residual solid carbon and the steel casing of the tyre. The yield of pyrolytic oil can be up to 58 wt% of the original tyre rubber and the oil has broad fuel properties similar to commercial grade light fuel oil/gas oil fuel (Table 1). The oil also has the advantages of a liquid fuel in its ease of handling, storage and transport. The carbon has potential as a solid fuel, or can be used as low grade activated carbon or carbon black (Table 2). The derived gas is composed mainly of hydrogen, methane and other hydrocarbons and has a sufficiently high calorific value that it can provide the energy requirements for the pyrolysis process (Table 2). The steel is easily separated from the residual carbon after pyrolysis and may be recycled via the scrap metal industry. As such the pyrolysis process is attractive environmentally in that all of the products of pyrolysis may be recycled.

The process conditions of pyrolysis may be altered to produce the desired char, gas or oil end-product, with pyrolysis temperature, heating rate and gas residence time having the most influence on the product distribution. Heating to between 400–600 °C and at very slow heating rates maximises the yield of char. Moderate heating rates in the range of about 20–100 °C/min and maximum temperatures of 600 °C gives an approximate equal distribution of oils, char and gases. At high temperatures in the region of 750–850 °C the oils are largely thermally degraded to produce a mainly gas product. Pyrolysis has utilised, a wide range of technologies including, fixed bed, fluidised bed, entrained flow, ablative, rotary kiln, vacuum *etc*.

Table 2 Typical properties of tyre pyrolysis carbon and gas composition from the pyrolysis of scrap tyres at 500 °C

Carbon	Pyrolysis (500 °C) (wt%)	Gas	Pyrolysis (500 °C) (wt%)
Moisture content (wt%)	0.4	Methane	0.81
Volatiles (wt%)	2.8	Ethane	0.30
Ash content	11.9	Propane	0.32
Carbon (wt% daf)	90.6	Isobutane	0.14
Hydrogen (wt% daf)	0.9	Butane	0.11
Nitrogen (wt% daf)	0.7	Ethene	1.16
Sulfur (wt% daf)	2.3	Propene	0.51
Gross CV (MJ kg^{-1})	30.5	Butene	0.13
BET Surface area (m^2 g^{-1})	64	Butadiene	1.92
Mesopore surface area (m^2 g^{-1})	33	Isobutene	0.19
Average mesopore radius (Å)	60	Hydrogen	0.16
		Carbon monoxide	0.09
		Carbon dioxide	0.32

Table 1 Typical fuel properties of the tyre pyrolysis oil compared to petroleum derived gas oil and light fuel oil

Fuel Test	Tyre Oil	Gas oil	Light Fuel Oil
Carbon Residue (%)	2.2	<0.35	—
Mid B.Pt. (°C)	264	300	347
Viscosity			
60 °C (cs)	2.38	1.3	4.3
40 °C (cs)	6.30	3.3	21.0
Density (kg m^{-3})	0.91	0.78	0.89
API Gravity	15.51	31	26.6
Flash Point (°C)	20	75	79
Hydrogen (%)	9.4	12.6	12.4
Nitrogen (%)	0.45	0.05	0.15
Carbon (%)	88.0	87.1	85.5
Sulfur (%)	1.45	0.2	1.4
Oxygen (%)	0.5	0.05	0.5
Fluorine (ppm)	110	—	—
Chlorine (ppm)	170	—	—
Initial B.Pt. (°C)	100	180	200
10% B.Pt. (°C)	140	—	—
50% B.Pt. (°C)	264	300	347
90% B.Pt. (°C)	355	—	—
CV (MJ kg^{-3})	42.1	46.0	44.8
Ash (wt%)	0.002	0.01	0.02
Moisture content (%vol.)	4.6	0.05	0.1
Burning rate coefficient (mm^2 s^{-1})	0.75	0.88	0.82

However, the quality of the product oil and carbon produced from the tyre pyrolysis process are generally low. The oil has to compete in the market place with fuels derived from traditional petroleum derived fuels. There are some drawbacks to the use of the oil as a fuel in that it has a high sulfur content and a low flash point and often contains fine carbon char particles. Similarly, the carbon after pyrolysis is generally only useful for low grade use, such as carbon black filler for plastic pipes and plastic shoes or as a solid fuel. If the pyrolysis process could be further developed to produce higher value products, the economic viability of the process would be enhanced.

Upgrading the pyrolysis process

Recent research at the University of Leeds has examined process routes which seek to upgrade the pyrolysis carbon to activated carbon and to use catalyst technology to upgrade the oil with the

aim of producing higher value end products.

Activated carbons are produced from traditional feedstocks such as wood, coal and coconut husks via either physical or chemical activation. The tyre derived carbons were investigated through a physical activation upgrading route. The carbon produced from the tyre pyrolysis was activated in either steam or carbon dioxide at temperatures up to 950 °C. Activation involves the reaction of the steam with the carbon to produce CO, CO_2, H_2 and CH_4. This removes the carbon in the reaction products and thereby widens the pores of the carbon and increasing surface area. Higher degrees of burn off are achieved by longer reaction times. The degree of carbon loss (burnoff) achieved is calculated from:

$$\text{Burnoff wt\% daf} = \left(\frac{W_1 - W_2}{W_1}\right) \times 100$$

where w_1 = Initial carbon mass on a dry, ash free (daf) basis, g. w_2 = Mass of carbon remaining after activation on daf basis, g.

It is thought that the activation of tyre char proceeds through two stages, a higher rate of weight loss at low degrees of burn-off, followed by a linear period of burn-off, occurring at a lower rate. It has been shown that disorganised carbon reacts more quickly than better organised carbon exhibiting a more graphitic structure. For tyre pyrolysis carbons it has been shown that a significant proportion of the carbon consists of carbonised hydrocarbon residue, in addition to the carbon black originally used in tyre manufacture. The disorganised carbon is preferentially burnt off in the initial stages of the activation process followed by burn off of the more ordered carbon black.

The relationship between the developed surface area of the activated carbons in relation to burn off for steam and carbon dioxide activating gas is shown in Fig. 1. The surface area reached a maximum in the range 60 to 65 wt% burn off at over 600 $m^2\ g^{-1}$, then decreased. Commercially available activated carbons are highly porous carbonaceous materials with high surface areas, typically in the range 400 to 1500 $m^2\ g^{-1}$. Activated carbon is an excellent adsorbent. It can absorb large quantities of gases and is commonly used to remove pollutants from gas or liquid streams.

It was found that steam was more reactive than carbon dioxide as an activating agent. The reduced reactivity in carbon dioxide has been attributed to the lower reactivity of carbon dioxide to diffusion effects, brought about by the larger size of the carbon dioxide molecule. Other workers have postulated that carbon dioxide forms more stable oxygen groups on the carbon surface than steam, which remain longer on the surface and result in a slower reaction rate.

Of further significance, the activated carbons have a porosity and sulfur content which is particularly suitable for the removal of mercury from industrial aqueous waste-waters and flue gases. The activated carbons are highly mesoporous in nature with pore sizes in the range of 2–50 nm which is a range particularly useful for the removal of mercury from industrial waste streams. In addition, the high sulfur content of the tyre derived activated carbons also aids the removal of mercury by chemical adsorption through the formation of mercuric sulphide in addition to removal by physical adsorption. The removal of mercury from waste streams is particularly important to industry since the metals are known to be toxic, but also the emission levels are heavily regulated and require expensive clean-up. The use of a low cost activated carbon derived from a waste such as scrap tyres would off-set the costs of clean-up.

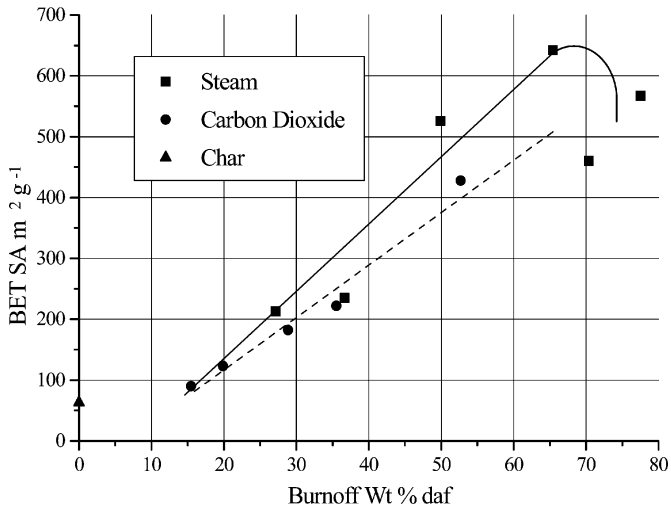
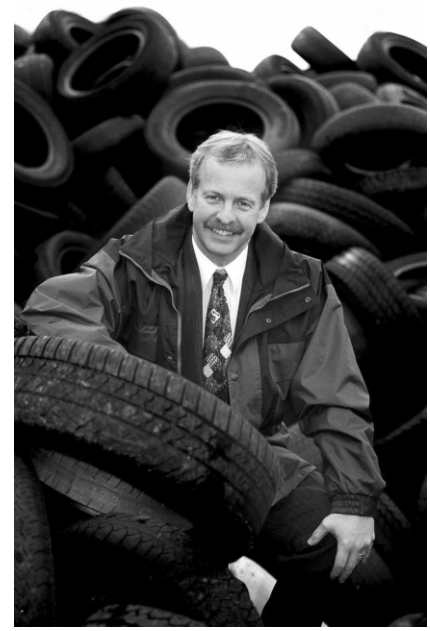


Fig. 1 Influence of burn-off on the development of surface area for steam and carbon dioxide activating gas at 935 °C activation temperature.

Oil from tyre pyrolysis

The oil derived from tyre pyrolysis is very complex, containing alkanes, alkenes and aromatic compounds with molecular masses which range from 50 to over 1000. Conventional zeolite type catalysts have been investigated in a pyrolysis-catalysis reactor to produce an oil which can be used as a chemical feedstock rather than a fuel. The catalyst is placed in the hot exit zone of the pyrolysis reactor so that the pyrolysis gases and oil vapours pass over the catalyst. The catalyst promotes the formation of low molecular weight aromatic compounds in high yields. The aromatic chemicals found in the product oil include, benzene, methylbenzene and dimethylbenzenes. These chemicals are major industrial chemical feedstocks. For example, the products from benzene are derivatives such as ethylbenzene, cyclohexane and (1-methylethyl)benzene which are used as basic materials for the production of plastics, resins, fibres, surfactants, dyestuffs and pharmaceuticals.



Dimethylbenzenes (xylenes) are regarded as major industrial chemicals and have applications in the plastics industry. 1,2-Dimethylbenzene is used to produce benzene-1,2-dicarboxylic anhydride (phthalic anhydride), which in turn is used to produce plasticisers, dyes and pigments. 1,3-Dimethylbenzene derivatives have applications in the polyester resin and fibre industries and 1,4-dimethylbenzene derivatives are used in the production of polyester fibres. Methylbenzene (toluene) has a wide range of applications as a chemical feedstock and is used for example, in the production of pesticides, dyestuffs, surfactants and solvents.

Levels of benzene, methylbenzene and dimethylbenzenes totalling of over 50% by mass have been produced in the oil (Fig. 2). This represents a 15–20 % conversion of the scrap tyre rubber to these chemicals. Such concentrations makes it possible to separate them from the oil using conventional methods, making the process commercially viable.

The pyrolysis process has the potential to recycle tyres to produce high value products which make recycling not only environmentally attractive, but also *commercially* attractive. With the new Landfill Directive that is going to ban tyres from being buried, we need to find alternatives which will recycle the products back into the environment. Pyrolysis is not the complete replacement – it's just part of the mix of different processes that will provide the solution to the problem.

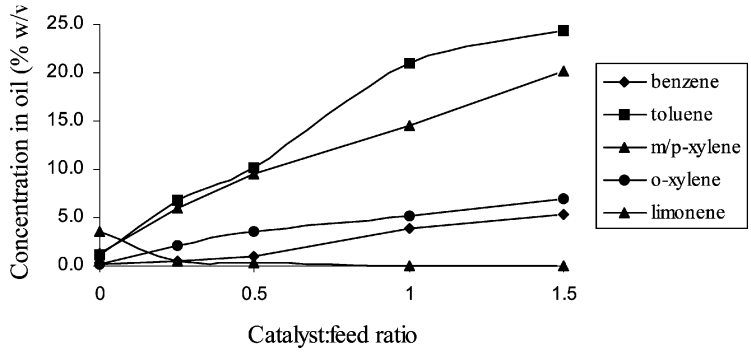


Fig. 2 Effect of Zeolite catalyst:feed ratio on the yields of benzene, toluene, xylene and limonene.

References

1 P. T. Williams and A. J. Brindle, 'Aromatic chemicals from the catalytic pyrolysis of scrap tyres', *J. Anal. Appl. Pyrolysis*, 2003, **67**, 143–164.

2 P. T. Williams and A. J. Brindle, 'Catalytic pyrolysis of tyres: influence of catalyst temperature', *Fuel*, 2002, **81**, 2425–2434.

3 A. M. Cunliffe and P. T. Williams, 'Influence of process conditions on the rate of activation of chars derived from the pyrolysis of used tyres', *Energy Fuels*, 1999, **13**, 166–175.

4 A. M. Cunliffe and P. T. Williams, 'Properties of chars and activated carbons derived from the pyrolysis of used tyres', Environ Technol., 1998, **19**, 1177–1190.

5 P. T. Williams, R. P. Bottrill and A. M. Cunliffe, 'Combustion of tyre pyrolysis oil', *Transactions of the Institution of Chemical Engineers, Part B, Process, Safety and Environmental Protection*, 1998, **76**, 291–301.

6 A. M. Cunliffe and P. T. Williams, 'Composition of oils derived from the batch pyrolysis of tyres', *J. Anal. Appl. Pyrolysis*, 1998, **44**, 131–152.

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The Summer School on Green Chemistry

The Summer School on Green Chemistry, devised by the Italian Interuniversity 'Chemistry for the Environment' (INCA), is a high level training school for young chemists. Its purpose is to teach the design of intrinsically clean chemical processes to solve pollution concerns at the source. The innovative approach lies in teaching to use chemistry for pollution prevention, as an alternative to the end-of-pipe remediation, which is costly both economically, and in terms of health, safety, and of the environment.

The School runs since 1998, and is held in the centre of Venice. It is funded by the European Commission's Framework Programmes, and by the Italian Ministry for Foreign Affairs. Admitted students benefit from complete scholarships. It has attracted many young scientists: in 2002 the number of applicants has topped 90 for a little over 60 available slots. European participants, aged 25 to 35, represented academia and industry.

The first five editions of the school are contained in a volume (Collection of Lectures of the Summer Schools on Green Chemistry) which serves as textbook for the course and which is available free of charge through the INCA web site (http://www.unive.it/inca).

The schools consist of 12–14 lectures over a one week period, plus ample discussion time, a poster session, awards for posters, and some practical problem solving. The atmosphere is informal, there are social dinners, boat trips around Venice, mixers, *etc.*, effectively making the school pleasurable as well as profitable. Attendance is required but ample free time allows participants to take advantage of the opportunity to be in Venice.

The auspice is that in the future the Summer School on Green Chemistry will become a stepping stone in the career of many young researchers, wishing to combine state-of-the-art research in chemistry and environmental awareness.

Mass efficiency as metric for the effectiveness of catalysts

Marco Eissen* and Konrad Hungerbühler from the Swiss Federal Institute of Technology in Switzerland,† and Stefan Dirks and Jürgen Metzger from the Universitat Oldenburg in Germany‡ **argue that metrics such as mass intensity, environmental factor and cost index indicate weak points with respect to environmental impact and cost efficiency in synthesis design. These weak points give a precise picture of the progress being made with alternative catalytic systems, and show how, for example, a switching to a heterogeneous system can affect efficiency, both positively and negatively**

Environment- and resource-saving syntheses and processes contribute significantly to sustainable development.[1,2] Catalysis plays an important role and is, therefore, applied frequently in synthesis. Efficient use of resources and lowering costs can be achieved not only by improving the conversion of substrates to a product, but also by recycling the catalyst.[3] Different approaches have been taken to recycling homogeneous catalysts, *e.g.* aqueous systems,[4] fluorous biphase chemistry[5] or multicomponent solvent systems.[6] Another possibility is the immobilization of homogeneous catalysts on a solid support.[7,8] However, maximal recycling of catalyst material should not lose sight of the disadvantages that are potentially connected with it. For example, reverting to environmentally friendly aqueous media always means to include a new compartment in which possibly hazardous substances will be emitted and, thus, a new disposal route to be treated. As well as costs, the intensive production of new alternative (*e.g.* fluoric and ionic[9]) solvents has an impact on the environment, to which even a minimal loss of substances and/or their disposal contribute. Therefore, the fourth of the twelve 'more' green chemistry principles of N. Winterton claims to measure catalyst and solvent losses in air and aqueous effluent.[10] Moreover, a full mass-balance should be established (third principle[10]), which makes use of reagents, auxiliary materials, etc. A holistic view is necessary.[11,12] Mass balances of alternatives can be compared using metrics such as the *E* factor[13] and mass index S^{-1}.[11,14] The *E* factor (ratio of waste [kg] to product unit [kg]) is an output orientated indicator, whereas the mass index S^{-1} (ratio of all raw materials [kg] to the product [kg]) is an input orientated indicator. These metrics and the cost index CI (CURRENCY UNIT per kg product) clarify the benefits and drawbacks of changes in synthesis design, *i.e.* the strong and weak points, which must be addressed.

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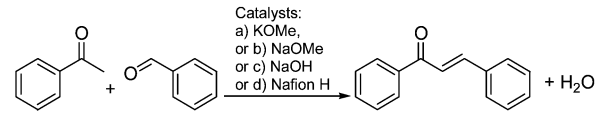
Two examples of important synthesis protocols for carbon-carbon bond formation, aldol condensation and Michael reaction are examined. The aldol reaction of acetophenone and benzaldehyde is usually base-catalyzed, as demonstrated in Scheme 1a) −c).



Scheme 1 Aldol reaction catalyzed by a base (a),[15] (b),[16] (c)[17] or by the recyclable Nafion H (d).

The yields resulting from the use of protocols a) to d) are 75, 71, 85 and 78%, respectively. The base must be neutralized and/or washed out during the work-up procedure. The solid-acid Nafion H,§ on the other hand, can be reused (Scheme 1d).

Fig. 1 shows a quantitative comparison of methods a) to d) (Scheme 1) and, especially, that protocol d) is the most effective procedure with regard to mass efficiency: S^{-1} = 2.7 kg kg^{-1} compared to 5.6 (a), 7.8 (b) and 6.8 (3.0 without water) (c) and E = 1.7 kg kg^{-1} compared to 4.6 (a), 7.0 (b) and 5.8 (2.0 without water) (c). Not only solvents and auxiliary materials can be saved according to protocol d), but the catalyst too, is reusable (at least ten times, therefore, see 'Recycling') without having a negative effect on the yield. This leads to a decrease in

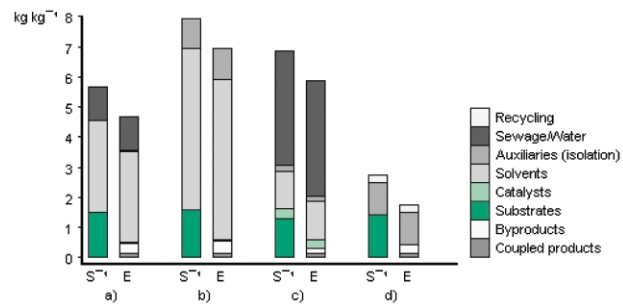


Fig. 1 Mass index S^{-1} and environmental factor E of the a) KOMe, b) NaOMe, c) NaOH and d) Nafion H catalyzed synthesis of chalcone according to Scheme 1 using the software EATOS.[11]

DOI: 10.1039/b301753m

the E factor to 1.5 kg kg^{-1} in synthesis d). Correspondingly, resources are saved as can be seen from the mass index S^{-1}. It is possible to avoid an additional disposal route, the waste water treatment that will be mandatory especial in synthesis c). To obtain an idea of how to estimate the material costs of raw materials in alternative systems, the cost index CI is used to identify the relevant cost drivers (Fig. 2). If the materials are

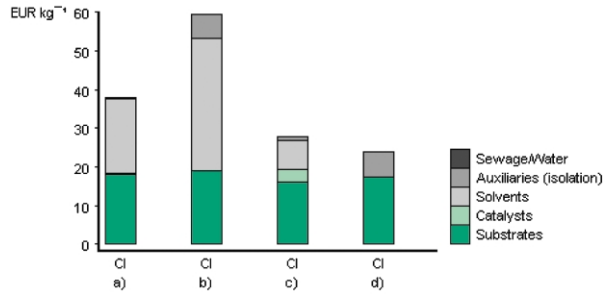
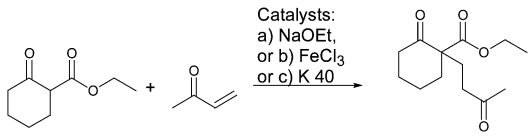


Fig. 2 Cost index CI of the a) KOMe, b) NaOMe, c) NaOH and d) Nafion H catalyzed synthesis of chalcone according to Scheme 1 using the software EATOS.[11]

purchased from Aldrich (see current catalogue) and assuming that Nafion H is recycled, synthesis d) is the most economical (23.7 EUR kg^{-1}). However, because the costs of substrates (d) are slightly higher than in c), measures should be taken to increase yield.

The second example, the Michael-reaction (Scheme 2), can also be base- or Lewis acid- catalyzed. Because procedures a) and b) (Scheme 2) have the disadvantages of catalyst loss in



Scheme 2 Michael reaction catalyzed by a base (a),[15] a Lewis acid (b) or a solid Lewis acid K 40 ($FeCl_3$ supported on montmorillonite) (c).

homogeneous catalysis, the heterogeneous Lewis acid, K 40, a $FeCl_3$-supported montmorillonite, was examined (Scheme 2c). Yields of protocols a) to c) are 70, 85 and 76%, respectively.

According to Fig. 3 protocol a) with S^{-1} = 3.6 kg kg^{-1} requires between twice and three times the amount of raw material as b) and c). Protocol b) avoids a resource intensive

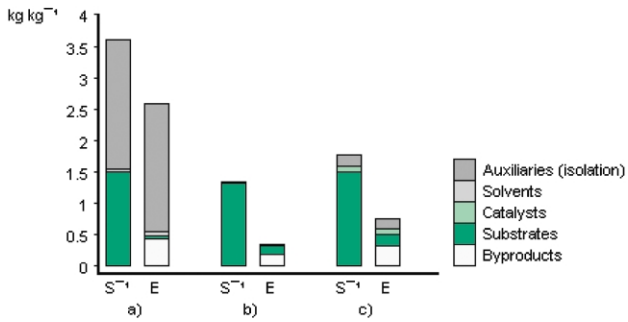


Fig. 3 Mass index S^{-1} and environmental factor E of the a) NaOEt, b) $FeCl_3$ and c) K 40 catalyzed synthesis of ethyl 2-oxo-1-(3-oxo-butyl)-cyclohexanecarboxylate according to Scheme 2 using the software EATOS.[11]

work-up, therefore, the generation of waste (see E factor) is lower by about one order of magnitude compared to a).

The consequence of using protocol c) and implementing a reusable catalyst (K 40) is a decrease in yield as shown in the yellow segment 'Byproducts' in synthesis c). This, of course, has an impact on the amount of substrates necessary to produce one kilogramme of product (compare 'Substrates'). Additional solvents are necessary to extract the product from the catalyst after filtration. Because the activity of the catalyst decreases significantly already in the third run, this catalyst cannot be attributed to the segment 'Recycling' like Nafion H (Fig. 1). Spent K 40 must be disposed of or be treated after a few runs. In contrast, very small amounts of cheap iron(III) chloride are required in synthesis b). Therefore, compared to chemical problems of other catalytic systems, the effort required to save the catalyst in the Michael reaction (Scheme 2) is unjustified.

In conclusion, Nafion H seems to be an efficient catalyst for performing aldol condensation to yield chalcone in an environmentally friendly manner, i.e. avoiding the use of water and reducing the amount of solvent. In contrast, application of K 40 to the Michael reaction has advantages over traditional base catalysis but does not effectuate an increase in mass efficiency, in contrast to the protocol for homogeneous catalysis using iron(III) chloride. These examples demonstrate that the application of alternative catalytic systems must always be looked at from a holistic point of view that takes the full mass-balance into account. In systems more complicated than those described here for demonstration purposes, the integration of preliminary processes will possibly become necessary. For instance, we examined three four-step routes and one three-step route to ethyl (*R*)-2-hydroxy-4-phenylbutyrate, which is an important intermediate in pharmaceutical industry for Angiotensin Converting Enzyme (ACE) inhibitors; *e.g.* Benazepril (Novartis) and Cilazapril (Roche). Interestingly, based on the data available the route showing an overall yield of 50% and an enantiomeric excess of 76% performs better with regard to mass efficiency than an alternative showing a yield and enantiomeric excess of 99%. Main reasons are solvent demand and other substrates than the key-substrate to which the yield refers.[18]

Acknowledgement

M. Eissen thanks the Deutsche Bundesstiftung Umwelt for support within the framework of the scholarship program.

Notes and references

§ Nafion H (7–9 mesh) and K 40 were obtained from Aldrich and Süd-Chemie, respectively. In one experiment, catalyst bleeding, 'leaching', of $FeCl_3$ was not observed.[19] Products were characterized by ^{1}H NMR and mass spectrometry as well as by comparing their physical properties with those reported in the literature.

Chalcone by means of Nafion H (Scheme 1d): Acetophenone (3 g, 24.96 mmol) and benzaldehyde (2.65 g, 24.96 mmol), both freshly distilled, were stirred for two days at 97 °C in the presence of Nafion H (1 g). Using a Pasteur pipette, the reaction mixture was separated from the Nafion H pellets. The catalyst was washed twice with 2 ml ethanol that was used to crystallize the product. More product was obtained from the mother liquor via crystallization (1.5 ml ethanol) and Kugelrohr distillation (160-170°C, 10^{-1} mbar) to give a total amount of 4.06 g (78%).

Verification of the recyclability of Nafion H in the chalcone synthesis: In presence of Nafion H (0.25 g), benzaldehyde (0.5 g, 4.71 mmol) and acetophenone (0.25 g, 2.08 mmol) were stirred at 105 °C (oil bath) for 8 h. Using a Pasteur pipette, the mixture was removed from the catalyst, which was washed with few acetone. Another nine cycles were performed with the same catalyst. The yields were

practically identical (75% and 76%).

Ethyl 2-oxo-1-(3-oxo-butyl)-cyclohexanecarboxylate (Scheme 2c, *i.e.* in presence of K 40): In several portions 2-butenone (5.76 g, 82.2 mmol) was added to ethyl 2-oxocyclohexanecarboxylate (9.8 g, 57.6 mmol) containing K 40 (0.98 g). The mixture was stirred for two days at room temperature. The catalyst was filtered off through a fine filter paper and washed with 2 ml of ethanol. The distillation yielded 10.56 g (76%) of the product. The protocol of Scheme 2b was followed[19] as described in the literature.[20]

1 M. Eissen, J. O. Metzger, E. Schmidt and U. Schneidewind, *Angew. Chem., Int. Ed.*, 2002, **114**, 402–425.
2 M. Poliakoff, J. M. Fitzpatrick, T. R. Farren and P. T. Anastas, *Science*, 2002, **297**(5582), 807–810.
3 A. Hassan and S. Richter, *Chem. Eng. Technol.*, 2002, **25**(12), 1141–1148.
4 W. A. Herrmann and C. W. Kohlpaintner, *Angew. Chem., Int. Ed. Engl.*, 1993, **32**(11), 1524–1544.
5 I. T. Horvath, *Acc. Chem. Res.*, 1998, **31**(10), 641–650.
6 A. Behr and C. Fängewisch, *Chem. Eng. Technol.*, 2002, **25**(2), 143–147.
7 J. H. Clark and D. J. Macquarrie, *'Supported Catalysts'*. In *Kirk-Othmer Encyclopedia of Chemical Technology*, John Wiley & Sons, Inc., 2002.
8 R. Haag, *Angew. Chem., Int. Ed. Engl.*, 2002, **41**(3), 520.
9 D. Zhao, M. Wu, Y. Kou and E. Min, *Catal. Today*, 2002, **74**, 157–189.
10 N. Winterton, *Green Chem.*, 2001, **3**(6), G73–G75.
11 M. Eissen and J. O. Metzger, *Chem. Eur. J.*, 2002, **8**(16), 3580–3585.
12 M. Eissen, J. O. Metzger, EATOS, Environmental Assessment Tool for Organic Syntheses; the software can be obtained free of charge *via* http://www.chemie.uni-oldenburg.de/oc/metzger/eatos/.
13 R. A. Sheldon, *Chemtech*, 1994, **3**, 38–47.
14 The mass index is also referred to as MI: D. J. C. Constable, A. D. Curzons and V. L. Cunningham, *Green Chem.*, 2002, **4**, 521–527.
15 H. G. O. Becker, *Organikum: Organisch-chemisches Grundpraktikum*, Wiley-VCH, Weinheim, 2001.
16 L. F. Tietze and T. Eicher, *Reaktionen und Synthesen*, Georg Thieme Verlag, Stuttgart, New York, 1991.
17 E. P. Kohler and H. M. Chadwell, *Org. Synth., Coll. Vol. I*, **78**.
18 H.-U. Blaser, M. Eissen, P. F. Fauquex, K. Hungerbühler, E. Schmidt, G. Sedelmeier and M. Studer, *'Comparison of Four Technical Syntheses of Ethyl (R)-2-Hydroxy-4-Phenylbutyrate'*. In *Large-Scale Asymmetric Catalysis*, eds. H.-U. Blaser and E. Schmidt, Wiley-VCH, Weinheim, 2003.
19 M. Eissen. Bewertung der Umweltverträglichkeit organisch-chemischer Synthesen, PhD, 2001, p. 141; http://docserver.bis.uni-oldenburg.de/publikationen/bisverlag/2002/eisbew01/eisbew01.html.
20 J. Christoffers, *J. Chem. Soc., Perkin Trans. 1*, 1997, (21), 3141–3149.

Green solvents for catalysis

Walter Leitner, Kenneth R. Seddon and Peter Wasserscheid introduce this special issue on a conference held from 13–16 October 2002 at Bruchsal in Germany

Over the last decade, green chemistry has been a topic of numerous conferences and workshops all over the world. These symposia have provided excellent opportunities for the scientific community to exchange ideas, to foster the concept, and to develop the field to its current fertile state. The large majority of these events have tried to demonstrate the full variety of possible approaches to sustainable chemistry, covering a wide range of disciplines and methodologies. The fast growing activities in the field of green chemistry encouraged us to organise a more specifically targeted conference, bringing together researchers for a focussed and in-depth discussion of an individual area in its full scientific detail. Under the auspices of DECHEMA, and with the constant support of Drs. Kurt Wagemann, Dana Schleyer and Barbara Feisst, a conference was devoted to *Green Solvents for Catalysis* from 13–16 October 2002, in Bruchsal, Germany.

The vast majority of chemical transformations occur in the solution phase, and the solvent is a strategic parameter in the implementation of such processes on a laboratory and industrial scale. On a molecular level, the solvent helps to bring reagents in direct contact and stabilises or destabilises intermediates and transition states. In process design, the use of solvents determines the choice of work-up procedures and recycling or disposal strategies. The interplay of molecular and process engineering is particularly important for reactions involving organometallic catalysts. Within the framework of green chemistry, innovative concepts for the substitution of volatile organic solvents in organometallic catalysis have become the focus of interdisciplinary research activities all over the world. Promising approaches include catalysis utilising aqueous biphasic systems, ionic liquids, supercritical media, fluorinated phases or thermoregulated systems.

The response to the announcement of *Green Solvents for Catalysis* far exceeded our expectations: the conference attracted over 220 scientists from 24 countries out of 4 continents. One third of the participants came from industry, demonstrating the high relevance of the topic for technical application. The share of students reached almost 25% and 14 young scientists were brought in with the aid of industrially sponsored travel grants. The scientific programme consisted of 30 oral presentations and 71 posters. To overcome classical borders, the programme was structured according to reaction types and chemical processes, which theme ran throughout the meeting. In many presentations, the potential of individual concepts to open new opportunities beyond solvent replacement became clearly visible. The present volume of *Green Chemistry* contains a selection of contributions from the Bruchsal Meeting. All the papers published here were subject to the normal RSC peer review system, and the topics discussed give a flavour of the broad variety of reactions and processes that were discussed at the symposium.

In addition to the scientific discussion, there was plenty of room for informal exchange of ideas and networking. One highlight was certainly the candlelight dinner in the beautiful baroque castle of Bruchsal. At this occasion, the local wines were discovered as another attractive solution phase by most participants.

The final day reflected the fruitful scientific discussion throughout the conference with overview lectures from industrialists, comparing and contrasting the various solvent systems. The conference closed with a panel discussion, collecting an extremely enthusiastic feedback from the audience. As a natural consequence, it was decided to hold a follow-up conference on *Green Solvents for Synthesis* at the same location from 3–6 October 2004.

LEFT to RIGHT – Walter Leitner (Lehrstuhl fur Chemie und Petrolchemie, RWTH, Aachen, Germany), Kenneth Seddon (Queens University Belfast Ionic Liquids Laboratory (QUILL)) and Peter Wasserscheid (Institut für Technische Chemie und Makromolekulare Chemie, RWTH Aachen, Germany.

DOI: 10.1039/b302757k

Meeting the challenges to sustainability through green chemistry

Paul T. Anastas of the Chemistry Department, University of Nottingham in the UK discusses green chemistry as an approach toward meeting the goals of sustainability

Background

During the course of the past year, there has been a heightened degree of focus on sustainability due in some part to the World Summit on Sustainable Development in Johannesburg, South Africa. The discussions in preparation for that meeting as well as the statements and declarations that resulted provide ample evidence of a growing consensus that the world faces serious challenges to its sustainability. Sustainability for the purposes of this discussion will be defined as according to the Brundtland Commission, 'The ability to meet the needs of the current generation while preserving the ability of future generations to meet their needs.' A simpler way of expressing this idea may be, 'Preserving the things you cannot live without and preserving them forever.'

Any listing of the major challenges facing the sustainability of Earth will generate debate and refinement. However, most may agree that among the most pressing issues facing the planet would be the following:

- Population growth
- Energy
- Food supply
- Resource depletion
- Global climate change
- Water
- Toxics generation and dispersion

It would be reasonable to argue that the above list, both individually and collectively, constitute the major challenges to sustainability. As such, these issues must constitute our highest priorities since the failure to meet these challenges will mean that the human society may not be around to meet any others. What role does green chemistry have to play in meeting these challenges and the ultimate goal of sustainability? Green chemistry fulfills a fundamental and crosscutting role that is essential to the critical pathway toward sustainability. Simply stated, it is difficult to imagine a way to address the challenges of sustainability without engaging in green chemistry.

To understand some of the challenges our society must confront, it is useful to recognize that society has previously been on an unsustainable trajectory. In fact, one hundred years ago there were predictions that the volume of waste produced by the increasing number of horses in the New York City would virtually bury the entire population. This future was not avoided by placing a legal ban on horses. Rather, it was through the engagement of science and technology and the invention of alternative personal transportation means that the trajectory was changed.

Furthermore, meeting the challenges requires a planning perspective of the century or longer timeframe rather than merely focusing on years or decades. For example, a resource planner in the year 1900 would want to ensure that there was an ample supply of whale oil in the year 2000 for lighting, wood for fuel, rock salt for refrigeration and horses for personal transportation. By relying on such resources, society was on an arguably unsustainable trajectory. Again, it was through the engagement of science and technology that shifted society toward greater growth and sustainability. Similarly, in order to shift society from the current projected unsustainable trajectory, it is once again necessary to engage science and technology to achieve the goal of sustainability with green chemistry as part of the foundation.

Discussion

In using green chemistry as the approach toward meeting the goals of sustainability, there is embedded the recognition that all that is available in the universe is energy and matter. Since the hazards we confront are based in the physical/chemical properties of the molecules we make, it is the manipulation of these very physical/chemical properties that is the most powerful method we have to confront these hazards. Through the design of matter at the molecular level, we can deal with fundamental problems such as toxicity, renewability and global impact. Even our energy concerns are based on the matter (materials) that are used to generate, store and transport our energy supply.

Green chemistry shifts the approach to addressing issues, such as environmental problems, from the *circumstantial* to the *intrinsic*. Virtually every significant approach to dealing with environmental issues has tried to change the circumstances or the conditions of the problem. By changing conditions, we attempt to ensure that hazardous chemicals, for instance, cannot escape in high concentrations to the environment or that these chemicals are treated before disposal. The difficulty with simply attempting to change the conditions of a given process is the additional expense, often in the form of engineering controls that are simply a cost drain. These attempts at trying to make unsustainable products, processes and systems a little less bad through changing the conditions can be costly. In addition, if

DOI: 10.1039/b211620k

conditions change such as in the case of accidents or malice, the consequences are at a maximum because the hazard remains intact.

Typically, regulations specify maximum limits and best available technologies to control conditions. Trends in regulation (Fig. 1) and in the costs of compliance with these regulations and other environmental expenditures by industry (Fig. 2) over time illustrate the economic burden of this approach even in light of the benefits it has brought about. This methodology should stand in contrast to the approach that green chemistry proposes, namely, to deal with the issues at the intrinsic level.

Green chemistry addresses hazards, whether physical (flammability, explosivity), toxicological (carcinogenicity, endocrine disruption), or global (ozone depletion, climate change) as an inherent property of a molecule. Therefore the hazard can be addressed through appropriate design of the structure and its associated physical/chemical properties at the molecular level. This approach has the advantage of not requiring expenditures of non-productive capital such as is the case in waste treatment plants. Again, by minimizing the inherent nature of the hazard you reduce the potential for catastrophic events through accident or breakdown.

Population

The first of the challenges to sustainability, population, drives many other challenges as well. While it took all of human history until 1930 to reach a population of 2 billion (Fig. 3) it has taken only 70 years to triple that number to 6 billion. If United Nations population projections are accurate, we will have another billion people on the planet in the next 10 years with China adding the equivalent of the current population of the United States. It is important to understand where this population growth is taking place. As seen in Fig. 4, while population growth in the most developed economies with the highest standard of living is virtually stagnant, the population growth in developing nations with the lowest standard of living is increasing at a significant rate.

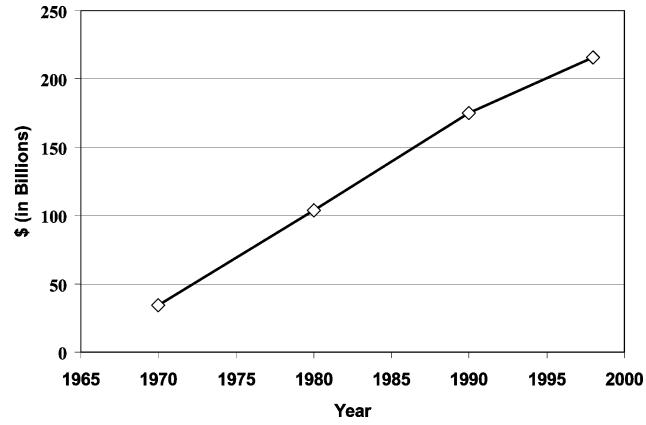


Fig. 2 Environmental expenditures in billions of dollars from 1970–1998. Source.[25]

Drawing from the empirical data on this very complex issue, it is difficult to ignore the correlation between increased quality of life and sustainable population growth. Employing a strategy of achieving more sustainable population growth through an increased quality of life in developing nations is one that is compelling but not without drawback. The drawback is reflected in the historical trend that increased quality of life was often associated with increase resource utilization and degradation of the environment (Fig. 5). Therefore, one needs to recognize that any approach to population stabilization involving an increase in quality of life must be inextricably linked to doing so in a way that minimizes the impact on human health and the environment (Fig. 6). Green chemistry possesses the framework, techniques and methodologies to achieve this goal as seen in examples of

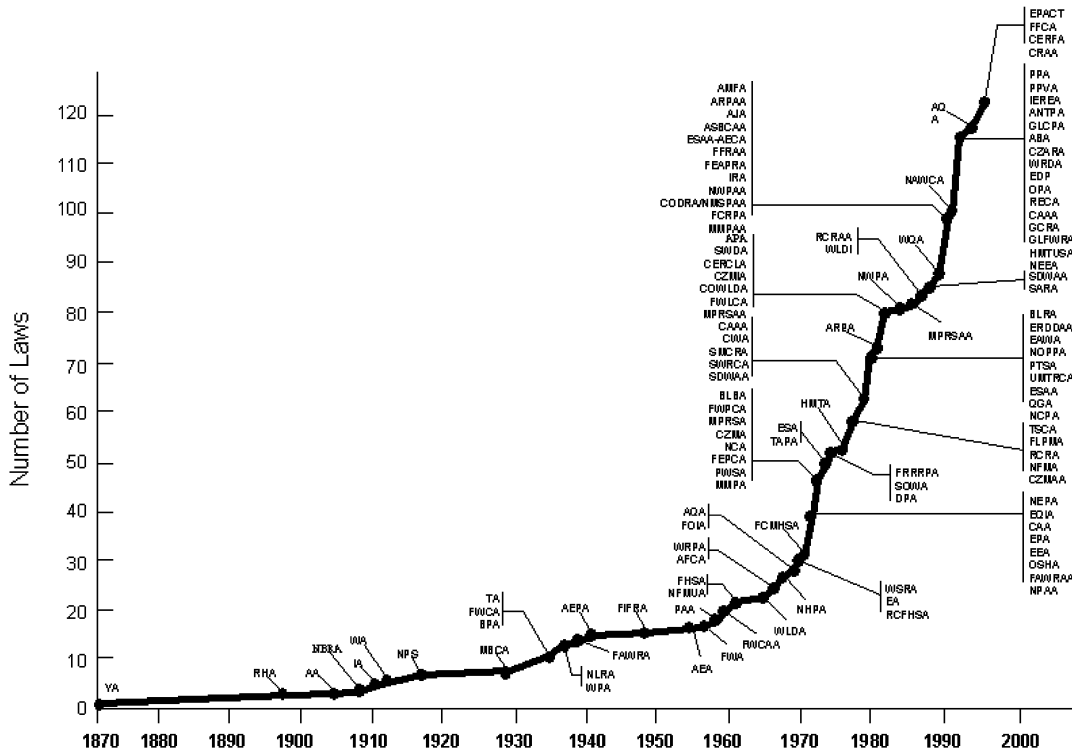


Fig. 1 Expansion of environmental regulation in the United States from 1970 to present. Source:[24]

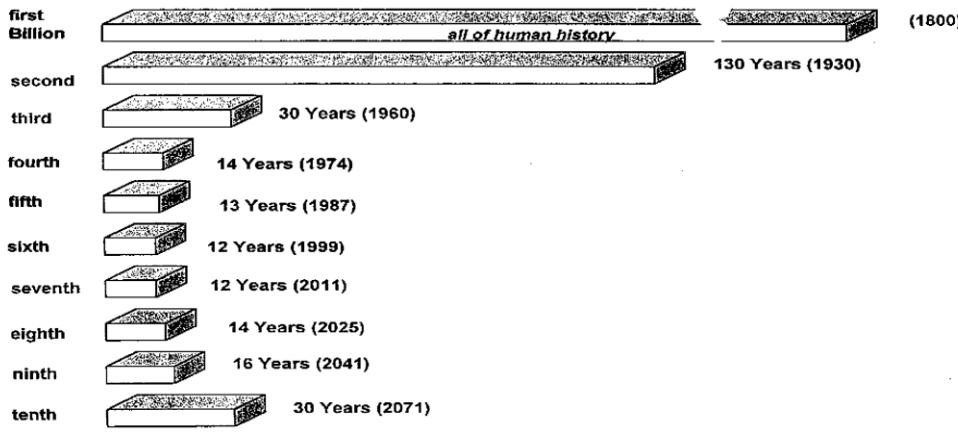


Fig. 3 Number of years required to add each billion to the world population. Source.[26]

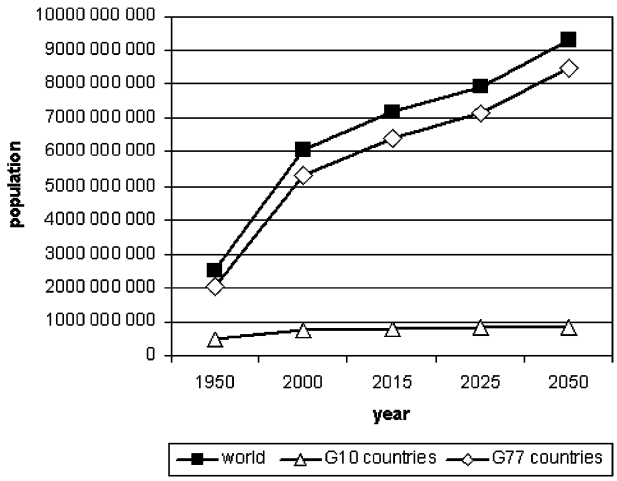


Fig. 4 Projected population growth in industrialized (G10) and developing (G77) nations based. 2000 projections, medium variant. Source.[27]

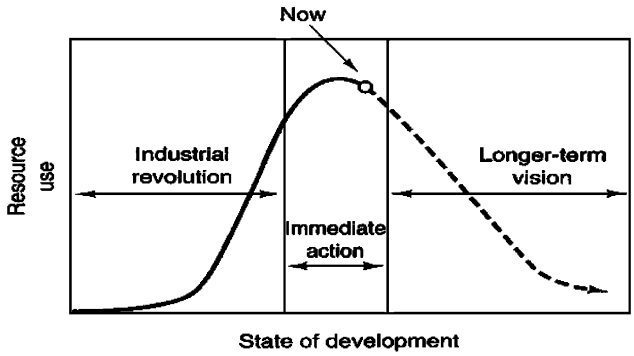


Fig. 5 Schematic of resource use versus state of development. Source.[28]

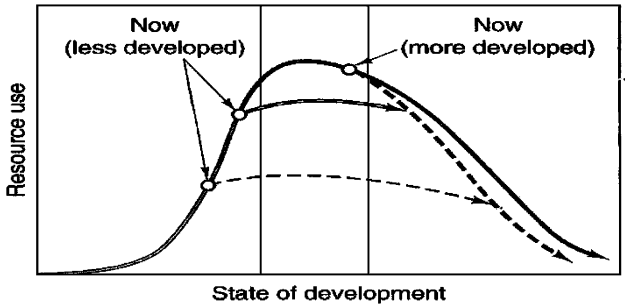


Fig. 6 Schematic of alternative leap frog technology for development. Source.[28]

the engagement of green chemistry on the other challenges listed below.

Energy

Currently, the energy supply of the world is largely based on the combustion of carbon. The extraction and collection of carbon through mining, drilling, processing, etc. has well documented environmental consequences. The production of carbon dioxide and other gases has been cited as contributing to global warming both by the International Panel on Climate Change (IPCC), as well as the National Academy of Sciences in the U.S.[1,2] While the exact impacts of the generation of associated toxics during the production of fossil fuels and the rate at which this finite resource is being depleted will perhaps always be the topic of varying analyses, these are also areas of environmental concern.

Projections of energy needs suggest that energy demands will continue to increase in order to support development and a growing population (Fig. 7). The question is 'What type of energy future will supply these energy needs?'. Current projections (Fig. 8) would suggest a continued domination by fossil fuels. Green chemistry, however, is engaged in addressing energy needs through the development of more sustainable energy technologies.

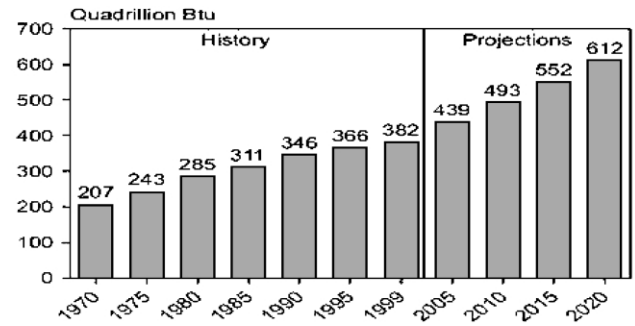


Fig. 7 World energy consumption from 1970 to present and projected to 2020 in quadrillion btu. Source.[29,30]

The principles of green chemistry[3] are being employed in the development of the hydrogen economy and fuel cells. The sustainable sources of hydrogen generation in an economically sustainable manner are an area of active research both in green chemistry and green engineering.[4,5] The design and development of photovoltaics and solar energy devices that are both economically viable and also ensure a positive energy balance through their manufacture and use is being pursued.[6] Materials

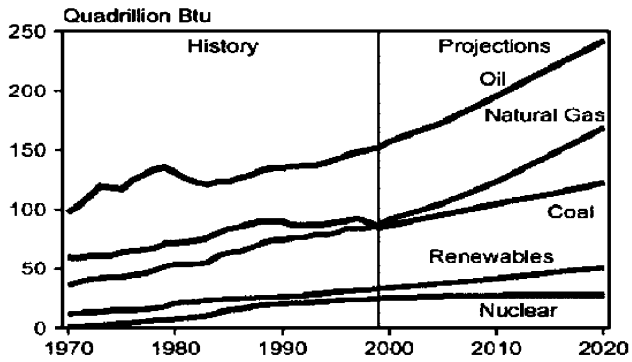


Fig. 8 World energy consumption by fuel type from 1970 to present and projected to 2020. Source.[29,30]

that are needed to make wind and geothermal energy systems possible are being developed through green chemistry research. The energy future will need to be shifted to a more sustainable balance and green chemistry is essential in making that shift happen.

Food supply

Currently, the world produces enough food to feed its population. While regional starvation exists for reasons ranging from distribution to economics to politics, the miracle of the efficiency of modern agriculture is undeniable (Fig. 9).

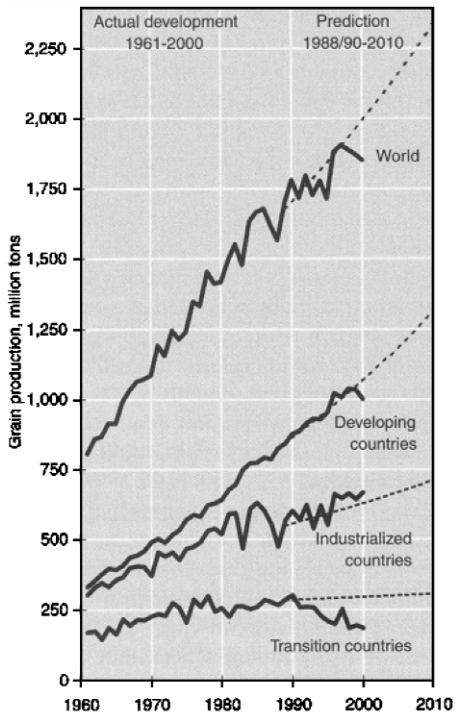


Fig. 9 Actual grain production in million tons from 1961 to 2000 and projected grain production from 2000 to 2010. Source[31,32]

However, the historical methods used to achieve this efficiency have not generally been sustainable. The use of pesticides (Fig. 10) and fertilizers (Fig. 11) has grown substantially with the environmental consequences of agricultural run-off well documented. Green chemistry has witnessed advances in the development of new and more sustainable pesticides that are both targeted very specifically to only pest organisms and do not

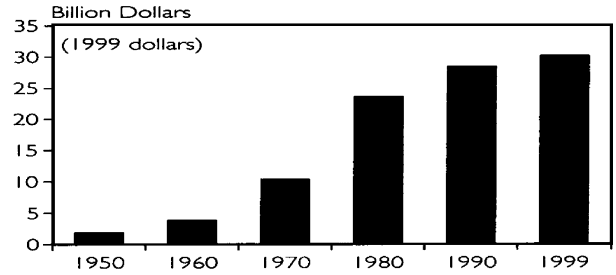


Fig. 10 Global pesticide sales from 1950–1999 in billion 1999 dollars. Source.[33]

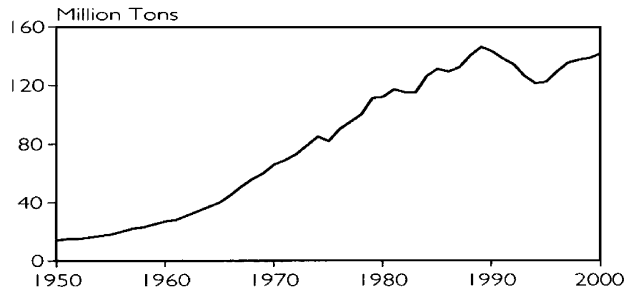


Fig. 11 Global fertilizer use in million tons from 1950–2000. Source.[33]

persist in the environment.[7–10] In addition, fertilizers and fertilizers adjuvants are significantly decreasing the amount of material that needs to be applied to the land in order to achieve the same beneficial activity.[11] Continued development of compounds to improve agricultural efficiency by green chemistry will be one essential component of achieving sustainable agricultural systems to meet the needs of the additional billions of people expected to populate the planet.

Global climate change

While projections of climate change show a global warming trend, most models show that some places may get warmer while some get cooler; some places will get drier while some get wetter. Exactly where and at exactly what rate these projections will be manifested is still the subject of reasonable debate. What is certain, however, is that approaches to minimize the generation and release of greenhouse gases to the atmosphere will require new science and technology that deals with the issue in an economically and environmentally sustainable manner. There is current research on simple sequestration technologies for carbon dioxide. While there will be attempts to make this as least costly as possible, these technologies will still be a **cost** rather than **value adding.** Green chemistry research is seeking to design and develop methods that will utilize carbon dioxide in fixative ways that are value adding, such as in polymer materials[12] and on potentially much larger scales such as building materials and concrete.[13] Changing the equation from carbon dioxide as a waste to using it as a value added feedstock would be an essential pathway to dealing with the goal of controlling carbon dioxide in a manner that is both economically and environmentally sustainable.

Resource depletion

The use of limited finite resources becomes and increasingly important issue as population increases. It has been stated that in order for the current population of the Earth to live at the same

quality of life as the industrialized nations, it would require the resources of four 'Earth equivalents'.[14] Other analyses state that sustainability will require a least a four-fold (others say ten-fold) increase in material efficiency, that is getting the same function for one-quarter or one tenth the material.

Renewable resource utilization is a central tenet of green chemistry and a very active area of engagement. Use of biomass as feedstock is being developed in everything from polymers,[15] materials[16] and fuels.[17] The use of nanoscience is beginning to be pursued to achieve material efficiency through green chemistry that will have potential applications from computing to energy storage and others not yet imagined to meet the goal of sustainability.[18] Non-conventional biomass such as seafood by-products, *e.g.*, chitin, continue to be developed into materials like chitosan.[19] However, an overarching theme may be that green chemistry strives to turn materials and energy sources that may have once been viewed as waste into value added renewable materials.

Water

Water, perhaps the molecule most associated with life on Earth, is also one of the greatest challenges to sustainability in the 21st century. Thirty percent of the world's population will face water shortages by the year 2050, according to the United Nations Environment Program (UNEP).[20] The water crisis is so severe that, according to UNEP:

- Every eight seconds, a child dies from a water-related disease
- 50 percent of people in developing countries suffer from one or more water related diseases
- 80 percent of the diseases in the developing world are caused by contaminated/polluted water;
- 50 percent of people on Earth lack adequate sanitation

In many countries, water shortages stem from inefficient use, degradation of the available water by pollution and the unsustainable use of underground water in aquifers. Green chemistry is improving water supply and water quality through the prevention of contamination and more environmentally benign treatment methodologies. In addition to finding alternatives to unsustainable water use in applications like manufacturing, Green chemistry is also being engaged to find more sustainable ways to purify drinking water. Through the use of totally chlorine-free disinfection agents, water can both be pure and also not contribute to the generation of toxic and bioaccumulating substances.[21]

Toxics in the environment

The generation and release of toxic substances to the environment remains a global issue. In the U.S. alone, over 7 billion pounds were released directly to the air, water and land in the most recent TRI reporting.[22] Persistent, bioaccumulating and endocrine disrupting chemicals are of serious concern in both the industrialized and developing world. One of the greatest strengths of green chemistry is its focus on the molecular basis of toxicity. Through an understanding of the mechanisms of action of toxicity both in the body and within ecosystems, green chemistry engages to design molecular structures that are inherently either incapable of manifesting a particular toxic endpoint, or at a minimum, greatly disfavoring these toxic mechanisms.[23] These principles and techniques have been applied to substances ranging from dyes to pesticides to plastics to pharmaceuticals.

There are those that often quote the 16th century physician and patriarch of toxicology, Paracelsus in his admonition that 'Everything is toxic, it is simply a matter of the dose.' This obvious citation is taken a reminder that we can never say that something possesses **absolutely no** toxicity. It is important while recognizing the immense complexity of toxicological mechanisms, not to overstate this trivial but true fact. While we may never be able to reach perfection, it is an extremely worthwhile goal to move from extremely potent toxic substances to those that are many orders of magnitude less hazardous. Stated another way:

Ode to Paracelsus

It's important to heed Paracelsus
'All's toxic, just depends on the dose'
And to condemn those who tell us,
it means hazard can't be controlled.

While all things may be able to harm us.
It does not mean that all are the same.
to scientifically disarm us
would do us all great shame.

The substances we need to design
would make Paracelsus proud.
Then we can drink 10 liters of 'benign'
And perhaps we may only drown.

Conclusion

The challenges of sustainability are among the most complex and daunting ever faced by society. It may well be that only by working at the most fundamental level, the molecular level, that we can address these complex, global issues in an environmentally and economically sustainable manner. Green chemistry is engaged and needs to be increasingly engaged in facing these challenges by addressing the intrinsic nature of our materials and energy to make them more sustainable. No one is arguing that green chemistry alone will lead to sustainability. However, with green chemistry as an essential element, the path toward sustainability can be traversed, without the engagement of green chemistry, the existence of a path is not clear.

Acknowledgement

The author wishes to thank Juliet Zimmerman for her assistance and contributions to this work, without which this paper would not have been possible.

References

1 R. T. Watson, a.t.C.W.T., *Climate Change 2001: Synthesis Report. 2001*, *Intergovernmental Panel on Climate Change*: Cambridge, p. 398.
2 NRC Board on Sustainable Development (editor) *Our Common Journey: A Transition Toward Sustainability*, ed. N.B.o.S. Development, National Academy Press, Washington D.C., 2000, 384 pp.
3 P. Anastas and J. Warner, *Green Chemistry: Theory and Practice*, Oxford University Press, London, 1998, 144.
4 R. D. Cortright, R. R. Davda and J. A. Dumesic, *'Hydrogen from catalytic reforming of biomass-derived hydrocarbons in liquid water'*, *Nature*, 2002, **418**, 964–967.
5 B. E. Logan, *et al.*, *'Biological hydrogen production measured in batch anaerobic respirometers'*, *Environmental Science and Technology*, 2002**, 36**, 2530–2535.
6 K. Kato, A. Murata and K. Sakuta, *'Energy Payback Time and Life-Cycle CO_2 Emission of Residential PV Power System with Silicon PV Module'*, *Progress in Photovoltaics, Research and Applications*, 1998, **6**, 105–115.

7 Dow Agrosciences LLC *Spinosad, A New Natural Product for Insect Control, in Presidential Green Chemistry Challenge Award Recipients*, ed. United States Environmental Protection Agency, Washington, D.C., 1999.

8 Dow Agrosciences LLC *Sentricon™ Termite Colony Elimination System, A New Paradigm for Termite Control, in Presidential Green Chemistry Challenge Award Recipients*, ed. United States Environmental Protection Agency, 2000, Washington, D.C.

9 Rohm and Haas Company *Designing an Environmentally Safe Marine Antifoulant, in Presidential Green Chemistry Challenge Award Recipients*, ed. United States Environmental Protection Agency, Washington, D.C., 1996.

10 Rohm and Haas Company, *Invention and Commercialization of a New Chemical Family of Insecticides Exemplified by CONFIRM™ Selective Caterpillar Control Agent and the Related Selective Insect Control Agents MACH 2™ and INTREPID™*, in *Presidential Green Chemistry Challenge Award Recipients*, United States Environmental Protection Agency, Editor. 1998: Washington, D.C.

11 Donlar Corporation *Production and Use of Thermal Polyaspartic Acid, in Presidential Green Chemistry Challenge Award Recipients*, ed. United States Environmental Protection Agency, Washington, D.C., 1996.

12 M. Cheng, E. B. Lobkovsky and G. W. Coates, *'Catalytic Reactions Involving C1 Feedstocks: New High-Activity Zn(II)-Based Catalysts for the Alternating Copolymerization of Carbon Dioxide and Epoxides'*, *Journal of the American Chemical Society*, 1998, **120**(42), 11018–11019.

13 R. Jones, *Supercritical CO_2 carbonation of cement and cement-fiber composites: The supramics process, in Green Engineering*, ed. P. Anastas, T. C. Williamson and L. Heine, American Chemical Society, Washington, DC, 2002, 124–135.

14 W. E. Rees, P. Testemale and M. Wackernagel, *Our Ecological Footprint*, New Society Publisher, British Columbia, Canada, 1995, 176.

15 R. A. Gross and B. Kalra, *'Biodegradable Polymers for the Environment'*, *Science*, 2002, **297**, 803–807.

16 R. P. Wool, *et al.*, *Affordable Composites and Plastics from Renewable Resources, in Green Materials*, ed. EPA-ACS, American Chemical Society, Washington, D.C., 2001.

17 M. T. Holtzapple, *et al.*, *Biomass Conversion to Mixed Alcohol Fuels Using the MixAlco Process, Applied Biochemistry and Biotechnology*, 1999, **77–79**, 609–631.

18 L. Lave, *Lifecycle/Sustainability Implications of Nanotechnology in Societal Implications of Nanoscience and Nanotechnology*, National Science Foundation, Washington, D.C., 2001, 162–166.

19 O. C. Agboh and Y. Qin, *Chitin and chitosan fibers, Polymers for Advanced Technologies*, 1997, **8**(6), 355–365.

20 *United Nations Environment Program, Global Environmental Outlook 2000*, United Nations, New York, 1999.

21 S. C. Gupta, *et al.*,*'The Design of Catalysts for Green Oxidation Processes'*, *Science*, 2002, **296**, 326–328.

22 *United States Environmental Protection Agency, Toxics Release Inventory for 2000*, Washington, D.C., 2002.

23 Ed. Stephen C. Devito and Roger L. Garrett, *Designing Safer Chemicals: Green Chemistry for Pollution Prevention, ACS Symposium Series, No 640*, Washington, D.C., American Chemical Society, 1996.

24 J. A. Cusumano, *'New Technology for the Environment'*, *Chemtech*, 1992, **22**(8), 482–489.

25 R. H. Bezdek, *'State of the Industry: Jobs and Sales Created by Environmental Protection'*, *New England's Environment*, 1999, (8).

26 Population Division of the Department of Economic and Social Affairs *World Population Projections to 2150*, United Nations Secretariat, New York, 1998.

27 Population Division of the Department of Economic and Social Affairs *World Population Prospects: The 2000 Revision*, United Nations Secretariat, New York, 2000.

28 T. E. Graedel and B. R. Allenby, *Industrial Ecology*, Prentice Hill, Englewood Cliffs, 1995, 341.

29 Energy Information Adminstration and Office of Energy Markets and End Use. 2001, Department of Energy: Washington D.C.

30 Energy Information Adminstration and Office of Energy Markets and End Use, *World Energy Projection System*, 2002.

31 Food and Agriculture Organization, *The State of Food and Agriculture*, United Nations, Rome, 2001.

32 N. Alexandratos, *The world food outlook: a review essay*, Population and Development Review, 1997, **23**, (4), p. 877–888.

33 Linda Stark (editor), *State of the World*, ed. W. Institute, New York: W. W. Norton and Company, 2002, 256.

Perspective

Chemical reactions in supercritical carbon dioxide: from laboratory to commercial plant†

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Received 12th December 2002
First published as an Advance Article on the web 3rd March 2003

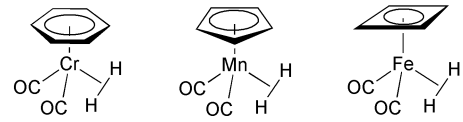
The application of supercritical carbon dioxide in continuous, fixed bed reactors has allowed the successful development of a variety of industrially viable synthetic transformations. The world's first, multi-reaction, supercritical flow reactor was commissioned in 2002 as a direct result of the successful collaboration between the Clean Technology Group at the University of Nottingham and the fine chemicals manufacturer, Thomas Swan & Co. Ltd. We highlight the development of this project from laboratory to plant scale, particularly in the context of the hydrogenation of isophorone. Phase data for the system; isophorone + H_2 + CO_2, are presented for the first time. Overall, we present a progress report about an on-going Green Chemistry initiative that has successfully forged strong links between Industry and Academia.

Introduction

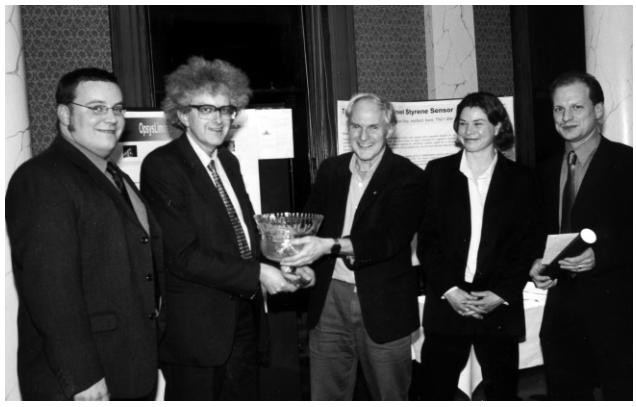
This is an unusual paper because it traces a project from simple experiments in the laboratory right up to the construction of a full scale plant capable of producing 1000 tons *per annum*. We believe that the story is important because a major aim of Green Chemistry is the implementation of new technologies on a large scale and, as yet, there are very few concrete examples of this aim being realised in practice.[1,2] The project is important for a second reason, namely that the plant itself is a large-scale Green Chemistry experiment and a rare example of a new technology being put to the test in public. Like all such projects, the full history is quite convoluted. Here we highlight only the most significant events.

The project involves chemical reactions in supercritical fluids (SCFs) which have been recognised for some time as possible replacements for environmentally less acceptable solvents.[2,3] In particular, supercritical CO_2 ($scCO_2$) has been used widely for extraction processes,[4] for example for the extraction of caffeine from coffee beans. The decaffeination of coffee is an outstanding example of a green technology that has largely supplanted earlier processes.[3,4] Most importantly, for this project, the pre-existence of a mature SCF extraction industry meant that most, if not all, of the equipment needed for chemistry in SCFs was already available well before the official start of the project in 1995. However, the project itself has a much longer history.

Originally, the motivation at Nottingham for carrying out chemical reactions under supercritical conditions was to provide a better route for the photochemical generation of unstable organometallic dihydrogen[5] and dinitrogen complexes such as those shown in Scheme 1.[6,7] One of the keys to the success of this early work was the relatively high concentrations of H_2 and N_2 that could be readily achieved, because such gases



Scheme 1 Examples of unstable organometallic species prepared in supercritical fluids.[6]



Representatives of the Nottingham/Thomas Swan team receiving the First Prize in the RSC 2002 Industrial Innovation Team Award from the RSC President, Sir Harry Kroto (centre), for their production scale process in supercritical carbon dioxide. (From the right) Dr Stephen Ross and Dr Murielle Sellin of Thomas Swan & Co., and Prof. Martyn Poliakoff and Dr Peter Licence of the University of Nottingham. The picture was taken immediately after Sir Harry had lightheartedly placed the upturned glass trophy as a helmet on Martyn's head!

† This work was presented at the Green Solvents for Catalysis Meeting held in Bruchsal, Germany, 13–16th October 2002.

Green Context

The success of Green Chemistry depends on the development of commercial scale processes based on the principles of green chemistry. The replacement of volatile organic solvents with more environmentally benign reaction media is one of the most exciting ideas to emerge from green chemistry research and here we can read about its successful transition to commercial production. The paper also demonstrates the potential value to both parties of academic industrial collaboration. ***JHC***

are totally miscible with most SCFs. This concentration effect was later exploited for catalytic hydrogenation in SCFs by Noyori *et al.*[8] and others.[9]

We quickly extended our experiments to other SCF photoreactions including C–H activation[10] and the synthesis of metal ethene complexes.[11] All of these reactions[6] were initially carried out in small spectroscopic cells (volume < 2 mL) which afforded little chance of isolating the 'unstable' products, even though many of them appeared to be surprisingly long-lived. This inspired us to devise miniature continuous reactors for carrying out such reactions on a preparative scale (see Fig. 1),[11–13] which subsequently enabled us to isolate a number of novel ethene and dihydrogen complexes, one of the few occasions when *new* compounds have been successfully isolated with the aid of SCFs.[6]

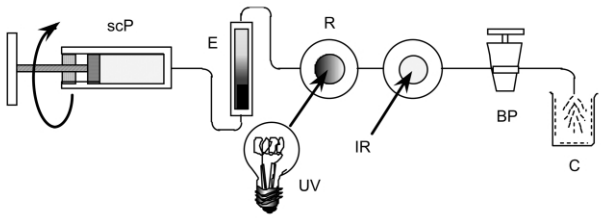


Fig. 1 Schematic view of a flow reactor[11] used for the isolation of $Cr(CO)_5(C_2H_4)$ from supercritical C_2H_4, scC_2H_4. Parts are labelled as follows: scP, the scC_2H_4 pump; E, reservoir for solid $Cr(CO)_6$; R, the photolysis chamber for converting reactant to product; UV, photolysis lamp; IR, IR cell for optimising the reaction, BP, back-pressure regulator to release the pressure and to precipitate the product into the container C. (Note that, strictly, this is a batch type reactor being run in a flow mode because the reservoir E will eventually run out. In practise E could hold enough reactant for several experiments.)

Then came an unusual twist to the story. The work at Nottingham was included by David Bradley in his New Scientist feature article[14] on SCFs entitled *'Solvents get the Big Squeeze'*. The article covered a number of applications of SCFs, ranging from the decaffeination of coffee[4] to the development of new reactions and polymerisation techniques.[15] Crucially to this project, it also included M. Poliakoff's semi-humorous vision of SCF chemistry in the future as being *'as simple as operating a drinks vending machine. The chemist will simply press a button and the machine will add the appropriate reagents to the supercritical CO_2 and pump the mixture into the reactor'*. This frivolous statement caught the eye of Professor Tom Swan OBE, owner of the fine chemicals manufacturer, Thomas Swan & Co. Ltd., who recognised the potential that such 'dial a chemical' technology could bring to his business. He was also attracted by $scCO_2$ as a cleaner solvent because, at that time, it was feared that all chlorinated solvents might be banned. He contacted Nottingham, nine months of discussions began, and a collaboration was set up.

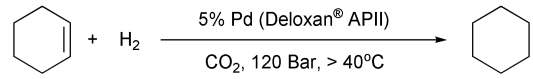
The strategy

It was decided to target continuous hydrogenation in $scCO_2$ using heterogeneous catalysts. This built on existing Nottingham expertise[11,12] in constructing flow reactors involving H_2 and, if successful, would lead to a new capability for Thomas Swan & Co. Ltd. Heterogeneous rather than homogeneous catalysis was chosen because it was experimentally simpler and there were more obvious routes to scale up under high pressure conditions. The objectives were ambitious: to develop a technology for hydrogenating a wide range of organic functionalities, with high selectivity, and on *a scale equivalent to tons per annum in the laboratory*.

It rapidly became clear that a multidisciplinary team would be required including organic chemists, high pressure engineers and catalyst developers. Thus, links were formed, at an early stage, with the German catalyst manufacturers, Degussa AG, who had experience of catalysis in SCFs,[16] and with Dr K.-H. Pickel whose company, NWA GmbH, specialises in the manufacture of high pressure SCF apparatus.[17,18] Finally, a German post-doctoral researcher, Dr Martin Hitzler, was recruited to co-ordinate the research efforts.

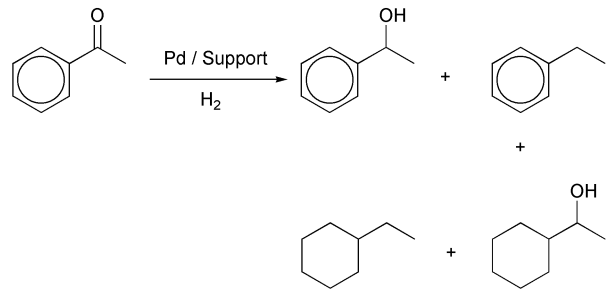
Proof of concept

The project started in November 1995. The first reaction involved the hydrogenation of cyclohexene in supercritical CO_2, (Scheme 2). The results were striking, with a quantitative conversion being observed. The reaction proceeded with a very high linear hourly space velocity (LHSV) (*e.g.* 300 h^{-1} from a 5 mL reactor),[19,20] equivalent to a rate of 1200 mL per h or 7.5 tons *per annum*.



Scheme 2 The hydrogenation of cyclohexene under supercritical conditions, the reaction proceeded quantitatively with a very high LHSV (*e.g.* 300 h^{-1} from a 5 mL reactor).

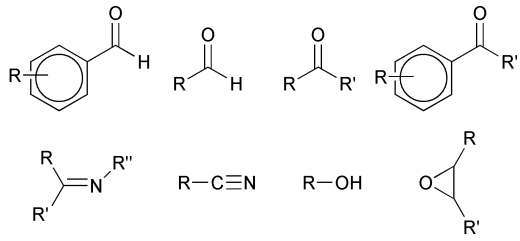
These results complemented those of Härröd and co-workers who were working on the hydrogenation of oleochemicals in supercritical propane.[9,21] A detailed investigation at Nottingham into the hydrogenation of acetophenone (Scheme 3),



Scheme 3 The range of products obtained in the hydrogenation of acetophenone. Conditions could be chosen to maximize the yield of any one of these products.[19,20]

showed that $scCO_2$ allowed reaction conditions to be optimised very effectively to maximise the yield of particular hydrogenation products.[19] An interesting aspect was that the reactor delivered product free from any solvent. Thus, early in this project, all analysis was performed merely by diluting the product with deuterated solvent and running the ^1H NMR spectrum.[19,20] Later, the analysis was switched to more conventional methods, *e.g.* GC-FID, and GC-MS.

$scCO_2$ differs from conventional solvents in that its density is highly pressure dependent[4] and it is totally miscible with H_2 (see above). Furthermore, even if $scCO_2$ does not dissolve an organic liquid completely, CO_2 can dissolve into the liquid[22] causing it to expand considerably in volume, with a concomitant increase in the solubility of H_2 in the liquid phase. In general, our results suggested that, despite the unusual features of $scCO_2$ as a solvent, the overall selectivity of a given catalyst was not necessarily changed compared to its behaviour in conventional solvents but rather that conditions could be optimised more effectively in $scCO_2$.[23] The range of functionalities which could be hydrogenated in this way was quickly extended[19] and soon included those shown in Scheme 4. Most of these could be hydrogenated with high selectivity. There were some limitations, inherent to $scCO_2$, particularly the fact that aliphatic amines react with CO_2 to form insoluble carbamates,[3,4] which effectively terminate the reactions by precipitating and blocking the reactor.



Scheme 4 Some of the functionalities that have been successfully hydrogenated under supercritical conditions as part of our project.[20]

Extending the chemistry

It was quickly realised that the SCF reactor was not restricted to hydrogenation reactions and could, in principle, be adapted to any type of solid or supported catalyst. Successful reactions included Friedel Crafts alkylation,[24] etherification,[25] hydroformylation[26] and base-catalysed transesterification.[27] The success of such reactions prompted Thomas Swan & Co. to set up their own SCF equipment in their research laboratories at Consett, UK. At the end of the first year, a PhD student, Fiona Smail was recruited to the project, Fig. 2. Further PhD students have been recruited annually.

Fig. 2 Picture of Dr F. R. Smail operating the first SCF reactor in Nottingham, (for a schematic view see Fig. 3). She joined the project in 1996 as a postgraduate student and, on completion of her PhD, joined Thomas Swan & Co. Ltd. where she is now Senior Research Chemist. In 2002, she won the CIA-SOCSA Innovation Prize for Young Chemists in recognition of her work in SCFs.

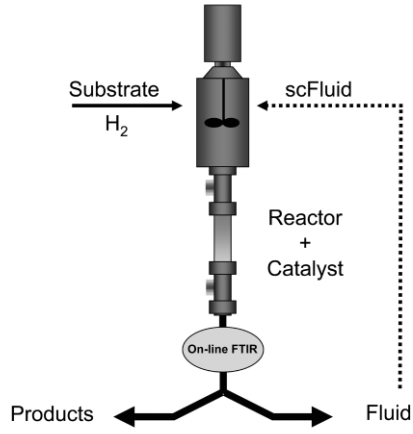
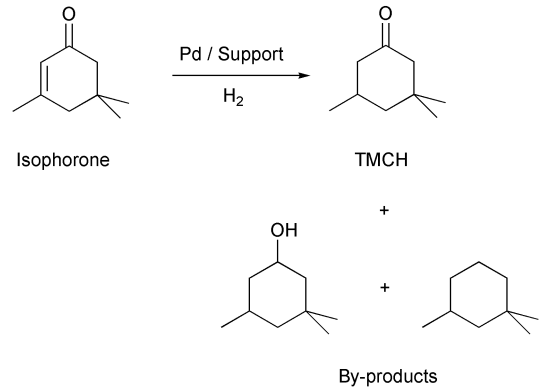


Fig. 3 Block diagram of the key components of the continuous reactor for hydrogenation of organic compounds at Nottingham.[19] $scCO_2$, H_2 and the organic substrate were mixed in a heated mixer. The mixture was then passed through a reactor containing a fixed bed catalyst (usually a supported noble metal). There was optional on-line FTIR monitoring before the product and CO_2 were separated by expansion. More recent reactors have used static rather mechanical premixers.

The development of a process

It was now important to identify a model compound, which could be used by the two laboratories, Nottingham and Thomas Swan & Co., as the basis for developing a viable SCF process. It was also important to choose a reaction of potential commercial interest where the ease of optimisation in $scCO_2$ could be exploited. The chosen reaction was the hydrogenation of isophorone to trimethylcyclohexanone (TMCH) (Scheme 5).[19] This reaction is a good model because the industrial end-



Scheme 5 Reaction scheme illustrating the range of products obtained in the hydrogenation of isophorone.

users require high purity product. The problem with conventional hydrogenation technologies is that they can easily lead to a mixture of TMCH and the over-hydrogenated by-products, trimethylcyclohexanol and trimethylcyclohexane.[28] All of these compounds, and isophorone itself, have similar boiling points, and the need to separate and purify TMCH from these mixtures adds greatly to both the cost and the environmental impact of the overall process.

This reaction was initially carried out on a laboratory-scale at Nottingham where it was found that conditions in $scCO_2$ could be adjusted to give quantitative conversion of isophorone to TMCH at a rate of up to 7 ml per min.[19] Clearly, if this process could be scaled up, one would eliminate the need for any purification steps following the hydrogenation. The work was then transferred to the laboratories at Thomas Swan & Co. where the industrial environment was better suited to investigating the feasibility of scale-up to a production scale. These investigations focussed particularly upon the choice of catalyst and catalyst lifetime.

Catalyst. The initial studies at Nottingham were carried out using catalysts supported on Deloxan®, a polysiloxane material from Degussa.[16] Deloxan® was found to be very durable and gave a good catalyst lifetime with up to 3 kg of product produced per gram of catalyst without significant loss of selectivity.[19] At this point, the decision was taken to commission a full-scale plant from the Swedish engineering company Chematur Engineering.

Then, there was a major setback. The Deloxan® range of catalysts was suddenly withdrawn from commercial production; an alternative source of catalysts was urgently required. Having screened a variety of catalysts, it was evident that a wide range of conversions and catalyst lifetimes could be obtained for a given noble metal, depending on the nature of the support. It was quickly recognised that the key criterion was the yield of TMCH *per g of Pd* rather than the yield *per g of catalyst*. These results supported previous work carried out by Hutchenson *et al.* in that Deloxan® outperformed most other catalysts with respect to conversion.[29] Eventually, alternative catalysts were identified that gave excellent catalyst life whilst retaining a level of conversion and product selectivity comparable to Deloxan®, see Table 1.

Table 1 Catalyst screening results for the selective hydrogenation of isophorone to trimethylcyclohexanone (TMCH)

Catalyst	Metal loading	kg TMCH/ g cat.	kg TMCH/ g Pd	Selectivity (%)
Deloxan®	Pd 5%	3.0	60	100
A	Pd 5%	0.4	8	91
B	Pd 2%	1.2	60	100
C	Pd 2%	1.1	55	>99
D	Pd 5%	3.0	60	98
E	Pd 2%	0.05	1	94

Reaction optimisation

Table 2 summarises the optimised conditions for the hydrogenation of isophorone in the laboratory. Particularly striking is the range of concentrations of isophorone which can be successfully reacted, 2–48 wt%. Supercritical reactions generally involve high pressures and considerable compression costs, in contravention of the 6th principle of Green Chemistry.[1,30] Clearly, maximising the concentration of isophorone will minimise the energy requirements of the process. At the same time, working with such high concentrations raises the whole issue of phase behaviour in the reaction mixture.

Table 2 Optimised laboratory conditions for hydrogenation of isophorone to TMCH

Reactor size	0.85 cm id, 25 cm long
Catalyst	2% Pd
Temperature	Inlet 56 °C
	Outlet 100 °C
Hydrogen	1.7–2.75 equivalents
Substrate feed	2–48 wt%

Phase behaviour. Considerable scientific argument has revolved around the question of whether supercritical hydrogenation reactions proceed faster and more efficiently in either a single or multiple phases; indeed conflicting reports have been published.[22,31–33] Much of this debate has revolved around the LHSV of a reaction, but this parameter only addresses part of the issue from an industrial perspective. Other important factors which have to be taken into account include catalyst lifetime, overall conversion and product selectivity as well as solvent compression costs. The situation has been at least partly resolved by a key paper by Nunes da Ponte and co-workers.[34] They have shown that biphasic reactions can sometimes be faster than monophasic ones, because the concentration of substrate (as opposed to H_2) is lower under monophasic conditions.

Because of the difficulty in measuring the high-pressure phase equilibrium of complex fluids, data on critical points and phase separations are scarce, especially for multi-component mixtures. Furthermore, the composition of a reaction mixture changes as the reaction proceeds.[35,36] Dissolving a substrate in a SCF mixture complicates the phase diagram of the system, when compared to that of a pure substance. Consequently, variations in temperature and pressure can have a much more pronounced effect on the phase behaviour of a fluid mixture than that of a pure substance.

Therefore we have undertaken a study[37] of the phase behaviour of four mixtures of varying composition, isophorone–CO_2–H_2 across six experimentally determined isotherms at 40, 60, 80, 100, 120 and 140 °C. This has established the boundary between the one and two phase regions of the phase diagram for this system; see Fig. 4.

The measurement of these phase equilibria clearly reveals that, for mixtures with a composition in excess of around 5% isophorone, quite substantial pressures and temperatures are required to render the system monophasic, a condition that has been reported to be essential for efficient and rapid hydrogenation.[32] By contrast, we have shown that this reaction can be carried out with excellent selectivity and conversion with as much as 50% isophorone in the reaction stream, conditions that are clearly not single phase. Furthermore, when conditions that facilitate single phase reactions are employed, a loss of desired product selectivity is observed as the high temperatures that are required often lead to the formation of unwanted side products.

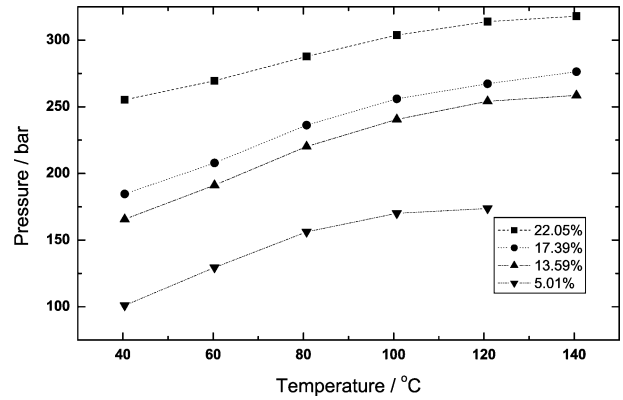


Fig. 4 Plot illustrating the experimentally determined phase boundaries of four mixtures of isophorone–CO_2–H_2 of varying composition. (Isophorone w/w 5–22 % w/w, molar ratio of isophorone : H_2 was fixed at 1 : 1.7).

The plant

Fig. 5 shows the schematic design of the Thomas Swan & Co. plant. It has a production capacity of *ca.* 100 kg per hour (1000 tons *per annum*). It therefore represents a ×400 scale-up of the laboratory reactor in terms of production.

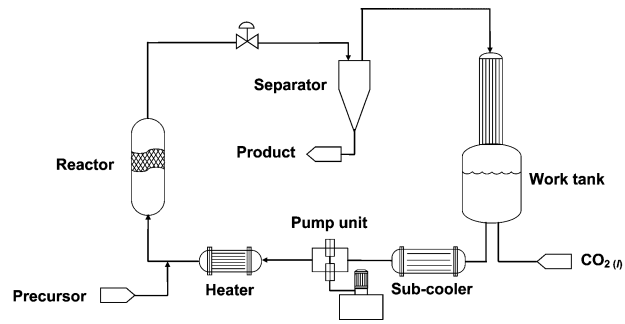


Fig. 5 Schematic flow diagram of the SCF plant at Thomas Swan & Co. Ltd., constructed by Chematur Engineering.

The plant is multi-purpose. The catalysts within the reactor can be changed to change the chemistry. A photograph of the actual reactors may be seen in Fig. 6. It is designed to work only with CO_2 as the SCF. (A new plant for reactions in supercritical propane is currently being built in Göteborg).[38] The Thomas Swan & Co. plant went on stream in June 2002.

The hydrogenation of isophorone was the first reaction to be run on the plant. The optimised conditions are shown in Table 3, and it is immediately clear that these conditions are very close to the optimised conditions in the laboratory, Table 2. If this transferability applies to other reactions, it will have considerable significance; reactions can be optimised in the laboratory and transferred almost directly to the plant.

Table 4 summarises the customer specifications for TMCH and an actual analysis of the raw product, direct from the plant. It can be seen that the product exceeded the specification in all five categories, although the acid value is only reached after residual CO_2 is removed by a brief application of vacuum. Thus,

Fig. 6 Photograph of the reactor array in the Thomas Swan & Co. SCF reactions plant.

Table 3 Optimised plant conditions for hydrogenation of isophorone to TMCH

Catalyst	2% Pd
Temperature	Isothermal 104–116 °C
Hydrogen	1.7 equivalents
Substrate feed	9–17 wt%

Table 4 Customer specification and product analysis for TMCH produced under supercritical conditions

Specification	Customer	SwanSCF
Colour (Hazen scale)	10 max	< 10
Assay (%)	99 min	99.4
Trimethylcyclohexanols (%)	1 max	0.3
Isophorone (%)	0.4 max	0.08
Acid value/mg KOH g^{-1}	0.1 max	0.08[a]

[a] Value measured after discharge of dissolved CO_2, corresponding value before discharge was 8.

in the case of TMCH, SCF technology has eliminated the need for any downstream purification of the product.

Conclusion

The first phase of our collaboration has reached a successful conclusion. The reaction methodology developed in the laboratory has been successfully scaled up to a commercial scale. The academic and industrial partners have generated appropriate outcomes in the form of publications and patents respectively. At the same time there has been a physical transfer of Green Chemistry know-how from university to industry; apart from M.G. Hitzler, all of the post-docs and students sponsored by Thomas Swan, have joined the company after completing their work at Nottingham. Last year Thomas Swan & Co. Ltd. were nominated as one of the top 20 most innovative speciality chemical companies in the world[39] and the work at Nottingham has been recognised by the awarding of an RSC Interdisciplinary Award (MP). In January 2003, the Nottingham-Thomas Swan & Co. research teams won first prize in the Industrial Innovation Team Award of the Industrial Affairs Division of the Royal Society of Chemistry for their work on 'developing production scale chemistry in supercritical carbon dioxide'.

Overall, we believe not only that our collaboration has been scientifically rewarding to the participants but also that we have demonstrated what can be achieved by a committed academic/industrial partnership. However, the most exciting phase is just beginning. The technology works; now we have to demonstrate whether it is commercially competitive. Such demonstrations are vital to the future of Green Chemistry. Manufacturers will not adopt new, cleaner technologies unless they also provide genuine commercial advantages.

Acknowledgements

Apart from the authors, this project has involved contributions from Drs M. G. Hitzler, J. R. Hyde, W. K. Gray, F. R. Smail and N. J. Meehan and Messrs D. N. Carter, R. Amandi, B. Walsh, P. Stephenson, A. O. Chapman and P. Clark, at Nottingham and Drs F. R. Smail, N. J. Meehan and M. Sellin and Ms D. Adair and Ms N. Canceil at Thomas Swan & Co. Ltd. We thank Messrs M. Guyler, M. Dellar, J. Whalley, R. Wilson, P. Fields and K. Stanley for technical support at Nottingham. We are grateful to Profs D. J. Cole-Hamilton, M. W. George, S. M. Howdle and M. Nunes da Ponte and Drs K.-H. Pickel, O. Aaltonen, A. Burgess and P.A. Hamley for helpful discussion.We thank all those who have supported this research including EPSRC (Grant Nos. GR/M73644, GR/R02863), EU Marie Curie programme (Contract No. ERBFMRXCT970104), EU Framework 5 projects (CPF-CO2 and SUPERSYN), the Royal Society, the CRYSTAL Faraday Partnership, the British Council, Degussa AG, Chematur Engineering and NWA GmbH.

References

1 M. Poliakoff, J. M. Fitzpatrick, T. R. Farren and P. T. Anastas, *Science*, 2002, **297**, 807.
2 J. M. DeSimone, *Science*, 2002, **297**, 799.
3 W. Leitner and P. G. Jessop, *Chemical synthesis using supercritical fluids*, Wiley-VCH, Weinheim, 1999.
4 M. A. McHugh and V. J. Krukonis, *Supercritical fluid extraction: principles and practice*, Butterworth-Heinemann, Boston, MA, 1994.
5 R. K. Upmacis, M. Poliakoff and J. J. Turner, *J. Am. Chem. Soc.*, 1986, **108**, 3645.
6 J. A. Darr and M. Poliakoff, *Chem. Rev.*, 1999, **99**, 495.
7 S. M. Howdle, M. A. Healy and M. Poliakoff, *J. Am. Chem. Soc.*, 1990, **112**, 4804.
8 P. G. Jessop, T. Ikariya and R. Noyori, *Nature*, 1994, **368**, 231.
9 M. Härröd, M.-B. Macher, J. Högberg and P. Møller, *Proceedings of the 4th Conference on Supercritical Fluids and Their Applications*, Capri, Italy, 1997, p. 319.
10 J. A. Banister, A. I. Cooper, S. M. Howdle, M. Jobling and M. Poliakoff, *Organometallics*, 1996, **15**, 1804.
11 J. A. Banister, S. M. Howdle and M. Poliakoff, *J. Chem. Soc., Chem. Commun.*, 1993, 1814.
12 J. A. Banister, P. D. Lee and M. Poliakoff, *Organometallics*, 1995, **14**, 3876.
13 P. D. Lee, J. L. King, S. Seebald and M. Poliakoff, *Organometallics*, 1998, **17**, 524.
14 D. Bradley, *New Sci.*, 1994, **143**, 32.
15 J. M. DeSimone, E. E. Maury, Y. Z. Menceloglu, J. B. McClain, T. J. Romack and J. R. Combes, *Science*, 1994, **265**, 356.
16 T. Tacke, S. Wieland and P. Panster, *Process Technol. Proc.*, 1996, **12**, 17.
17 B. Minder, T. Mallat, K. H. Pickel, K. Steiner and A. Baiker, *Catal. Lett.*, 1995, **34**, 1.
18 K.-H. Pickel and K. Steiner, *Proceedings of the 3rd International Symposium on Supercritical Fluids*, Strasbourg, France, 1994, p. 25.

19 M. G. Hitzler, F. R. Smail, S. K. Ross and M. Poliakoff, *Org. Proc. Res. Dev.*, 1998, **2**, 137.
20 M. G. Hitzler and M. Poliakoff, *Chem. Commun.*, 1997, 1667.
21 M. Härröd and P. Møller, *Process Technol Proc.*, 1996, **12**, 43.
22 A. Bertucco, P. Canu, L. Devetta and A. G. Zwahlen, *Ind. Eng. Chem. Res.*, 1997, **36**, 2626.
23 M. Poliakoff, N. J. Meehan and S. K. Ross, *Chem. Ind.*, 1999, 750.
24 M. G. Hitzler, F. R. Smail, S. K. Ross and M. Poliakoff, *Chem. Commun.*, 1998, 359.
25 F. R. Smail, W. K. Gray, M. G. Hitzler, S. K. Ross and M. Poliakoff, *J. Am. Chem. Soc.*, 1999, **121**, 10711.
26 N. J. Meehan, A. J. Sandee, J. N. H. Reek, P. J. C. Kamer, P. W. M. N. van Leeuwen and M. Poliakoff, *Chem. Commun.*, 2000, 1497.
27 K. W. Gray, D. N. Carter and M. Poliakoff, unpublished results.
28 See, for example: D. P. Cotrupe, W. E. Wellman and P. E. Burton, Patent No., US 3446850, 1969.
29 K. W. Hutchenson, F. E. Herkes, D. J. Walls, T. K. Das and J. F. Brennecke, *Abstr. Pap. Am. Chem. Soc.*, 2001, **221**, 342.
30 P. T. Anastas and J. Warner, *Green Chemistry Theory and Practice*, Oxford University Press, Oxford, UK, 1998.
31 L. Devetta, A. Giovanzana, P. Canu, A. Bertucco and B. J. Minder, *Catal. Today*, 1999, **48**, 337.
32 M. Härröd, S. Van der Hark and A. Holmqvist, *Proceedings of the 8th Meeting on Supercritical Fluids*, Bordeaux, France, 2002, p. 133.
33 M. Nunes da Ponte, A. Milewska, D. Gourgouillon, D. Chouchi and I. Fonseca, *Proceedings of the 8th Meeting on Supercritical Fluids*, Bordeaux, France, 2002, p. 129.
34 D. Chouchi, D. Gourgouillon, M. Courel, J. Vital and M. Nunes da Ponte, *Ind. Eng. Chem. Res.*, 2001, **40**, 2551.
35 J. Ke, B. X. Han, M. W. George, H. K. Yan and M. Poliakoff, *J. Am. Chem. Soc.*, 2001, **123**, 3661.
36 J. Ke, M. W. George, M. Poliakoff, B. X. Han and H. K. Yan, *J. Phys. Chem. B*, 2002, **106**, 4496.
37 The gas–liquid phase boundary of this system was measured in a variable-volume view cell, which consists of a horizontal cylinder mounted with a sapphire window in the front end. The cell volume is changed by moving a piston placed within the cylinder. A sample, with known composition, was then loaded into the cell; any changes in phase behaviour, as a function of temperature and pressure, were monitored. For further details of the experimental technique employed, see reference 4.
38 M. Härröd, S. Van der Hark, A. Holmqvist and P. Møller, *Chem. Eng. Trans.*, 2002, **2**, 537.
39 *Chemical Specialty*, 2001, Sept./Oct., 25.

Perspective

Multiphase catalysis and its potential in catalytic processes: the story of biphasic homogeneous catalysis†

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Received 6th January 2003
First published as an Advance Article on the web 1st April 2003

Homogeneous catalysis in comparison to heterogeneous catalysis is burdened by the use of a solvent, which makes catalyst recycle and product separation costly and difficult. This is probably one of the main reasons that industry prefers heterogeneous catalysis.

Besides heterogenizing homogeneous catalysts, immobilization of the homogeneous catalysts in multiphase operation (*e.g.* two-liquid phase approach) offers promising opportunities. The two-liquid phase approach rests on the proper choice of distribution coefficients of the products with immiscible solvents. The following cases can be considered:

• The catalyst operates in a polar phase and the products form the second immiscible phase which can be "spooned off".
• Two immiscible solvents yielding two phases are used in the reactor. The catalyst remains in one phase, the products are extracted into the second phase.
• The homogeneous catalysis is carried out conventionally followed by extraction of the products with a second solvent, which is immiscible with the solvent of the phase containing the catalyst.

Examples are presented for all three cases. For case one, besides polar organic solvents, water, perfluorinated solvents, ionic liquids and supercritical CO_2 will be discussed.

Ionic liquids, having no vapour pressure and supercritical CO_2 can be used in a continuous operation. The catalyst must be soluble in the ionic liquid phase. The product will be extracted by the $scCO_2$. After separation, the CO_2 can easily be recycled. The combination of ionic liquids and compressed CO_2 provides a unique new approach of great promise.

In general — in contrast to heterogeneously catalyzed reactions such as the conversion of ethylene to ethylene oxide — homogeneously catalyzed reactions require, for economic reasons, high conversions. This can be overcome by using the "recycle two-phase approach" as will be demonstrated for the conversion of butadiene–ammonia to the primary octadienylamine. Especially processes with consecutive reactions can benefit here.

Introduction

In the development of chemistry the use of solvents has always played a crucial role. To the earliest solvents applied belong water, alcohol and terpentine. The many processes of transmutation, known to the medieval chemists, would have been impossible without solvents. Hermannus Boerhave wrote in 1733: *"Besides the four elements fire, water, air and soil we must consider a fifth one, the solvent, which is essential for chemists in conducting all their beautiful reactions."*

As the chemical industry developed more and more solvents were used on a larger and larger scale and solvents became a

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† This work was presented at the Green Solvents for Catalysis Meeting held in Bruchsal, Germany, 13–16th October 2002.

Green Context

Industry commonly prefers heterogeneous catalysis largely because of the separation difficulties associated with homogeneous catalysts that require added process stages, and leads to waste and inevitable loss of valuable catalyst. Multiphase catalysis involving two immiscible liquid phases offers a way around these problems and this methodology is reviewed in this article. The use of water, perfluorinated solvents, ionic liquids and supercritical carbon dioxide are all considered in this context. As the authors point out, through the combined expertise and imagination of chemists and engineers we can seek to take advantage of the enhanced activity that homogeneous catalysts can offer without the associated problems. ***DJM***

burden to the environment, which caused S. Lippard to demand: *"Develop the art of conducting chemical reactions without solvents"*. Also one of the targets in Green Chemistry is new solvents and reaction media. There is no question: the best solvent is no solvent.

Homogeneous catalysis is especially effected by the need for solvents. This is probably one of the main reasons that industry prefers heterogeneous catalysis in the gas phase. From Fig. 1 the problems of homogeneous catalysis are understandable. In a hypothetical reaction A + B → C, A and B are mixed in a solvent containing the homogeneous catalyst.

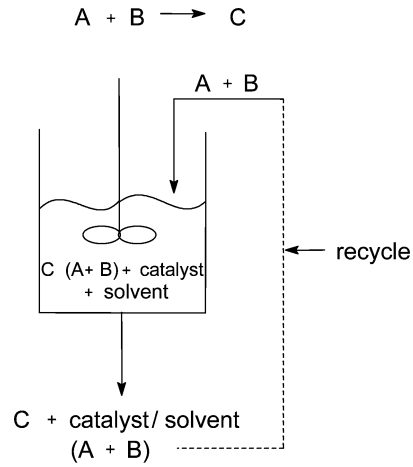


Fig. 1 Stirred tank reactor for homogeneous catalysis.

At 100% conversion no A and B are left, but there is still the problem of separating the product C from the catalyst/solvent phase, namely catalyst recycle . This problem is intensified at lower conversions with unreacted A and B present. Therefore, in homogeneous catalysis one prefers high conversions, but encounters all the difficulties of consecutive reactions.

In Table 1 advantages and disadvantages of homogeneous and heterogeneous catalysis are shown.

Multiphase catalysis

Various strategies have been developed to circumvent the problems of catalyst recycle

- Thermal and chemical methods
- Catalyst heterogenization

Supported solid phase (SSPC)
Supported liquid phase (SLPC)

- Membrane technology
- Multi-Phase (Biphasic liquid–liquid systems)

1. Thermal and chemical methods:

Here the Monsanto process for making acetic acid *via* the carbonylation of methanol may serve as an example practised at large scale. The rhodium catalyst stays in the reactor while the product acetic acid is distilled off. Obviously this works only when the product can be distilled off without decomposition of the products or harming the catalysts.

2. Catalyst heterogenization:

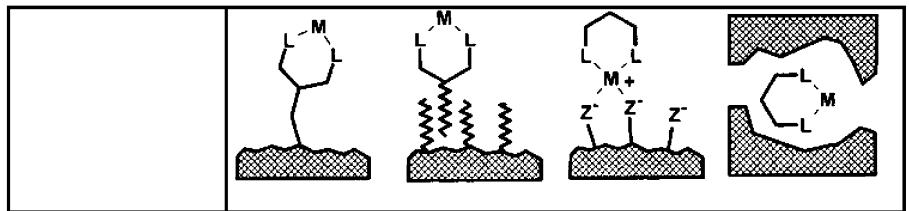
Numerous papers deal with heterogenizing homogeneous catalysts on an organic or inorganic support. Here various immobilization methods have been applied shown in Fig. 2.

Covalent binding, adsorption, ion pair formation, entrapment (ship in a bottle concept) and many more have been investigated. Summarizing, one can discuss the following advantages and disadvantages:

Advantages

Table 1 Advantages and disadvantages of homogeneous versus heterogeneous catalysis in catalyst removal

	Stirred tank Homogeneous operation	Fixed bed Heterogeneous operation
Conversion	High conversion	Low conversion
Separation	Filtration after chemical decomposition Distillation Extraction	No separation problems
Additional equipment required	Yes	No
Catalyst recycling	Difficult	Not neccessary
Costs of catalyst losses	High	Minimal
Catalyst concentration in product	Low	



Immobilization method	covalent binding	adsorption	ion pair formation	entrapment or 'ship in a bottle'
Applicability	broad	restricted	restricted	restricted
Problems	preparation	competition with solvents, substrates	competition with ionic substrates, salts	size of substrate, diffusion

Fig. 2 Heterogenization of homogeneous catalysts.

• ease of catalyst recycle
• homogeneous catalysts with unique ligand surroundings can be stabilized
• multifunctional catalysts are possible by supporting various organometallic complexes
• stabilization of uniform active species (single site catalysts)

Disadvantages
• bleeding of metal and/or ligand
• activity loss

So far, success in heterogenization is modest but possible as is evident from heterogenizing single site metallocene catalysts for gas phase ethene polymerization.

3. Membrane technology:

In this technology molecular size enlarged organometallic complexes (*e.g.* dendrimers[1] or colloids[2] are separated by a membrane thus divorcing the product phase from the catalyst phase. It is too early to evaluate this approach and the reader is referred to the elegant research by D. Vogt[1], G. van Koten[1] and S. Mecking.[2]

4. Multiphase (biphasic, liquid/liquid) catalysis

The principle of this technology expresses that the catalyst is immobilized in one liquid phase and the products separate in a second phase like water and oil. The product phase possessing no catalyst can be "spooned off" (decanted) easily thus enabling easy recycle of the catalyst phase. In this way, the solvent applied for the catalyst phase does not enter into the environment and meets the requirements of the "green solvent" concept. The solvent can be costly due to recycle and the engineers can treat them as an investment making economic calculations easier. Three cases can be considered in this approach.[3,4,7]

• Products separate during catalysis
• Catalysis is followed by extraction
• Solvent for extraction is already added during catalysis

4.1. Products separate during catalysis

The principle of this concept is illustrated with a general reaction between substrate A and B to the product C in Fig. 3.

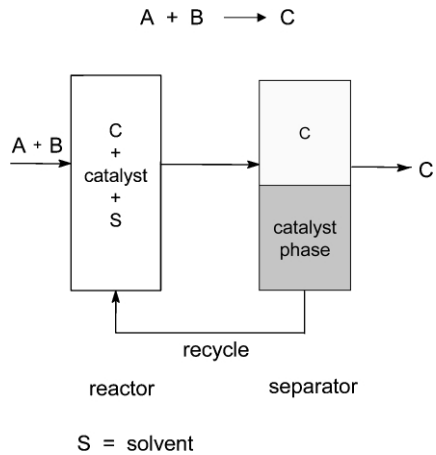
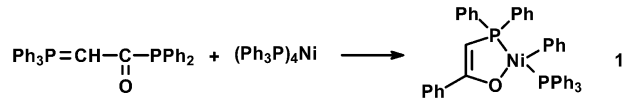


Fig. 3 Biphasic catalysis: products separate during catalysis.

The catalyst is dissolved in the solvent S. The products C formed during catalysis float on top of the solvent S because of their insolubility in this solvent and can be "spooned off" (decanted). Product–catalyst separation follows in a separator (settler); catalyst recycling to the reactor is easy.

This principle of catalyst recycle was discovered by the author during the development of Shell's SHOP-Process.[5]

When the author joined Shell Development at Emeryville, California in 1965, he was challenged with the task of linearly oligomerizing ethene to α-olefins, which in the C_{12}–C_{18} range were needed by Shell for detergent use. Being educated in the tradition of the K. Ziegler/C. Wilke school, the author synthesized P∩O-chelate- Ni-complexes as is shown for one example in Scheme 1.



Scheme 1 Synthesis of a square planar P∩O-chelate- Ni-complex.

Complex **1**, dissolved in toluene, reacted with ethene yielding α-olefins in >98% selectivity and >99% linearity. Catalyst cost and the need to recycle the catalyst brought the industrial development of this highly selective reaction to a near death. Than serendipity helped, but one should remember: *"In the fields of observation, chance favours only the prepared mind"* (L. Pasteur). One day the authors laboratory assistant, A. Nabong, used by mistake acetonitrile instead of toluene. "Eureka!" When opening the autoclave there were two phases, a yellow one containing the catalyst, and a water clear phase consisting only out of α-olefins. This was the discovery of biphasic catalysis. But problems remained. *"For it is one thing to invent a basically correct process, another to introduce it into industry"* (Hermann Ost 1907). Before a pilot plant could be built, a solvent with the right distribution coefficients having good solubility for ethene and poor solubility for α-olefins, a solvent in which the catalyst was stable at temperatures necessary for appropriate heat exchange still had to be found. Here it proved extremely useful that Shell at the same time has developed the Shell-Sulfolane-Extraction-Process and knowledge of this technology could enter into the development of SHOP. Many solvents were tested. The generality of the concept of biphasic catalysis was recognized. One site reaction was the observation that the use of water as solvent led to the formation of polyethylene. This probably was the first single site catalyst applied for ethene polymerization[6]. Finally, the first plant was constructed and a flow-scheme of the oligomerization part is shown in Fig. 4.

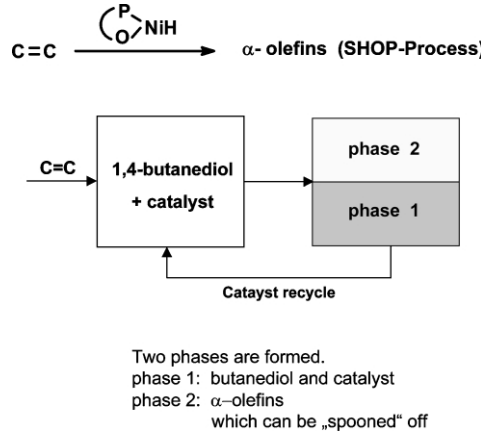


Fig. 4 Flow scheme of the SHOP-Process (oligomerization part).

Phase 1 contains the P∩O–Ni–H catalyst, phase 2 consists of pure α-olefins. This process with a capacity of 1 mio t, built in two big plants in England and USA, is the largest single feed application of homogeneous catalysis. Only hydroformylation starting from various olefins is bigger.

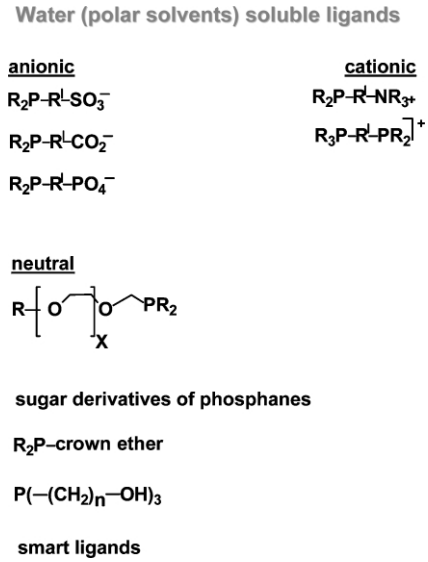
It is obvious that besides polar organic solvents also other solvents must be applicable. Having returned to the RWTH Aachen, the author started a general program in biphasic catalysis as early as 1973. Here the author is deeply indebted to A. Behr, who collaborated in so many fruitful ways when investigating biphasic catalysis at RWTH Aachen. The first report of our work appeared in 1976[7]. In our paper of 1987[3], nearly all the concepts disclosed later by many authors are already described.

Looking back from today, the biphasic concept is demonstrated for various solvents:

- Two immiscible organic liquids
- Water
- Fluor based solvents
- Ionic liquids
- Supercritical CO_2
- Supercritical solvents

4.1.1. Water. Here, as also reported in numerous literature examples, two large commercial processes evolved namely the hydroformylation of propene and butene by Rhône-Poulenc/Ruhrchemie (Hoechst)[8] and the synthesis of octadienols by Kuraray[9]. In both cases water soluble, sulfonated R_3P ligands are used.

The search for water soluble ligands has led to many ligand systems from which a selection is shown in Scheme 2.



Scheme 2 Water soluble ligands.

One of the earliest academic researchers in biphasic catalysis with water was F. Joó, Institute of Physical Chemistry, University of Debrecen, Hungary, who as early as 1975 started to work in this area. Here I also want to draw the attention of the reader to the work of B. Drießen-Hölscher of our institute.[10] Also the reader is referred to the book by B. Cornils and W. Herrmann "Aqueous-Phase Organometallic Catalysis".[11]

4.1.2 Fluor based solvents. In collaboration with Hoechst, we started in 1988 to use the fluorinated solvent Hostinert ® for the dimerization of 1-butene and for the oxidation of olefins.[12,13,14] The solvent and the catalyst used in the dimerization of 1-butene is shown in Fig. 5.

The results were not too exciting, mainly due to bleeding of the catalyst into the product phase, thus we did not publish this work outside of the thesis. Later, I. T. Horváth and J. A. Gladysz demonstrated in their beautiful work the usefulness of fluorinated solvents and complexes with fluorinated ligands.

4.1.3. Ionic liquids. The history of ionic liquids may be viewed as a relatively recent one, or one extending back to the 19th century. Its early use in homogeneous catalysis goes back

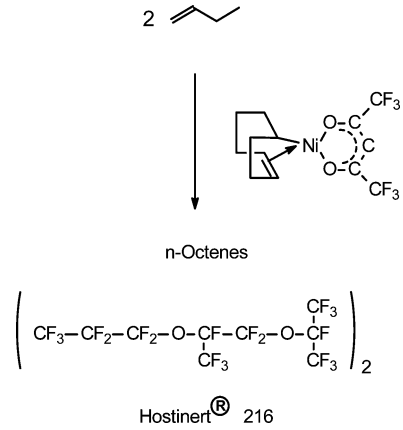


Fig. 5 Dimerization of 1-butene in Hostinert ® 216.

to G. Parshale[15] and J. F. Knifton.[16] The currently popular ionic liquids based on quaternary heterocyclic cations such as alkylpyridinium or dialkylimidazolium have been pioneered by J. S. Wilkes. It is the great merit of K. Seddon to have recognized the great potential of ionic liquids in chemistry. In a number of pioneering publications dealing with physics and chemistry of ionic liquids, he brought ionic liquids to the attention of more scientists as, for instance, the author. Here, also great credit must be given to M. Green, who used ionic liquids very early at BP and who also has inspired the author to investigate them. It became obvious, that ionic liquids could be used in a biphasic approach for homogeneous catalysis and in 1990, nearly parallel to J. S. Wilkes, Y. Chauvin[17] carried out the first reactions to polymerize and oligomerize olefins. Based on the work of Y. Chauvin, the Institut Francais du Pétrole (IFP) has developed a biphasic version of their established "Dimersol" technology by using ionic liquids, namely the "Difasol" process.[18]

We at Aachen started our work applying ionic liquids in 1995 with a Ph.D thesis of P. Wasserscheid[19,20] converting 1-butene to n-octenes. A self explanatory reaction scheme is exhibited in Fig. 6.

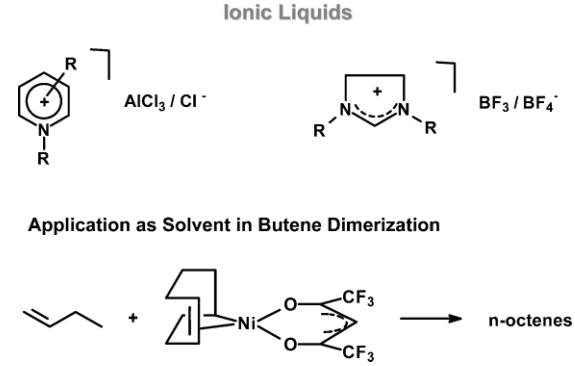


Fig. 6 Dimerization of butenes in ionic liquids.

The catalyst consisted out of a C_8H_9Ni-hexafluoroacetylacetonate complex known to dimerize butene linearly. The ionic liquids shown in Fig. 6 were used.

This work proved successful and was extended to ethylene oligomerization[20] and hydroformylation.[21] P. Wasserscheid selected the research on ionic-liquids for his Habilitation.[22] He advanced the field to a remarkable level. Today his name is closely associated with the development of ionic liquids, and he is well known for his many outstanding scientific contributions.

4.2. Catalysis is followed by extraction

This second approach of biphasic catalysis is rather general and is demonstrated in Fig. 7.

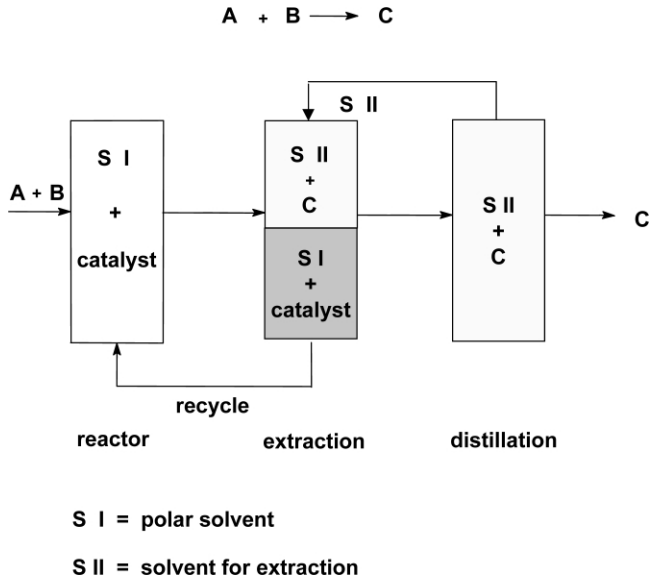


Fig. 7 Extraction of products from the catalyst phase by an appropriate solvent.

The hypothetical homogenous reaction A + B ⟶ C is carried out in solvent S I. After the reaction, solvents S II, immiscible with solvent S I, is added and the product C is extracted into solvent S II. The solvent S II is distilled off and recycled as is the catalyst phase with solvent S I. This working scheme, in principle, can be applied to any homogeneous catalysis as long as the appropriate solvent for extraction is available. It can also be used to recover costly ligands or metals as in enantioselective reactions, a domain of homogeneous catalysis.

4.3. Solvent for extraction is added during catalysis

The general principle of this method is elucidated in Fig. 8.

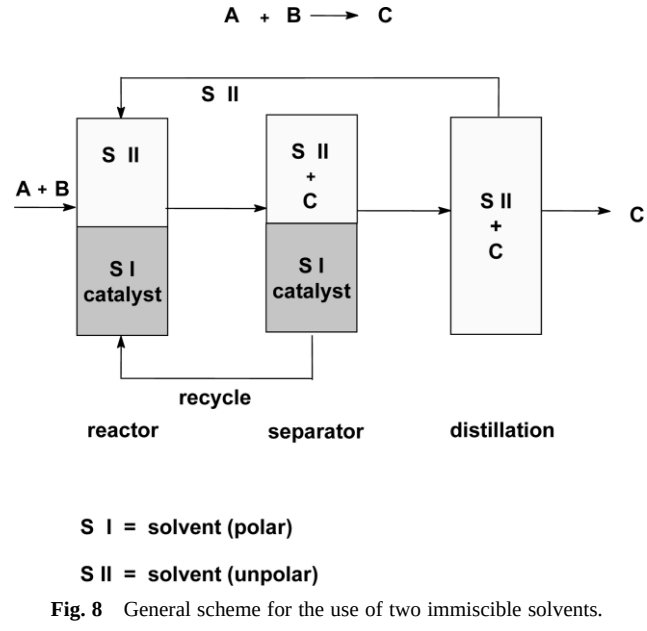


Fig. 8 General scheme for the use of two immiscible solvents.

The extraction solvent S II is already present in the reactor during catalysis. It must form a second phase with the solvent S I, which contains the catalyst. The product C formed during catalysis is removed from the catalyst phase S I into the extraction phase S II. In a separator (decanter) both phases are separated. S I/catalyst is recycled, S II/C is split *via* distillation into product C and pure solvent S II, which is brought back into the reactor.

We could demonstrate the usefulness of this method as early as 1976 in a telomerization reaction of butadiene with phthalic acid as shown in Fig. 9.[7]

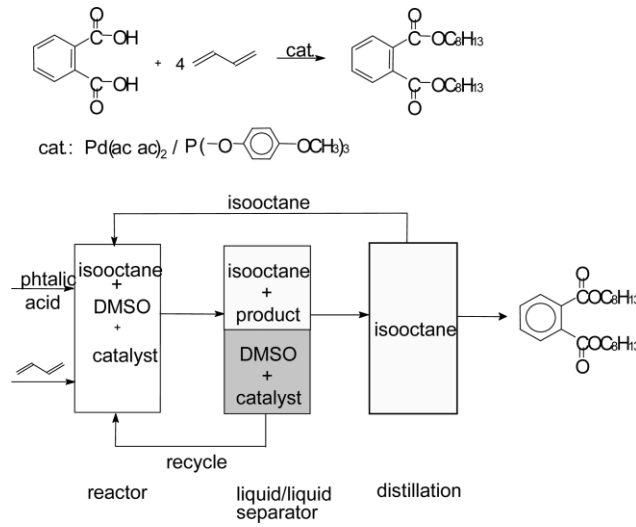
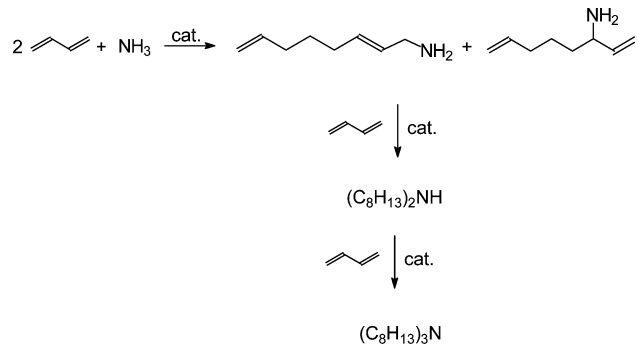


Fig. 9 Synthesis of phthalates in a biphasic approach.

The terephthalates obtained by telomerizing phthalic acid with butadiene — due to the high boiling points — cannot be distilled off. By adding the solvent isooctan to the reaction phase DMSO-catalyst, the telomeric octylphthalates are extracted away from the catalyst/DMSO phase into the isooctane extraction phase. The latter one is separated in the liquid/liquid separator. The catalyst phase is recycled, the isooctane/product phase is separated *via* distillation and the solvent for extraction isooctane is brought back into the reactor.

In this way it is possible to remove the products *via* extraction at low conversions from the reaction phase, which can be very useful in consecutive reactions. From a technical point of view, this method is cumbersome but it offers the advantages of carrying out reactions at low conversions. Normally, in homogeneous catalysis, high conversions and high selectivities are necessary to make the homogeneous process economic. High selectivity and high conversion, however, are very demanding on the catalyst applied. Especially in processes where consecutive reactions occur, homogeneous systems are at a disadvantage.

An example of such a process is the telomerization of butadiene with ammonia which was nicely demonstrated by B. Drießen-Hölscher and which is shown in Scheme 3.[23]



Scheme 3 Telomerization of butadiene with ammonia.

The product of technical interest is the primary octadienylamine $C_8H_{13}NH_2$. However, because of its higher nucleophilicity compared to ammonia, it is very reactive and is therefore subject to further consecutive reactions with butadiene yielding the secondary $(C_8H_{13})_2NH$ and the tertiary amine $(C_8H_{13})_3$ N.

B. Drießen-Hölscher could show that the primary octadienylamine can be synthesized selectively by the catalytic two-phase-telomerization of butadiene and ammonia, provided that the primary products are immediately extracted from the aqueous catalyst phase after their synthesis, using a solvent with appropriate polarity. In this way, one avoids consecutive reactions to higher amines in the aqueous phase. The catalyst system applied consists of palladium acetate/tppts (tppts – Trisodium salt of 3,3′,3″-phosphanetriylbenezene-sulfonic acid) dissolved in water. The second phase is an organic solvent such as toluene (Fig. 10).

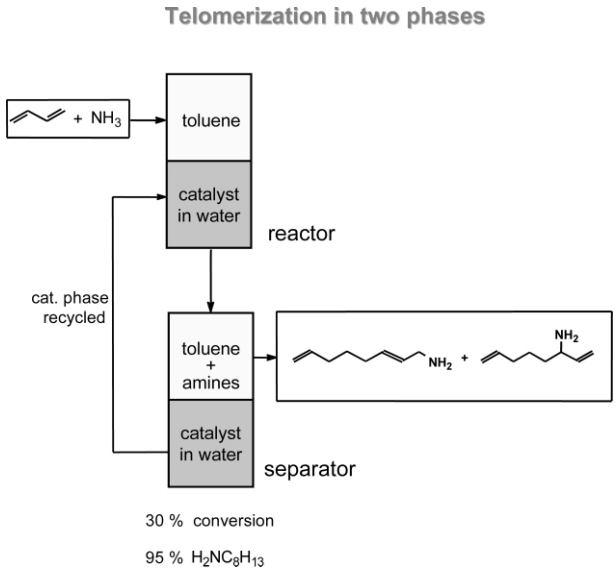


Fig. 10 Telomerization of ammonia with butadiene.

This concept can also be very useful, when product inhibition occurs in a chemical reaction.

4.3.1. Use of supercritical CO_2. Supercritical CO_2 can be used to separate the products from the catalyst upon depressurizing, a burgeoning new approach in catalysis.[24] A unique novel approach is based on the use of supercritical CO_2 and ionic liquids. The ionic liquid, having no vapour pressure, contains the catalyst. The products formed during catalysis are separated *via* supercritical CO_2 extraction.

E. J. Beckmann,[25] first realized that the combination of $scCO_2$ and ionic liquid can offer special advantages. The first application in catalysis goes back to P. G. Jessop.[26] W. Tumas published a hydrogenation in biphasic systems with $scCO_2$ with simultaneous product extraction.[27] D. J. Cole-Hamilton, for the first time, demonstrated the simultaneous product extraction in continuous catalytic reaction using ionic liquid/$scCO_2$.[28]

W. Leitner and P. Wasserscheid demonstrated this novel promising approach for the enantioselective hydrovinylation of styrene.[29]

In the author's understanding this is a remarkable contribution to the field of catalysis. Now homogeneous catalysts can be immobilized in ionic liquids and a bridge between homogeneous and heterogeneous catalysis is provided.

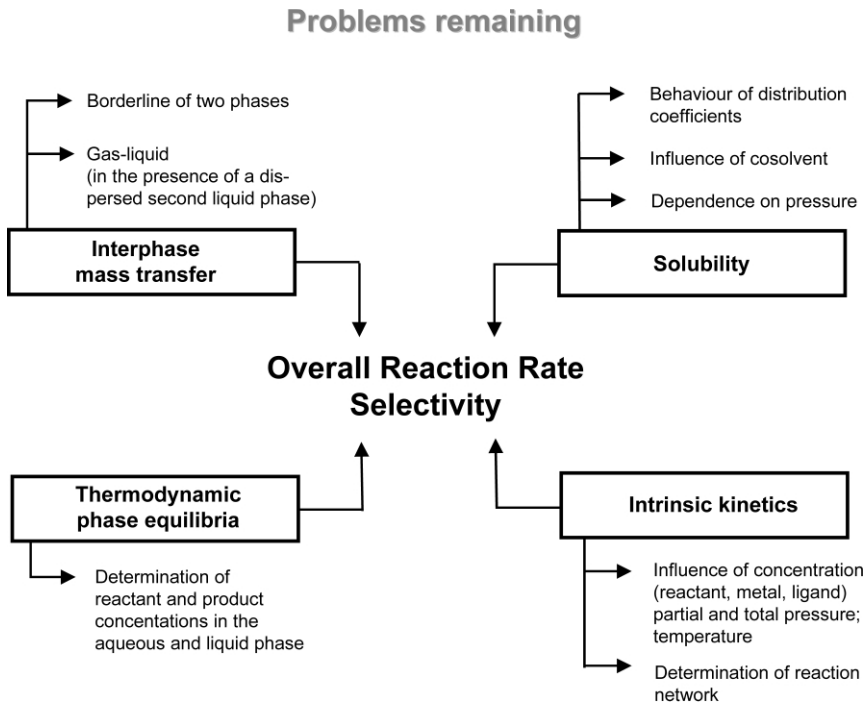
Conclusions

Biphasic catalysis can be a very powerful tool to solve the problems of catalyst recycle in homogenous catalysis. It is applied already industrially. One of the challenging difficulties still rests with engineering a system to a degree that all of the catalyst stays in the catalyst phase. This requires a fine tuning of many parameters. Chemists and engineers must collaborate here in a truly interdisciplinary way. A list of problems remaining is shown in the self explanatory Scheme 4.[11]

The author believes that the future will hold much promise for the biphasic approach and that Max Planck may have been wrong when he has said: *"A new scientific discovery doesn't triumph because the opponents are convinced, it will win when the opponents finally die"*.

Especially the use of ionic liquids offers great opportunities for catalyst modifications, for bio-inspired research. For instance, one can build ligands into the backbone of ionic liquids. Also in reactions where product inhibition (poisoning) occurs, the biphasic approach can be very beneficial.

Finally it should be pointed out that the approach of biphasic catalysis is also applicable to heterogeneous catalysis as was



Scheme 4 Problems remaining in biphasic catalysis.[11]

demonstrated in a beautiful way by Asahi Kasei[30] in their commercialized process of hydrogenation of benzene to cyclohexene. This approach is shown in Fig. 11.

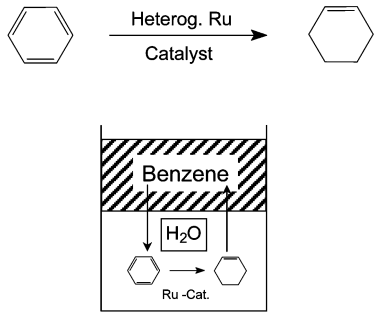


Fig. 11 Hydrogenation of benzene to cyclohexene.

Here the fine tuning and interplay of distribution coefficients is demonstrated in an impressive way. Benzene forms one phase, water the second. The solubility of benzene in water is used to bring it to the heterogeneous Ru-catalyst, where it is hydrogenated to cyclohexene, which is then extracted into the benzene phase thus removing it from the catalyst and preventing further hydrogenation to cyclohexane, the most stable product.

Acknowledgement

"Science requires a cooperative approach, whereby one person's knowledge enriches the discoveries of the next." (José Ortega y Gasset)

The author is very grateful to his many co-workers, which have contributed in an outstanding way. First of all there are to name A. Behr, D. Vogt, B. Drießen-Hölscher and P. Wasserscheid, all of them are continuing research in biphasic catalysis advancing it to novel understanding and applicability. It is impossible to enumerate all the names whose research — carried out in many master theseses and Ph.D. theses — is behind this article. Many, many thanks!

Many thanks go to my colleges and here I want to refer to I. Tkatchenko and K. Cavell. To both I am grateful for a valuable partnership.

My many thanks go to the companies and institutes which have funded our work in such a generous way: Shell, BP, Hoechst, Degussa, Bayer, Deutsche Forschungsgemeinschaft (DFG), Fond der Chemie.

Finally, I want to express my apologies to those, whose names I haven't mentioned in this article. Here I feel especially guilty regarding the beautiful work on smart ligands and thermoregulated phase transfer catalysis.

References

1 (*a*) M. Albrecht, N. J. Hovestad, J. Boersma and G. van Koten, *Chem. Eur. J.*, 2001, **7**, 1289; (*b*) N. J. Hovestad, E. B. Eggeling, H. J. Heidbüchel, J. T. B. H. Jastrzebski, U. Kragl, W. Keim, D. Vogt and G. van Koten, *Angew. Chem., Int. Ed.*, 1999, **38**, 1655–1657.
2 S. Mecking, R. Thomann, H. Frey and A. Sunder, *Macromolecules*, 2000, **33**, 3958.
3 A. Behr and W. Keim, *Erdöl, Erdgas, Kohle*, 1987, **103**, 126.
4 B. Drießen-Hölscher, P. Wasserscheid and W. Keim, CATTECH June 1998, 47–51.
5 W. Keim, *Angew. Chem., Int. Ed. Engl.*, 1990, **29**, 235–244.
6 R. S. Bauer, H. Chung, P. W. Glocker, W. Keim and H. van Zwet, US 3.635.937 (Shell Oil Company 1972).
7 A. Durocher, W. Keim and P. Voncken, *Erdöl und Kohle, Erdgas, Petrochemie*, 1976, **29.1**, 31.
8 (*a*) E. Wiebus and B. Cornils, *Chem. Ing. Techn.*, 1994, **66**, 916; (*b*) E. G. Kuntz, Rhône Poulenc Patent, FR 2.314.1910 (1975); (*c*) E. G. Kuntz, *Chem. Tech.*, 1987, **17**, 570.
9 Y. Tokitoh and N. Yoshimura, (Kuraray Co.), US 5.057.631 (1991) and EP 0.436226 (1990).
10 B. Drießen-Hölscher, Habilitation RWTH Aachen (03/2000).
11 B. Cornils and W. Herrmann, *Aqueous-Phase Organometallic Catalysis*, Wiley-VCH Weinheim, 1998.
12 M. Vogt. Ph. D. Thesis RWTH Aachen 1991.
13 W. Keim, M. Vogt, P. Wasserscheid and B. Drießen-Hölscher, *J. Mol. Catal., A: Chem.*, 1999, **139**, 171.
14 (*a*) B. Cornils, *Angew. Chem.*, 1995, **107**, 1709; (*b*) B. Cornils, *Angew. Chem.*, 1997, **109**, 2147.
15 G. W. Parshall, *J. Am. Chem. Soc.*, 1972, **95**, 8716.
16 J. F. Knifton, *J. Mol. Cat.*, 1987, **43**, 65.
17 Y. Chauvin, B. Gilbert and I. Guibard, *J. Chem. Soc., Chem. Commun.*, 1990, 1715.
18 H. Olivier, *J. Mol. Catal. A. Chem.*, 1999, **146**, 285.
19 P. Wasserscheid and T. Welton, *Ionic liquids in Synthesis*, Wiley-VCH, Weinheim 2002.
20 P. Wasserscheid and W. Keim, *Angew. Chem., Int. Ed.*, 2000, **39**, 3772.
21 W. Keim, D. Vogt, H. Waffenschmidt and P. Wasserscheid, *J. Catal.*, 1999, 481.
22 P. Wasserscheid, Habilitation RWTH Aachen 2002.
23 T. Prinz, W. Keim and B. Drießen-Hölscher, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 1708.
24 J. P. G. Jessop and W. Leitner, (Eds) *Chemical Synthesis Using Supercritical Fluids*, Wiley-VCH Weinheim, 1999.
25 L. A. Blanchard, D. Hancu, E. J. Beckmann and J. F. Brennecke, *Nature*, 1999, **299**, 28.
26 A. Brown, P. Pollet, E. McKoon, C. A. Eckert, C. L. Liotta and P. G. Jessop, *J. Am. Chem. Soc.*, 2001, **123**, 1254.
27 F. Liu, M. B. Abrams, R. T. Baker and W. Tumas, *Chem. Commun.*, 2001, 433.
28 M. F. Sellin, P. W. Webb and D. J. Cole-Hamilton, *Chem. Commun.*, 2001, 781.
29 A. Bösmann, G. Franció, E. Janssen, M. Solinas, W. Leitner and P. Wasserscheid, *Angew. Chem., Int. Ed. Engl.*, 2001, **40**, 2697.
30 Asahi Kasei, US Pat. 5457251 (1996).

Catalysis for fine chemicals: who needs (will use) new solvents?†

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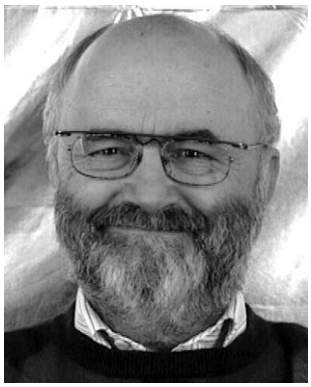
Received 2nd January 2003
First published as an Advance Article on the web 14th March 2003

The need for new solvents for catalysis in the production of fine chemicals is discussed. After a short description of the different needs of fine chemicals and bulk chemicals manufacture, the role of the solvent in catalytic processes is shown, illustrated by examples from Solvias' process development. It is concluded that for the catalytic production of fine chemicals, new types of solvents such as supercritical CO_2, ionic liquids, aqueous or fluorous media will be applied only under special circumstances and that much more information on scope and limitations (chemical, ecological, economical) is required.

Introduction/background

Organic chemistry is by tradition chemistry in solution – and for very good reasons. Whenever possible, organic chemists try to carry out reactions with dissolved, well defined homogeneous reactants. All theories on reactivity are based on the existence of ideally solvated, molecularly defined species – either stable molecules, metastable intermediates or unstable transition states. Last but not least, this experimental technique was and still is immensely successful. However, for ecological reasons using a solvent has an obvious downside because after the reaction the products have to be separated from the reaction solution and the solvent has to be either recycled or discarded. For these reasons, the question whether to use a solvent at all and if yes, which one, is obviously very important. Why then the somewhat provocative title? If we ask chemists in various fields of catalysis, whether new solvents are needed, it is likely that we get two kind of answers (see Table 1). From our extensive experience (first with the in-house catalysis group of Ciba-Geigy/Novartis and now in Solvias, a medium sized company offering catalyst and process development to customers in the fine chemicals industry) we suspect that most production managers, but especially those in fine chemicals manufacture will be rather skeptical. In this contribution we will discuss the reasons for our conjecture.

Hans-Ulrich Blaser carried out his doctoral research with A. Eschenmoser at the Federal Institute of Technology (ETH) Zürich, from which he received the PhD degree in 1971. Between 1971 and 1975 he held postdoctoral positions at the University of Chicago (J. Halpern), Harvard University (J. A. Osborn), and Monsanto (Zürich). During 20 years at Ciba-Geigy (1976–1996) he gained practical experience at R&D in the fine chemicals and pharmaceutical industry, which continued at Novartis (1996–1999) and at Solvias where he presently is chief technology officer. During his industrial carrier, he has developed and implemented numerous catalytic routes for agrochemicals, pharmaceuticals and fine chemicals (both as project leader and section head).



† This work was presented at the Green Solvents for Catalysis Meeting held in Bruchsal, Germany, 13–16th October, 2002.

Characteristics of fine chemicals manufacture[1]

While there is no generally accepted definition for fine chemicals, in this article we will use the following terminology: "Rather complex molecules (isomers, stereochemistry, functional groups) with limited thermal stability, high value and a short product life" as schematically depicted in Fig. 1. The manufacture of fine chemicals and especially of pharmaceuticals and agrochemicals is characterized in Table 2. Traditionally, most fine chemicals are synthesized without a catalyst because reagents with a sufficiently high reactivity are used and if a catalyst is necessary at all, in most cases either a proton or a simple base is sufficient. The application of metal based catalysts is relatively rare for the synthesis of complex molecules, not only in academic laboratories but also in the fine chemicals industry.[1,2] This is very much in contrast to the situation in the bulk chemicals or polymer industry where catalytic methods dominate.[3] On the other hand, the use of solvents is much more common in fine chemicals production because many starting materials and products are solids and do not tolerate high temperatures.

Green Context

This fascinating article gives a great deal of insight into the issues of solvent selection in industry, and illustrates the pros and cons of choosing a solvent very nicely. Case studies are presented which help to delineate the central influence of solvent choice, and the more general discussion neatly puts these scientific considerations into an industrial production context. It is clear that there is a strong case for better solvents, but that their eventual impact may be heavily focussed on certain applications with little impact on others.
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 DOI: 10.1039/b300028c

Table 1 Possible answers to the question: Do we need new solvents?

Answer 1: Not really, because	**Answer 2: Yes, because**
there are already enough solvents	there can be never enough good solvents
we have learnt to live with them	we need solvents with better ecology
we know their good and bad properties	we need designed/tailored solvents
we know how to regenerate/recycle	see this special issue of *Green Chemistry*
BUT: We will apply them in special cases	OF COURSE: A lot of research is necessary
Who is likely to say NOT REALLY?	**Who is likely to say Yes?**
process developers for fine chemicals	process developers for bulk chemicals
most managers in chemical production	people with unsolved catalytic problems
researchers with other priorities	researchers developing new solvents

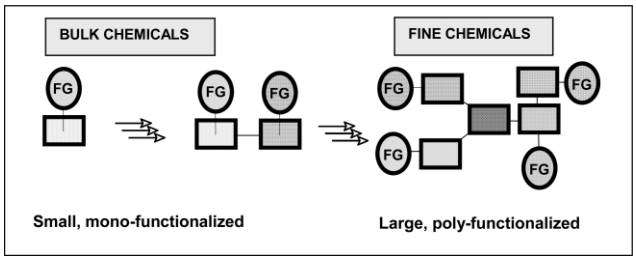

Fig. 1 Schematic structures of bulk and fine chemicals.

Another important factor is the limited time and effort for process development. In the life science industry, the time for the development of the production process for a new chemical entity is often rather short, between a few months in the pharmaceutical industry (see Fig. 2) to 1–2 years for agrochemicals since time to market can significantly affect the profitability of a new product. In addition, the money spent to develop a process for one particular product is also limited since at the stage where the definitive process has to be established, the fail rate of the product is still high. The consequences of these constraints on the choice of the process technology is obvious: first choice is always the technology that is well proven, where scope and limitations are well known to the process chemist to make it predictable. In addition, reagents and solvents with known safety and toxicology will be used if practicable. This means that if ever possible standard catalysts or solvents will be used and tailor-made new solutions with too many unknown parameters will be avoided.

The role of the solvent in the toolbox of the catalytic chemist

In this section, we briefly discuss the instruments of the development chemist in case a catalyst is required for a specific transformation. In our experience once the type of catalyst (homogeneous metal complex, heterogeneous catalyst, bio-catalyst) is chosen, there is a hierarchy of influences. The most important elements for the design of homogeneous catalysts are depicted schematically in Fig. 3. Predominant are the type of the metal and the ligand(s), the nature of the anion and also additives can sometimes play a role. For heterogeneous catalysts it is also the type of metal, the nature of the support (if any) which dominate the catalyst performance and sometimes the presence of modifiers and promoters can also have a major effect. While the solvent (and also the experimental conditions) can have a significant influence on the catalyst performance as well as the overall process efficiency, generally, it is of

Table 2 Characteristics of fine chemicals

	Fine chemicals	Bulk chemicals
Number of products	large	small
Volume	small/medium (1–10000 t y^{-1})	large
Products patented	very often	no
Life time	short/medium	long
Main F&E effort	molecule	process
Consequences for processes	multi step (3 – >10) solution, multipurpose batch equipment	often continuous, gas phase, dedicated plant
	competitive process (cost tolerant)	best process (cost decisive)
	development must be fast	development time and cost not critical
	usually not patented	patented
Consequences for catalysts	commercial standard catalysts	tailored catalysts
	good activity at low *T*	patented

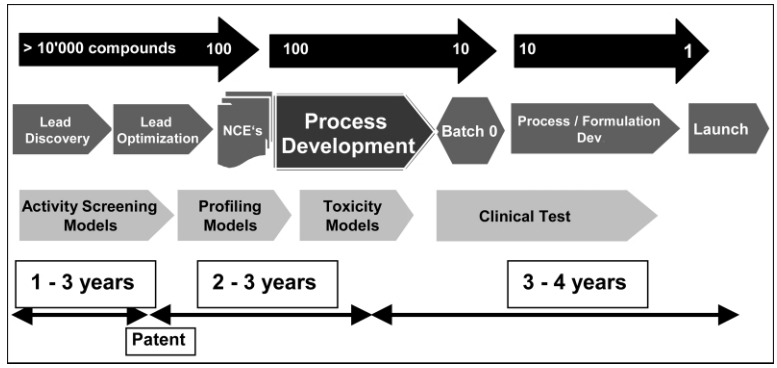

Fig. 2 Development process of a pharmaceutical.

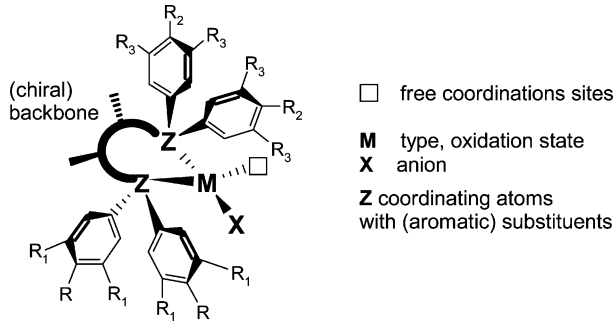

Fig. 3 Design elements for (chiral) metal complexes.

secondary importance. In other words, the wrong solvent can diminish the performance of a good catalyst while even the best solvent can not turn an unsuitable catalyst into a star performer.

Solvent effects: four case studies

The following small case histories from our own laboratories serve to demonstrate our conjecture.

Chemoselective hydrogenations of aromatic nitro groups[4]

The chemoselective catalytic hydrogenation of the nitroallyl ester depicted in Fig. 4 was a major problem because in contrast to the stoichiometric Béchamp reduction, only very few classical catalysts are capable of reducing an aromatic nitro group in presence of a monosubstituted C=C bond. Table 3 and Fig. 5 show relevant results obtained during the development of a new catalytic system. The choice of the metal as well as of the modifier had a decisive effect on both yield and selectivity. With the optimal catalyst (5%Pt–1%Pb/$CaCO_3$) the solvent did not affect the selectivity at all, but had a strong effect on catalyst activity and a moderate one on yield. The final compromise was methyl ethyl ketone (MEK) as solvent even though some imine formation with the resulting aniline slightly decreased the yield.

Homogeneous enantioselective hydrogenation of α-keto esters[5,6]

The enantioselective hydrogenation of α-keto esters is a topic of current interest since the resulting α-hydroxy esters are important building blocks. In our laboratories we pursued two approaches, one using homogeneous Rh–diphosphine catalysts[5] and the second with heterogeneous Pt catalysts modified with cinchona alkaloids[6] (see Fig. 6). Both showed interesting solvent effects.

A screening program using 7 diphosphines, 3 solvents and 4 different reaction conditions showed that norphos gave ee's up to 91%, whereas ee's for the other tested ligands ranged from 5% for bppfoh to 71% for bppm. Surprisingly, the solvent had a dramatic effect on both the extent and the sense of induction. Table 4 shows the solvent effect on enantioselectivity and catalytic activity for Rh–(2*S*;3*S*)-norphos, the most selective

Table 3 Reduction of a nitroallyl ester: effect of metal, support and modifier on aniline yield and selectivity

Catalyst	Modifier	Yield (%)	% allyl retained
Béchamp	—	90	100
Raney Nickel	—	50	61
Raney Nickel	DCDA	53	96
5% Pd/$CaCO_3$		n.d.	0
5% Pd/$CaCO_3$	3% Pb	n.d.	3
5% Pt/C		n.d.	0
5% Pt/C	3% Bi	n.d.	61
5%Pt/$CaCO_3$	1% Pb	> 92	> 99

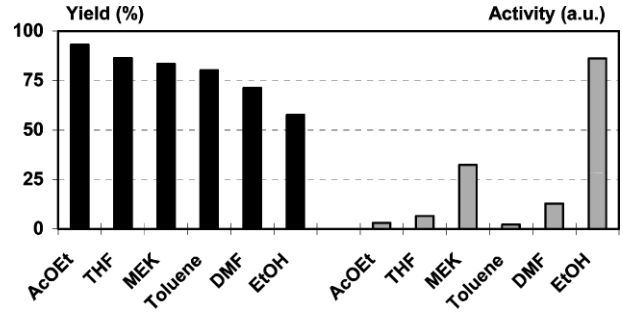

Fig. 5 Reduction of a nitroallyl ester with a 5%Pt–1%Pb/$CaCO_3$ catalyst: effect of solvent on yield and relative activity.

catalyst. For ethyl 2-hydroxy-4-phenylbutyrate (R = $PhCH_2CH_2$) we observed a large decrease in conversion and even a reversal of the absolute configuration when changing from toluene to methanol! The use of the cationic Rh–norphos–BF_4 catalyst in methanol caused a significant drop in both the activity and the enantioselectivity. While alcohols had a positive effect on both rate and ee, water or small amounts of triethylamine were detrimental. Similar, if less pronounced, effects were also observed for ethyl pyruvate. These results were quite different from those described for the hydrogenation of ketones where aprotic solvents gave the highest enantioselectivities and a rare case where the solvent dominates the catalyst performance.

In the case of the cinchona modified heterogeneous catalysts, the metal and the modifier are decisive for good enantioselectivities. Whereas ee's up to 98% can be reached with Pt catalysts, all other noble metals give much lower activities and enantioselectivities (best ee's for Rh *ca.* 60%, Ir 39%, Pd 29%, Ru 0%)[6a]. Solvent effects were important but not dominant as shown in Fig. 7, where the effect of the dielectric constant on ee is shown. Acetic acid very often has a small but significant advantage over toluene for the hydrogenation of several α-functionalized ketones.

Enantioselective manufacture of (*S*)-metolachlor[7]

The enantioselective hydrogenation of the imine depicted in Fig. 8 is the key step for the industrial manufacture of (*S*)-metolachlor on a > 10000 t y^{-1} scale. The preferred catalyst is an Ir–Xyliphos complex which was specifically devolved for this important transformation. During catalyst development we found that three factors were important for good catalyst

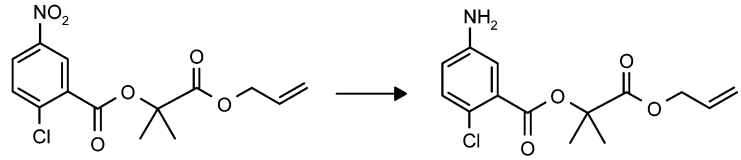

Fig. 4 Chemoselective hydrogenation of a nitroallyl ester.

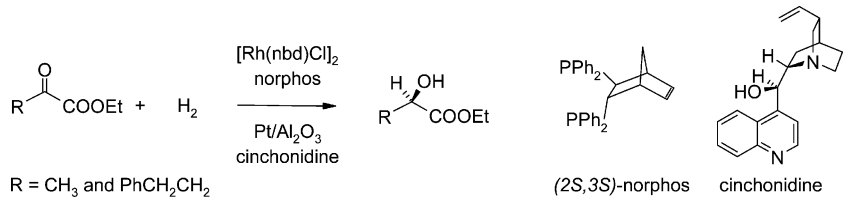

Fig. 6 Enantioselective hydrogenation of α-keto esters with Rh–norphos.

Table 4 Hydrogenation of ethyl 2-hydroxy-4-phenylbutyrate with [Rh(nbd)Cl]2/(2*S*,3*S*)-norphos. (s/c 200, 30 °C, 100 bar).

Solvent	Time/h	Conversion (%)	ee (%)
Toluene	24	17	12 (*R*)
MeOH–Toluene 1 : 1	21	25	73
EtOH	21	27	82
MeOH	21	35	86
MeOH[a]	21	10	11
MeOH[b]	3	95	96
MeOH–5% H_2O	19	22	69
MeOH–1 equiv. NEt_3[c]	22	99	5

[a] s/c = 50, 25 °C. [b] $[Rh(nbd)_2]BF_4$. [c] 60 °C.

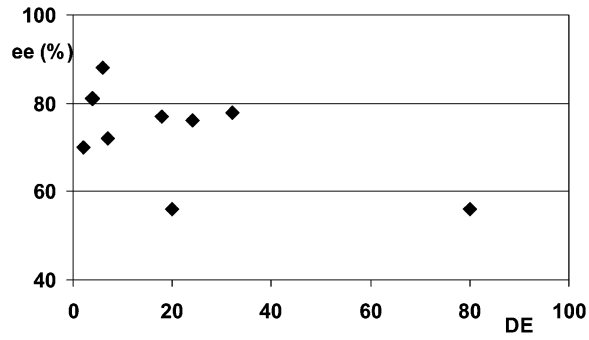

Fig. 7 Effect of the dielectric constant of the solvent on the ee for the hydrogenation of ethyl pyruvate using cinchonidine modified Pt/Al_2O_3 catalysts.[6b]

performance: Ir as central metal atom, the ferrocenyl diphosphine ligand and the presence of iodide. When the effect of solvents was tested (see Table 5), acetic acid significantly enhanced catalyst activity and productivity. The effect of the presence of both iodide and acetic acid is quite dramatic as can be seen in Fig. 9. However, we later found that this is not really a solvent, but rather a general acid effect and in the actual production process very small amounts of a strong acid but no solvent at all are used.[7b]

New solvents for catalysis

In the last few years, several types of new solvents have been shown to be compatible with and useful for catalytic applications. Here we will not review the chemical results described for various types of new solvents, some of these can be found in the cited references and in the contributions to this special issue of *Green Chemistry*. Generally, our impression is that similar chemical results can be obtained as with conventional solvents and that the main distinction concerns environmental (recycling, toxicology, safety) and engineering (catalyst separation, solubility, vapor pressure) factors.[8–12] Rather we want to compare the advantages claimed for the application of new media with the problems we see when considering their use for the manufacture of fine chemicals. In Table 6 we have summarized these points for supercritical fluids (especially sCO_2), ionic liquids, water and fluorous solvents in the context of fine chemicals manufacture.

Generally it can be stated that every production manager has a conservative attitude – and for good reasons. Since he or she has to deliver the required quantities of a product on time and

Table 5 Enantioselective hydrogenation with Ir–Xyliphos

Solvent	*t* (100%)/h	Initial rate/ mmol min^{-1}	ee (%)
thf	7	0.3	73.6
CH_2Cl_2	4	0.3	73.8
$(CH_3)_3COCH_3$	12	0.2	75.4
acetone	6	0.4	72.8
toluene	12	0.4	72.5
i-PrOH	0.75	1.1	79.0
t-BuOH	1	1.0	77.1
CH_3COOEt	8	0.7	71.5
none	10	0.3	72.7
CH_3COOH	0.5	1.5	78.5

Reaction conditions: s/c: 800; 150 mg $(Bu)_4NI$; solvent: 2 ml; 25 bar H_2; 30 °C.

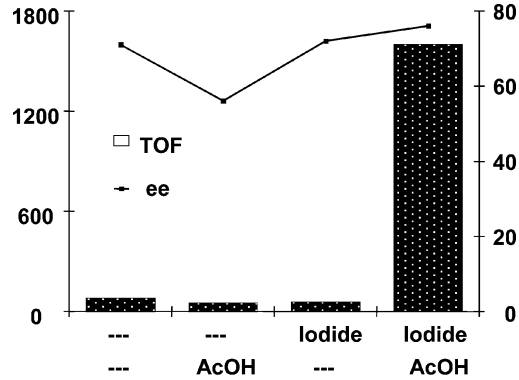

Fig. 9 Enantioselective hydrogenation with Ir–Xyliphos, effect of iodide and acetic acid on ee and TOF.

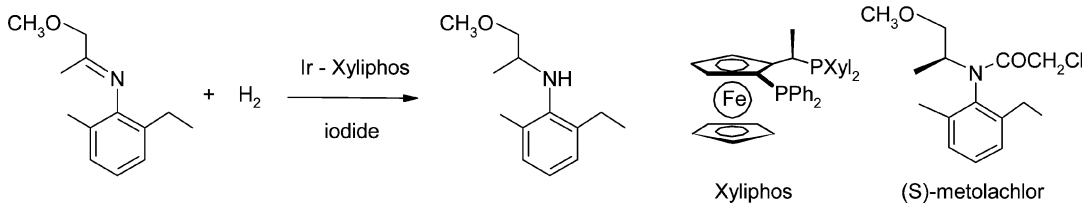

Fig. 8 (*S*)-Metolachlor manufacture: structures of starting material, ligand and products.

Table 6 Opportunities and problems for the application of new media

Medium	Opportunities	Critical issues for fine chemicals applications
Supercritical solvents, especially sCO_2[9]	Relatively cheap, green, available, non-toxic	
	Easy catalyst and product separation (except when both have the same state)	Relatively high pressure (and temperature)
	Very high solubility of hydrogen	Special equipment needed
	Properties are tunable with additives	Often low solubility of starting materials (no longer supercritical)
	Expanded liquids	High development effort
Ionic liquids[10]	Unusual/new reactions and selectivities possible	Price
	Separation/recycling of catalyst (combination with sc extraction)	Toxicity unknown
	No vapor pressure	Recycling/leaching of ionic liquid can be problematic
	Chemical tunability	Quality of ionic liquids vary, can be problematic for catalysis
Water[11]	Low price	Refractory contaminations difficult to remove (burning)
	Environmentally friendly solvent	Difficult to evaporate
		Use of detergents often necessary
		Functionalized ligands necessary
Fluorous/biphasic[12]	Unusual/new reactions and selectivities	Production/disposal might be problematic
	Separation/recycling of catalyst	Price of solvent and specially functionalized ligands
	Some tunability	

with the specified quality, the issue of predictability is extremely important. An established process with known weaknesses is better accepted than a much better one where the effect of too many parameters are not (yet) known. In addition, technologies requiring special equipment (pressure, temperature, construction material) not yet installed in the plant have a much higher barrier for acceptance. The question of reliable supply, of known toxicological data and last but not least of the price will be probably very important issues for new media such as ionic liquids and fluorous solvents.

It must be realized that while tunability is an advantage, the number of parameters to be optimized increases and so will the time and the costs for process development. The same holds true when special equipment (*e.g.* for supercritical fluids or for continuous processes) must be used. Catalyst separation and recycling are often cited as motivation for replacing homogeneous catalysts with heterogeneous analogs or for using biphasic conditions. In our experience both with enantioselective hydrogenation and various Pd catalyzed C–C coupling reactions, removal of the catalyst was often not critical and was accomplished using distillation, crystallization or adsorption/reduction on charcoal. Nevertheless, this will not always be possible and in this case alternatives are welcome. A last comment concerns catalyst recycling as a strategy for increasing the turnover numbers, another advantage often claimed when describing new reaction technology. In our development work we optimize our catalysts for high tons; recycling is always the second choice and is avoided if ever possible. The main reasons are the difficulty in controlling the quality of the recycled catalyst (especially important for production under cGMP regime) and also the much longer development time because catalyst tests must always involve recycles which can be very time consuming.

These issues are most important when (i) the time and expense for process development that can be invested in a particular product are relatively low, (ii) the fail rate of a particular development product is high and (iii) when the cost of goods are only a small part of the price of the final product. This is especially pronounced for new pharmaceuticals, somewhat less for agrochemicals. The advantages described in Table 6 become more meaningful for larger scale products with a long lifetime where the quality of the process is the dominant issue. In these cases, the time and expenses for process development are not so essential and the opportunity to tailor not only the catalyst but also the solvent to the needs of a particular process become genuine advantages. The recent commercialization of catalytic hydrogenations in supercritical carbon dioxide by the Thomas Swan company is (up to now) one of the few example of the commercial use of a 'new' solvent.[13]

Conclusions

We think that the best opportunities for new solvents arise when the catalyst performance in classical solvents is not satisfactory, catalyst separation with classical methods is difficult and probably also for new catalytic transformations. Based on our experience, we think that selective oxidations (especially with oxygen) and aromatic substitution reactions such as Friedel Crafts acylation or nitration might have the best potential for the application of new media.

On the other hand, there are several prerequisites that must be met if new solvents (or new catalysts) should be considered by the development chemists. Its scope and limitations should be well known (functional group tolerance, compatibility with catalyst *etc.*). The solvent must be commercially available at acceptable prices and with guaranteed quality. Its toxicity and other ecological factors (recycling, disposal) must be well known.

Applications of new solvents (and new catalysis) has a good chance to be applied on an industrial level if the "solvent community" succeeds in

- better educating/convincing R & D chemists and production managers
- developing more technically feasible reactions/new solvents (keep up research!)
- speeding up process development, so that development time is no longer an issue (efficient solvent screening)

References

1 H. U. Blaser and M. Studer, *Appl. Catal. A: Gen.*, 1999, **189**, 191.
2 *Fine Chemicals through Heterogeneous Catalysis*, ed. R. A. Sheldon and H. van Bekkum, Wiley-VCH, Weinheim, 2001, p. 3.
3 *Handbook of Heterogeneous Catalysis*, ed. G. Ertl, H. Knötzinger and J. Weitkamp, Wiley-VCH, Weinheim, 1997; J. Hagen, *Industrial Catalysis*, Wiley-VCH, Weinheim, 1999.

4 U. Siegrist, P. Baumeister, H. U. Blaser and M. Studer, *Chem. Ind. (Dekker)*, 1998, **75**, 207.

5 F. Spindler, U. Pittelkow and H. U. Blaser, *Chirality*, 1991, **3**, 370; H. U. Blaser, H. P. Jalett and F. Spindler, *J. Mol. Catal. A: Chem.*, 1996, **107**, 85.

6 (*a*) For a review see M. Studer and H. U. Blaser, *Adv. Synth. Catal.*, 2003, **345**, 45; (*b*) H. U. Blaser, H. P. Jalett and J. Wiehl, *J. Mol. Catal.*, 1991, **68**, 215.

7 (*a*) F. Spindler, B. Pugin, H. P. Jalett, H. P. Buser, U. Pittelkow and H. U. Blaser, *Chem. Ind. (Dekker)*, 1996, **68**, 153; (*b*) H. U. Blaser, H. P. Buser, K. Coers, R. Hanreich, H. P. Jalett, E. Jelsch, B. Pugin, H. D. Schneider, F. Spindler and A. Wegmann, *Chimia*, 1999, **53**, 275.

8 See for example M. Freemantle, *Chem. Eng. News*, May 28, 2002, 30; Q.-H. Fang, Y-M. Li and A. S. C. Chan, *Chem. Rev.*, 2002, **102**, 3385.

9 Selected publications on catalysis in supercritical fluids J. Xiao, S. C. A. Nefkens, P. G. Jessop, T. Ikariya and R. Noyori, *Tetrahedron Lett.*, 1996, **37**, 2813; S. Wang and F. Kienzle, *Ind. Eng. Chem. Res.*, 2000, **39**, 4487; D. Zhao, M. Wu, Y. Kou and E. Min, *Catal. Today*, 2002, **74**, 157; A. Baiker, *Chem. Rev.*, 1999, **99**, 453; D. Zhao, M. Wu, Y. Kou and E. Min, *Catal. Today*, 2002, **74**, 157.

10 Selected publications on catalysis in ionic liquids J. Dupont, R. F. de Souza and A. Z. Suarez, *Chem. Rev.*, 2002, **102**, 3667; D. Zhao, M. Wu, Y. Kou and E. Min, *Catal. Today*, 2002, **74**, 157; A. Berger, R. F. de Souza, M. R. Delgado and J. Dupont, *Tetrahedron: Asymmetry*, 2001, **12**, 1825; R. Sheldon, *Chem. Commun.*, 2001, 2399.

11 Selected publications on catalysis in aqueous media D. Sinou, *Adv. Synth. Catal.*, 2002, **344**, 221; T. Dwars and G. Oehme, *Adv. Synth. Catal.*, 2002, **344**, 239.

12 Recent publications on catalysis in fluorous media I. T. Horvath, *Acc. Chem. Res.*, 1998, **31**, 641 and reference 8.

13 P. Licence, J. Ke, M. Sokolova, S. K. Ross and M. Poliakoff, *Green Chem.*, 2003, **5**, DOI: 10.1039/b300028c; For a discussion see M. Freemantle, *Chem. Eng. News*, 2001, May 28, 31. See also www.thomas-swan.co.uk.

Asymmetric hydrogenation with perfluoroalkylated monodentate phosphorus(III) ligands in supercritical CO_2 and CH_2Cl_2†

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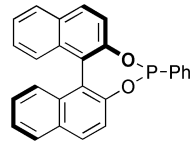
Received 11th December 2002
First published as an Advance Article on the web 27th March 2003

Four chiral perfluoroalkylated monodentate phosphorus(III) ligands have been prepared and characterised. These ligands have been evaluated in the rhodium-catalysed asymmetric hydrogenation of dimethyl itaconate in both dichloromethane and supercritical CO_2 ($scCO_2$) and compared with the parent, non-perfluoroalkylated, catalyst systems.

Introduction

We have been investigating the application of perfluoroalkylated phosphorus(III) ligands for catalysis under fluorous biphase conditions,[1,2] in perfluorocarbon solvents[3–5] and in $scCO_2$[6,7] as alternative media to conventional organic solvents and have now turned our attention to asymmetric catalysis. We have recently reported the synthesis of (*R*)-6,6′-bis(tridecafluorohexyl)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl and (*R*)-6,6′-bis(1*H*,1*H*,2*H*,2*H*-tridecafluorooctyl)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl and their application in the ruthenium-catalysed hydrogenation of dimethyl itaconate in methanol.[8] However, the requirement of >60% fluorine by weight for preferential perfluorocarbon solubility[9] and the relatively poor reactivity of catalysts including our derivatised BINAP ligands in $scCO_2$‡ indicated that it was unlikely that a viable fluorous- and $scCO_2$-compatible BINAP-based catalyst system could be prepared. Recently, however, there has been significant interest in the applications of chiral monodentate phosphonite, phosphoramidite and phosphite ligands based upon (*R*)- and (*S*)-binaphthol as cheap, easily accessible ligands for rhodium-catalysed enantioselective hydrogenation of prochiral olefins. Independently, Reetz[10] and Pringle[11] report ee's of up to 94% for the hydrogenation of dimethyl itaconate and methyl-2-acetamidoacrylate using mono- and bis-phosphonite ligands with a variety of alkyl and aryl substituents (*e.g.* **1**). Feringa and de Vries,[12] Chan[13] and Zhou[14] report comparable enantioselectivities using the *N*,*N*-dimethyl-phosphoramidite ligand (**2**), whilst Reetz[15,16] and Xiao[17] report the best asymmetric induction in this series using monodentate phosphite ligands (*e.g.* **3**) particularly those incorporating chiral alcohols. Here, we report the synthesis of four perfluoroalkylated chiral monodentate phosphorus(III) ligands and their application in rhodium-catalysed asymmetric hydrogenation in conventional solvents and supercritical CO_2.



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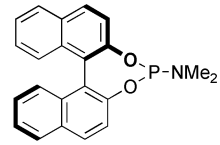

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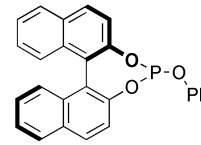


(3)

Experimental

Proton, ^{19}F and ^{31}P NMR spectroscopies were carried out on a Bruker ARX250 spectrometer at 250.13, 235.34 and 101.26 MHz or a Bruker DPX300 spectrometer at 300.14, 282.41 and

Eric Hope graduated with a B.Sc. (1982) and Ph.D. (1985) from the University of Southampton and moved to the University of Leicester in 1987. He has been awarded an SERC NATO Fellowship (1987), an EPSRC Advanced Fellowship (1989) and a Royal Society University Research Fellowship (1994) to investigate the synthesis and application of fluorine-containing inorganic and organic compounds, and was promoted to a Chair of Inorganic Chemistry in 2000. This work led to an interest in the application of fluorinated species and solvents for catalysis in alternative reaction media and the Leicester group has published widely in the areas of fluorous and supercritical solvents.

Green Context

The development of catalytic processes involving metal-cented catalysts in $scCO_2$ requires the development of novel CO_2-soluble ligands for the complexes involved. This paper describes the preparation in high yield of some such ligands, as well as initial attempts to utilise them in enantioselective hydrogenations under supercritical conditions. So far, enantioselectivities were moderate and lower than in the conventional system. However, the work helps to point the way forward in this area ***DJM***

† This work was presented at the Green Solvents for Catalysis Meeting held in Bruchsal, Germany, 13–16th October 2002.

 DOI: 10.1039/b212313b

121.50 MHz respectively and were referenced to external $SiMe_4$ (^1H), external $CFCl_3$ (^{19}F) and to external H_3PO_4 (^{31}P) using the high frequency positive convention. Elemental analyses were performed either by Butterworth Laboratories Ltd. or the Elemental Analysis Service at the University of North London. Mass spectra were recorded on a Kratos Concept 1H mass spectrometer. The products from the catalytic experiments were analysed on a Varian CP-3380 GC equipped with a Chiraldex G-TA (40 m × 0.25 mm) column for the determination of ee values.

(*R*)-6,6′-Bis(tridecafluorohexyl)-2,2′-dihydroxy-1,1′-binaphthyl[8] and 4-tridecafluorohexylphenol[1] were prepared as described previously. Diethyl ether was dried by refluxing over sodium under dinitrogen. Dichloromethane and triethylamine were dried by refluxing over calcium hydride under dinitrogen. Each was then distilled under nitrogen, stored in closed ampoules over molecular sieves and freezed–pumped–thawed three times to remove all dissolved gases before use. Phosphorus trichloride, dichlorophenylphosphine and hexamethylphosphorus triamide (Aldrich) were distilled under nitrogen prior to use. The gases CO_2 and H_2 (BOC), used in the catalytic experiments, were used without purification.

Preparation of phenyl-(*R*)-1,1′-binaphthyl-6,6′-tridecafluorohexyl -2,2′-diyl-phosphonite, (4)

(*R*)-6,6′-Bis(tridecafluorohexyl)-2,2′-dihydroxy-1,1′-binaphthyl (759 mg, 0.823 mmol) and triethylamine (115 µl, 0.826 mmol) were dissolved in CH_2Cl_2 (10 cm³) and dichlorophenylphosphine (112 µl, 0.825 mmol) was added slowly *via* syringe. After stirring the solution for 3 h, the solvent was removed *in vacuo*, the residue dissolved in ether–dichloromethane (ratio: 1:1) and filtered. After removing the solvent, the pale yellow product was washed with acetonitrile (3 × 5 cm³) and dried for 2 h at 50 °C under vacuum to obtain the product as a white solid (0.804 g, 95%). (Found: C, 44.15; H, 1.32. $C_{38}H_{15}F_{26}O_2P$ requires C, 44.36; H, 1.46%). MS (FAB): *m*/*z* = 1028 [M⁺]. ^1H NMR (C_6D_6): δ 6.90 (1H, d, $^3J_{HH}$ = 8.7 Hz), 7.17 (3H, m), 7.36 (3H, m), 7.41 (1H, s), 7.48 (1H, d, $^3J_{HH}$ = 8.7 Hz), 7.49 (1H, d, $^3J_{HH}$ = 8.7 Hz), 7.65 (2H, m), 7.74 (1H, d, $^3J_{HH}$ = 8.9 Hz), 8.19 (1H, s), 8.27 (1H, s). $^{31}P\{^1H\}$ NMR (C_6D_6): δ 186.6 (s). $^{19}F\{^1H\}$ NMR (C_6D_6): δ −81.44 (6F, t, $^4J_{FF}$ = 10.6 Hz), −110.26 (4F, m), −121.67 (8F, m), −123.08 (4F, m), −126.50 (4F, m). $[\alpha]_D^{17}$ −77.4 (*c* 0.5, $CHCl_3$).

Preparation of (*R*)-1,1′-binaphthyl-6,6′-tridecafluorohexyl -2,2′-diyl-dimethylamino-phosphoroamidite, (5)

(*R*)-6,6′-Bis(tridecafluorohexyl)-2,2′-dihydroxy-1,1′-binaphthyl (630 mg, 0.683 mmol) was dissolved in dichloromethane (10 cm³) and $P(NMe_2)_3$ (125 µl, 0.689 mmol) added. After stirring the solution for 3 h, the solvent was removed *in vacuo*, the residue dissolved in ether–dichloromethane (ratio: 1:1) and filtered. After removing the solvent, the slight yellow product was washed with acetonitrile (5 cm³) and dried at 50 °C under vacuum to obtain the product as a white solid (0.639 g, 94%). (Found: C, 40.98; H, 1.57; N, 1.37. $C_{34}H_{16}F_{26}O_2PN$ requires C, 41.01; H, 1.61; N 1.41%). MS (FAB): *m*/*z* = 995 [M⁺]. ^1H NMR (C_6D_6): δ 2.51 (6H, d, $^3J_{PH}$ = 9.2 Hz, CH_3), 7.31 (2H, AB multiplet, $^3J_{HH}$ = 9.4 Hz), 7.38 (2H, AB multiplet, $^3J_{HH}$ = 9.4 Hz), 7.45 (1H, d, $^3J_{HH}$ = 8.7 Hz), 7.56 (1H, d, $^3J_{HH}$ = 8.7 Hz), 7.96 (1H, d, $^3J_{HH}$ = 8.7 Hz), 8.05 (1H, d, $^3J_{HH}$ = 8.7 Hz), 8.15 (1H, s), 8.17 (1H, s). $^{31}P\{^1H\}$ NMR (C_6D_6): δ 150.0 (s). $^{19}F\{^1H\}$ NMR (C_6D_6): δ −81.27 (6F, t, $^4J_{FF}$ = 10.6 Hz), −110.59 (4F, m), −121.89 (4F, m), −123.22 (4F, m), −128.14 (4F, m). $[\alpha]_D^{17}$ −225.6 (*c* 1.2, CH_2Cl_2).

Preparation of phenyl-(*R*)-1,1′-binaphthyl-6,6′-tridecafluorohexyl -2,2′-diyl-phosphite, (6)

Phosphorus trichloride (200 µl; 2.30 mmol) and triethylamine (280 µl; 2.01 mmol) were dissolved in dichloromethane (10 cm³) and a solution of (*R*)-6,6′-bis(tridecafluorohexyl)-2,2′-dihydroxy-1,1′-binaphthyl (937 mg, 1.02 mmol) in dichloromethane (10 cm³) was added slowly. After stirring the solution for 3 h, the solvent was removed *in vacuo* and the yellow solid dried for 2 h at 80 °C under vacuum. Complete removal of the excess PCl_3 *in vacuo* was followed by ^{31}P NMR spectroscopy. The yellow solid was dissolved in CH_2Cl_2 and triethylamine (125 µl; 0.899 mmol) and phenol (86 mg; 0.915 mmol) in CH_2Cl_2 (5 cm³) added. After stirring the solution for 3 h, the solvent was removed *in vacuo*, the residue dissolved in ether–dichloromethane (ratio: 1:1) and filtered. After removal of the solvent, the slight yellow product was washed with acetonitrile (2 × 5 cm³) and dried for 2 h at 50 °C under vacuum to afford the product as a white solid (0.85 g, 89%). (Found: C, 43.76; H, 1.44. $C_{38}H_{15}F_{26}O_3P$ requires C, 43.68; H, 1.44%). MS (FAB): *m*/*z* = 1044 [M⁺]. ^1H NMR ($CDCl_3$): δ 7.28 (2H, m), 7.09 (3H, m), 7.36 (2H, AB multiplet, $^3J_{HH}$ = 11.7 Hz), 7.38 (2H, AB multiplet, $^3J_{HH}$ = 11.7 Hz), 7.45 (1H, d, $^3J_{HH}$ = 8.95 Hz), 7.62 (1H, d, $^3J_{HH}$ = 8.95 Hz), 7.99 (1H, d, $^3J_{HH}$ = 8.95 Hz), 8.08 (1H, d, $^3J_{HH}$ = 8.95 Hz), 8.14 (1H, s), 8.17 (1H, s). $^{31}P\{^1H\}$ NMR (C_6D_6): δ 145.7.$^{19}F\{^1H\}$ NMR (C_6D_6): δ −81.42 (6F, t, $^4J_{FF}$ = 9.72 Hz), −110.24 (4F, t, $^4J_{FF}$ = 16.0 Hz), −121.63 (8F, m), −123.06 (4F, m), −126.48 (4F, m). $[\alpha]_D^{17}$ −96.4 (*c* 1.4, CH_2Cl_2).

Preparation of 4-tridecafluorohexylphenyl-(*R*)-1,1′-binaphthyl-6,6′-tridecafluorohexyl -2,2′-diyl-phosphite, (7)

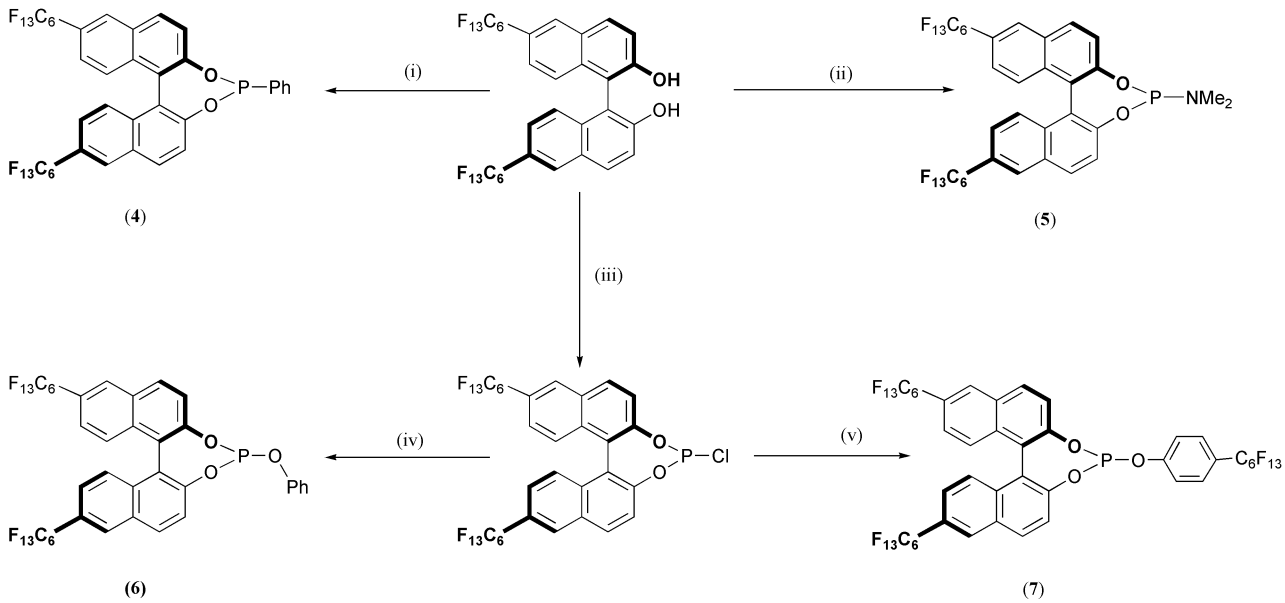
This was prepared following the method for (**6**) in 90% yield using 4-tridecafluorohexylphenol. (Found: C, 38.69; H, 0.98. $C_{44}H_{14}F_{39}O_3P$ requires C, 38.77; H, 1.03%). MS (FAB): *m*/*z* = 1362 [M⁺]. ^1H NMR ($CDCl_3$): δ 7.19 (2H, m), 7.47 (6H, m), 7.55 (1H, d, $^3J_{HH}$ = 8.78 Hz), 7.72 (1H, d, $^3J_{HH}$ = 8.78 Hz), 8.02 (1H, d, $^3J_{HH}$ = 8.78 Hz), 8.19 (1H, d, $^3J_{HH}$ = 8.97 Hz), 8.22 (1H, s), 8.28 (1H, s). $^{31}P\{^1H\}$ NMR (C_6D_6): δ 141.0 (s). $^{19}F\{^1H\}$ NMR (C_6D_6): δ −81.27 (9F, m), −110.10 (2F, m), −110.25 (4F, m), −121.62 (12F, m), −123.03 (6F, m), −126.45 (6F, m). $[\alpha]_D^{17}$ −89.1 (*c* 2.0, CH_2Cl_2).

General procedure for hydrogenation in $scCO_2$

The catalyst was prepared by adding the monodentate ligand (20.7 µmol) to a solution of $[Rh(cod)_2][BF_4]$ (10 µmol) in CH_2Cl_2 (10 cm³). The solution was stirred for 10 minutes before the solvent was removed *in vacuo*. The preformed catalyst (0.6–2.4 µmol) was placed directly into an autoclave and dimethyl itaconate (104 mg) loaded in a small glass sample tube was placed upright in the autoclave to avoid catalysis prior to pressurisation with carbon dioxide. The vessel was flushed several times with hydrogen and pressurized to 20 bar. After heating to the desired reaction temperature, carbon dioxide was pressurized to a total pressure of 200 bar. After stirring the reaction mixture for 2–24 h, the vessel was cooled in an ice bath and slowly depressurized. The reaction mixture was dissolved in CH_2Cl_2, the catalyst removed via a short silica gel column and the product(s) solution directly analyzed by GC.

General procedure for hydrogenation in CH_2Cl_2

The catalyst was prepared by adding the monodentate ligand (35.0 µmol) to a solution of $[Rh(cod)_2][BF_4]$ (17 µmol) in



Scheme 1 (i) $PhPCl_2$, Et_3N, CH_2Cl_2, rt; (ii) $P(NMe_2)_3$, CH_2Cl_2, rt; (iii) PCl_3, Et_3N, CH_2Cl_2, rt; (iv) C_6H_5OH, Et_3N, CH_2Cl_2, rt; (v) HOC_6H_4-4-C_6F_{13}, Et_3N, CH_2Cl_2, rt.

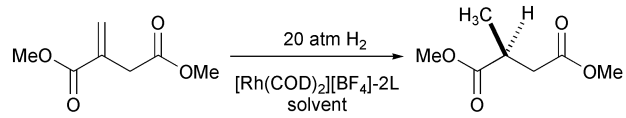
CH_2Cl_2 (10 cm^3). Dimethyl itaconate (104 mg), the required volume of the catalyst solution and dichloromethane (to a total volume of 4 cm^3) were loaded into the pressure vessel. The vessel was flushed several times with hydrogen and pressurized to 20 bar. After reaction, the vessel was depressurized, the catalyst removed *via* a short silica gel column and the product(s) solution directly analysed by GC.

Results and discussion

The synthesis of a range of chiral monodentate perfluoroalkylated phosphorus(III) ligands incorporating chelation at the phosphorus centre has been achieved by the high yielding reaction of the perfluoroalkylated-(*R*)-binaphthol[8] with phosphorus chloride reagents (in the presence of triethylamine) or hexamethylphosphorus triamide (Scheme 1). For the reaction of perfluoroalkylated-(*R*)-binaphthol with PCl_3, it is important to add the triethylamine before the derivatised binaphthol to get the desired $(ArO)_2PCl$ compound. Addition of phenol or derivatised phenol results in ligands **6** and **7**.

Whilst the phosphoramidite (**5**) is air- and moisture-stable, the phosphonite (**4**) and phosphites (**6**, **7**) are highly moisture sensitive. The ^1H NMR spectroscopic data for these ligands reveal complicated, overlapping, resonances in the aryl region of their ^1H NMR spectra associated with the binaphthyl and phenyl protons. The ligands show six or five, highly characteristic, resonances in their ^{19}F NMR spectra associated with the tridecafluorohexyl ponytails, diagnostic singlets in their $^{31}P\{^1H\}$ NMR spectra (at 187, 150, 146 and 141 ppm respectively) and parent ions in their FAB mass spectra. The optical purity of the products was confirmed by CD which, for (**5**), interestingly gave the opposite rotation to that reported for the parent, non-perfluoroalkylated phosphoramidite.[18] During the course of this work, we have remade both (*R*)- and (*S*)-1,1′-binaphthyl-2,2′-diyl-dimethylaminophosphoroamidite and measured their optical rotations. We have found that the optical rotations for these ligands also have the opposite signs to those reported in the literature which concurs with our data for (**5**).

We have evaluated the reactivity and enantioselectivity of these ligands in the rhodium-catalysed hydrogenation of dimethyl itaconate in dichloromethane and supercritical CO_2 (Scheme 2). The rhodium catalysts formed with ligands



Scheme 2

containing two perfluoroalkyl groups (**4,5,6**) are readily soluble in dichloromethane and, hence, their catalytic activities and enantioselectivities (Table 1) can be compared directly with

Table 1 Asymmetric Rh-catalysed hydrogenation of dimethyl itaconate using (*R*)-perfluoroalkylated phosphorus(III) ligands in CH_2Cl_2.[a]

Ligand	*t*/h	Substrate/ Catalyst	Conversion (%)	% ee
4	14	500	100	84
4	3	500	98	82
4	1	500	90	84
1[b]	n.r.	1000	100	29
5	3	250	100	> 99
5	3	500	100	> 99
2[c]	20	20	100	87
6	3	500	45	91
6	3	100	100	91
(*S*)-3[d]	20	1000	100	97
7	16	500	14	< 1

[a] (*R*)-ligands unless otherwise stated; Ligand:Rh = 2:1; room temperature. [b] Ref. 10; n.r. = not reported. [c] Ref. 12; % ee increases to 94.4 at 0 °C. [d] Ref. 15.

those for the parent literature, non-perfluoroalkylated, catalyst systems. Unfortunately, the tris-derivatised phosphite is not sufficiently soluble in dichloromethane, as a consequence of the perfluoroalkyl sidechains, and gave very poor conversion and asymmetric induction even after 16 hours, which is probably a result of background reaction due to unligated rhodium. Complete conversion could be achieved with the ligands **4–6** depending on the substrate : catalyst ratios and reaction times and, interestingly, the introduction of the perfluoroalkyl groups directly on to the binaphthyl backbone appears to have a significant influence on the enantioselectivities in comparison to those for the perprotio parents. Thus, ee's of 84% and > 99%

Table 2 Asymmetric Rh-catalysed hydrogenation of dimethyl itaconate using (*R*)-perfluoroalkylated phosphorus(III) ligands in supercritical CO_2.[a]

Ligand	*t*/h	*T*/°C	Substrate/ Catalyst	Conversion (%)	% ee	Additive
4	3	40	1000	9	8	
5	3	40	1000	11	10	
5	5	40	500	85	15	NaBARF (1.1 equiv)
5	3	40	250	84	31	NaBARF (1.1 equiv)
5	2	60	500	6	16	NaBARF (1.1 equiv)
5	3	80	500	9	5	NaBARF (1.1 equiv)
5	13	40	500	67	1	NaBARF (1.1 equiv) + $C_6F_{13}C_2H_4OH$ (30 mg)
6	3	40	1000	8	7	
7	13	40	250	21	34	
7	13	40	250	28	65	NaBARF (1.1 equiv)

[a] Ligand : Rh = 2 : 1.

to the (*R*) enantiomer were observed with **4** and **5** respectively. In contrast, their parental analogues were reported to give ee's at only 29% and 87% respectively.[10,12] The data indicate that, in these systems, the introduction of the perfluoroalkyl groups directly on to the binaphthyl backbone has relatively little influence on the reactivities but can result in enhanced enantioselectivities in comparison with their perprotio parents.

Previous work on the coordination properties of perfluoroalkylated phosphite ligands, has shown that the additional oxygen linker atom was not sufficient to completely insulate the phosphorus donor atoms from the electronic influence of the fluorous ponytails.[19] Here, we believe that the electron-withdrawing effects of the fluorous ponytails is having a beneficial influence on these monodentate phosphorus(III) ligands in terms of their enantioselectivities. In our previous work on the ruthenium catalysed asymmetric hydrogenation of dimethyl itaconate,[8] we found whilst a tridecafluorohexyl group imposed no detectable effect on enantioselectivity, it was necessary to introduce an additional C_2H_4 insulating spacer group between the fluorous ponytails and the binaphthyl rings in order to get reactivity comparable to that for the parent Ru-BINAP complex. The difference between the monodentate ligands described here and our derivatised BINAPs could be ascribed to the two different types of ligand systems being compared. With the BINAP system good σ donor phosphine ligands were investigated whereas, here, we are examining the applications of poor σ donor phosphonite, phosphoramidite and phosphite ligand.

Unfortunately, this level of reactivity has not been retained in supercritical CO_2 (Table 2). The reactivity and enantioselectivity in $scCO_2$ using the bis-derivatised ligands (**4,5,6**) are much lower than in CH_2Cl_2. After 3 h the conversion is around 10% and the ee value is also around 10% for all three ligands in $scCO_2$. This dramatic decrease in reactivity and selectivity is unlikely to be purely a solvent effect and is probably caused by poor solubility of the catalysts in the supercritical fluid. Following the addition of the fluorinated anion, BARF, as used by Burk and Tumas for asymmetric hydrogenation using the Et-DUPHOS ligand[20] and by Leitner *et al.* for asymmetric hydrogenation using a bisperfluoroalkylated phosphinite ligand,[21] enhanced reactivities and enantioselectivities can indeed be achieved for the phosphoramidite ligand (**5**), showing that the low reactivity of these catalysts results mainly from their low solubility in the reaction medium. To achieve a higher solubility in $scCO_2$ the catalysis was attempted at a higher temperature; but, instead of an increase in reactivity and selectivity, both values were decreased due to decomposition of the catalysts, which was visible by deposition of black metal particles after the reaction. Although reactivity can be improved by the addition of a small amount of a fluorous alcohol, this is at the expense of selectivity, probably due to decomposition of the ligand by the acidic alcohol. For a similar reason, menthyl binaphthylphosphite was shown to be ineffective in the same reaction in MeOH.[17] However, fluorous alcohols have previously been shown to enhance the enantioselectivity in Ru(II)-BINAP catalysed asymmetric hydrogenation reactions in $scCO_2$.[22] Consistent with the solubility argument, much higher enantioselectivities were observed with the tris-derivatised phosphite ligand (**7**) in the presence of the BARF counterion in $scCO_2$, 65%, and the phosphoroamidite ligand (**5**) in hexane, 92%. At 65% ee the enantioselectivity is still much lower than that for ligand **6** in CH_2Cl_2 but this could be explained by a combination of solvent effects and the potential influence of the third perfluoroalkyl chain and is not necessarily a solubility problem. Our explanation for this rests with the apolarity of carbon dioxide as a solvent which may argue against its application in asymmetric hydrogenation using binaphthyl-backboned ligands. However, it is not clear if, or to how great a degree, the solvent polarity contributes to the observed low ee's in $scCO_2$. In attempts to resolve these issues, further work on ligands with larger numbers of fluorous ponytails for enhanced solubility in $scCO_2$ and asymmetric catalysis in alternative supercritical fluids is underway.

Conclusions

The synthesis of chiral perfluoroalkylated monodentate phosphorus(III) ligands has been achieved in high yield. In the rhodium-catalysed asymmetric hydrogenation of dimethyl itaconate in dichloromethane the perfluoroalkyl substituents have a considerable influence upon the enantioselectivities of the catalyst. However, in $scCO_2$ even in the presence of the fluorinated BARF anion, activities as well as enantioselectivities in this asymmetric hydrogenation reaction are modest.

Acknowledgement

We thank the Royal Society (EGH, AMS), the EPSRC (DJA, WC, SL, AW), the Leverhulme Centre for Innovative Catalysis and its Industrial Partners (JX) for financial support.

References

‡ In the ruthenium-catalysed asymmetric hydrogenation of dimethyl itaconate in $scCO_2$ with (*R*)-6,6′-bis(tridecafluorohexyl)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl and (*R*)-6,6′-bis(1*H*,1*H*,2*H*,2*H*-tridecafluorooctyl)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl, good enantioselectivities (73 and 75% ee respectively) were obtained but the reactions took 24

hours to go to 100% completion compared to just 15 minutes in methanol.

1 P. Bhattacharyya, D. Gudmunsen, E. G. Hope, R. D. W. Kemmitt, D. R. Paige and A. M. Stuart, *J. Chem. Soc., Perkin Trans. 1*, 1997, 3609–3612.
2 E. G. Hope, R. D. W. Kemmitt, D. R. Paige and A. M. Stuart, *J. Fluorine Chem.*, 1999, **99**, 197–200.
3 A. M. Stuart, D. Gudmunsen, E. G. Hope, G. P. Schwarz, D. F. Foster and D. J. Cole-Hamilton, *International Patent*, WO 00/33956, 2000.
4 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.
5 D. F. Foster, D. J. Adams, D. Gudmunsen, A. M. Stuart, E. G. Hope and D. J. Cole-Hamilton, *Chem. Commun.*, 2002, 722–723.
6 A. Banet, W. Chen, E. G. Hope, R. D. W. Kemmitt, D. R. Paige, A. M. Stuart, J. Xiao and L. Xu, *J. Chem. Soc., Dalton Trans.*, 2000, 4052–4055.
7 Y. Hu, W. Chen, A. M. Banet Osuna, A. M. Stuart, E. G. Hope and J. Xiao, *Chem. Commun.*, 2001, 725–726.
8 D. J. Birdsall, E. G. Hope, A. M. Stuart, W. Chen, Y. Hu and J. Xiao, *Tetrahedron Lett.*, 2001, **42**, 8551–8553.
9 L. P. Barthel-Rosa and J. A. Gladysz, *Coord. Chem. Rev.*, 1999, **190–192**, 587–605.
10 M. T. Reetz and T. Sell, *Tetrahedron Lett.*, 2000, **41**, 6333–6336.
11 C. Claver, E. Fernadez, A. Gillon, K. Heslop, D. J. Hyett, A. Martorell, A. G. Orpen and P. G. Pringle, *Chem. Commun.*, 2000, 961–962.
12 M. van den Berg, A. J. Minnaard, E. P. Schudde, J. van Esch, A. H. M. de Vries, J. G. de Vries and B. L. Feringa, *J. Am. Chem. Soc.*, 2000, **122**, 11539–11540.
13 X. Jia, R. Guo, X. Li, X. Yao and A. S. C. Chan, *Tetrahedron Lett.*, 2002, **43**, 5541–5544.
14 A.-G. Hu, Y. Fu, J.-H. Xie, H. Zhou, L.-X. Wang and Q.-L. Zhou, *Angew. Chem., Int. Ed. Engl.*, 2002, **41**, 2348–2350.
15 M. T. Reetz and G. Mehler, *Angew. Chem., Int. Ed. Engl.*, 2000, **39**, 3889–3890.
16 M. T. Reetz, G. Mehler, A. Meiswinkel and T. Sell, *Tetrahedron Lett.*, 2002, **43**, 7941–7943.
17 W. Chen and J. Xiao, *Tetrahedron Lett.*, 2002, **42**, 2897–2899.
18 R. Hulst, N. Koen de Vries and B. L. Feringa, *Tetrahedron: Asymmetry*, 1994, **5**, 699–708.
19 D. J. Adams, D. Gudmunsen, J. Fawcett, E. G. Hope and A. M. Stuart, *Tetrahedron*, 2002, **58**, 3827–3834.
20 M. J. Burk, S. Feng, M. F. Gross and W. Tumas, *J. Am. Chem. Soc.*, 1995, **117**, 8277–8278.
21 S. Lange, A. Brinkmann, P. Trautner, K. Woelk, J. Bargon and W. Leitner, *Chirality*, 2000, **12**, 450–457.
22 J. Xiao, S. C. A. Nefkens, P. G. Jessop, T. Ikariya and R. Noyori, *Tetrahedron Lett.*, 1996, **37**, 2813–2816.

Neoteric solvents for asymmetric hydrogenation: supercritical fluids, ionic liquids, and expanded ionic liquids†

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Received 29th November 2002
First published as an Advance Article on the web 25th March 2003

Neoteric (new) solvents such as supercritical CO_2 ($scCO_2$), ionic liquids (ILs), ILs with cosolvents, and CO_2-expanded ionic liquids (EILs) offer flexible physical properties, which allow chemists and engineers to select the optimal solvent system for a specific reaction process. Homogeneously-catalyzed asymmetric hydrogenation of α,β-unsaturated carboxylic acids was chosen for its economic interest and its multiple H_2-concentration dependent behaviours. For example, with ruthenium BINAP-type catalysts, type I substrates require high H_2 concentration in solution, while type II require low H_2 concentration. $ScCO_2$, ILs and EILs are highly attractive because of their contrasting properties and their potential flexibility in improving or reducing hydrogen transfer rates and thus concentrations. Several ILs were tested and compared with EILs, IL–cosolvent mixtures, $scCO_2$, and normal methanol as media for these reactions to establish the most effective system for each substrate type. Atropic acid (type I) was hydrogenated up to 92% ee which is not better than in methanol. However, tiglic acid (type II) was hydrogenated up to 93% ee in the optimized IL system, which is significantly better than was observed in MeOH. CO_2-expansion of ionic liquids affected the selectivity for both substrates, improving the selectivity for atropic acid and lowering it for tiglic acid. The solubility of the catalyst in $scCO_2$ was measured and the antisolvent effect of H_2 in $scCO_2$ was demonstrated and discussed.

Introduction

Neoteric (new) solvents such as supercritical carbon dioxide[1] and ionic liquids[2–5] are not only potentially more environmentally friendly than volatile organic compounds (VOCs) as solvents but also can dramatically affect reaction rate and selectivity because of their unusual physical and chemical properties. Comparisons between ionic liquids (ILs) and supercritical CO_2 ($scCO_2$) are particularly interesting because these two media contrast in almost every physical property. Supercritical CO_2 is volatile, nonviscous, nonconducting, nonpolar, and unable to dissolve large and unsaturated compounds. Many ionic liquids such as 3-butyl-1-methylimidazolium hexafluorophosphate ([bmim]PF_6, Scheme 1) have exactly the opposite properties. It is therefore to be expected that reaction performance in the one solvent should differ greatly from that in the other. It is also expected that reaction performance should differ in different ionic liquids, in ionic liquids with cosolvents, and in ionic liquids with CO_2 dissolved therein. This study was designed to evaluate the effect of the different properties of various neoteric solvents on the enantioselectivity of a test reaction.

Industrial application of environmentally-benign solvents is more likely to take place if economic motivators exist. Economic advantages of these solvents include potential rate and selectivity increases, facilitated catalyst–product separa-

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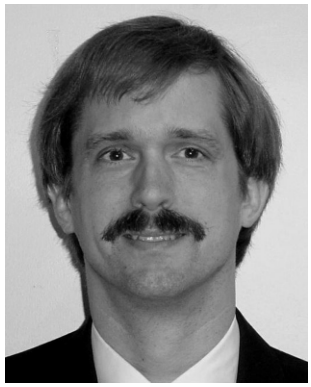
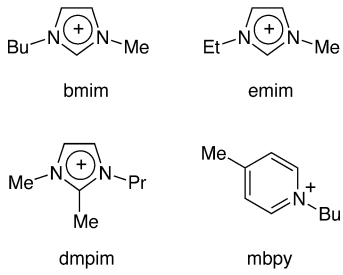


† This work was presented at the Green Solvents for Catalysis Meeting held in Bruchsal, Germany, 13–16th October 2002.

Green Context

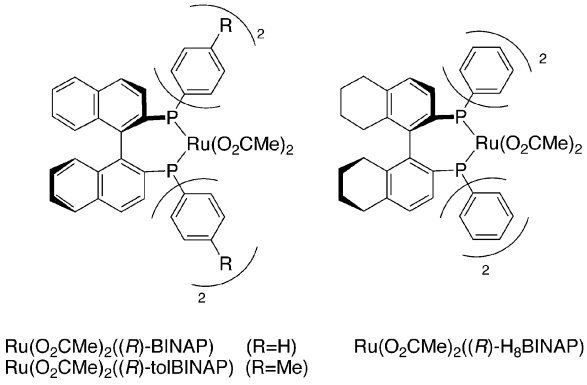
While we can read many articles about non-volatile organic solvents it is less easy to find useful comparisons between these different alternative solvent systems. Here a number of different solvents were studied in order to evaluate the most effective system for the enantioselective hydrogenation of α,β-unsaturated acids. As would be expected, the solubility of hydrogen is a prime factor. Good results were obtained using methanol and methanol–CO_2 systems for atropic acid where good H_2 solubility is important. In contrast the best results for tiglic acid are in ionic liquids where low H_2 solubility is advantageous. Thus there is no universally favourable solvent but we need to consider the requirement of each reaction in turn. ***JHC***



Scheme 1 The structures of the ionic liquid cations. The anions are BF_4, PF_6, O_3SCF_3, and $N(O_2SCF_3)_2$.

tion, facilitated solvent and catalyst recycling (addressed in our preliminary communication[6]), and reduced waste disposal costs. If such economic advantages drive the industrial adoption of neoteric solvents, then environmental advantages can be expected, including reduced evaporative losses, reduced reliance on petrochemical-derived solvents (at least for $scCO_2$ and expanded liquids), reduced liquid hazardous waste, and increased solvent recycling.

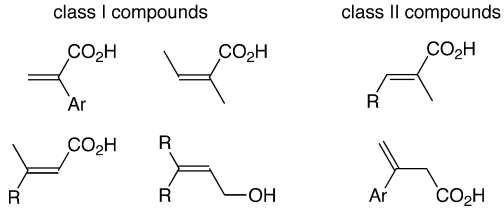
Asymmetric hydrogenation catalyzed by chiral transition metal complexes, a classic enantioselective reaction, was selected as the test reaction for a comparison of these various reaction media. Ruthenium BINAP complexes (Scheme 2)



$Ru(O_2CMe)_2$((*R*)-BINAP) (R=H) $Ru(O_2CMe)_2$((*R*)-H_8BINAP)
$Ru(O_2CMe)_2$((*R*)-tolBINAP) (R=Me)

Scheme 2 Structures of the BINAP-type ruthenium catalysts.

catalyse the enantioselective hydrogenation of a range of functionalized olefins,[7] traditionally in methanol solution. The substrates can conveniently be grouped into two categories: class I substrates are hydrogenated in high enantioselectivity at high H_2 concentration while class II substrates are hydrogenated in high enantioselectivity at low H_2 concentration (Scheme 3).



Scheme 3 Structures of typical class I and class II substrates.

In practice, the H_2 concentration in the MeOH is a function of the H_2 pressure[7] and the stir rate (*i.e.* mass transfer limitations exist).[8] In solvents other than methanol, the trends may be the opposite, or there may be no H_2 pressure dependence. Among the most important of the class I substrates are atropic acid (α-phenylacrylic acid) and its derivatives; the hydrogenation products include the anti-inflammatory drugs Ibuprofen and Naproxen.

Selection of the appropriate neoteric solvents for an asymmetric hydrogenation of a particular substrate is likely to depend on which class the substrate belongs to. For substrates in class I, one would predict that high enantioselectivity would be obtained in supercritical CO_2, because of that medium's complete miscibility with H_2 gas[9] and its lack of mass transfer limitations. In contrast, for substrates in class II, ionic liquids would seem to be the more logical choice, because of their very low ability[10] to dissolve H_2 and their high viscosity.[11,12] We performed the following study in order to evaluate these predictions. A preliminary communication from part of this study has already appeared.[6a]

Experimental

Ionic liquids were obtained from commercial sources and degassed by being kept under strong vacuum for a period of 48–72 h. Bis(trifluoromethylsulfonyl)amide ionic liquids were a generous gift from Covalent Associates. Organic solvents and water were degassed with N_2 by repeated freeze–vacuum–thaw cycles. The $Ru(OAc)_2$(tolBINAP) catalyst was prepared by the literature method.[13] Reactions were performed under inert gas (N_2 or CO_2) conditions.

Safety warning

Operators of high pressure equipment such as that required for these experiments should take proper precautions, including but not limited to the use of blast shields and pressure relief mechanisms, to minimize the risk of personal injury.

Method for synthesis of atropic acid

Atropic acid was prepared by vacuum distillation of atrolactinic acid (the method of McKenzie and Wood).[14] 3.00 grams of atrolactinic acid were placed in a 100 ml round bottom flask attached *via* a short length of glass pipe to a 50 ml round bottom collection flask which was connected to a gas–vacuum manifold. While under strong vacuum the flask containing the atrolactinic acid was heated by flame; after 5 min a powdery white residue began to collect on the sides of the collection flask. After 25 min all that remained in the distilling flask was a small amount of amber residue. The white solid sublimate was dissolved in 40 ml of 1:1 hot water:ethanol. The product was precipitated as white crystals by the slow addition of 40 ml of hot water and subsequent cooling of the solution. The solid was filtered under vacuum and collected (yield 1.48 g). The identification of the product was confirmed by comparison of the ^{1}H NMR spectrum with literature data.[15]

Hydrogenation of atropic acid

Under a nitrogen atmosphere, ionic liquid or methanol (1.8 g, degassed), $Ru(O_2CCH_3)_2$(R-tolBINAP) (3.0 mg, 3.3 μmol), atropic acid (14.5 mg, 97.8 μmol) and stir bar were combined in a 1 dram glass uncapped vial. At this time additional cosolvents (1 g) were added if used. Ten such vials were then placed in a 160 mL steel vessel kept at 25 °C. Hydrogen gas was added up to the desired pressure, followed by CO_2 gas pressure if needed. The reported CO_2 pressures are in fact the difference between the total pressure and the H_2 pressure. The reaction was performed at various pressures of hydrogen and CO_2 at a temperature of 25 °C. After approximately 24 h the gas was slowly vented from the vessel over a period of 2.5 h. To each vial was added 1.5 ml of toluene and the contents were stirred for 1 h. The toluene layer was then removed and condensed to 0.5 mL. From this extract a 1 μL sample was taken and analyzed using chiral capillary GC. Hydrogenations of tiglic acid were

performed by a similar method but with 9.0 mg tiglic acid (90 μmol) and 2.0 mg $Ru(O_2CCH_3)_2$(R-tolBINAP) (2.2 μmol).

Measurement of the solubility of $Ru(O_2CMe)_2$(tolBINAP) in $scCO_2$

The solubility of $Ru(O_2CMe)_2$(tolBINAP) in $scCO_2$ was determined using UV/visible spectroscopy. The solubility experiment was carried out at 205 bar and 40 °C, in a high-pressure optical cell with quartz windows. The cell was made of stainless steel SS316, with an internal volume of 20 ml. A stir bar was placed at the bottom of the cell to promote mixing and to keep the conditions uniform inside the cell. The temperature was measured by an Omega type-K thermocouple in contact with the fluid. The pressure was read from a Druck pressure gauge DPI 260 and a Druck pressure transducer PDCR 4010, connected to the cell through a short line of tubing. The cell temperature was controlled to within 0.5 K by an Omega CN9000A temperature controller with four cartridge heaters.

A known amount of solid catalyst was loaded into the cell in a glove box which is purged constantly with nitrogen. The cell was then placed under vacuum (approximately 100 Pa) for one hour. After vacuum, the cell was heated to 40 °C, and CO_2 was added into the cell using an Isco syringe pump, model 500D. The equilibrium of the mixture was observed *in situ* by measuring the UV/Vis spectrum of the solution periodically using the HP 8453 UV/Vis spectrophotometer. CO_2 pressure was ramped up until there was no further significant increase in the peak absorbance. At this point, all the solid was dissolved in the fluid phase, and the solubility was thus determined.

Measurement of the anti-solvent effect of H_2 on the solubility of $Ru(O_2CMe)_2$(tolBINAP) in $scCO_2$

The experimental setup was similar to the one described for measuring the catalyst solubility, with one exception. In this case, H_2 was added to the cell first. The pressure and temperature of the system were then allowed to be stable before adding in CO_2. The number of moles of H_2 added was calculated using the Modified Benedict–Webb–Rubin equation of state.[16]

Results and discussion

Solubility of $Ru(O_2CMe)_2$(tolBINAP) catalyst in $scCO_2$

The synthesized $Ru(O_2CMe)_2$(tolBINAP) catalyst was shown by ^1H NMR to contain 85% of pure catalyst and 15% of (tolBINAP) free ligand. The solubility of (tolBINAP) free ligand in $scCO_2$ was not detectable by UV/Vis spectroscopy because it has no absorbance at the wavelength used for these experiments. The catalyst solubility was measured to be 2.59×10^{-5} mole pure catalyst per mole CO_2, with 6% uncertainty, at CO_2 pressure of 205 bar and 313 K (corresponding to a CO_2 density of 19.2 mole l^{-1}). The molar absorptivity for the solution was calculated to be 234 l $mole^{-1}$ cm^{-1}, at a maximum wavelength of 388 nm.

Anti-solvent effect of H_2 on catalyst solubility

Hydrogen and nitrogen are anti-solvents in CO_2 solution,[17,18] meaning that they decrease the solubility of other solutes. To illustrate the anti-solvent effect of H_2, we used the Peng–Robinson equation of state to calculate the change in solubility of naphthalene in $scCO_2$ at 40 °C.[19] The data calculated are shown in Fig. 1. At 220 bar total pressure, the mole fraction solubility of naphthalene in 10% H_2–CO_2 mixture is predicted to be half of its solubility in pure $scCO_2$. The antisolvent effect is far stronger at lower pressures. To further illustrate the antisolvent effect, and the fact that it can be overcome by higher CO_2 pressure, an experiment was performed in which CO_2 pressure was increasingly applied to a H_2–MeOH–Nile Red mixture (Fig. 2, the structure of Nile Red is shown below).

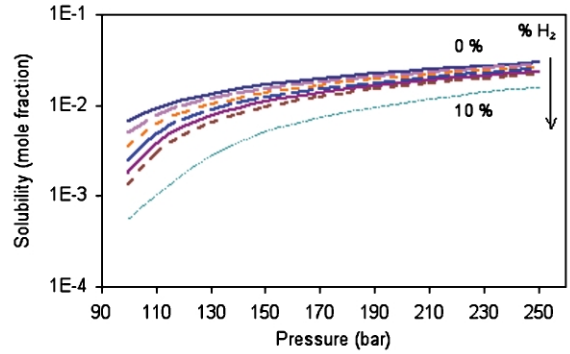


Fig. 1 H_2 anti-solvent effect on the solubility of naphthalene in $scCO_2$, at 40 °C and 0, 1, 2, 3, 4, 5, and 10 mol% H_2.

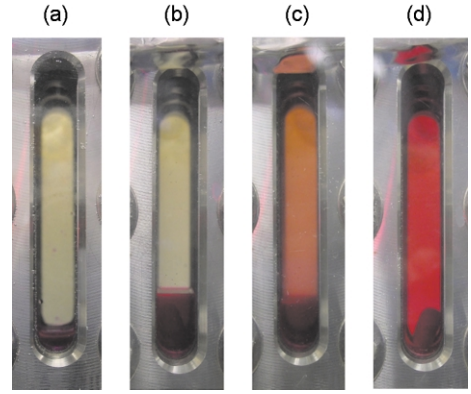
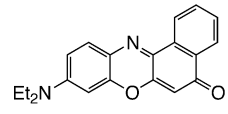


Fig. 2 The effect of CO_2 pressure on the phase behaviour of a CO_2–H_2–Nile Red–MeOH mixture. A 3 mL methanol solution of Nile Red was placed in the 31 mL vessel and hydrogen gas (100 bar) was added at 31 °C. CO_2 pressure was then progressively added. a) 0 bar CO_2, b) 137 bar CO_2, c) 178 bar CO_2, d) 215 bar CO_2. (CO_2 pressure being the difference between total pressure and the original H_2 pressure). The stir bar evident in two of the photos is also present in the other two but is in a small space below the level of the window.

Although methanol is normally miscible with $scCO_2$ in any proportions above about 80 bar,[20–22] in the presence of 100 bar H_2 gas the complete dissolution of methanol in the CO_2 occurs only at much higher pressures (approximately 300 bar total pressure). Note however that at this pressure all of the methanol and even the Nile Red are entirely dissolved in the CO_2–H_2 phase (Fig. 2d).



Nile Red

To test the effect of H_2 on the solubility of the catalyst in $scCO_2$, two experiments were carried out, with 6 mmol and 16 mmol of H_2. In both experiments, we observed consistently that the UV absorption peak at 388 nm (corresponding to the ruthenium complex) disappeared between 6 and 15 h after contact of the solution with CO_2 and H_2. Fig. 3 shows the disappearance of the UV peak at 388 nm. To test whether this

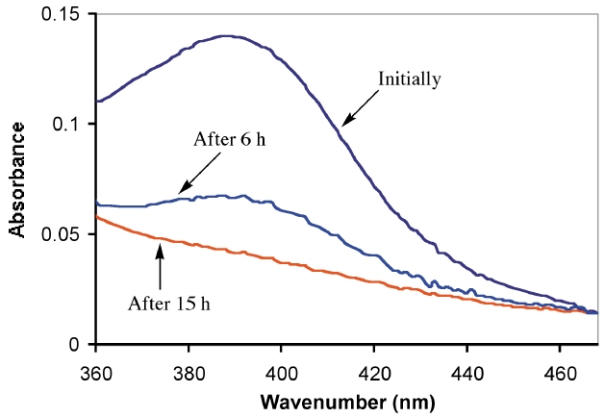


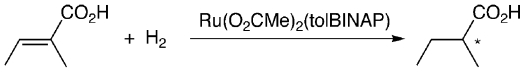
Fig. 3 UV/Vis absorption of the $Ru(O_2CMe)_2$(tolBINAP) catalyst in H_2–CO_2 solution, initially (top curve), after 6 h, and after 15 h (bottom curve). Conditions: 40 °C, 150 bar total pressure, 5 mole% H_2.

behaviour is a result of the antisolvent effect, helium, an inert anti-solvent, was used in place of H_2. In this case, the Ru-peak at 388 nm remained in the UV/Vis spectrum of the solution for more than 24 hours. Therefore the anti-solvent effect is not sufficient to force the catalyst entirely out of solution.

Based on these results, the $Ru(O_2CMe)_2$(tolBINAP) catalyst is believed to have reacted with the H_2 gas and formed a new Ru-containing species of reduced solubility in $scCO_2$ which dropped out of the solution or had no absorbance at these wavelengths. Despite the potential antisolvent effect, we were still able to achieve good yields and selectivity for the hydrogenation reaction in the presence of the catalyst, H_2, CO_2, and methanol. Methanol may have helped keep the active catalyst in solution because methanol is a good solvent for the catalyst and methanol is known to be an effective cosolvent for enhancing the solubility of aromatic species in $scCO_2$.[23–25]

Asymmetric hydrogenation in $scCO_2$

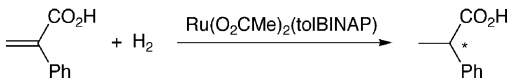
Previous work by Xiao *et al.*[26] found that the asymmetric hydrogenation of tiglic acid (a class II substrate; eqn. 1) at low



(1)

H_2 pressure (5–7 bar) with $Ru(O_2CMe)_2$(H_8BINAP) was more selective in MeOH (95%) than in $scCO_2$ (71%), although the enantioselectivity in the supercritical phase could be increased to 89% by the addition of a fluorinated alcohol as a cosolvent. We obtained 88% using the $Ru(O_2CMe)_2$(tolBINAP) precursor in $scCO_2$ with MeOH cosolvent (3 mL or 74 mmol MeOH, 40 °C, 5 bar H_2, 220 bar total, 31 mL volume).

We have now evaluated the asymmetric hydrogenation of a class I substrate, atropic acid, in $scCO_2$ (eqn. 2). In these



(2)

experiments, however, methanol was used as a cosolvent instead of the fluorinated alcohol. We found that with all other factors equal, the enantioselectivity in $scCO_2$ with MeOH cosolvent was 88% (40 °C, 100 bar H_2, 300 bar total), significantly lower than the best results we have obtained in MeOH (94% at 40 °C, 97% at 25 °C). There is no increase in selectivity obtained by performing the reaction in the supercritical phase. Note that even at 100 bar H_2 pressure, the methanol is soluble in the H_2–CO_2 mixture as long as the total pressure of CO_2 and H_2 is at least 300 bar (Fig. 2d).

Asymmetric hydrogenation in ionic liquids

Asymmetric hydrogenation using BINAP-type catalysts in ILs was first reported by the group of Dupont,[27] who studied reaction 2 in $[bmim]BF_4$ with alcohol cosolvents. They found that the alcohol cosolvent was necessary in order to obtain reasonable enantioselectivity, that the selectivity was roughly H_2-pressure independent, and that the catalyst–IL solution could be recycled by extraction of the product with 2-propanol. The lack of an H_2-pressure dependence in an alcohol–IL mixture was surprising given that the reaction is known to be strongly H_2-pressure dependent in pure alcohols.[7]

We have now evaluated the hydrogenation of class I and class II substrates in various ILs.

a) Tiglic acid. We compared the enantioselectivity of asymmetric hydrogenation of tiglic acid in several ionic liquids. Tiglic acid is one of those substrates which requires a low H_2 concentration, or low H_2 pressure and mass transfer rates, for optimum selectivity.[7,8] We recently confirmed that the ee for this reaction is H_2-pressure dependent in $[bmim]PF_6$–H_2O and in $[bmim]PF_6$–^{i}PrOH mixtures.[6] Therefore one would expect reasonably good enantioselectivity in viscous ionic liquids, as we have observed (Table 1). The enantioselectivity in these different solvents increased in the order:

Table 1 The asymmetric hydrogenation of tiglic acid catalysed by $Ru(O_2CMe)_2$(*R*-tolBINAP)

Entry	Solvent/mL	CO_2, bar	H_2, bar	% ee
1	MeOH	0	5	88
2		70	5	79
3	$[bmim]PF_6$	0	5	93
4		0	70	79
5		70	5	85
6	$[bmim]PF_6$–toluene	0	5	88
7		70	5	81
8	$[bmim]PF_6$–^{i}PrOH	0	5	76
9		70	5	72
10	$[bmim]BF_4$	0	5	88
11		0	70	77
12	$[mbpy]BF_4$	0	5	88
13	$[emim]O_3SCF_3$	0	5	84
14	$[emim]N(O_2SCF_3)_2$	0	5	95
15	$[dmpim]N(O_2SCF_3)_2$	0	5	93

$$[emim]O_3SCF_3 < [bmim]BF_4 = [mbpy]BF_4 < [bmim]PF_6 = [dmpim]N(OTf)_2 < [emim]N(OTf)_2$$

where the structures of the ionic liquids are shown in Scheme 1. Note that the choice of cation has only a weak effect on the enantioselectivity, unsurprising because the cations used are structurally similar. However, the choice of anion has a strong effect. None of these ionic liquids performed very poorly, the worst being $[bmim]BF_4$. That ionic liquid is less viscous than $[bmim]PF_6$ (viscosities of 154 and 371 centipoise respectively, at 20 °C),[12] has a lower surface tension,[28] and is better able to dissolve H_2 gas.[29] For all three reasons one would expect greater concentrations of H_2 in the liquid $[bmim]BF_4$ during the hydrogenation and consequently a lower enantioselectivity.

Methanol as a medium for this reaction is inferior to most of the ionic liquids in terms of the enantioselectivity that is obtained. This was expected based upon the argument that solvents which are highly capable of dissolving H_2 and have low diffusion and surface tension should give the lowest ee's for this class of substrates. Similarly, the hydrogenation in a $[bmim]PF_6$–cosolvent mixture is less selective than the hydrogenation in $[bmim]PF_6$ alone (compare entries 3, 6, and 8). Addition of cosolvents is known to decrease the viscosity of ionic liquids,[11] and is therefore expected to improve the mass transfer of H_2 into the liquid phase. Note that isopropanol as a cosolvent had a stronger selectivity-lowering effect than did toluene, possibly because of the alcohol's protic character, which could influence the mechanism of the hydrogenation.

The use of higher pressures of H_2 decreases the enantioselectivity of the reaction in [bmim]PF_6 and in [bmim]BF_4, as is known to be the case in methanol.[7]

b) Atropic acid. Atropic acid hydrogenation, which requires a high concentration and high mass transfer rate of H_2,[7] was more enantioselective in methanol than in any of the ionic liquids (Table 2), probably because the viscosity of the ionic liquids is much higher than that of methanol. The selectivity was also higher in a methanol–ionic liquid mixture than in pure ionic liquid (Table 2, entries 7 and 16), consistent with the argument that added methanol is expected to lower the viscosity of the ionic liquid, to increase the solubility of hydrogen, and to supply a source of protons to assist in the hydrogenation mechanism. Addition of isopropanol has the same effect on selectivity (entries 7 and 13), even though it has poor miscibility with [bmim]PF_6. Toluene was also tested as a cosolvent in the IL because it has the same ability to reduce the viscosity but it can not affect the reaction mechanism by supplying protons. Interestingly, the addition of toluene as a cosolvent does not increase the ee (entries 5 and 8 or 7 and 10), suggesting that the protic character of the alcoholic cosolvents was important to the selectivity-enhancing effect.

Table 2 The asymmetric hydrogenation of atropic acid catalysed by $Ru(O_2CMe)_2$(*R*-tolBINAP)

Entry	Solvent/mL	H_2, bar	CO_2, bar	% ee
1	MeOH	50	0	92
2		50	50	90
3		100	0	91
4	[bmim]PF_6	5	0	22
5		50	0	32
6		50	50	57
7		100	0	49
8	[bmim]PF_6–toluene	50	0	19
9		50	50	3
10		100	0	21
11	[bmim]PF_6–^{i}PrOH	50	0	33
12		50	50	57
13		100	0	75
14	[bmim]PF_6–MeOH	50	0	54
15		50	50	87
16		100	0	82
17	[bmim]BF_4	5	0	37
18		50	0	15
19	[emim]O_3SCF_3	50	0	25
20	[emim]$N(O_2SCF_3)_2$	50	0	31
21	[dmpim]$N(O_2SCF_3)_2$	50	0	39

For the reactions in ionic liquids without added cosolvents, the enantioselectivity was low. Selectivity in [bmim]PF_6 increased, but not dramatically, with increased H_2 pressures (entries 4, 5, and 7). This, however, was not observed in [bmim]BF_4 (entries 17 and 18, *cf*. the results of Dupont in [bmim]BF_4–alcohol mixtures), for reasons that are not clear.

For the reactions in ILs, the selectivity depended on the choice of IL, increasing in the order:

$$[bmim]BF_4 < [emim]O_3SCF_3 < [bmim]PF_6 = [emim]N(OTf)_2 < [dmpim]N(OTf)_2$$

Even though the ee's are rather low and therefore the accuracy is fairly poor, it is evident that the trend is similar to that obtained with tiglic acid. This is surprising, because an argument based upon viscosity, surface tension or upon ability to dissolve H_2 gas would have predicted that the trend for atropic acid (a class I substrate) would be opposite to that observed for tiglic acid (a class II substrate). We have found that the trends are almost the same, which suggests that viscosity/mass transfer and H_2 solubility are not the only parameters. In particular, the viscosity[12] of [emim]O_3SCF_3 is only 13% of that of [bmim]PF_6 and one would therefore expect better H_2 transport into the former ionic liquid and consequently much better enantioselectivity for atropic acid hydrogenation.

Differences in H_2 solubility or mass transfer are therefore not a satisfactory explanation for the trend in effectiveness of the IL's. An alternative explanation has not yet been identified, but must lie among the many solvent parameters we have not yet explored, including polarity, coordinating ability, and hydrophobicity.

Asymmetric hydrogenation in CO_2-expanded ionic liquids

If CO_2 is present during a reaction in a liquid solvent, then the presence of the CO_2 can have a substantial effect on the reaction rate by a phenomenon called gas-expansion of the liquid phase. Dissolution of CO_2 into an organic liquid phase at pressures above 40 bar causes an observable and typically multi-fold increase in the volume of the liquid phase,[30–32] accompanied by changes in the physical properties of the liquid phase mixture. Most relevant to this study, molecular (non-ionic) liquid solvents are known to have increased gas–liquid diffusion rates[33] and increased ability to dissolve H_2,[34] upon expansion with CO_2. Viscosity reductions caused by dissolved CO_2 in highly viscous liquids have been used for a number of applications.[35,36] Reactions in liquid solvents are known to be affected by expansion of the solvent with a gas,[37,38] probably as a direct result of such physical property changes. Carbon-dioxide expansion of *ionic liquids* does occur (although the volume change is small),[39] resulting in a change in the melting point[40] and other properties. We have observed visually that the viscosity of [bmim]PF_6 is decreased under CO_2 pressure. Seddon *et al*.[11] observed that the viscosity of [bmim]BF_4 dropped 10 fold when a cosolvent was added at a concentration of 50 mole%, the change in viscosity being roughly independent of the choice of cosolvent. Brennecke *et al*. showed that CO_2-expanded [bmim]PF_6 has a CO_2 mole fraction of 50% at 50 bar. We could thus expect that under the conditions in our experiments, the viscosity of the ionic liquid could be lowered by an order of magnitude by the presence of CO_2. Accompanying the drop in viscosity, we also expect an increase in gas–liquid mass transfer rates and an increase in the solubility of H_2 in the liquid phase; both of these factors should affect enantioselectivity. There are recent reports of the effect of CO_2 expansion on the selectivity of 1-hexene oxidation[41] and hydroformylation[6c] in [bmim]PF_6.

For tiglic acid hydrogenation, expansion of [bmim]PF_6 caused a significant drop in the enantioselectivity compared to that in normal [bmim]PF_6, consistent with the anticipated higher H_2 solubility and rate of mass transfer (Table 1, entries 3 and 5). CO_2-expansion of [bmim]PF_6–cosolvent mixtures caused smaller drops in the enantioselectivity (entries 6–9). For atropic acid hydrogenation, CO_2-expansion of [bmim]PF_6 caused an increase in enantioselectivity, again consistent with greater H_2 solubility and mass transfer rate (Table 2, entries 5 and 6). Simply increasing the H_2 pressure instead of adding CO_2 also increased the selectivity but not to as great an extent (entries 5 and 7). Expansion of [bmim]PF_6–alcohol mixtures also increased the enantioselectivity, but once again the [bmim]PF_6–toluene mixture was an exception. Dissolving CO_2 in MeOH did not cause a significant change in the enantioselectivity relative to that in normal MeOH.

Conclusions

A number of different solvents were studied in order to evaluate the most effective system for enantioselective hydrogenation of α,β-unsaturated acids (Figure 4). As expected, solvents thought to dissolve a significant concentration of hydrogen gas gave

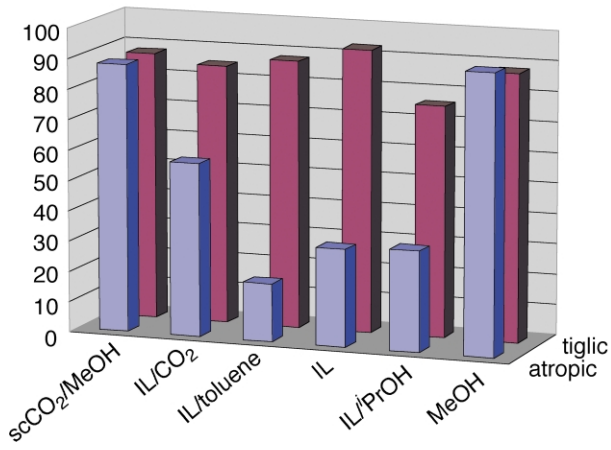


Fig. 4 Graphic comparison of the enantioselectivity obtained for hydrogenation of tiglic and atropic acid in various solvents. Conditions for nonsupercritical runs: 25 °C, 5 bar H_2 (tiglic acid), 50 bar H_2 (atropic acid). Conditions for supercritical runs: 40 °C, 5 bar H_2 (tiglic acid), 100 bar H_2 (atropic acid).

favorable enantioselectivities for substrates known to be dependent on high H_2 concentrations. Also, solvents dissolving low concentrations of hydrogen were ideal for those substrates dependent on minimal amounts of dissolved H_2. Specifically, atropic acid was hydrogenated in 92, 90, and 88% ee in methanol, CO_2-expanded methanol, and $scCO_2$ with methanol cosolvent, respectively. Since hydrogenation of atropic acid is known to be H_2 concentration dependent, it can be assumed that these three solvents are more readily able to dissolve hydrogen than the other solvents in the study. In particular, the ionic liquids in the study were unsatisfactory for this reaction; reasonable ee's being observed only in a CO_2-expanded ionic liquid–methanol mixture. Tiglic acid, on the other hand, was hydrogenated with enantioselectivities of 93 to 95% ee in each of the ILs, [bmim]PF_6, [emim]$N(O_2SCF_3)_2$, and [dmpim-]$N(O_2SCF_3)_2$, with inferior results in other ILs, methanol, CO_2-expanded methanol, and CO_2-expanded ILs. These results were again expected since it is assumed that IL's dissolve only small amounts of H_2 gas and that higher enantioselectivities for the tiglic acid hydrogenation are in accordance with low H_2 concentration.

Thus, in general, following comparison of the various neoteric solvents in terms of feasibility for use as reaction media for asymmetric hydrogenation, we have found that no one solvent clearly outperforms all others for all substrates. The question as to which neoteric solvent will allow the greatest selectivity for a particular reaction depends on the choice of substrate. The question as to which neoteric solvent is best to use will also require consideration of process and separation factors. A suite of neoteric solvents will clearly be a necessity for future applications.

Acknowledgements

This material is based upon work supported by the National Science Foundation under Grant No. 9815320. NMR spectrometers used in this study were funded by NSF CRIF program (CHE-9808183). We thank Dr David Bush of Georgia Institute of Technology for his valuable advice on equations of state. Covalent Associates are thanked for their generous donation of ionic liquid samples.

References

1 *Chemical Synthesis using Supercritical Fluids*, ed. P. G. Jessop and W. Leitner, VCH–Wiley, Weinheim, 1999.
2 P. Wasserscheid and W. Keim, *Angew. Chem., Int. Ed.*, 2000, **V39**, 3773–3789.
3 T. Welton, *Chem. Rev.*, 1999, **99**, 2071–2083.
4 P. A. Z. Suarez, S. Einloft, J. E. L. Dullius, R. F. deSouza and J. Dupont, *J. Chim. Phys. Phys.-Chim. Biol.*, 1998, **95**, 1626–1639.
5 J. G. Huddleston, A. E. Visser, W. M. Reichert, H. D. Willauer, G. A. Broker and R. D. Rogers, *Green Chem.*, 2001, **3**, 156–164.
6 (*a*) R. A. Brown, P. Pollet, E. McKoon, C. A. Eckert, C. L. Liotta and P. G. Jessop, *J. Am. Chem. Soc.*, 2001, **123**, 1254–1255; (*b*) Other reports combining ILs and $scCO_2$ for catalyst recycling include: F. C. Liu, M. B. Abrams, R. T. Baker and W. Tumas, *Chem. Commun.*, 2001, 433–434; (*c*) M. F. Sellin, P. B. Webb and D. J. Cole-Hamilton, *Chem. Commun.*, 2001, 781–782; (*d*) A. Bösmann, G. Franciò, E. Janssen, M. Solinas, W. Leitner and P. Wasserscheid, *Angew. Chem., Int. Ed.*, 2001, **40**, 2697–2699.
7 R. Noyori, *Asymmetric Catalysis in Organic Synthesis*, John Wiley and Sons, New York, 1994.
8 Y. Sun, R. N. Landau, J. Wang, C. LeBlond and D. G. Blackmond, *J. Am. Chem. Soc.*, 1996, **118**, 1348–1353.
9 C. Y. Tsang and W. B. Streett, *Chem. Eng. Sci.*, 1981, **36**, 993–1000.
10 J. L. Anthony, E. J. Maginn and J. F. Brennecke, *J. Phys. Chem. B*, 2002, **106**, 7315–7320.
11 K. R. Seddon, A. Stark and M. J. Torres, *Pure Appl. Chem.*, 2000, **72**, 2275–2287.
12 K. R. Seddon, A. Stark and M. J. Torres, in *Clean Solvents*, ed. M. Abraham, ACS, Washington, 2002.
13 M. Kitamura, M. Tokunaga and R. Noyori, *J. Org. Chem.*, 1992, **57**, 4053–4054.
14 A. McKenzie and J. K. Wood, *J. Chem. Soc.*, 1919, **115**, 828.
15 I. Zadrozna, J. Kurkowska and I. Makuch, *Synth. Commun.*, 1997, **27**, 4181–4191.
16 B. A. Younglove, *J. Phys. Chem. Ref. Data*, 1982, **11** (Supplement No. 1).
17 H. J. Gahrs, *Ber. Bunsenges. Phys. Chem.*, 1984, **88**, 894.
18 A. De Jong, A. Eftaxias, F. Trabelsi, F. Recasens, J. Sueiras and F. Stuber, *Ind. Eng. Chem. Res.*, 2001, **40**, 3225–3229.
19 Although the cubic equations of state are known to be less precise for H_2 than for most other species, it is still the best available alternative and should certainly show trends reliably.
20 T. S. Reighard, S. T. Lee and S. V. Olesik, *Fluid Phase Equil.*, 1996, **123**, 215–230.
21 C. J. Chang, C. Kou-Lung and D. Chang-Yih, *J. Supercrit. Fluids*, 1998, **12**, 223–237.
22 K. Bezanehtak, G. B. Combes, F. Dehghani, N. R. Foster and D. L. Tomasko, *J. Chem. Eng. Data*, 2002, **47**, 161–168.
23 A. Tavana, J. Chang, A. D. Randolph and N. Rodriguez, *AIChE J.*, 1989, **35**, 645–648.
24 J. M. Dobbs, J. M. Wong, R. J. Lahiere and K. P. Johnston, *Ind. Eng. Chem. Res.*, 1987, **26**, 56–65.
25 T. T. Ngo, D. Bush, C. A. Eckert and C. L. Liotta, *AIChE J.*, 2001, **47**, 2566–2572.
26 J. Xiao, S. C. A. Nefkens, P. G. Jessop, T. Ikariya and R. Noyori, *Tetrahedron Lett.*, 1996, **37**, 2813–2816.
27 A. L. Monteiro, F. K. Zinn, R. F. DeSouza and J. Dupont, *Tetrahedron: Asymmetry*, 1997, **8**, 177–179.
28 G. Law and P. R. Watson, *Langmuir*, 2001, **17**, 6138–6141.
29 A. Berger, R. F. de Souza, M. R. Delgado and J. Dupont, *Tetrahedron Asymmetry*, 2001, **12**, 1825–1828.
30 P. S. Gallagher, M. P. Coffey, V. J. Krukonis and N. Klasutis, in *Supercritical Fluid Science and Technology*, ed. K. P. Johnston and J. M. L. Penninger, American Chemical Society, Washington, D. C., 1989.
31 C. J. Chang and A. D. Randolph, *AIChE J.*, 1990, **36**, 939–942.
32 A. Kordikowski, A. P. Schenk, R. M. Van Nielen and C. J. Peters, *J. Supercrit. Fluids*, 1995, **8**, 205–216.
33 C. Dariva, L. A. F. Coelho and J. V. Oliveira, *Fluid Phase Equilib.*, 1999, **160**, 1045–1054.
34 N. P. Freitag and D. B. Robinson, *Fluid Phase Equilib.*, 1986, **31**, 183–201.
35 S. D. Yeo and E. Kiran, *Macromolecules*, 1999, **32**, 7325–7328.
36 S. Sarrade, L. Schrive, D. Gourgouillon and G. M. Rios, *Separation and Purification Technology*, 2001, **25**, 315–321.
37 C. A. Thomas, R. J. Bonilla, Y. Huang and P. G. Jessop, *Can. J. Chem.*, 2001, **79**, 719–724.
38 M. A. Kane, G. A. Baker, S. Pandey, E. P. Madziarz III, D. C. Hoth and F. V. Bright, *J. Phys. Chem. B*, 2000, **104**, 8585–8591.
39 L. A. Blanchard, Z. Gu and J. F. Brennecke, *J. Phys. Chem. B*, 2001, **105**, 2437–2444.
40 S. G. Kazarian, N. Sakellarios and C. M. Gordon, *Chem. Commun.*, 2002, 1314–1315.
41 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**, 1246–1248.

Mercury(II) partitioning from aqueous solutions with a new, hydrophobic ethylene-glycol functionalized bis-imidazolium ionic liquid†

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Received 23rd January 2003
First published as an Advance Article on the web 20th March 2003

A room temperature ionic liquid containing a bis-imidazolium cation incorporating a short ethylene-glycol spacer, 1,1′-[1,2-ethanediylbis(oxy-1,2-ethanediyl)] bis[3-methyl-1*H*-imidazolium-1-yl]bis(trifluoromethanesulfonyl)imide, has been prepared from the corresponding chloride salt, and the X-ray crystal structure of the low-melting hexafluorophosphate salt has been determined. The crystal structure reveals the ether linkage to be quite flexible and to participate in strong C2–H···O hydrogen bonds leading to asymmetry. The crystal structure of the bis-imidazolium salt incorporating a decyl-spacer, 1,1′-[1,10-decyl]bis[3-methyl-1*H*-imidazolium-1-yl] hexafluorophosphate, has also been determined and displays an all-*trans* (symmetric) conformation except at the beta carbon positions where a characteristic kink is observed. Introducing the ethylene-glycol functionality dramatically increases the distribution ratio of mercury ions, but not caesium, from aqueous solution to the hydrophobic ionic liquid, and from basic solution. This is the first example of pH dependent partitioning and stripping of mercury from ionic liquid/aqueous two-phase systems. The crystal structure of the related mercury(II) carbene complex, obtained from the reaction of mercury(II) acetate with 1,1′-[oxybis(2,1-ethanediyloxy-2,1-ethanediyl)]bis[3-methyl-1*H*-imidazolium-1-yl] tosylate, containing a three-ether spacer, in acetonitrile, reveals the possibility of a carbene extraction mechanism.

Introduction

Task Specific Ionic Liquids[1] (TSILs) contain specific functionality covalently incorporated within one of the ionic components of the ionic liquid (IL), typically within the cation. The TSIL approach (either as bulk IL, or as the active component in a composite solvent) can be used to develop new ILs containing functionalized extractants by alkylation of an imidazole with agents bearing complexants in which the IL, or IL-like groups, increase the affinity of active species for the IL over a second phase (either aqueous or organic). Examples include metal complexants and extractants, CO_2-sequestering materials, and ILs incorporating pendant polyether groups used to tether IL-immobilized reagents for organic synthesis.[2] Recently, Branco and co-workers[3] have prepared a number of ether-appended ILs and have reported that these are significantly better solvents for dissolving $HgCl_2$ and $LnCl_3$ than the corresponding alkyl-substituted analogs.

Our interest in metal–ether complexants (*e.g.*, with Group 1–2 metals of relevance to electrochemistry), salt-induced phase separation and structuring in polyethylene glycol (PEG)-based aqueous biphasic systems (ABS),[4] and separation and extraction of heavy metals,[5,6] led us to investigate a range of ILs incorporating ether functionality as extraction media. Here, we report initial results for the synthesis of a new example of an IL containing the bis-imidazolium cation, 1,1′-[1,2-ethanediylbis(oxy-1,2-ethanediyl)]bis[3-methyl-1*H*-imidazolium-1-yl] (**1**), in which a proto-extractant functionality (an ethylene glycol unit) is incorporated between the two cationic groups (Fig. 1). We also report three relevant crystal structures and the partitioning behavior of Hg^{2+} and Cs^{+} to the hydrophobic IL phase from aqueous acid, base, and salt solutions.

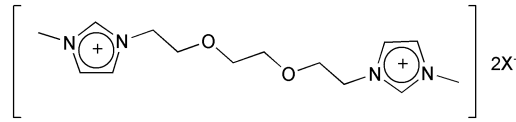

Fig. 1 Structure of the ILs prepared containing the 1,1′-[1,2-ethanediylbis(oxy-1,2-ethanediyl)]bis[3-methyl-1*H*-imidazolium-1-yl] cation: **1a** X = Cl; **1b** X = [NTf_2]; **1c** X = [PF_6].

Results and discussion

Polyethylene glycols containing quaternized terminal functions (ammonium, benzimidazolium and imidazolium salts) have previously been prepared and investigated as polymer–salt

Green Context

One of the most interesting features of ionic liquids is the very large range of properties that can be achieved even with the commonly used imidazolium cationic units. Here we see described new room temperature ionic liquids based on bis(methylimidazolium) cations involving ethylene glycol spacers. The distribution ratio for Hg^{2+} to the ionic liquid is high compared to normal alkyl-substitute/imidizolium ionic liquids although it is not optimal compared to polydentate ethers. ***JHC***

† This work was presented at the Green Solvents for Catalysis Meeting held in Bruchsal, Germany, 13–16th October 2002.

Dr Robin D. Rogers' research interests are diverse and include structural chemistry, green separation science and technology, ionic liquids, aqueous biphasic separations, dissolved metal ion separations, environmental applications, pollution prevention, pollution remediation, design and synthesis of porous solids, radiochemistry, and environmental inorganic chemistry. He is a Professor of Chemistry and Director of the Center for Green Manufacturing at UA, and Editor-in-Chief of the ACS journal Crystal Growth and Design. He has led efforts to organize the IL community, promoting effective communication of results and stimulating additional research activities by other groups. The most visible of these have been co-organization of a NATO ARW, national ACS meeting symposia on ionic liquids (221st in San Diego, 224th in Boston, and up-coming 226th in New York, Sept 2003) with Prof Ken R. Seddon and the publication of edited proceedings from these meetings. The current members of this team, including staff scientists in the Center for Green Manufacturing, postdoctoral and graduate students, have produced over 50 reviewed papers on ionic liquids research.

Members of the RDR group (UA) contributing to this paper, left to right; J. D. H., W. M. R., R. P. S., R. D. R., S. K. S., G. A. B., A. E. V. (inset).

hybrid polyelectrolytes.[7,8] The salts **1a–c** (Fig. 1), synthesized here, are the shortest discrete polyethylene oligomers of these related systems.

The 1,1′-[1,2-ethanediylbis(oxy-1,2-ethanediyl)]bis[3-methyl-1*H*-imidazolium-1-yl] cation was initially prepared as the chloride salt (**1a**) by alkylation of 1-methylimidazole with 1,2-bis(2-chloroethoxy)ethane in 1,1,1-trichloroethane. The chloride salt formed as a viscous, dense phase which was sparingly soluble in water, or CH_2Cl_2–MeCN. After drying *in vacuo*, **1a** was used directly for conversion to the corresponding bis(trifluoromethanesulfonyl)imide (**1b**, $[NTf_2]^-$) and hexafluorophosphate (**1c**, $[PF_6]^-$) salts in water. Metathesis of **1a** with an aqueous solution of $LiNTf_2$, yielded **1b** as a hydrophobic liquid. In contrast, **1c** precipitated as a low melting crystalline solid (mp 87 °C) on treating an aqueous solution of **1a** with HPF_6–NaOH.

In comparison to bis-imidazolium salts containing alkane spacer groups,[9,10] the ether linkage imparts a greater degree of flexibility (resulting in lower melting points) and increased hydrophilicity as shown by the higher equilibrium water content of **1b** (2.6 wt%) compared to ILs containing 1-alkyl-3-methylimidazolium ($[C_n mim]^+$) cations (for example 1.4 wt% in $[C_4 mim][NTf_2]$[11]).

Structural studies

Crystals of **1c** suitable for single crystal X-ray diffraction were collected by filtration, washed with water, and air dried. The cations form hydrogen-bonded dimers (Fig. 2) containing a strong intermolecular cation–cation hydrogen-bond from one imidazolium C(2)-hydrogen to an ether oxygen of the second cation (H16A···O12^b, 2.32 Å, C16–H16A···O12^b = 159°; Table 1). The second ether oxygen (O9) appears to be directed toward two possible acidic hydrogens, although the contacts are

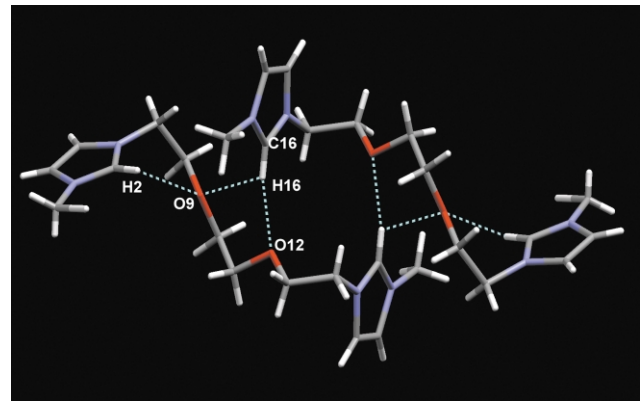

Fig. 2 Cation–cation hydrogen-bonding interactions in the crystal structure of **1c**. Addition of the ether hydrogen-bond acceptor functionality to the hydrophobic ionic liquid cation enables formation of the cation–cation hydrogen-bonded dimer by hydrogen-bonds from one acidic imidazolium C(2)–H donor to the ether-oxygens of the other cation with the ether chains adopting two opposing helices in the dimer.

long (O9^b···H16A = 2.83 Å (intermolecular) and O9···H2A = 2.89 Å (intramolecular)).

Within each dimer, the two ethylene-oxide chains form helices with opposing pitches (+ve and −ve). In common with many complexed crown ethers, the torsion angles around the O–C bonds within the chain are anti, while the torsion angles around the C–C bonds are gauche. Interestingly, the C2–N3–C7–C8 and C16–N15–C14–C13 torsion angles differ (the former being −83.8°, the latter 114.6°), perhaps reflecting the orientation necessary to bring H16A into position for its much stronger intermolecular hydrogen bond.

The intermolecular cation–cation hydrogen-bonding results in asymmetry with each ligand in the solid state structure (Fig. 3). The two anions associated with each cation are also non-equivalent. The ring hydrogen atoms (bonded to C4, C5, C18,

Table 1 Selected hydrogen bonds in the crystal structures of **1c** and **2**

1c Donor-H···Acceptor	D–H/Å	H···A/Å	D···A/Å	D–H···A/deg
C2–H2A···O9	0.95	2.89	3.092(5)	93
C2–H2A···F2		2.52	3.116(5)	121
C2–H2A···F4[a]		2.65	3.109(5)	110
C16–H16A···O12[b]	0.90	2.32	3.174(4)	159
C16–H16A···O9[b]		2.83	3.295(4)	114
2 Donor-H···Acceptor	D–H /Å	H···A /Å	D···A /Å	D–H···A /deg
C1–H1A···F6	0.95	2.32	3.266(2)	176
C2–H2A···F5[c]	0.95	2.42	3.355(2)	170
C3–H3A···F4[d]	0.95	2.70	3.406(2)	131
C3–H3A···F5[d]		2.77	3.496(2)	134

Symmetry Codes: [a] a = x, 0.5 − y, −0.5 + z [b] b = 1 − x, 1 − y, 2 − z [c] c = −x, 0.5 + y, 0.5 − z [d] d = −1 − x, 1.5 − y, 0.5 + z

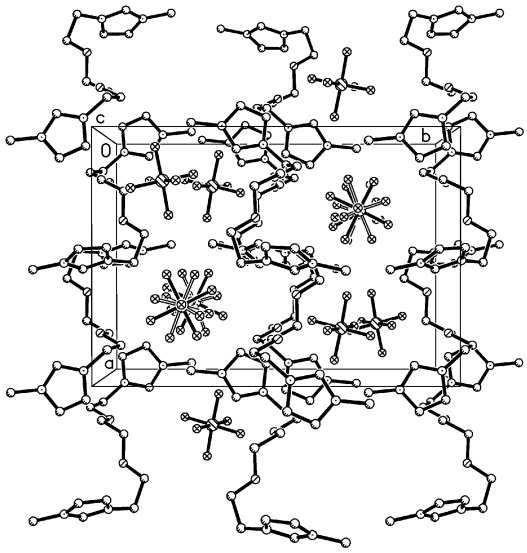

Fig. 3 Packing diagram of the crystal structure of **1c** showing the asymmetry in the cation and the two different hexafluorophosphate anions, one ordered and the second in a rotationally disordered site. (Hydrogen atoms have been removed for clarity.)

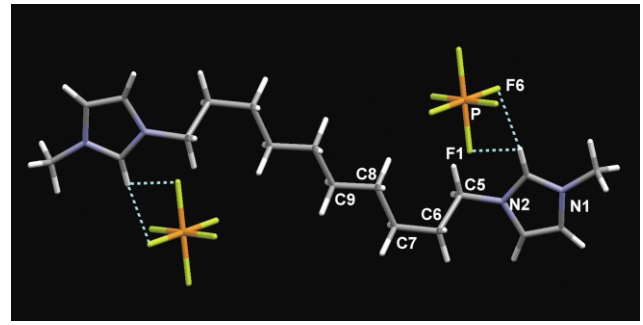

Fig. 4 Structure of 1,1′-[1,10-decyl]bis[3-methyl-1*H*-imidazolium-1-yl] hexafluorophosphate (**2**), containing an alkyl-spacer between the two imidazolium sub-units. Within the decyl chain all of the C–C–C–C (or N–C–C–C torsion angles are *anti*, except for the C5–C6–C7–C8 torsion angle which is *gauche* and gives a characteristic kink in the imidazolium's long chain alkyl substituent. The shortest contacts from the imidazolium cation to the hexafluorophosphate anions are shown.

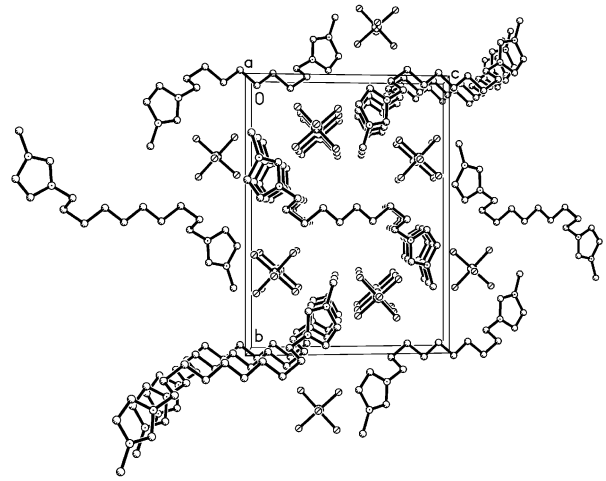

Fig. 5 Packing diagram for **2**. The main hydrogen bonding occurs between the ring hydrogen atoms and the fluorine atoms in the anions. (Hydrogen atoms have been removed for clarity.)

C19), the methyl hydrogen atoms (bonded to C6, C20) and the linker alpha hydrogen atoms (bonded to C7, C14) have many contacts indicative of weak hydrogen bonds to the two anions. The geometrically significant H···F contacts range from 2.32 to 2.9 Å. Site disorder in one of the two anions and the lack of disorder in the other suggests differences in the hydrogen-bonding scheme. The liquid state most likely also exhibits variable hydrogen-bonding and the resulting disorder could account for the unexpectedly low melting points we observe.

For comparison, the salt, 1,1′-[1,10-decyl]bis[3-methyl-1*H*-imidazolium-1-yl] hexafluorophosphate[10] (**2**, mp 71 °C), containing two imidazolium units linked with an alkyl-spacer, was synthesized and the crystal structure obtained. In contrast to **1c**, there is no association of cations in the crystal structure of **2**, the central methylene groups of the alkyl-spacer in the cation have an all-*trans* conformation, while a characteristic kink is observed at the C(5)–C(6) position, beta to the imidazolium ring as shown in Fig. 4.

The configuration of the decyl-spacer in **2** (Fig. 5), allows the cations to pack in symmetric arrangements that maximize close contacts between the ring hydrogen atoms and the anions (Table 1). Thus, the most acidic position and one of the remaining ring hydrogen atoms form single hydrogen bonds to F atoms, while the third hydrogen atom forms a bifurcated interaction with two fluorine atoms on a single anion. Each head group thus forms hydrogen bonds to three different anions. The methyl (C4) and decyl alpha carbon (C5) hydrogen atoms have additional contacts with the anions ranging from 2.58 to 2.9 Å. The lack of hydrogen bond acceptors in the cation results in the dramatically different solid state structure, and may have additional implications in the liquid state which require further investigation.

Partitioning studies

The hydrophobic room temperature IL, **1b**, was utilized in contact with several aqueous phases to demonstrate the

potential for using simple glycol-containing ILs as metal complexants and extractants. It is important to note here, that despite introducing some hydrophilic functionality into the IL cation *via* the ether groups, the $[PF_6]^-$ salt when melted and the liquid $[NTf_2]^-$ salts remain relatively hydrophobic.

Crown ethers and polyethylene glycols (PEGs) are reasonable ligands for Hg^{2+} coordination.[12] Even short chain triethylene glycol can coordinate $HgCl_2$ as the crystal structure shown in Fig. 6 demonstrates. The bidentate coordination of one ethylene oxide unit to mercury in the crystal structure of $[(HgCl_2)_3$(triethylene glycol)] provides at least some evidence that the same unit in **1b** may be capable of coordination despite its short length.

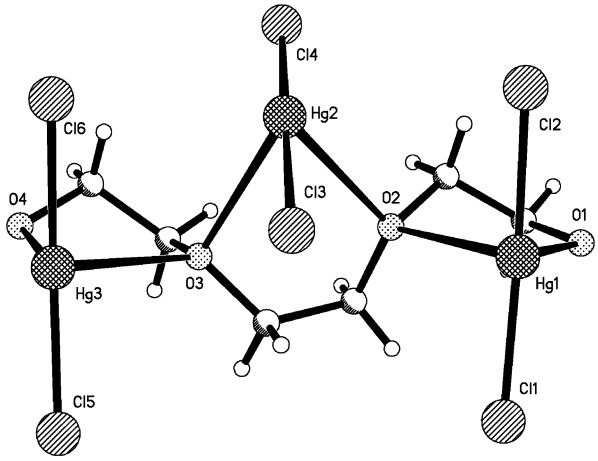

Fig. 6 Bidentate coordination of triethylene glycol to three $HgCl_2$ units in $[(HgCl_2)_3$(triethylene glycol)]. (This figure was produced from the coordinates provided in reference 12.)

We have attempted the use of short and long chain PEGs in the hydrophobic IL $[C_4mim][PF_6]$ as an extractant for Hg^{2+}. The radiochemically determined distribution ratios for Hg^{2+} were all rather low (Fig. 7) and only exceed unity when PEG oligomers with molecular weight greater than 200 (*i.e.*, larger than tetraethylene glycol) were used, although the *D* values did increase with the more hydrophobic polypropylene glycol as the extractant.

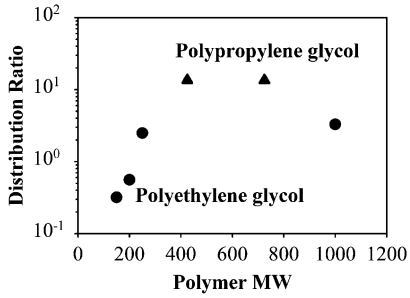

Fig. 7 $^{203}Hg^{2+}$ distribution ratios in $[C_4mim][PF_6]$–water mixtures where the IL phase initially contained 3 wt% polyethylene glycol (●) or polypropylene glycol (▲), as a function of polymer molecular weight.

Further studies (Fig. 8) on the partitioning of a ^{14}C-labeled polyethylene glycol-3400 indicated that the loss of the water-soluble PEG to the aqueous phase would be a major concern. Note that the data in Fig. 8 suggest higher distribution ratios for the PEG moiety as the hydrophobicity of the IL increases, however, the highest *D* observed (*ca.* 30) is still too low for an effective extractant.

It was hoped, therefore, that the new TSIL, **1b**, in which the extractant moiety is incorporated as part of the IL cationic component would drastically reduce leaching to the aqueous

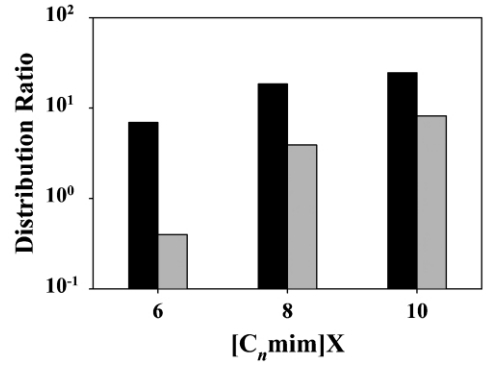

Fig. 8 Distribution ratios for ^{14}C-labelled PEG-3400 in $[C_n$mim]X IL–water mixtures, containing $[PF_6]$ (black) and $[BF_4]$ (grey) anions.

phase. Since hydrophobicity of the IL was not compromised by adding the ethylene oxide linker, the distribution ratios for Cs^+ and Hg^{2+} were determined as a function of aqueous phase nitric acid, hydrochloric acid, sodium hydroxide, sodium nitrate, and sodium chloride concentration (Fig. 9).

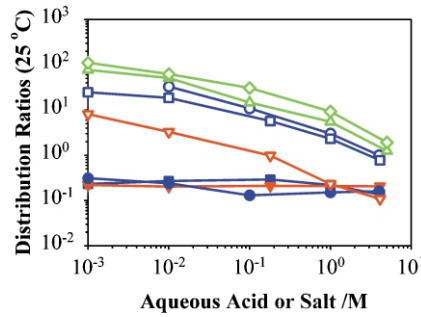

Fig. 9 Distribution ratios at 25 °C for $^{137}Cs^+$ (solid symbols) and $^{203}Hg^{2+}$ (open symbols) between **1b** from aqueous phases as a function of aqueous HNO_3 (○), NaOH (▽), $NaNO_3$ (□), HCl (◇), and NaCl (△) concentration. The colors denote the anion type in the aqueous phase, chloride (green), nitrate (blue), and hydroxide (red).

The distribution ratios between **1b** and pure H_2O for Cs^+ and Hg^{2+} are 0.33 and 54, respectively. The Cs^+ distribution ratios remain essentially invariant between 0.13–0.33 with the concentration of acid, base, or salt in the aqueous phase, perhaps indicating the inability of the short PEG moiety to completely wrap up and dehydrate the large, hard Cs^+ coordination sphere. This is consistent with data for other hydrophobic IL-aqueous systems in which Cs^+ remains in the aqueous phase in the absence of complexants (*e.g.*, crown ethers).[13]

In contrast to Cs^+ data, the distribution ratio for Hg^{2+} in the **1b**-aqueous systems is relatively high (54 compared to 0.81 for $[C_4mim][PF_6]$–aqueous[5]). These values are comparable with results obtained previously in IL–aqueous systems containing specific Hg^{2+}-complexing extractants either dissolved in the IL,[5] or incorporated as a task specific function.[6]

The distribution ratios for Hg^{2+} between **1b** and the various aqueous phases (Fig. 9) show a marked anion concentration dependence. The distribution coefficient for Hg^{2+} to the IL phase was greatest from chloride-containing aqueous phases, and decreases in the order $Cl^- > NO_3^- > OH^-$. The partitioning of Hg^{2+} to the IL phase **1b** decreases with increasing ion concentration in the aqueous phase with no apparent pH dependence; the distribution coefficients decrease at both high and low pH, and also at high salt concentrations.

The dependency of the distribution ratio on extractant concentration was determined by using **1b** as an extractant in 1-decyl-3-methylimidazolium bis(trifluoromethanesulfonyl)imide as the bulk IL phase (D_{Hg} in the absence of extractant = 0.7). For Hg^{2+} extraction from nitric acid solutions, a line of slope unity was obtained, indicating partitioning at a 1:1

Hg^{2+}:extractant ratio (Fig. 10). In general, Hg^{2+} ions form high coordination number complexes with multidentate crown-ethers and PEGs,[12] however, rare examples of Hg^{2+} with a single bidentate glycol-containing ligand in the metal coordination shell have been reported (see, for example, Fig. 6).[12,14]

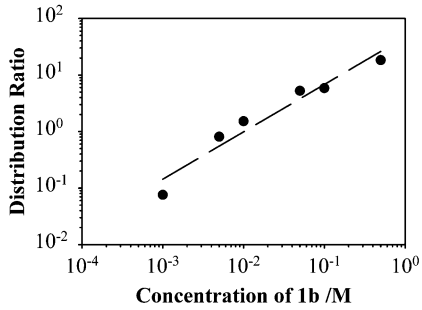

Fig. 10 Distribution ratios for $^{203}Hg^{2+}$ as a function of extractant concentration using **1b**, between $[C_{10}mim][NTf_2]$ IL and 0.001 M aqueous HNO_3.

The response to nitric acid concentration is consistent with that observed in IL-aqueous systems with added extractants such as crown ethers,[15,16] however, the mechanism for extraction proposed when the neutral complexant is dissolved in the IL phase (cation transfer and exchange[16]) can not be so easily rationalized when the extractant functionality and the potential cation-exchange unit (imidazolium moiety) are covalently bound. One possible mechanism would be the formation of a Hg–carbene complex[17] through deprotonation of the imidazolium moieties and coordination to the Hg^{2+} ion.

Polyether-linked bis-imidazolium cations can readily form crystalline 1:1 Hg–carbene complexes in nonaqueous solvents and we have illustrated this by preparing and structurally characterizing a dihydrate complex (**3**, Fig. 11) obtained from

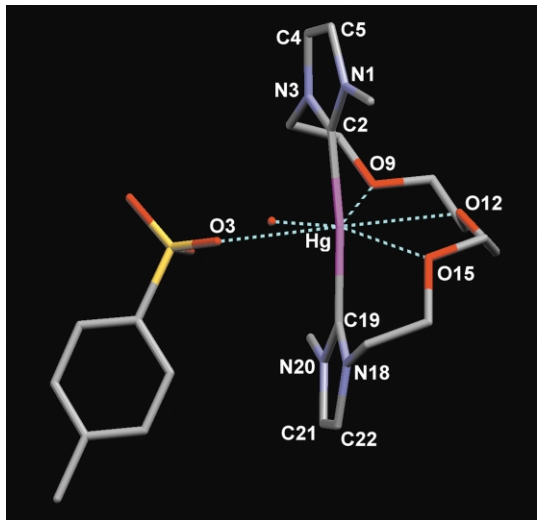

Fig. 11 The mercury atom environment in the Hg-carbene complex **3**. (Hydrogen atoms are omitted for clarity.)

the reaction of $Hg(OAc)_2$ and a triether-linked bis-imidazolium salt, 1,1′-[oxybis(2,1-ethanediyloxy-2,1-ethanediyl)]bis[3-methyl-1*H*-imidazolium-1-yl] tosylate in acetonitrile. The Hg atom has a seven-coordinate environment, showing approximately linear C–Hg–C bonds (Hg–C = 2.054(6) and 2.055(6) Å; C–Hg–C = 173.1(2)°). The metal occupies a pocket within the helical cavity formed by the ether-bis(carbene) ligand with Hg–O distances of 2.839(5), 2.964(5), and 2.938(5) Å. The remaining face of the metal is capped by one tosylate anion (Hg–O(tosylate) 2.924(6) Å) and a water molecule (H_2O–Hg 3.010(5) Å). Interestingly, the *N*-heterocyclic rings (N18–C19–N20–C21–C22) of adjacent ligands interact via head-to-tail π-stacking (ring-ring separation 3.46 Å) reminiscent of the stacking observed in the crystal structures of free imidazolium salts.

The Hg–O distances are all within the range of such distances observed in a series of HgX_2 crown ether and PEG complexes.[12] The Hg-carbene distances are also normal (see, for example, the 2.086 Å average in bis[(1-methyl-3-pyrimidinyl)imidazoline-2-ylidene]mercury(II) bis(hexafluorophosphate) and the 2.060 Å in bis[2-(1,3-diphenyl)imidazolyl]mercury(II) perchlorate.)[18]

The hydrogen bonding in **3** illustrates what happens when strong acceptors are present. Both water molecules make strong single hydrogen bonds to the tosylate oxygen atoms with H–O–H···O(anion) contacts ranging from 1.94 to 2.31 Å and H–O–H···O(anion) angles ranging from 162 to 171°. Three of the four ring protons also hydrogen bond to the anions (H···O = 2.43 to 2.72 Å; C–H···O = 142 to 154°). The fourth ring proton makes a bifurcated hydrogen bond to both an anion (H···O = 2.57 Å; C–H···O = 130°) and to the non-coordinated water molecule (H···O = 2.80 Å; C–H···O = 134°).

Despite the crystallographic evidence above, carbene formation is base-promoted, while the partitioning results in the presence of base (NaOH data in Fig. 9) show a decrease in distribution ratio under highly basic conditions which does not support the formation of a promoted metal–carbene complex in aqueous media. Notably, the distribution ratios in the presence of NaOH show that Hg^{2+} partitioning to the aqueous phase is favored ($D < 1$) when the hydroxide concentration is increased above *ca.* 0.5 M. *This is the first example where mercury can be partitioned to an IL, and then stripped back to an aqueous phase using a pH, or salt concentration shift.*

Thus, the extraction mechanism is not clear, and requires further investigation. Mercury(II) ions have a strong tendency to form complexes, principally linear two-coordinate, or tetrahedral four-coordinate systems. In aqueous solution, speciation of Hg(II) complexes leads to the formation of a range of species following the equilibrium shown in the equation:

$$Hg^{2+} \rightleftharpoons HgX^{+} \rightleftharpoons HgX_2 \rightleftharpoons [HgX_3]^{-} \rightleftharpoons [HgX_4]^{2-}$$

At high $[X]^-$ concentration, the anionic species to the right of the equilibrium predominate, for example, in 1 M Cl^-, $[HgCl_4]^{2-}$ is the predominant species, whereas at 10^{-1} M Cl^-, $HgCl_2$, $HgCl_3^-$, and $HgCl_4^{2-}$ are in approximately equal concentrations.[19] It seems likely that neutral HgX_2 compounds are partitioned to the IL phase, by complexation in a four-coordinate HgX_2O_2 environment coordinated to the IL ether-oxygens.

The distribution of metal ions (in this case, Hg^{2+}) between the two phases depends on a number of factors, including ionic strength, with an additional anion dependence and binding of the metal species to the extractant. The distribution coefficients for Hg^{2+} to **1b** are much higher than with generic IL–aqueous systems which were doped with differing MW PEG oligomers as extractants (Fig. 7) and also PEG-ABS systems in the absence of extra complexing ions.[20] The ability to introduce, and maintain PEG-like functionality in a hydrophobic IL phase without leaching of water soluble PEG leads to an enhancement in partitioning.

Conclusions

Simple ILs containing two alkylimidazolium groups in the cation portion, linked by a diether spacer have been prepared. The salt containing hexafluorophosphate anions is a crystalline solid, whereas when the anions are substituted with bis(trifluoromethanesulfonyl)imide, a hydrophobic liquid is obtained. The crystal structure of the hexafluorophosphate salt shows that

introduction of the ether groups which contain hydrogen-bond acceptor sites into the cation allows cation–cation hydrogen bonding from an acidic C(2)-hydrogen on one imidazolium ring to the ether oxygen atoms. It is worth noting that the distribution ratio for Hg^{2+} to the IL is high compared to ILs containing only alkyl-substituents,[5] for which, the distribution ratios are all less than 1. This indicates the validity of the TSIL concept in preparing this simple extractant, however, both the complexing environment and size of the chelating functions (only bidentate) in these ionic liquids are not optimal for metal extraction in contrast to polydentate ethers (either PEG or crown-ethers) which can more easily 'wrap-up' metal ions. Extending the PEG length, or introducing other chelating atoms (S or N) could be anticipated to yield, through synthetically simple protocols, an expanded range of TSIL extractants that can be simply prepared and utilized for selective complexation and extractions; but enhanced complexation constants between the IL cation and metals may also hinder stripping to recover the metals.

Experimental

1,2-Bis(2-chloroethoxy)ethane was purchased from Fluka, $LiNTf_2$ was a gift from 3M and HPF_6 was a gift from Ozark Fluorine Specialties (Tulsa, OK). All other reagents were purchased from Aldrich (Milwaukee, WI). Chemicals were used as received, all aqueous solutions were prepared with deionized water, purified with a Barnsted deionization system (Dubuque, IA) and polished to 18.3 MΩ cm^{-1}. Aqueous solutions of HNO_3, $NaNO_3$, HCl, NaCl, and NaOH were prepared as molar concentrations by transferring a known amount of material to a volumetric flask and diluting to the specified volume with deionized water. $^{203}HgCl_2$ and $^{137}CsCl$ were obtained from Amersham Life Sciences (Arlington Heights, IL). Gamma-ray emission analysis was used for all isotopes and carried out on a Packard Cobra II Auto-Gamma Spectrometer (Packard Instrument Company, Downers Grove, IL). Distribution experiments were performed at 25 °C.

Distribution ratios for $^{203}Hg^{2+}$ and $^{137}Cs^{+}$ were determined by contacting 1 mL of **1b** and 1 mL of an appropriate aqueous phase followed by vortexing (2 min) and centrifuging (2000 *g*, 2 min) to equilibrate the phases. Addition of the metal ion tracer (*ca*. 0.005 μCi, 5 μL of the chloride form of each) was followed by two intervals of vortexing (2 min) and centrifuging (2000 *g*, 2 min) to ensure that the phases were fully mixed and separated. The phases were separated and dispensed into shell vials from which 100 μL of each phase was removed for radiometric analysis. Since equal volumes of both phases were removed for analysis, the distribution ratio for the metal ions (*D*) was determined as the ratio of radioactivity in the lower (IL) phase to the upper (aqueous) phase. Each experiment was done in duplicate and the results agreed to within 5%.

Synthesis of 1,1′-[1,2-ethanediylbis(oxy-1,2-ethanediyl)]bis-[3-methyl-1*H*-imidazolium-1-yl] chloride (1a)

A solution of 1,2-bis(2-chloroethoxy)ethane (100 g, 0.535 mol) and 1-methylimidazole (87.75 g, 1.07 mol) in 1,1,1-trichloroethane (150 mL) was heated at 80 °C for 2 days, the ionic liquid formed as a viscous, dense phase. After removal of the upper organic phase, residual solvent was removed under reduced pressure on a rotary evaporator to yield a viscous gum, slightly soluble in water and in CH_2Cl_2. The dichloride salt was used directly, without further purification to prepare **1b** and **1c**.

Metathesis to the bis(trifluorosulfonyl)imide salt (1b)

1a (52.0 g, 0.148 mol) was dissolved in water (200 mL) and a solution of $Li[NTf_2]$ (54.6 g, 0.22 mol) in water (100 mL) was added. The mixture was stirred for 10 min, then allowed to settle into two phases. The lower, ionic liquid phase was collected, washed with water (3 × 75 mL), dissolved in CH_2Cl_2 (100 mL), and residual water was removed by decantation. The organic phase was dried over anhydrous $MgSO_4$, filtered, and the organic solvents then evaporated under reduced pressure at 75 °C to give the product as a pale brown liquid (71 g, 0.09 mol, 82% conversion based on the anion). T_g −69 °C (DSC, heating), T_{dec} 400 °C (TGA 10 °C min^{-1} under N_2). ^1H (500 MHz, DMSO-d_6) 3.57 (2H, s, O–CH_2), 3.77 (2H, t, O–CH_2), 3.89 (3H, N–CH_3), 4.36 (2H, t, N–CH_2), 7.64, 7.66 (2H, C(4,5)–*H*), 9.07 (1H, C(2)–*H*). ^{13}C 35.69 (N–CH_3), 48.92 (N–CH_2), 68.22 (CH_2–O), 69.51 (CH_2–O), 119.7 (q CF_3), 122.70, 123.37 (*C*(4,5)), 136.87 (*C*(2)).

Metathesis to the hexafluorophosphate salt (1c)

To a solution of **1a** (2 g, 7.1 mmol) in a water (20 mL) cooled ice-bath, was added dropwise, with rapid stirring, hexafluorophosphoric acid (64 wt% solution in H_2O). *Caution! Adequate ventilation is required, HPF_6 fumes readily in moist air liberating HF*. A solution of NaOH in water was added to neutralize the aqueous acid to pH 7. The resulting hexafluorophosphate salt precipitated as colorless crystals (mp 87 °C) which were collected by filtration, washing with distilled water, and then air dried. ^1H (500 MHz, DMSO-d_6) 3.54 (2H, s, O–CH_2), 3.74 (2H, t, O–CH_2), 3.86 (3H, N–CH_3), 4.32 (2H, t, N–CH_2), 7.67, 7.68 (2H, C(4,5)–*H*), 9.03 (1H, C(2)–*H*). ^{13}C 35.72 (N–CH_3), 48.72 (N–CH_2), 68.12 (CH_2–O), 69.32 (CH_2–O), 122.62, 123.38 (*C*(4,5)), 136.72 (*C*(2)).

Synthesis of 1,1-[1,10-decyl]bis[3-methyl-1*H*-imidazolium-1-yl] hexafluorophosphate (2)

The hexafluorophosphate salt was prepared by metathesis from an aqueous solution of the chloride salt with aqueous hexafluorophosphoric acid. After minimal stirring of the resulting molten salt-aqueous biphasic mixture, the hexafluorophosphate salt crystallized. Crystals were collected, washed with deionized water and air dried. Mp (71 °C) and ^1H NMR were comparable with those reported in ref 10.

Synthesis of the mercury–carbene complex (3)

1,1′-[Oxybis(2,1-ethanediyloxy-2,1-ethanediyl)]bis[3-methyl-1*H*-imidazolium-1-yl] tosylate was prepared by the reaction of triethylene glycol ditosylate and 1-methylimidazole (1 : 2 molar ratio) in toluene, heated at reflux for 2 days. The product was formed as a vicous dense phase. After removal of the upper organic phase, the residual solvent was removed under reduced pressure on a vacuum line yielding the solid ditosylate salt, which was used directly to form the mercury–complex **3**. ^1H (360 MHz, DMSO-d_6) 9.33 (1H, s, C(2)*H*), 7.95, 7.920 (2H, 2×s, C(4,5)*H*), 7.74 (2H, d, OTs), 7.35 (2H, d, OTs), 4.55 (2H, t, N–CH_2), 4.05 (3H, s, N–CH_3), 3.96 (2H, t, NCH_2–CH_2–O), 3.73, 3.67 (4H, *aa′bb′*, OCH_2CH_2O), 2.50 (3H, s, OTs).

The tosylate salt (0.50 g, 0.8 mmol) was dissolved in acetonitrile (10 mL) and a solution of mercury(II) acetate (0.26 g, 0.8 mmol) in acetonitrile (10 mL) was added. The mixture was heated at reflux for 2 days. The resulting solution was then allowed to cool to room temperature. The acetonitrile was then allowed to slowly evaporate over a two-day period which resulted in the formation of small poor quality crystals which were taken, dissolved in CH_2Cl_2 (10 mL) and layered with pentane (10 mL) and after two days good quality crystals of the carbene complex (**3**) were obtained.

X-Ray structure of 1c

A colorless single crystal (0.22 × 0.13 × 0.06 mm) of **1c** was obtained on metathesis of **1a** with HPF_6–NaOH in water. Diffraction data were collected on a Siemens CCD area detector-equipped diffractometer with Mo Kα (λ = 0.71073 Å) radiation at −100 °C using a stream of nitrogen gas. The crystal structure was solved by direct methods using the SHELXTL software package. All non-hydrogen atoms were anisotropically refined and all hydrogen atoms were located using difference Fourier maps and isotropically refined. *Crystal data for* **1c**: formula $C_{14}H_{24}F_{12}N_4O_2P_2$, *Fw* = 570.31, monoclinic, *a* = 11.761(4), *b* = 16.685(6), *c* = 11.864(4) Å, β = 90.504(7)°, *V* = 2328.0(15) Å^3, *T* = 173 K, space group $P2_1/c$, Z = 4, μ(Mo–Kα) = 0.302 mm^{-1}, Reflection collected 5523, Independent/observed reflections 3168 (R_{int} = 0.0220)/ 2210 ($I > 2\sigma(I)$), R_1 = 0.0458, wR_2 = 0.1165 ($I > 2\sigma(I)$ data).

X-Ray structure of 2

A colorless single crystal of **2** (0.15 × 0.12 × 0.10 mm) was obtained by recrystallization from methanol–water. Diffraction data were collected and the crystal structure was solved as above. All non-hydrogen atoms were anisotropically refined. Hydrogen atoms were placed in calculated positions and allowed to ride on the bonded carbon atoms. *Crystal data for* **2**: formula $C_{18}H_{32}F_{12}N_4P_2$, *Fw* = 594.42, monoclinic, *a* = 6.4611(2), *b* = 16.5436(5), *c* = 12.1828(4) Å, β = 99.445(1)°, *V* = 1284.56(7) Å^3, *T* = 173 K, space group $P2_1/c$, *Z* = 2, μ(MoKα) = 0.271 mm^{-1}, Reflections collected 8031, Independent/observed reflections 2990 (R_{int} = 0.0149)/ 2639 ($I > 2\sigma(I)$), R_1 = 0.0364, wR_2 = 0.0965 ($I > 2\sigma(I)$ data).

X-Ray structure of 3

A colorless single crystal (0.23 × 0.16 × 0.10 mm) of **3** was obtained by recrystallization from dichloromethane–pentane. Diffraction data were collected and the structure refined as above. All non-hydrogen atoms were anisotropically refined and all hydrogen atoms with the exception of the methyl hydrogen atoms were located using difference Fourier maps and isotropically refined. Methyl hydrogen atoms were refined as a rigid group using a riding model. *Crystal data for* **3**: formula $C_{30}H_{44}HgN_4O_{11}S_2$, *Fw* = 901.40, triclinic, *a* = 10.086(3), *b* = 12.459(3), *c* = 15.204(4) Å, α = 83.209(4), β = 84.160(4), γ = 67.666(5)°, *V* = 1751.4(8) Å^3, *T* = 173 K, space group *P*1, *Z* = 2, μ(Mo–Kα) = 4.576 mm^{-1}, Reflections collected 7935, Independent/observed reflections 5002 (R_{int} = 0.0407)/ 4540 ($I > 2\sigma(I)$), R_1 = 0.0369, wR_2 = 0.0895 ($I > 2\sigma(I)$ data). CCDC reference numbers 202389–202391. See http://www.rsc.org/suppdata/gc/b3/b300971h/ for crystallographic data in .cif or other electronic format.

Acknowledgments

This research has been supported by the U.S. Environmental Protection Agency's STAR program through grant number R-82825701-0. (Although the research described in this article has been funded in part by EPA, it has not been subjected to the Agency's required peer and policy review and therefore does not necessarily reflect the views of the Agency and no official endorsement should be inferred.) Additional support was provided to the Center for Green Manufacturing from the National Science Foundation Grant EPS-9977239 and the Environmental Management Science Program of the Office of Environmental Management, US Department of Energy, Grant DE-FG07-01ER63296.

References

1 A. E. Visser, R. P. Swatloski, W. M. Reichert, R. D. Rogers, R. Mayton, S. Sheff, A. Wierzbicki and J. H. Davis, Jr., *Chem. Commun.*, 2001, 135; E. D. Bates, R. D. Mayton, I. Ntai and J. H. Davis, Jr., *J. Am. Chem. Soc.*, 2002, **124**, 926.
2 J. Fraga-Dubreuil, M.-H. Famelart and J. P. Bazureau, *Org. Proc. Res. Devel.*, 2002, **6**, 374.
3 L. C. Branco, J. N. Rosa, J. J. M. Ramos and C. A. M. Afonso, *Chem. Eur. J.*, 2002, **8**, 3671.
4 H. D. Willauer, J. G. Huddleston and R. D. Rogers, *Ind. Eng. Chem. Res.*, 2002, **41**, 2591.
5 A. E. Visser, R. P. Swatloski, S. T. Griffin, D. H. Hartman and R. D. Rogers, *Sep. Sci. Technol.*, 2001, **36**, 785.
6 A. E. Visser, R. P. Swatloski, W. M. Reichert, R. Mayton, S. Sheff, A. Wierzbicki, J. H. Davis, Jr. and R. D. Rogers, *Env. Sci. Tech.*, 2002, **36**, 2523.
7 N. Yoshikazo, K. Ito and H. Ohno, *Solid State Ionics*, 1998, **113–115**, 199.
8 M. Ono, K. Wariishi, T. Yasuda and C. Qian, US Pat. Appl., 2002, US 20020055046.
9 R. S. Varma and V. V. Namboodiri, *Chem. Commun.*, 2001, 643.
10 A. B. McEwan, World Pat., WO 01/04097, 2001.
11 P. Bonhôte, A.-P. Dias, N. Papageorgiou, K. Kalyanasundaram and M. Grätzel, *Inorg. Chem.*, 1996, **35**, 1168.
12 R. D. Rogers, A. H. Bond and J. L. Wolff, *J. Coord. Chem.*, 1993, **29**, 187.
13 A. E. Visser, R. P. Swatloski, W. M. Reichert, S. T. Griffin and R. D. Rogers, *Ind. Eng. Chem. Res.*, 2000, **39**, 3596.
14 K. Kubo, N. Kato, A. Mori and H. Takeshita, *Heterocycles*, 2000, **53**, 535.
15 S. Dai, Y. H. Ju and C. E. Barnes, *J. Chem. Soc., Dalton Trans.*, 1999, 1201.
16 M. L. Dietz and J. A. Dzielawa, *Chem. Commun.*, 2001, 2124.
17 W. Herrmann and C. Köcher, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 2162; J. C. C. Chen and I. J. B. Lin, *J. Chem. Soc., Dalton Trans.*, 2000, 839.
18 Data from the Cambridge Structural Database, F. H. Allen, *Acta Cryst.*, 2002, **B58**, 380.
19 F. A. Cotton and G. Wilkinson, *Advanced Inorganic Chemistry*, Fifth Edition, Wiley-Interscience, New York, 1988, p 612.
20 R. D. Rogers and S. T. Griffin, *J. Chromatogr. B, Biomed. Sci. Appl.*, 1998, **711**, 277.

How hazardous are ionic liquids? Structure–activity relationships and biological testing as important elements for sustainability evaluation†

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Received 3rd December 2002
First published as an Advance Article on the web 10th March 2003

For ionic liquids only few toxicological and/or ecotoxicological data are available until now. A strategy is presented which aims at an environmental risk assessment of chemicals, using a combination of structure–activity relationships (SAR), toxicological and ecotoxicological tests and modelling. The parts "test-kit-concept" and "multidimensional risk analysis" are described in detail by means of selected imidazolium ionic liquids. The iterative process of this strategy offers a tool for sustainable product design.

Prof. Dr. B. Jastorff was born in 1942. He studied chemistry at the University of Kiel starting in 1962 and obtained his PhD degree in 1970. Until 1973 he was research assistant at the Max-Planck-Institute for experimental medicine in Göttingen. Since 1973 he has been Professor at the University of Bremen, from 1996 to 2002 he served as Managing Director of the UFT Center of Environmental Research and Technology. His international collaborations led to guest professorships in The Netherlands, Poland and Romania, a Dr. h.c. from the University of Timisoara, Romania, and a Medal of Merit of the Medical University of Gdansk. He is head of the UFT Department of Bioorganic Chemistry, closely cooperating within the interdisciplinary UFT unit "Risk Research for Man and the Environment".

† This work was presented at the Green Solvents for Catalysis Meeting held in Bruchsal, Germany, 13–16th October 2002.

Introduction

Ionic liquids are a fascinating group of new chemicals with the potential to improve development in organic chemistry and chemical technology,[1,2] stimulating a lot of research fields. Over the past few decades the number of publications concerning ionic liquids has increased substantially.[3] However, until now only few toxicological and/or ecotoxicological data are available for this group of chemicals. More information is needed to assess ionic liquids with regard to sustainability and to the principles of green chemistry. An adequate product design for this promising group of chemicals should consider not only technological needs but also toxicological and ecotoxicological risks. Fig. 1 depicts three ways to look at the structural elements of a substance. The "Technicophore" comprises structural elements which are mandatory for a technical application (*e.g.* function, synthesis, extraction). "Toxicophore" defines elements associated with risk for man

Green Context

The development of ionic liquids as non-volatile solvents promises a group of solvents for synthesis whose dispersal into the environment should be more readily controlled and minimised. But how problematic are they if they do get into the environment? This article discusses the toxicity and ecotoxicity of ionic liquids using structure–activity relationships. Such tools can be used to aid the rational design of optimal solvents from a technical and environmental perspective. ***DJM***

 DOI: 10.1039/b211971d

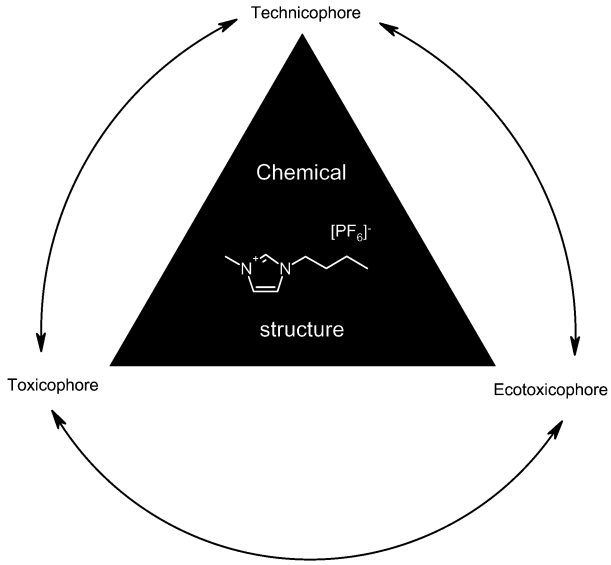

Fig. 1 Aspects of structural elements of chemicals to be optimized within a process of sustainable product design.

and "Ecotoxicophore" correspondingly elements associated with risk for the environment.

In an iterative process the technological needs have to be reconciled with a minimization of hazards for man and the environment. Here we report our strategy to identify the toxic and ecotoxicological potential of structural elements comprising ionic liquid structures and show the first results in the form of a preliminary comparative risk assessment of selected ionic liquids. Our strategy aims at an environmental risk assessment of chemicals, using a combination of structure–activity relationships (SAR), toxicological and ecotoxicological tests and modelling. Ionic liquids are a chemically diverse group of substances with a high potential for technical application which makes them an ideal model group for applying our strategy for sustainable design of chemicals.

In order to improve the data basis for the assessment of sustainability we formed a cooperation network including chemists, biologists, ecologists and epidemiologists. According to the "test-kit-concept" developed first for nucleotide analogues,[4] specific compounds are synthesized in a first step. Furthermore physical and chemical properties of all these compounds are determined and toxicological as well as ecotoxicological data are generated utilizing test systems on different biological complexity levels (*e.g.* enzymes, cells, organisms, mesocosm studies).

1. A multidisciplinary working group has been established within the "Centre of Environmental Science and Environmental Technology (UFT)". Due to cooperation with external partners the expertise was successfully extended (*e.g.* synthesis, physico-chemical and chemical properties, additional biological test systems).

2. To understand properties and activities of chemicals, we are using a rational approach of thinking in terms of structure–activity relationships (SAR).[5]

3. A theoretical prediction algorithm for presumed metabolites in biological systems is included in our approach.[6]

4. The "test battery ecotoxicity/toxicity" allows a systematic evaluation of (eco)toxicological properties of chemicals on biological systems of different complexity.

5. The findings from our own investigations are combined with information gained from literature in order to establish the process of multidimensional risk analysis.[7,8]

The interdisciplinary research unit "Risk Research for Man and the Environment" which is part of the "Centre of Environmental Research and Environmental Technology" (http://www.uft.uni-bremen.de) employs three infrastructural units:

1. SAR-QSAR
2. Analytics
3. Test battery ecotoxicity/toxicity

In the following, strategic concepts and first results obtained by these units are reported.

First the structural formula of a chemical has to be evaluated systematically to understand the structure–activity relationships. Applying an algorithm, the following properties (Table 1) can be obtained:

Table 1 Qualitative and semiquantitative information that can be gathered from every chemical structure[5]

1	Atom types present
2	Bond types present
3	Hybridisation of all atoms
4	Location of non-bonding electron pairs
5	Steric hindrance and conformational freedom
6	Possibility for geometric isomerism
7	Chirality
8	Ionic molecular interaction potential
9	Local dipole moments
10	Hydrophobic molecular interaction potential
11	Hydrogen bond donor potential
12	Hydrogen bond acceptor potential
13	π–π-bond interaction potential (charge transfer interaction potential)
14	Ring systems
15	Dissociating functional groups and estimated pK_a-values
16	Functional groups which promote prototropic shift
17	All other functional groups and their potential reactions

Evaluation of these properties opens the way to understand much of life in rational terms because it is expressed in the language of chemistry.[9]

Fig. 2 shows four important classes of cations for ionic liquids. It is obvious that the variability of the residues (R_1, R_2, R_3, R_4) in connection with the choice of different anions will result in a tremendous number of possible compounds. A theoretical analysis of these chemical structures already allows a differentiation (according to the ring structures, *e.g.* imidazolium-component *versus* pyridinium-component or different central atoms, *e.g.* phosphorus *versus* nitrogen).

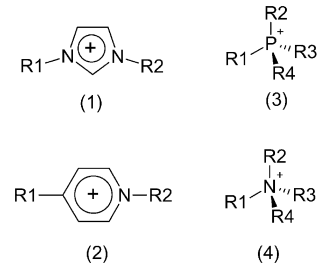

Fig. 2 Four important classes of cations for ionic liquids: (1) imidazolium, (2) pyridinium-, (3) phosphonium-, (4) ammonium-class.

The first target class we concentrated on was imidazolium derivatives (Fig. 3) of ionic liquids which exemplify our way of analysis.

The central imidazolium ring is a delocalized aromatic system with high electron acceptor potential. Therefore, the nitrogen atoms are not able to form any hydrogen bonds. The system is very rigid and sterically inflexible. A methyl group in position R_1 does not change this sterically stable state. In contrast, elongation of residue R_2 (C_4-chain, C_{10}-chain) leads to a continuous increase of flexibility implying more conformational freedom. The R_2-residue of 2-phenylethyl-3-methylimidazolium chloride ([2-phenylethyl-mim][Cl]) contains an additional aromatic system. The phenyl ring shows a high electron density including electron donor potentials. Lipophilic parts

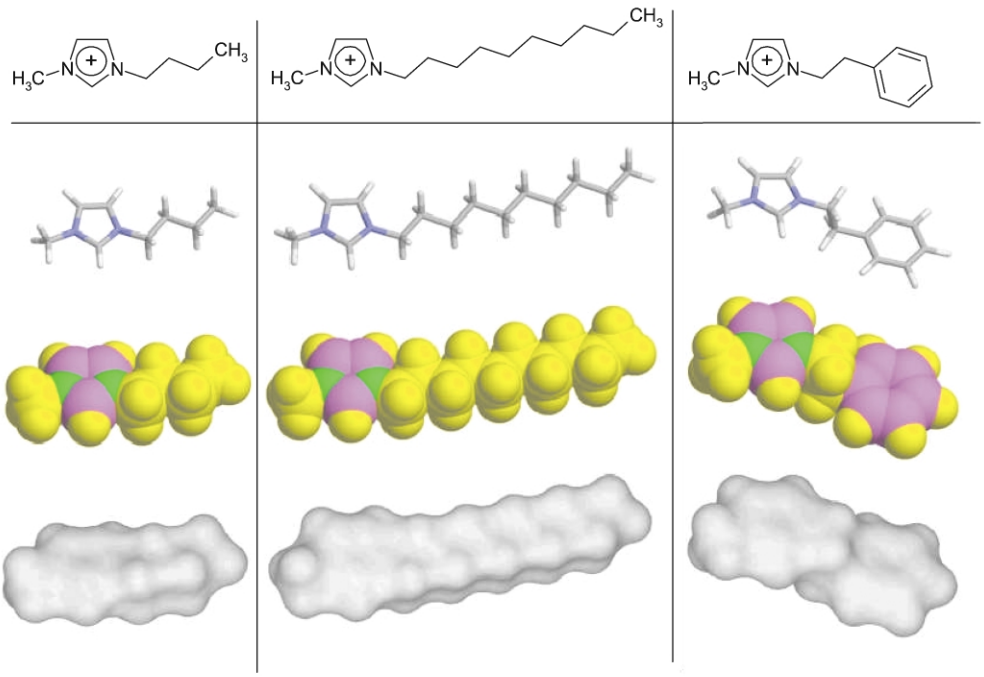

Fig. 3 Selection of three imidazolium cations: from left to right: bmim, dmim, 2-phenylethyl-mim. The top row shows their structural formulas. In the next three rows features of their 3-dimensional structures (optimized with MOPAC 2000, PM3 method[19]) are shown: first row, stick models in CPK-coloration; second row, models in which the colours denote molecular interaction potential (yellow: hydrophobic interaction potential, green: positive charge, and violet: charge transfer potential[5]); third row, water-accessible surface of the cations.[20]

within this molecule are the alkyl group and the phenyl structural element but some lipophilicity also resides in the aromatic imidazolium ring.

All three selected compounds reveal the steric feature of a flat cation which results in flexibility and prevents direct and easy binding of polar compounds.

Within our systematic algorithm the prediction of possible metabolites has to be considered. According to this theoretical approach several points of action can be identified. If these ionic molecules actually reach the cytochrome P_{450} system located in the endoplasmatic reticulum of any cell, they can be oxidized in different positions of the alkyl side chains. The resulting metabolites can further be broken down metabolically to biocompatible fatty acids and imidazole (for part of this proposed metabolism for the 1-butyl-3-methylimidazolium ([bmim]) cation see Fig. 4)

Of course it is possible that metabolites predicted theoretically may not be formed by nature. Nevertheless the prediction

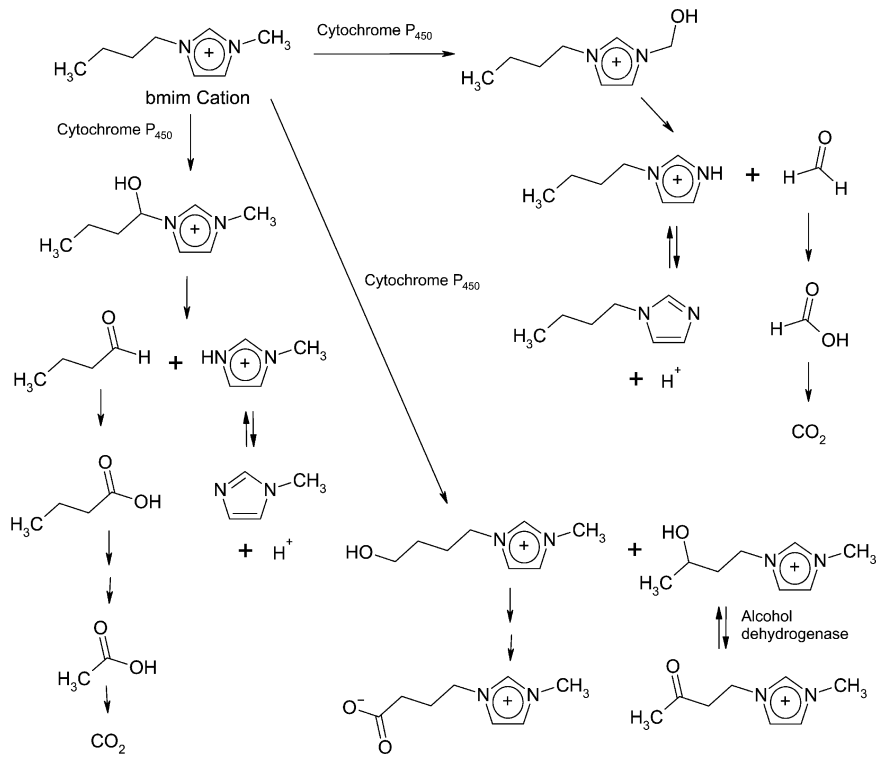

Fig. 4 Theoretically predicted metabolism scheme for [bmim] cation (according to ref. 5).

facilitates the analytical search for compounds while investigating the metabolic fate of ionic liquids in biological test systems. Such studies are under way within our cooperation network. Moreover, a computer supported expert system to predict metabolites of chemicals has been developed in collaboration with industry that might facilitate future work.[10]

Finally, two examples shall demonstrate the structure–activity relationship approach based on comparison of chemical structures. On the left side of Fig. 5, a pyridinium type of ionic

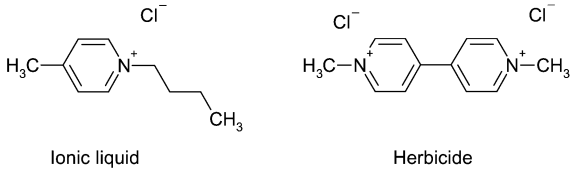

Fig. 5 Comparison of 4-butyl-1-methylpyridinium chloride and the herbicide "Paraquat".

liquid is presented in contrast to "Paraquat". The herbicide "Paraquat" is considered to exhibit substantial toxicological and ecotoxicological risk (due to high acute toxicity and high persistence) and has therefore been banned.

In the same way, 1-decyl-3-methylimidazolium chloride ([dmim][Cl]) and a patented plant growth regulator are depicted side by side in Fig. 6. Both examples indicate the structural similarity of some ionic liquids to already existing chemicals.

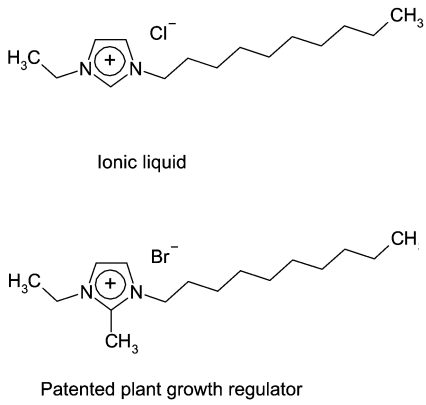

Fig. 6 Comparison of 1-decyl-3-methylimidazolium chloride ([dmim][Cl]) and a patented plant growth regulator.

Rationales for selection of test chemicals

Because of the high variability and indefinite number of possible ionic liquid species the choice of test compounds is difficult to perform. Therefore, we are using a so-called "test-kit-concept".[4] This concept has been used successfully over previous years to define nucleotide analogues as targets for systematic evaluation of enzymatic and cellular properties.[11]

Starting from the chosen basic imidazolium structure, in general there are two possibilities to change residues. The first approach is to increase chain length in the R_2-position keeping the R_1-residue constant (methyl group). Secondly, we keep R_2 constant but increase the length of R_1 from methyl to ethyl. The third set of test compounds concentrated on imidazolium compounds with methyl groups in the R_1-position and side-chains including a second aromatic ring (benzyl-, phenylethyl- and *p*-methylbenzyl moieties) in the R_2-position. These considerations resulted in the test kits 1, 2 and 3 (Fig. 7). Last not least we systematically varied the anion leaving the positively charged moiety constant, leading to test-kit 4 (Fig. 7).

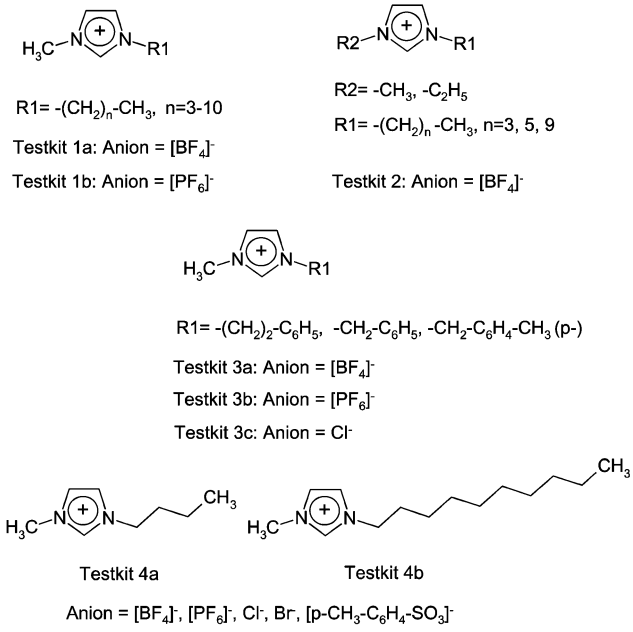

Fig. 7 Compounds of the test kits 1, 2, 3 and 4.

Rationales for selection of biological test systems

Due to the interdisciplinary approach described, a broad set of different methods to evaluate toxicological and/or ecotoxicological effects is available. Within the "Centre of Environmental Science and Environmental Technology (UFT)", a test battery has been arranged that comprises genetic, cellular and sub-cellular toxicology as well as aquatic and terrestrial ecotoxicology. The latter two consist of various approaches, differing in organisms, endpoints and complexity.[12] The test systems are selected according to regulatory requirements, questions under study and feasibility.

In the first step chemicals are tested by rapid screening methods (*e.g.* cell viability assay, luminescence inhibition test with bacteria). Acute or sub-lethal screening methods and chronic tests representing different biological levels (Fig. 8) are

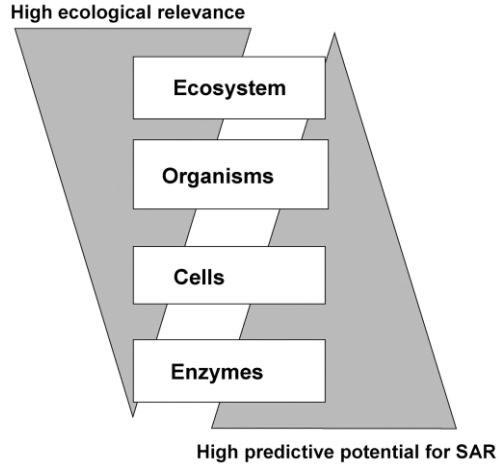

Fig. 8 Levels of complexity for the evaluation of the biological activity of chemicals.

available. Further tests are applied and designed on the basis of first results within a hierarchy of methods, starting with bacterial test systems and mammalian cell cultures up to complex mesocosms and human chromosomal aberration tests. All evaluated data will be compared to the effects predicted from SAR, including the metabolisation predictions.

First test battery results for different ionic liquid compounds of the chosen "test-kit" have already been generated. They will be explained in full detail in a different paper,[13] but the main results are included in the first attempt of a risk analysis reported below, specifically in the section "Biological Activity".

Multidimensional risk analysis

In the course of a case study about antifouling biocides, a multidimensional risk analysis based on five ecotoxicological indicators has been suggested.[7] The indicators are Release (R), Spatiotemporal Range (S), Bioaccumulation (B), Biological activity (A) and Uncertainty (U). They have been defined and explained in detail.[8]

The suggested multidimensional risk analysis is especially suitable for the comparison of chemical substances with a common scope of application. Since the imidazolium ionic liquids under investigation are being used as alternatives for conventional organic solvents, a first screening risk comparison of two selected substances with the common solvent acetone is presented here as a preliminary example. The chosen substances are 1-butyl-3-methyl-imidazolium tetrafluoroborate ([bmim][BF_4]) and 1-decyl-3-methyl-imidazolium tetrafluoroborate ([dmim][BF_4]), one for its abundance in organic synthesis literature, the other for its increased toxicity (see below). Each risk indicator is evaluated on a qualitative scale from 1 to 4, signifying a very low (1), rather low (2), rather high (3) and very high (4) risk. Additionally, the uncertainty of each evaluation is evaluated on a scale from very low (A), rather low (B), rather high (C) and very high (D). The scales are intended to be representative for solvents used in organic synthesis. The resulting five-dimensional risk profiles are depicted in Fig. 9.

Release R

In order to provide a just risk comparison, only the application of acetone and imidazolium ionic liquids as solvents for organic synthesis is taken into account. Acetone in general is a substance with a very high production volume, greater than one million metric tons per year, but only a fraction is being used in organic synthesis. Because of its high volatility, its tendency to be released from technical systems is quite high. Contrarily, pure ionic liquids are practically non-volatile. Therefore, their release from technical systems *via* air can be assumed to be much smaller. Their limited solubility in water, however, results in a release *via* wastewater, potentially making biological treatment possible, while acetone in waste water will mainly be volatilized into air, the rest being mineralized. An additional pathway, not for the ionic liquids themselves but for their decomposition products, is evaporation of dealkylated imidazole derivatives. In summary, release of acetone is found to be high, with very low uncertainty (4A), while release of imidazolium ionic liquids [bmim][BF_4] and [dmim][BF_4] is expected to be rather low, with high uncertainty due to lack of information regarding decomposition reactions leading to volatilization and biodegradation in treatment facilities (2D).

Spatiotemporal range S

The spatiotemporal range of the imidazolium ionic liquids is presumably governed by the interplay between water solubility, biotic and abiotic transformation and sorption to solid phases. No quantitative information about decomposition and biodegradation of any of the ionic liquids was accessible. Nevertheless it can be assumed that the [BF_4] anions eventually undergo hydrolysis. Also, the imidazolium cations can be expected to biodegrade eventually, following pathways similar to the ones suggested above, but with unknown timeframe. Acetone will almost completely partition into air under environmental conditions. It is known to be decomposed by reaction with OH radicals and ozone in air with a half-life of *ca.* 10 to 22 days.[14] Both properties in combination let its spatiotemporal range appear rather high, with rather low uncertainty (3B). The imidazolium cations also are likely to have a rather high spatiotemporal range, with a definitely very high uncertainty (3D).

Bioaccumulation B

Acetone is highly volatile and readily biodegradable and therefore does not tend to bioaccumulate in the common sense. Therefore, the bioaccumulation of acetone from the environment is scored very low, with very low uncertainty (1A). The tendency of [bmim][BF_4] and [dmim][BF_4] to bioaccumulate is unknown. However, [dmim][BF_4] can be presumed to have a tendency to be incorporated into membranes, because of its structural similarity to membrane lipids, comprising a charged head group with a nonpolar tail. Generally, the existing water solubility of the imidazolium tetrafluoroborates does not suggest high bioaccumulation. Bioaccumulation of [bmim][BF_4] is scored rather low, with very high uncertainty (2D), and bioaccumulation of [dmim][BF_4] is scored rather high, with equally high uncertainty (3D).

Biological Activity A

A first study of biological activities of test kits 1, 2 and 4 has been conducted with three different test systems of the UFT test battery. Detailed results will be published elsewhere.[13] A

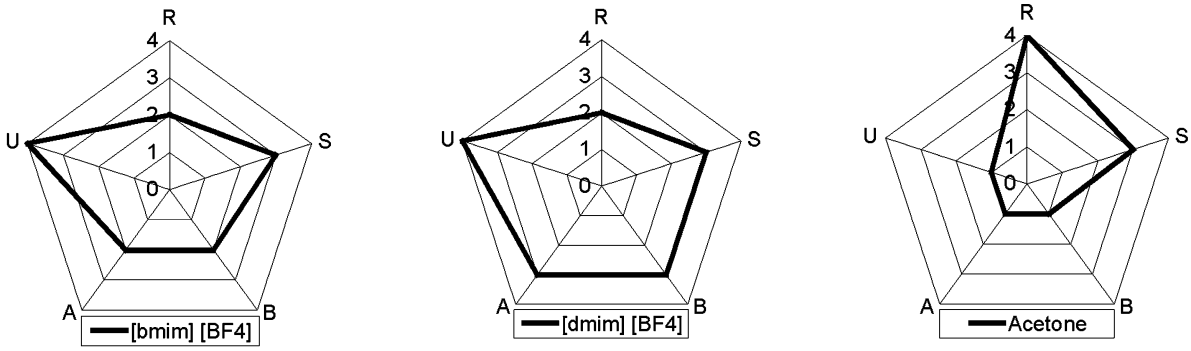

Fig. 9 5-Dimensional risk comparison of two ionic liquids with acetone. High risk scores are located on the outside of the graph, low risk scores towards the centre. R = Release, S = Spatiotemporal Range, B = Bioaccumulation, A = Biological activity, U = Uncertainty.

distinct influence of the length of the alkyl residues on toxicity was found. In all assays, ethyl imidazolium compounds were significantly more toxic than analogous methyl imidazolium compounds. Effect concentrations decreased by about 0.3 (IPC-81 leukemia cell lines) to about 0.6 (*Vibrio fischeri* luminescent bacteria) decadic log units for each additional carbon atom in the long n-alkyl chain. The biological activity of [dmim][BF_4] is therefore estimated to be rather high, which is partially corroborated by some of the first results from terrestrial and aquatic plant tests; still with a rather high uncertainty, since the results from standard ecotoxicological tests are not available (3C). The biological activity of [bmim][BF_4] is rather low, also with a rather high uncertainty (2C). In comparison, the biological activity of acetone is very low, in our own tests as well as in standard ecotoxicological tests, with very low uncertainty (1A).

Uncertainty

From the above, the remaining uncertainty of the risk evaluation is clearly very low for acetone (1), but very high for both [bmim][BF_4] and [dmim][BF_4] (4). This shows that the risk comparison can only be very preliminary at this stage of knowledge. To compensate for this a clearly defined strategy to gather additional risk relevant information is inevitable and it would be suitable to apply such a strategy completely in advance, before ionic liquids become high production volume chemicals.

Structure–activity relationships (SAR) and quantitative structure–activity relationships (QSAR) are powerful and rapid tools (Fig. 10) for a first theoretical assessment. Moreover, this

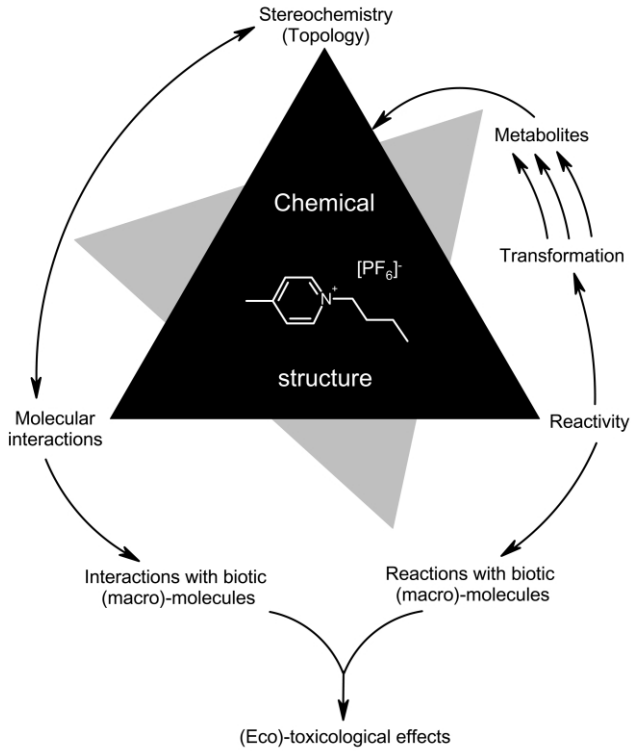

Fig. 10 Structure–activity relationship (SAR) triangle.[5]

approach allows us to define a clear chemical (synthesis and analysis), physical chemical (properties) and biological (effects on biological systems; see Fig. 8) experimental testing approach to check theoretical predictions and improve further predictions in an iterative way.

A strategy for sustainable product design

Sustainable development should bring about improvements in economical, ecological and social conditions for present and future generations. We agree with Diehlmann and Kreisel,[15] stating that these considerations can take place on a local, regional or global level, which are all important.

Looking at the sustainable development of ionic liquids, the integration of companies from the very beginning will open up the chance to consider technological needs while avoiding hazardous structures in the early steps to development of new industrial chemical products. Together, chemists, biologists and technologists have to find appropriate compounds based on the results of the SAR- and QSAR-algorithm. The structures of these compounds will be compared to each other and the properties will be assessed theoretically.[4] In this step, all computer aided prediction systems can be integrated like toxicity (*e.g.* DEREK,[16] TOPKAT[17]) and degradability prediction (*e.g.* EPIWIN[18]) or prediction of physico-chemical properties and others.[19,20] This evaluation will lead to a selection of a first set of compounds to be synthesized. Afterwards the predicted properties have to be validated experimentally, *i.e.* technological requirements have to be met and toxicological and ecotoxicological testing have to be integrated as well. It is also necessary to consider economic issues (benefits and cost effectiveness) in order to yield a complete assessment integrating economic, social and ecological dimensions (Fig. 11) as demonstrated in the Agenda 21.[21]

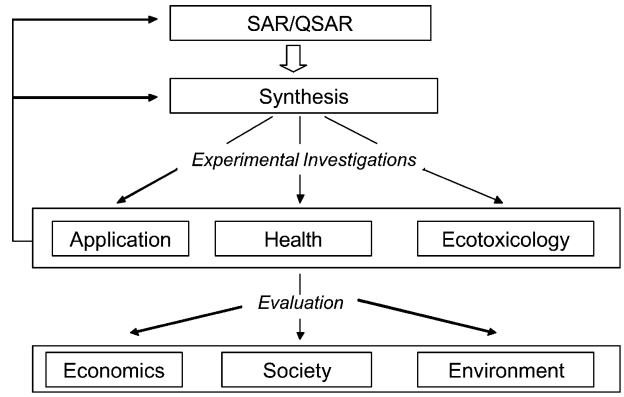

Fig. 11 A conceptual framework for a sustainable design of chemicals, showing our current focus (adapted from[8]).

Considering the whole life cycle of a chemical, waste treatment is another important aspect which has to be kept in mind. In close contact with the participating companies the field of application has to be evaluated, and differentiation between closed and open systems is necessary because the latter will implicate a broader release.

Conclusions

Using the iterative process described in this paper, the theoretical approach will help to reduce costs and to optimise the first and all following sets of compounds of interest. Although the procedure might appear very complicated and costly at first sight we propose to test its effectiveness. Our approach offers a promising tool to prevent undesirable effects of new technologies in advance of scaling up the production volume and may thus help to avoid remediation measures afterwards.[22]

The costs of an iterative multi- and trans-disciplinary approach to sustainable product design can be reduced substantially by the use of SAR and QSAR and by a time- and work-sharing collaboration between industry and academic

research. Using the example of designing ″green″ ionic liquids, we mainly aim at a continuous improvement of the strategy outlined here. For this purpose, our network is still open for further collaboration with other disciplines and people from academic research and from industry who are willing to add their expertise. We hope that ionic liquids in this way will become sustainable in the future.

Acknowledgement

Establishment and development of the "Test battery ecotoxicity/toxicity" is financially supported by the Senator for Women, Health, Youth, Social Affairs and Environmental Protection of the Freie Hansestadt Bremen.The discussion within the UFT directory board – Prof. Dr. Wolfgang Heyser, Prof. Dr. Norbert Räbiger, Prof. Dr. Dietmar Blohm, Prof. Dr. Armin Hildebrand, Prof. Dr. Rainer Frentzel-Beyme and Prof. Dr. Friedhelm Ventzke – contributed to the development of this concept.

References

1 P. Wasserscheid and T. Welton, *Ionic Liquids in Synthesis*, Wiley-VCH, Weinheim, Germany, 2002.
2 K. Seddon, *Green Chem.*, 2002, **4**, G35–G36.
3 R. D. Rogers and K. Seddon, *Ionic Liquids: Industrial Applications for Green Chemistry*, ACS Ser. 818, Oxford University Press, Oxford, UK, 2002.
4 B. Jastorff, E. G. Abbad, G. Petridis, W. Tegge, R. de Wit, C. Erneux, W. J. Stec and M. Morr, *Nucleic Acids Res., Symp. Ser.*, 1981, **9**, 219–223.
5 B. Jastorff, R. Störmann and U. Wölke, *Struktur-Wirkungsdenken in der Chemie – eine Chance für mehr Nachhaltigkeit*, Universitätsverlag Aschenbeck und Isensee, Oldenburg, Germany, 2003.
6 R. Störmann and B. Jastorff, *Sci. Total Environ., Suppl.*, 1993, 1657–1667.
7 J. Ranke and B. Jastorff, *Environ. Sci. Pollut. Res.*, 2000, **7**, 105–114.
8 J. Ranke, *Ecotoxicological Risk Profiles: Concept and Application to Antifouling Biocides*, PhD Thesis, Berlin, 2002.
9 A. Komberg, *Biochemistry,*, 1987, **26**, 6888–6891.
10 J. Franzen, B. Jastorff, R. Störmann and A. Germanus, German Patent Application 10145904.1, 2002.
11 F. Schwede, E. Maronde, H.-G. Genieser and B. Jastorff, *Pharmacol. Ther.*, 2000, **87**, 199–226.
12 T. Frische, *Environ. Pollution.*, 2003, **121**, 103–113.
13 J. Ranke, K. Mölter, F. Stock, U. Bottin-Weber, J. Poczobutt, J. Hoffmann, B. Ondruschka, J. Filser and B. Jastorff, in preparation.
14 *GDCh-Advisory Committee on Existing Chemicals of Environmental Relevance (BUA), Acetone*, S. Hirzel, Wissenschaftliche Verlagsgesellschaft, BUA reports **170**, Stuttgart, Germany, 1997.
15 A. Diehlmann and G. Kreisel, *Green Chem.*, 2002, **4**, G15–G17.
16 DEREK, v17.1, Lhasa Ltd., School of Chemistry, University of Leeds, Leeds, UK, 1998.
17 TOPKAT, Health Designs Inc., Rochester, New York, USA, 1996.
18 EPIWIN v3.10, Office of Pollution Prevention and Toxics, US EPA, 2000.
19 J. J. P. Stewart, MOPAC 2000, Fujitsu Limited, Tokyo, 1999.
20 MDL Chemscape Chime 2.6, MDL Information Systems, Inc., San Leandro, CA, USA, 1996–2001.
21 See http://www.un.org/esa/sustdev/agenda21.htm.
22 K. Hungerbühler, T. Mettier and J. Ranke, *Chemische Produkte und Prozesse – Grundkonzepte zum umweltorientierten Design*. Springer, Berlin, Germany, 1998.

Industrial preparation of phosphonium ionic liquids†

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Received 3rd October 2002
First published as an Advance Article on the web 4th December 2002

While a great deal of attention has been given to imidazolium ionic liquids in recent years, very few investigations involving phosphonium ionic liquids have been reported in the journal literature. The same is not true in the patent literature, where, in addition to filings concerning phosphonium ionic liquids specifically, filings concerning imidazolium ionic liquids routinely claim the manufacture and/or use of phosphonium ionic liquids as well. Despite this activity, commercial applications, and hence commercial production, have not materialized for any ionic liquids to date. Here we present an account of our research into ionic liquids from the perspective of a future, large-scale producer of ionic liquids for industrial applications. Several phosphonium ionic liquids are discussed with respect to synthesis and physical characteristics, and broad comparisons are made to relevant imidazolium systems. Full synthetic and characterization data are reported for several representative compounds including trihexyl(tetradecyl)phosphonium chloride, trihexyl(tetradecyl)phosphonium bis(2,4,4-trimethylpentyl)phosphinate, trihexyl(tetradecyl)phosphonium tetrafluoroborate, triisobutyl(methyl)phosphonium tosylate, and triisobutyl(methyl)phosphonium dimethylphosphate.

Standing, L-R: Donato Nucciarone, Wayde Teutenberg, Christine Kennedy, Cyril Bourget, Andrew Downard, Christine Bradaric, Yuehui (Joey) Zhou.
Seated, L-R: John Hillhouse, Mike Humeniuk, Angelo Melaragni, Janice Graham, Boban Jokovljevic.
Inset: Al Robertson.

Christine Bradaric received her Ph. D. in organic chemistry under the supervision of Prof. William Leigh at McMaster University in Hamilton, Canada, in 1998. Since then she has held the position of Research Chemist in the Phosphine Chemicals Group of Cytec Canada Inc., located in Niagara Falls. Christine is currently a Senior Research Chemist in the Mining Chemicals group of Cytec Industries, located in Stamford, Connecticut, USA.

Andrew Downard completed his Ph. D. in main-group chemistry under the supervision of Tristram Chivers at the University of Calgary, Canada, in September 2000. This was followed by post-doctoral studies with Ken Seddon at the Queen's University Ionic Liquid Laboratories in Belfast, Northern Ireland, as an NSERC Canada Fellow. He joined the research and development group at Cytec Canada Inc. in November 2001, working on the development and scale-up of ionic liquids. Currently, Andrew is a Master Black Belt candidate in Cytec's Six Sigma program.

Christine Kennedy completed her B.Sc. in Chemistry at Dundee University, Scotland. She worked as an analytical chemist in the local government water quality laboratory for five years before

Green Context

This article gives an overview of the field of ionic liquids, concentrating on the phosphonium based systems. These systems are much less well documented in academic papers, but there is a significant amount of industrial activity centred around them. Comparisons with the more common imidazolium systems are made. The paper is useful in that it flags up a further class of ionic liquids which should be considered as part of the portfolio of alternative reaction media which is emerging ***DJM***

† Portions of this work were presented at the following meetings: (a) 224th American Chemical Society Conference, Boston, USA, 2002; (b) Green Solvents for Catalysis Meeting, held in Bruchsal, Germany, 13–16th October 2002.

moving to Canada. Christine joined the research and development group at Cytec Canada Inc. in January 1997, and began ionic liquids research in 1998.

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Yuehui Zhou received his Ph. D. for the study of industrial organic chemistry at the Swiss Federal Institute of Technology of Zurich, Switzerland in October 1995. After post-doctoral studies in Germany, Canada, USA, and Switzerland in organoelemental chemistry, heterocyclic chemistry, materials chemistry, and pharmaceutical chemistry, he joined the research and development group at Cytec Canada Inc. in February 2001. Yuehui is now a leading research chemist for the development of new products.

1 Introduction

The field and phenomenon of room-temperature ionic liquids[1] are now well past infancy, but much work remains to be done to fulfill the true potential of these neoteric solvents. While ionic liquids containing quaternary nitrogen based cations have undergone extensive investigation in a myriad of applications over the last several years (see reviews by the groups of Gordon,[2] Rogers,[3] Seddon,[4] Sheldon,[5] Welton,[6] Wasserscheid,[7] and others[8]), studies involving quaternary phosphonium systems are much rarer.[9] As the global leader in the production of phosphine and phosphine derivatives, Cytec Industries has a great deal of experience in the manufacture of quaternary phosphonium salts that translates naturally to the manufacture of ionic liquids. For instance, Cytec routinely produces tetraalkylphosphonium halides such as the ionic liquid trihexyl(tetradecyl)phosphonium chloride, $[(C_6H_{13})_3P(C_{14}H_{29})]Cl$ (trade names: CYPHOS® 3653 and CYPHOS IL 101),[10] in tonne quantities.

Over the past several years our research program has developed a diverse range of phosphonium ionic liquids, pairing tetraalkylphosphonium cations with anions such as halides, tetrafluoroborate, hexafluorophosphate, dicyanamide, bis(trifluoromethanesulfonyl)amide, carboxylates, phosphinates, tosylates, alkylsulfates and dialkylphosphates, among others (Fig. 1). Here we summarize some of our work in this area and make comparisons to relevant nitrogen based systems with respect to physical characteristics, stability, and other important features. An informal overview of patent literature as it pertains to phosphonium ionic liquids is also presented.

The history of ionic liquids chemistry has been described in detail elsewhere,[2,11] but is worth reviewing briefly here. The first report of a room temperature molten salt was made by Walden in 1914, who noted the physical properties of ethylammonium nitrate (mp: 12–14 °C) formed by the reaction of ethylamine with concentrated nitric acid.[12] This discovery evidently did not arouse great or immediate interest in the scientific community of the day. Nonetheless, the next half century saw sporadic reports of the use of ionic liquids as media for electrochemical studies and, less commonly, as solvents for organic reactions.[2] Much of this work involved eutectic mixtures of chloroaluminate based salts such as $AlCl_3$–NaCl and pyridinium hydrochloride.[13] To our knowledge, no quaternary phosphonium cations were employed for such work during this period.

Ionic liquids did not reach a more general audience until seminal research efforts by the groups of Osteryoung[14] and Wilkes[11,15] in the 1970s, and Hussey[16] and Seddon[17] in the 1980s. This period also saw the first use of ionic liquids as reaction media for organic synthesis,[18] and, in 1990, for biphasic catalysis.[19] In the early 1990s, a report by Wilkes and co-workers describing the first air and moisture stable imidazolium salts, based on tetrafluoroborate, $[BF_4]^-$, and hexafluorophosphate, $[PF_6]^-$,[20] fueled further interest in the field. This interest has seen explosive growth during the past decade,[21] expanding to include diverse applications such as catalysis,[2,5,8a] separations,[22] electrochemistry,[23] electrodeposition,[24] photochemistry,[25] liquid crystals,[26] CO_2 capture,[27] desulfurization of fuel,[28] enzymatic syntheses,[5] lubrication,[29] rocket propulsion,[30] and thermal storage devices[31] to name just a few. Reflecting this, the number of papers published on ionic liquids has grown from approximately 40 per year in the early 1990s to multiple hundreds per year today.[21]

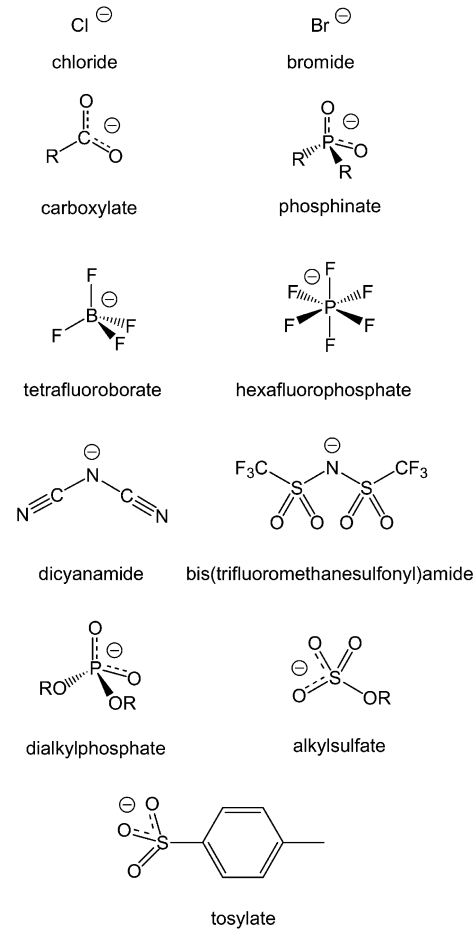


Fig. 1 Examples of anions that can be paired with tetraalkylphosphonium cations to produce ionic liquids.

Relative to their quaternary nitrogen based cousins, specific accounts of ionic liquids containing quaternary phosphorus cations are quite rare, a lacuna which is somewhat surprising given how often phosphonium ionic liquids are mentioned in review articles.[2–8] One recent report described some trialkylphosphonium salts, $[HPR_3]^+X^-$, that are liquid at room temperature.[32] Three accounts of catalysis in phosphonium ionic liquids have been reported: 1) tetraalkylphosphonium tosylates as solvents for hydroformylation;[9] 2) tetraalkylphosphonium halides as solvents for palladium catalyzed Heck reactions;[33] and 3) trihexyl(tetradecyl)phosphonium chloride as a solvent for palladium mediated Suzuki cross-coupling reactions.[34] In addition, work by Davis, Rogers and coworkers, initially focused on incorporated metal-ligating functionalities such as S, O, ureas and thioureas into imidazolium side chains

in a drive to produce ionic liquids suitable for the extraction of metal ions from aqueous solutions,[35] has subsequently expanded to include similarly derivatized phosphonium ionic liquids.[36] We note also that many low melting tetraalkylphosphonium salts are already well known as phase transfer catalysts.[37]

The relatively recent re-discovery of room-temperature ionic liquids has also been germane to a surge of patents filed in the field.[21] While the vast majority of these focus on nitrogen based cations (*e.g.* ammonium, imidazolium, pyridinium, *etc.*), there is a growing tendency to claim phosphonium cations as well (*vide infra*). Indeed, although it is not clear how much work has actually been done with the phosphorus based systems in most cases, the extension of coverage to include phosphonium salts now appears to be routine in almost any filing dealing with ionic liquids. In view of this situation, we feel that the need for further research involving phosphonium ionic liquids, both fundamental and applied, is critical to support the continuing advancement of the field as a whole.

2 Features and advantages of phosphonium ionic liquids

Asymmetrical tetraalkylphosphonium halides, $[R'PR_3^+]X^-$, are typically prepared by nucleophilic (S_N2) addition of tertiary phosphines, PR_3, to haloalkanes, [R′X (X = Cl, Br, I)] (eqn. (1)),[38] although other methods have been reported.[39]

$$PR_3 + R'X \rightarrow [R'PR_3]^+X^- \quad (1)$$

While the pK_as for tertiary phosphines are typically lower than the corresponding amines, their larger radii and more polarizable lone pair make them more nucleophilic. Hence the kinetics of salt formation are, in general, much faster than for amines.[40,41] The requisite tertiary phosphine starting materials can be prepared *via* free radical addition of phosphine gas, PH_3,[42] to α-olefins,[43] often in the presence of a suitable promoter such as DuPont's Vazo® series.[44]

The large number of commercially available haloalkanes and trialkylphosphines suggests a potentially large number of possible tetraalkylphosphonium salts. In our experience, however, there are some practical restrictions that limit the number of systems than can be synthesized easily. For example, only primary haloalkanes have reasonably fast kinetics. Furthermore, alkylphosphines containing branched alkyl chains also tend to be rather slow to react for what we believe are steric reasons. These restrictions notwithstanding, there are still a very large number of phosphonium salts that can be made by quaternization and/or anion exchange reactions.

While quaternization reactions such as those discussed above are well known (particularly for the syntheses of transfer catalysts and Wittig reagents), the realization that judicious selection of anion and cation can produce true room-temperature ionic liquids is comparatively recent. For example, we have found that quaternizing PR_3 (R = pentyl, hexyl, octyl) with 1-chloro- or 1-bromotetradecane produces phosphonium halides that are liquid at room temperature.[45] In addition, other phosphonium salts such as tetrabutylphosphonium chloride (mp: 67 °C), tetraoctylphosphonium bromide (mp: 45 °C) and tributyl(tetradecyl)phosphonium chloride (mp: 60 °C) are also low melting and fall within the generally accepted, broader definition of ionic liquids, *i.e.* salts which melt below ~100 °C. Though innumerable phosphonium cations can be imagined as constituents of phosphonium ionic liquids, we have utilized the trihexyl(tetradecyl)phosphonium cation, $[(C_6H_{13})_3P(C_{14}H_{29})]^+$, in much of our work. This is for reasons of cost and convenience, and because we have found it works well in many cases.

As is well known for imidazolium halides,[4,6,11] salts containing chlorometallate anions (*e.g.* $AlCl_4^-/Al_2Cl_7^-$, $FeCl_4^-$, *etc.*) are obtained by addition of metal chlorides (*e.g.* $AlCl_3$, $FeCl_3$, *etc.*) to phosphonium chlorides.[45] For example, we have prepared trihexyl(tetradecyl)phosphonium tetrachloropalladate, $[(C_6H_{13})_3P(C_{14}H_{29})]_2[PdCl_4]$, by simple addition of $PdCl_2$ to two equivalents of $[(C_6H_{13})_3P(C_{14}H_{29})]Cl$. This deep red ionic liquid has a melting point of –(50–48) °C, with onset of decomposition occurring above 400 °C. Although free flowing well below room temperature, the viscosity of trihexyl(tetradecyl)phosphonium tetrachloropalladate is approximately an order of magnitude greater than that of trihexyl(tetradecyl)phosphonium chloride (*e.g.* 104 P *vs.* 12 P at 30 °C). Its composition has been confirmed by NMR spectroscopy and elemental analysis.[46]

Phosphonium halides can also be converted by metathesis methods (see eqns. (2) and (3); R, R′ = alkyl; X = halogen; M = alkali metal; A = anion) to other anions such as phosphinate, carboxylate, tetrafluoroborate, hexafluorophosphate, *etc.* (Fig. 1).[47]

$$[R'PR_3]^+X^- + MA \rightarrow [R'PR_3]^+A^- + MX \quad (2)$$

$$[R'PR_3]^+X^- + HA + MOH \rightarrow [R'PR_3]^+A^- + MX + H_2O \quad (3)$$

While such methods are both powerful and versatile, the ionic liquids thus produced inevitably contain residual halide ions,[2–8,48] making them unsuitable for many applications. Halogen free systems can be produced by direct reaction of tertiary phosphines with alkylating agents such as benzenesulfonate, alkyltosylates, trialkylphosphates and dialkylsulfates (see eqns. (4)–(6)). These synthetic strategies, which together provide access to a large variety of 'tunable' phosphonium salts, are described in more detail below.

$$SO_2(OR)_2 + P(n\text{-Bu})_3 \rightarrow [RP(n\text{-Bu})_3]^+[SO_3(OR)]^- \quad \mathbf{1}\ (R = Me, Et, n\text{-Bu}) \quad (4)$$

$$O{=}P(OR)_3 + PR'_3 \rightarrow [RPR'_3]^+[PO_2(OR)_2]^- \quad \mathbf{2}\ (R = Me, Et, n\text{-Bu};\ R' = n\text{-Bu}) \quad \mathbf{3}\ (R = Me, Bu;\ R' = i\text{-Bu}) \quad (5)$$

$$O{=}PR(OR)_2 + P(n\text{-Bu})_3 \rightarrow [RP(n\text{-Bu})_3]^+[PRO_2(OR)]^- \quad \mathbf{4}\ (R = Me, n\text{-Bu}) \quad (6)$$

As suggested by eqn. (1), typical phosphonium cations have the general formula $[R'PR_3]^+$, in which three of the alkyl groups are identical while the fourth is different. However, this does not have to be the case. Primary and secondary alkylphosphines (RPH_2, R_2PH) are also available and can be converted to asymmetric tertiary phosphines (RR'_2P or $R_2R''P$) through free radical addition to olefins.[43] The resulting phosphonium cations have generic formulas of $RR'_2R''P^+$ and $R_2R'R''P^+$. This path offers another way to tune the properties of phosphonium ionic liquids.

One difference between phosphonium and ammonium salts is their stability with respect to degradation under various conditions.[9,49] For example, although both can decompose by internal displacement at higher temperatures (eqn. (7)), phosphonium salts are generally more thermally stable than ammonium salts in this respect.[49]

$$[R_4E]^+X^- \xrightarrow{\text{heat}} R_3E + R\text{-}X\ (E = N,P) \quad (7)$$

Unlike their ammonium counterparts, which can undergo facile Hoffmann- or β-elimination in the presence of base,[50] phosphonium salts decompose to yield a tertiary phosphine oxide and alkane under alkaline conditions (eqn. (8)).[51] Alternatively, depending on the nature of R and R′, stable phosphoranes can be formed (eqn. (9)); these are well known as Wittig reagents. While the decomposition of phosphonium salts by these pathways may occur even at room temperature in some cases, contrasting examples are known where tetraalkylphosphonium halides can be combined with concentrated sodium hydroxide well above room temperature without any degradation[49] (*e.g.* $[(C_{16}H_{33})P(C_4H_9)]Br$[52]).

$$[R_3P{-}CH_2{-}R']^+ + OH^- \rightarrow R_3P{=}O + CH_3{-}R' \quad (8)$$

$$[R_3P–CH_2–R']^+ + OH^- \rightarrow R_3P=CHR' + H_2O \quad (9)$$

While the decomposition point of neat phosphonium ionic liquids on heating varies somewhat depending on the anion, thermogravimetric analyses (TGA) indicate dynamic thermal stability in excess of 300 °C for many species.[53] Fig. 2 shows

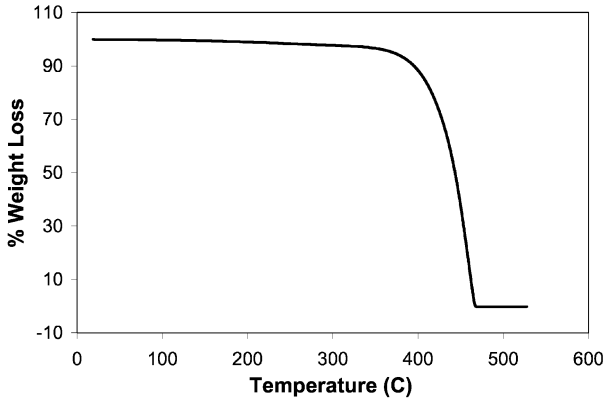


Fig. 2 Stability with respect to temperature, as demonstrated by thermogravimetric analysis (TGA), for trihexyl(tetradecyl)phosphonium tetrafluoroborate, $[(C_6H_{13})_3P(C_{14}H_{29})][BF_4]$.

TGA data for trihexyl(tetradecyl)phosphonium tetrafluoroborate, which exhibits a profile typical of most phosphonium salts. This enhanced thermal stability relative to quaternary nitrogen based salts is an important factor when, for example, reaction products must be removed from an ionic liquid by high temperature distillation.

Viscosity is a particularly important characteristic for solvents being considered in industrial applications. Phosphonium based ionic liquids tend to have viscosities somewhat higher than their ammonium counterparts, especially at or near room temperature. However, on heating from ambient to typical industrial reaction temperatures (*e.g.* 70–100 °C) their viscosities generally decrease to < 1 P. This is shown for trihexyl(tetradecyl)phosphonium chloride in Fig. 3 (see also Table 1).[54]

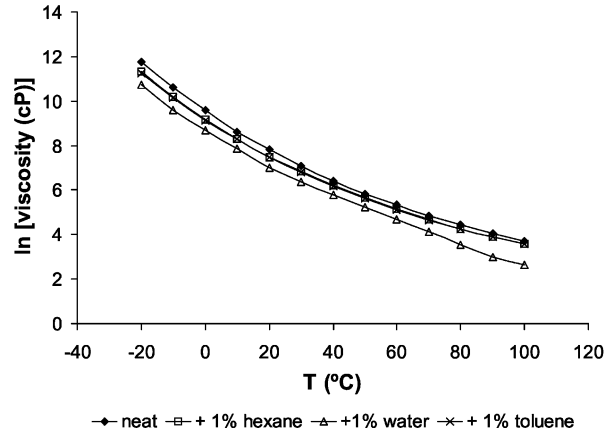


Fig. 3 Viscosity with respect to temperature for trihexyl(tetradecyl)phosphonium chloride, $[(C_6H_{13})_3P(C_{14}H_{29})]Cl$.

Ionic liquid viscosities are also very sensitive to solutes,[55] and the addition of reactants and/or catalysts can be expected to further reduce viscosity. For example, mixing trihexyl(tetradecyl)phosphonium chloride with 1% (w/w) of hexane, water or toluene[56] decreases the viscosity at all temperatures (Fig. 3, Table 1).

While the densities of many imidazolium ionic liquids have been reported previously,[55] few phosphonium ionic liquids are available for comparison. In contrast to most imidazolium ionic liquids (which generally have densities > 1 g ml^{-1}),[55] tetraalkylphosphonium salts tend to have densities in the range 0.8–1.2 g ml^{-1} with densities < 1 g ml^{-1} being the norm. Phosphonium cations containing more carbon atoms have slightly lower densities, as illustrated in Fig. 4, which shows density as a function of temperature for several tetraalkylphosphonium tosylates. The anion employed also has an impact on density; for example, Fig. 5 shows the order: Cl^- < $[BF_4]^-$ < Br^- < $[PF_6]^-$ with respect to density for trihexyl(tetradecyl)phosphonium cations paired with several anions.

Table 1 Viscosities of trihexyl(tetradecyl)phosphonium chloride (neat, and with designated mass percent of various impurities)

	Viscosity/P			
Temp./°C	Neat	+1% hexane	+1% water	+1% toluene
−20	1288.00	815.60	453.50	772.70
−10	414.80	268.00	146.60	254.80
0	144	93.69	58.65	90.79
10	56.03	39.61	25.61	39.42
20	24.69	17.81	11.10	17.66
30	11.84	9.40	5.87	9.14
40	6.09	4.97	3.25	4.83
50	3.37	2.83	1.86	2.75
60	2.08	1.70	1.07	1.65
70	1.25	1.07	0.62	1.06
80	0.85	0.71	0.34	0.71
90	0.58	0.49	0.20	0.49
100	0.41	0.36	0.14	0.35

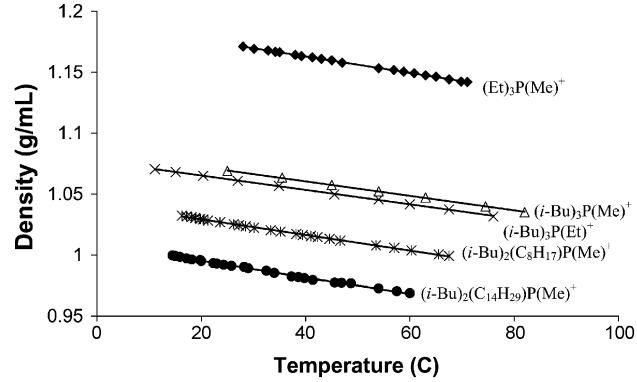


Fig. 4 Density as a function of temperature for several tetraalkylphosphonium tosylates.

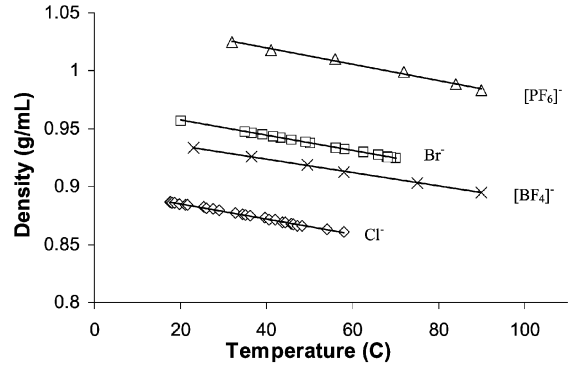


Fig. 5 Density as a function of temperature for several salts of the trihexyl(tetradecyl)phosphonium cation.

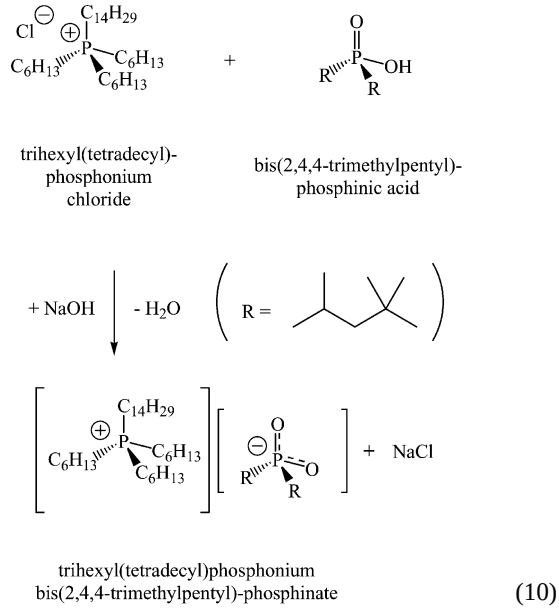
Another important difference between imidazolium and phosphonium salts are the acidic protons present in the former. Relative to phosphonium cations, imidazolium cations are not entirely inert and can interact with solutes either through hydrogen bonding interactions or through the aromatic nature of

the ring system.[57] Tetraalkylphosphonium salts do not have such acidic protons or aromatic rings, and consequently there is little potential for interaction with solutes.

3 Metathesis routes to phosphonium ionic liquids

Phosphonium salts, especially halides, have been available commercially for many years. They are typically made by quaternizing an alkylphosphine with a haloalkane,[38] and historically have had use as biocides[58] and phase transfer catalysts.[37] Burgeoning interest in ionic liquids prompted us to closely examine our own range of phosphonium salts in order to target their potential as ionic liquids. In fact, we discovered several ionic compounds that were liquid at or near room temperature. Furthermore, trihexyl(tetradecyl)phosphonium chloride was a commercial product for Cytec long before the term 'ionic liquids' achieved the prominence it currently enjoys. Trihexyl(tetradecyl)phosphonium chloride has subsequently been a starting material for the synthesis of numerous phosphonium based ionic liquids by anion exchange reactions.[47] These generally fall into two categories (as shown in eqns. (2) and (3)), representative examples of which are provided below. Ionic liquids containing the anions shown in Fig. 1 can be synthesized by one or the other of these routes.

Phosphonium phosphinates are of particular interest, both because they couple our existing expertise in phosphonium salt and phosphinic acid manufacturing, and because many are apparently novel ionic liquids. A notable example from this series is derived from bis(2,4,4-trimethylpentyl)phosphinic acid, better known as CYANEX® 272 Extractant (eqn. (10)). This is a well-known and popular solvent for the extraction of cobalt from nickel in both sulfate and chloride media,[59] and is currently used to produce more than half of the western world's cobalt.[60] Ionic liquids containing the bis(2,4,4-trimethylpentyl)-phosphinate anion are thus of interest not only for the usual reasons, but particularly for solvent extraction applications.



(10)

We note that both trihexyl(tetradecyl)phosphonium bis(2,4,4-trimethylpentyl)phosphinate and trihexyl(tetradecyl)-phosphonium chloride form a middle layer when combined with hexane (or petroleum ether) and water. This behaviour differs from that of the generally more dense dialkylimidazolium salts, which typically form the bottom phase in such three-layer systems.[61] An example of the advantageous nature of this feature was observed recently in the Suzuki cross-coupling of an aryl boronic acid with an aryl halide, shown to proceed under mild conditions in trihexyl(tetradecyl)phosphonium chloride.[34] Product separation was easily accomplished by washing with hexane and water to form a three-layer system; the palladium catalyst remained fully dissolved in the central phosphonium layer and could be easily recycled.

3.1 Synthesis of trihexyl(tetradecyl)phosphonium chloride

The synthesis of trihexyl(tetradecyl)phosphonium chloride is described here specifically, but similar methodology can be applied to the synthesis of other tetraalkylphosphonium halides. Trihexyl(tetradecyl)phosphonium chloride was synthesized by adding trihexylphosphine to one equivalent of 1-chlorotetradecane at 140 °C under nitrogen and stirring for 12 h. After the reaction was complete, the mixture was vacuum stripped to remove any volatile components such as hexene, tetradecene isomers, and excess 1-chlorotetradecane. This yielded a clear, pale yellow liquid in 98% yield (by mass), containing 93.9% trihexyl(tetradecyl)phosphonium chloride, 4.4% trihexylphosphonium hydrochloride and 0.3% hydrochloric acid. Other minor impurities include tetradecene isomers ($< 0.3\%$) and R_2PH ($< 0.7\%$).

Characterization of trihexyl(tetradecyl)phosphonium chloride. The product was characterized by ^1H, ^{13}C and ^{31}P NMR, and analyzed for halide concentration by titration with $AgNO_3$. ^1H NMR (300.13 MHz in $CDCl_3$): δ 2.49–0.86 (various m, 68 H). ^{13}C NMR (75.45 MHz in $CDCl_3$): δ 31.73–14.15 (s, 32 C). ^{31}P NMR (121.49 MHz in DCl_3): δ 33.39. These spectra are shown in Fig. 6.

3.2 Synthesis of trihexyl(tetradecyl)phosphonium bis(2,4,4-trimethylpentyl)phosphinate.[62]

Trihexyl(tetradecyl)phosphonium bis(2,4,4-trimethylpentyl)-phosphinate was prepared by combining trihexyl(tetradecyl)-phosphonium chloride (0.66 kg, 1.26 mol, Cytec Industries) and bis(2,4,4-trimethylpentyl)phosphinic acid (86.5% purity, 0.48 kg, 1.64 mol, Cytec Industries) in the presence of an excess of sodium hydroxide (40% w/w in water, 0.24 kg, 2.43 mol) and water (eqn. (9)). This mixture was heated to 55 °C with vigorous agitation for 4 h, and washed three times with water to remove sodium chloride. Vacuum stripping at 135 °C to remove any residual water gave the product, an orange/brown liquid, in 95% isolated yield (0.93 kg, 1.20 mol, chloride content 0.082% w/w by titration with $AgNO_3$).

Characterization of trihexyl(tetradecyl)phosphonium bis(2,4,4-trimethylpentyl)phosphinate. ^1H NMR (300.13 MHz in $CDCl_3$): δ 2.68–0.87 (various m, 85 H). ^{13}C NMR (75.45 MHz in $CDCl_3$): δ 54.71–14.26 (various s). ^{31}P NMR (121.49 MHz in 2-propanol): δ 34.39 (s, anion), 33.95 (s, cation). Impurities can also been seen in the ^{31}P NMR spectrum, *e.g.* at δ 46.41, 46.20, 37.99, 34.47. These arise from the bis(2,4,4-trimethylpentyl)phosphinic acid used, which typically contains small amounts of mono(2,4,4-trimethylpentyl)phosphinic acid and various phosphine oxides.

3.3 Synthesis of trihexyl(tetradecyl)phosphonium tetrafluoroborate.[62]

The tetrafluoroborate anion is well known for imidazolium ionic liquids, and syntheses of these compounds have been described elsewhere.[2–8,11] However, no phosphonium tetrafluoroborates have been reported previously. Here we describe the synthesis of trihexyl(tetradecyl)phosphonium tetrafluoroborate (eqn. (11)).

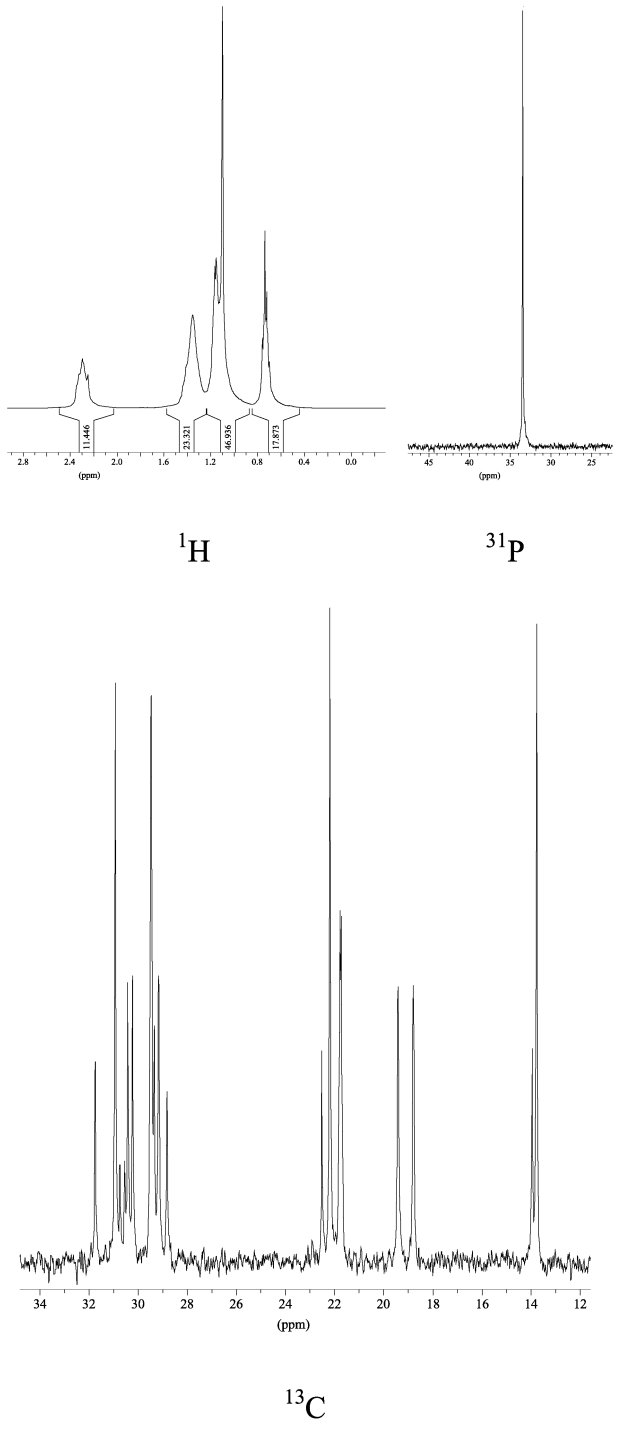


Fig. 6 ^{1}H, ^{13}C and ^{31}P NMR spectra of trihexyl(tetradecyl)phosphonium chloride in $CDCl_3$.

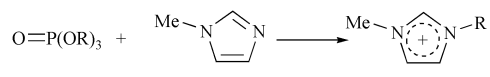
$$[(C_{14}H_{29})P(C_6H_{13})_3]Cl + Na[BF_4] \rightarrow [(C_{14}H_{29})P(C_6H_{13})_3][BF_4] + NaCl \quad (11)$$

Sodium tetrafluoroborate[63] (0.21 kg, 1.93 mol, Ozark Fluorine) and trihexyl(tetradecyl)phosphonium chloride (0.91 kg, 1.75 mol, Cytec Industries) were combined with a 1% (w/w) solution of NaOH in water (1.13 kg; this solution was used in the initial steps of the reaction in place of water to neutralize any HF formed). This mixture was heated to 55–60 °C for 2 h with agitation, after which the phases were allowed to separate at 60 °C for 1.25 h. The lower, aqueous layer was removed, leaving an emulsified product layer containing 1.55% chloride (w/w, by titration with $AgNO_3$); phase separation was slow at this temperature, and no distinct phase interface could be discerned. After being allowed to stand for another hour under ambient conditions, no further phase disengagement was observed. Another wash with 1% NaOH (0.50 kg) was commenced, with the mixture being heated to 55 °C for 1.5 h and then allowed to stand overnight under ambient conditions. After this time, the aqueous layer had fully separated from the product layer, and the former was easily drained, leaving a product layer containing 0.29% chloride. Water (1.0 kg) was used for the final wash cycle, and the reaction mixture agitated under ambient conditions for 2 h. The reaction mixture was left to disengage overnight under ambient conditions, after which time the product layer had solidified. After heating the reaction vessel to facilitate removal, the product (0.67 kg, 1.18 mol, 67% yield, chloride content 0.17%) was an opaque, faintly yellow liquid that solidified to form a white solid on standing. The low yield is presumed to be due to losses during transfer and washing rather than incomplete conversion.

Characterization of trihexyl(tetradecyl)phosphonium tetrafluoroborate. Mp: 26–27 °C. ^{1}H NMR (300.13 MHz in $CDCl_3$): δ 2.09–0.81 (various m). ^{11}B NMR (64.21 MHz in $CDCl_3$): δ −1.08 (s). ^{13}C NMR (75.45 MHz in $CDCl_3$): δ 31.91–13.91 (various s). ^{19}F NMR (188.31 MHz in $CDCl_3$): δ −150.49 (s), −150.55 (s). ^{31}P-NMR (121.49 MHz in $CDCl_3$): δ 33.25 (s).

4 Halide-free routes to phosphonium ionic liquids

As indicated above, many ionic liquids are prepared through quaternization of nitrogen or phosphorus centers to form chlorides, with subsequent anion exchange if other anions are required.[2–8] The materials thus prepared inevitably contain residual chloride ions, which may adversely affect metal catalysts[2–8,48] and/or contaminate reaction products. This is true, for example, of phosphonium ionic liquids used in the production of halogen-free epoxy resins[64] and polycarbonates.[65] In addition, anion exchange processes are typically wasteful and expensive, often involving the use of environmentally hazardous molecular solvents. Factors such as these increase the final cost of ionic liquids produced industrially, and effectively limit their application range. For these reasons and others, chloride-free routes to phosphonium salts are desirable.[66] Ren and coworkers, for example, have developed a direct route to imidazolium hexafluorophosphate without anion exchange.[67] Here we report several direct, solvent free, halide free routes to phosphonium ionic liquids *via* the quaternization of tertiary phosphines with dialkylsulfates (eqn. (4)), trialkylphosphates (eqn. (5)) and alkylphosphonates (eqn. (6)). Phosphonium dialkylphosphates and alkylphosphonates have been synthesized previously in a process employing molecular solvents.[68] Imidazoles may also be used as starting materials to produce ammonium salts by this route (eqn. (12)). In addition to these relatively novel anions, we have also prepared phosphonium tosylates (some examples of which have been described previously[9]) by a similar route. Table 2 summarizes a number of these compounds (**1**–**5**), and representative details pertaining to synthesis and characterization are described below. The structures of all compounds have been confirmed by multi-nuclear NMR spectroscopy, supplemented by other methods where appropriate.



5 (R = Me, *n*-Bu) (12)

In addition to being halide free, these synthetic routes also provide a way to tune the properties of phosphonium ionic liquids by varying the size of the anion (through the size of the alkyl groups attached to the anion moiety). This ability is useful for tailoring ionic liquids' properties to various application requirements. For example, we note that variation in R and R′

Table 2 Ionic liquids prepared by chloride-free routes (see eqns. (4)–(6) and (12))

Compound	R	R′	Reaction temp./°C	Time/h	Yield (%)	Appearance at room temp.
1a	Me	*n*-Bu	30–150	10	100	Colorless liquid
1b	Et	*n*-Bu	50–160	18	100	Colorless liquid
1c	*n*-Bu	*n*-Bu	100–190	24	75	Colorless liquid
2a	Me	*n*-Bu	120–200	20	100	Colorless liquid
2b	Et	*n*-Bu	160–200	25	91	Colorless liquid
2c	*n*-Bu	*n*-Bu	170–210	29	77.5	White waxy solid
3a	Me	*i*-Bu	160–180	10	100	White waxy solid
3b	Et	*i*-Bu	190–200	23	74.8	Colorless liquid
3c	*n*-Bu	*i*-Bu	190–200	25	68	Colorless liquid
4	Me	*n*-Bu	150–200	21	100	Colorless liquid
5a	Me		140–160	6	100	Yellow liquid
5b	*n*-Bu		170–180	5.5	98	Yellow liquid

allows melting points to be tuned to a certain extent. The phosphonium phosphate **2**, prepared from tri-*n*-butylphosphine (eqn. (5)), is liquid at room temperature when R = Me or Et, but solid when R = *n*-Bu. Conversely, **3**, prepared from triisobutylphosphine (eqn. (7)), is a solid when R = Me, and liquid when R = Et or *n*-Bu. Furthermore, as the alkyl chains become longer the product becomes increasingly hydrophobic in all cases.

4.1 General syntheses of 1–4

An equivalent of tertiary phosphine was added dropwise to the appropriate alkyl ester (dialkylsulfate, trialkylphosphate or trialkylphosphonate) under nitrogen and stirred at a temperature ranging from 30 to 200 °C, depending on the reactivity of the alkylating reagent. Short-chain alkylating reagents were generally more reactive than long-chain analogues, and tended to react at lower temperatures as indicated in Table 2. The speed of addition was adjusted such that no free tertiary phosphine could be observed in the reaction mixture. The reaction times, including the time for addition of the tertiary phosphine to the alkylating reagent, varied from 10 to 29 h (also depending on the chain length). After addition was complete and the mixture had been stirred for 2–3 h at the initial temperature, higher temperatures were used to accelerate the reaction. Reactions were essentially quantitative for shorter alkyl chain lengths, but yields became lower as the alkyl chains became longer (Table 2).

Characterization of triisobutyl(methyl)phosphonium dimethylphosphate (3a). All of the products listed in Table 1 have been fully characterized by appropriate methods. Here we give the NMR characterization of triisobutyl(methyl)phosphonium dimethylphosphate (**3a**) as a representative example. ^{1}H NMR (300.13 MHz in $CDCl_3$): δ 0.948 (18H, 6 CH_3, d), 1.91 (3H, 3CH, m), 1.96 (3H, P^+CH_3, d), 2.20 (6H, 3 CH_2, q), 3.37 (6H, 2 OCH_3, d). ^{13}C NMR (75.48 MHz in $CDCl_3$): δ 6.2 (P^+CH_3), 22.7 (CH), 23.6 (CH_3), 29.1 (CH_2), 51.2 (OCH_3). ^{31}P NMR (81.02 MHz in $CDCl_3$): δ 1.71 [$O{=}P^-(O)(OCH_3)_2$], 29.74 (P^+).

4.2 Synthesis of triisobutyl(methyl)phosphonium tosylate[62]

Methyl tosylate (mp: 27.5 °C, 0.71 kg, 3.83 mol, Esprix Technologies) was heated in a water-bath using a steam lance until fully liquefied. This was then charged into a jacketed, glass-lined reactor with paddle agitation as a neat liquid and heated to 80 °C. An equimolar amount of triisobutylphosphine (0.77 kg, 3.79 mol, Cytec Industries) was added dropwise, causing the temperature of the reaction mixture to rise. The jacketed reactor was cooled as necessary to keep the internal temperature near 100 °C (± 5 °C) throughout the course of the reaction. Addition was complete after 6 h, and the reaction mixture was allowed to stand under ambient conditions overnight. After this time, the product was heated to 160 °C under ~10 mmHg vacuum for 0.5 h to remove any residual starting material. The product was then cooled to 50 °C before being discharged as a clear, very faintly yellow liquid, identified as triisobutyl(methyl)phosphonium tosylate (1.43 kg, 3.67 mol, 97% yield). This product has a slight odor that can be removed, if needed, by oxidizing any residual triisobutylphosphine with a dilute solution of hydrogen peroxide to produce triisobutylphosphine oxide and water.

Characterization of triisobutyl(methyl)phosphonium tosylate. Appearance: clear, faintly yellow liquid at room temperature. ^{1}H NMR (300 MHz in $CDCl_3$): δ 7.69, 7.66 (2H, *ortho*-H, s); 7.04, 7.02 (2H, *para*-H, s); 2.24 (3H, H_3CP, s); 2.24 (3H, H_3C–Ar, s); 2.02–1.87 (3H, $(H_3C)_2CH$, m); 1.90 (6H, $–CH_2–$, d); 0.90 (18H, $(H_3C)_2CH$, d). ^{13}C NMR (975.45 MHz in $CDCl_3$): δ 144.31 (C4 of phenyl group), 138.74 (C1 of phenyl group), 128.33 (C2, C6 of phenyl group), 125.947 (C3, C5 of phenyl group); 30.35 ($–CH_2–$) 24.47 ($(H_3C)_2CH$), 23.62 (H_3CP), 21.17 ($(H_3C)_2CH$); 7.42 (H_3C–Ar). ^{31}P NMR (121.49 MHz in $CDCl_3$): δ 29.1 (s).

4.3 Synthesis of *N*,*N*-dimethylimidazolium dimethylphosphate (5a)

Trimethylphosphate (125.7 g, 0.87 mol, Aldrich) was added dropwise to a 300 ml flask containing *N*-methylimdazole (72.2 g, 0.87 mol, Aldrich) at room temperature. No temperature increase was observed on initial addition. However, when the temperature was slowly increased to 140 °C, a sudden temperature increase was observed. Addition was continued at 140 °C until all the material had been added to the flask, and the reaction mixture was subsequently stirred for another hour. The product was moved to a rotary evaporator and dried at 160 °C under an aspirated vacuum to yield a viscous, yellow oil identified as *N*,*N*-dimethylimidazolium dimethylphosphate (198 g, 0.87 mol, 100% yield).

Characterization of *N*,*N*-dimethylimidazolium dimethylphosphate (5a). Appearance: clear, faintly yellow liquid at room temperature. ^{1}H NMR (300.13 MHz in $CDCl_3$): δ 3.47 (6H, 2 OCH_3, d), 3.91 (6H, 2 CH_3, s), 7.43 (2H, 2 CH, s). ^{13}C NMR (75.48 MHz in $CDCl_3$): δ 36.1 (CH_3), 52.3 (OCH_3), 123.3 (CH), 139.6 (NCH_3). ^{31}P NMR (81.02 MHz in $CDCl_3$): δ 3.04 [$O{=}P^-(O)(OCH_3)_2$].

5 Patent literature[69]

Many patents concerning phosphonium ionic liquids have been filed in recent years. In general, the pertinent patents can be grouped into two broad categories: 1) those that cover the manufacture of ionic liquids; 2) those that cover the use of ionic liquids as solvents, catalysts, extraction media, and other materials.

In some cases both the manufacture and applications of ionic liquids are covered in a single patent; we have included these in the first category above. Only a few representative members of the second category are given—many more examples of each (particularly the second category, and particularly involving imidazolium cations) can be found in the patent and academic literature.

We note that the examples highlighted below reveal a growing trend towards claiming phosphonium ionic liquids in manufacturing and applications related patents, even when it

appears that only nitrogen based systems have been fully investigated. In some cases, potential future applications for phosphonium salts are already protected by patent despite the fact that much investigative work remains to be done to develop them.

5.1 Patents concerning the manufacture of phosphonium ionic liquids

Perhaps the broadest coverage of phosphonium ionic liquids in general is contained in Cytec's 'Phosphonium Salts,'[45] which claims phosphonium ionic liquids of the form $[R_1R_2R_3R_4P]^+[X]^-$ where R_{1-4} have 1–20 carbon atoms (and may also contain heteroatoms), and X^- is any anion other than a halide. A related patent held by Seddon and coworkers[70] protects a method of producing halide-free and metal-free ionic liquids *via* alkylation of organic bases (including tertiary phosphines) using either fluorinated esters (*e.g.* eqn. (13)) or methane sulfonates (eqn. (14)) as alkylating agents. The preparation of many quaternary phosphonium and ammonium salts by liquid–liquid extraction is covered in a patent assigned to the General Electric Company.[71]

$$PR_3 + CF_3COOR' \rightarrow [R_3PR']^+[CF_3COO]^- \quad (13)$$

$$PR_3 + R'OSO_2Me \rightarrow [R_3PR']^+[MeSO_3]^- \quad (14)$$

A number of optically active systems are claimed in various patents.[72] While these do include phosphonium salts, the claims are restricted in various ways. They do not cover, for example: 1) tetraalkylphosphonium salts that are not heterocyclic; 2) systems in which the asymmetric centre is not a carbon atom.[72] The same is not true of chiral ammonium ionic liquids, for which the manufacture and use in asymmetric synthesis, asymmetric catalysis, and racemate separation are all claimed.[73]

More specifically claimed phosphonium salts include those with Brønsted acidity but not Lewis acidity, the Brønsted acidity being either inherent to the anion or cation employed, or arising from the presence of a slight excess of the parent acid of the anion (*e.g.* eqn. (15)).[74] Such liquids are useful for reactions that are Brønsted acid catalyzed. All ionic liquids which are derived from the reaction of organonitrogen or organophosphorus compounds (that are not Lewis acidic) with a Brønsted acid are claimed, but only when the final product or product mixture is itself Brønsted acidic.

$$H_2SO_4 + PR_3 \rightarrow [HPR_3]^+[HSO_4]^- \quad (15)$$

Some patents distinguish particular phosphonium salts both by their composition and by their method of manufacture. For example, a number of phosphonium ionic liquids with common anions are protected if made by reacting the lead salt of an anion with the halide of a cation (eqn. (16), A = anion, C = cation, X = halogen)[75]

$$PbA_2 + 2CX \rightarrow 2CA + PbX_2 \quad (16)$$

Another example claims ionic liquids comprising ternary melts of: 1) alkyl metal (Al, Ga) halides; 2) imidazolium or pyridinium halides; and 3) quaternary ammonium or phosphonium halides.[76]

Finally, non-aqueous ionic liquids comprised of ammonium or phosphonium cations and sulfonated triarylphosphine anions are protected.[77] This coverage includes ionic liquids which comprise any cation containing a quaternary nitrogen or phosphorus centre with alkyl chains of 1–20 carbon atoms, and any sulfonated triarylphosphine anion, *e.g.* those derived from $M_3\{P[Ar(SO_3)]_3\}$ (M = Li, Na, *etc.*; Ar = aryl group). Wide variation in the cation and anion are covered. Ammonium or phosphonium salts are prepared using an excess of alkylating agent or acid, and these are converted to sulfonated triarylphosphine salts by metathesis. Mixtures containing 0–5 equivalents (excess) of the parent amine or phosphine, useful as solvents for catalysis, are also covered. A related patent claims ionic liquids comprised of ammonium cations and anions based on sulfonated or carboxylated triesters of phosphorous acid.[78]

5.2 Patents covering the use of phosphonium ionic liquids

The use of phosphonium ionic liquids for various applications is covered in a number of different ways in different patents. For example, several uses of ionic liquids for nuclear fuel reprocessing are protected in patents (assigned to British Nuclear Fuels Plc) which make no distinction based on composition.[79] Similarly, the use of any ionic liquids in inks for marker pens and ink jet printers has been claimed,[80] as has the use of any ionic liquid for removal of scale (typically $BaSO_4$ and $CaSO_4$, but also paraffin, wax and sludge) from wellbores in oilfield applications.[81]

While several other applications-related patents relevant to phosphonium ionic liquids have been filed in recent years, of particular note is the work of Institute Français du Petrole (IFP), who have commercialized the use of certain ionic liquids as solvents for catalysis for the dimerization, codimerization and oligomerization of olefins using transition metal catalysts (part of the Dimersol and Diafsol processes).[82] Ionic liquids containing an alkylaluminum dihalide with a quaternary ammonium or phosphonium halide wherein the alkyl chains are less than 12 carbon atoms long, and which are liquid below 80 °C, are covered.

Of particular interest for Friedel–Crafts chemistry, ionic liquids comprised of mixtures of R_nMX_{3-n} (R = C_{1-6}; M = Al, Ga; X = halide; n = 0, 1, 2) and ammonium, imidazolium, pyridinium or phosphonium halides, and the use of these in alkylation reactions, have also been claimed.[83]

Conclusions

While the future for ionic liquids is anything but certain, the potential for the field as a whole is undeniably enormous. We believe that successful commercialization of technologies utilizing these neoteric solvents will be a key driver for their continued development and integration into the chemical industry. Large-scale, industrial manufacture of the ionic liquids themselves is clearly a necessary precursor for this process. Here we have described a small part of our continuing efforts in this area.

Ionic liquids based on quaternary nitrogen cations such as imidazolium and pyridinium have been extensively investigated in the academic literature. By comparison, phosphonium ionic liquids have previously received scant attention. Judging by patent activity, however, there is significant interest in phosphonium ionic liquids for industrial use. We believe that phosphonium salts offer a good alternative to ammonium salts for many applications; while neither family is 'better' than the other, each will undoubtedly offer advantages and disadvantages for any particular function. This being the case, we anticipate that phosphonium ionic liquids will take their place alongside molecular solvents, imidazolium ionic liquids, and other modern materials in the toolboxes of chemists, chemical engineers, process developers, and inventors.

This is not to say, however, that further investigation of a more fundamental level is not required. Indeed, the physical behaviour of phosphonium ionic liquids still manages to surprise us regularly, and we look forward to continued research and discovery in this area.

Acknowledgements

We thank: Eduardo Kamenetzky, Chermeine Rivera, and William Mealmaker of Cytec Industries Research and Development for physical characterization of ionic liquids; Donato Nucciarone, John Hillhouse, and Mike Humeniuk of Cytec Canada Inc. for input in the preparation of this manuscript; Ken Seddon and Alwar Ramani of the QUILL Centre for continued collaboration in this area.

References

1 The terms 'ionic liquid' and 'room-temperature ionic liquid' are used here, interchangeably, to described ionic salts with melting points < ~100 °C. Many systems of interest have melting points around or below room temperature.
2 C. M. Gordon, *Appl. Catal. A*, 2001, **222**, 101.
3 J. G. Huddleston, A. E. Visser, W. M. Reichert, H. D. Willauer, G. A. Broker and R. D. Rogers, *Green Chem.*, 2001, **3**, 156.
4 (*a*) K. R. Seddon, *J. Chem. Tech. Biotech.*, 1997, **68**, 351; (*b*) J. D. Holbrey and K. R. Seddon, *Clean Products Proc.*, 1999, **1**, 223; (*c*) K. R. Seddon, A. Stark and M. J. Torres, *Pure Appl. Chem.*, 2000, **72**, 2275.
5 R. Sheldon, *Chem. Commun.*, 2001, 2399.
6 T. Welton, *Chem. Rev.*, 1999, **99**, 2071.
7 P. Wasserscheid and W. Keim, *Angew. Chem., Int. Ed.*, 2000, **39**, 3772.
8 (*a*) D. Zhao, M. Wu, Y. Kou and E. Min, *Catal. Today C*,, 2002, **74**, 157; (*b*) Y. S. Vygodskii, E. I. Lozinskaya and A. S. Shaplov, *Polym. Sci. Ser. C*, 2001, **34**, 236; (*c*) J. Dupont, C. S. Consorti and J. Spencer, *J. Braz. Chem. Soc.*, 2000, **11**, 337.
9 For example, see: N. Karodia, S. Guise, C. Newlands and J. Andersen, *Chem. Commun.*, 1998, 2341.
10 Cytec phosphonium salts are, in general, sold under the CYPHOS® trade name. Those specifically designated as ionic liquids will heretofore be known as CYPHOS IL phosphonium ionic liquids.
11 J. S. Wilkes, *Green Chem.*, 2002, 73.
12 P. Walden, *Bull. Acad. Imp. Sci. St. Petersbourg*, 1914, 1800.
13 R. M. Pagni, in *Advances in Molten Salt Chemistry, 1987*, ed. G. Mamantov, C.B. Mamantov and J. Braunstein, Elsevier, New York, 1987, vol. 6, pp. 211–346.
14 (*a*) H. L. Chum, V. R. Koch, L. L. Miller and R. A. Osteryoung, *J. Am. Chem. Soc.*, 1975, **97**, 3264; (*b*) J. Robinson and R. A. Osteryoung, *J. Am. Chem. Soc.*, 1979, **101**, 323.
15 J. S. Wilkes, J. A. Levisky, R. A. Wilson and C. L. Hussey, *Inorg. Chem.*, 1982, **21**, 1263.
16 T. B. Scheffler, C. L. Hussey, K. R. Seddon, C. M. Kear and P. D. Armitage, *Inorg. Chem.*, 1983, **22**, 2099.
17 D. Appleby, C. L. Hussey, K. R. Seddon and J. E. Turp, *Nature*, 1986, **323**, 614.
18 J. A. Boon, J. A. Levisky, J. L. Pflug and J. S. Wilkes, *J. Org. Chem.*, 1986, **51**, 480.
19 (*a*) Y. Chauvin, B. Gilbert and I. Guibard, *J. Chem. Soc., Chem. Commun.*, 1990, 1715; (*b*) R. T. Carlin and R. A. Osteryoung, *J. Mol. Catal.*, 1990, **63**, 125.
20 J. S. Wilkes and M. J. Zaworotko, *J. Chem. Soc., Chem. Commun.*, 1992, 965.
21 K. R. Seddon, *Green Chem.*, 2002, G25.
22 A. E. Visser, R. P. Swatloski and R. D. Rogers, *Green Chem.*, 2001, **2**, 1.
23 B. M. Quinn, Z. Ding, R. Moulton and A. J. Bard, *Langmuir*, 2002, **18**, 1734.
24 F. Endres, *Chem. Phys. Chem.*, 2002, **3**, 144.
25 C. M. Gordon and A. J. McLean, *Chem. Commun.*, 2000, 1395.
26 C. M. Gordon, J. D. Holbrey, A. R. Kennedy and K. R. Seddon, *J. Mater. Chem.*, 1998, **8**, 2627.
27 E. D. Bates, R. D. Mayton, I. Ntai and J. H. Davis, *J. Am. Chem. Soc.*, 2002, **6**, 926.
28 A. Bösmann, L. Datsevich, A. Jess, A. Lauter, C. Schmitz and P. Wasserscheid, *Chem. Commun.*, 2001, 2494.
29 (*a*) C. Ye, W. Liu, Y. Chen and L. Yu, *Chem. Commun.*, 2001, 2244; (*b*) W. Liu, C. Ye, H. Wang and L. Yu, *Tribology*, 2001, **21**, 482.
30 G. Gamero-Castaño and V. Hruby, *J. Propulsion Power*, 2001, **5**, 977.
31 B. Wu, R. G. Reddy and R. D. Rogers, *Sol. Eng.*, 2001, 445.
32 M. R. Netherton and G. C. Fu, *Org. Lett.*, 2001, **26**, 4295.
33 D. E. Kaufmann, M. Nouroozian and H. Henze, *Synlett*, 1996, 1091.
34 J. McNulty, A. Capretta, J. Wilson, J. Dyck, G. Adjabeng and A. Robertson, *Chem. Commun.*, 2002, 1986.
35 (*a*) A. E. Visser, R. P. Swatloski, W. M. Reichart, R. Mayton, S. Sheff, A. Wierzbicki, J. H. Davis and R. D. Rogers, *Chem. Commun.*, 2001, 135; (*b*) A. E. Visser, R. P. Swatloski, W. M. Reichart, R. Mayton, S. Sheff, A. Wierzbicki, J. H. Davis and R. D. Rogers, *Environ. Sci. Technol.*, 2002, **36**, 2523.
36 J. H. Davis, Jr., personal communication, November 27, 2001.
37 (*a*) A. W. Herriott and D. Picker, *J. Am. Chem. Soc.*, 1975, **97**, 2345; (*b*) C. M. Starks and C. Liotta, *Phase Transfer Catalysis*, Academic Press, Inc., New York, 1978; (*c*) M. O. Wolff, K. M. Alexander and G. Belder, *Chim. Oggi*, 2000, January/February, 29.
38 (*a*) W. A. Johnson, *Ylids and Imines of Phosphorus*, John Wiley and Sons, Inc., New York, USA, 1993; (*b*) *The Chemistry of Organophosphorus Compounds Vol. 3:Phosphonium Salts, Ylids and Phosphoranes*, ed. F. R. Hartley, John Wiley and Sons, Inc., New York, USA, 1994.
39 For example, see: V. P. Balema, J. W. Wiench, M. Pruski and V. K. Pecharsky, *Chem. Commun.*, 2002, 724.
40 S. A. Buckler and W. A. Henderson, *J. Am. Chem. Soc.*, 1960, **82**, 5791.
41 W. A. Henderson and C. J. Schultz, *J. Am. Chem. Soc.*, 1960, **82**, 5759.
42 We note that phosphine gas is highly toxic and pyrophoric, necessitating dedicated equipment and special handling techniques. The same is true, to a lesser extent, of many tertiary phosphines. Reactions involving these reagents should only be attempted by appropriately trained personnel.
43 M. M. Rahut, H. A. Currier, A. M. Semsel and V. P. Wystrach, *J. Org. Chem.*, 1961, **26**, 5138.
44 See http://www.dupont.com/vazo/.
45 A. J. Robertson, WO 01/87900, 2001 (Cytec Industries).
46 A. Downard and K. R. Seddon, unpublished results.
47 K. R. Seddon and A. J. Robertson, patent pending.
48 (*a*) P. C. Mørk and D. Norgård, *8th Scandinavian Symposium on Lipids, Helsinki, Proceedings*, 1975, 339; (*b*) P. C. Mørk and D. Norgård, *J. Am. Oil Chem. Soc.*, 1976, **53**, 506; (*c*) A. Menzel, K. Swamy, R. Beer, P. Hanesch, E. Bertel and U. Birkenheuer, *Surf. Sci.*, 2000, **454**, 88.
49 M. O. Wolff, K. M. Alexander and G. Belder, *Chim. Oggi*, 2000, 29.
50 (*a*) C. K. Ingold and O. Schumacher, *J. Chem. Soc.*, 1928, 3125; (*b*) W. Hanhart and C. K. Ingold, *J. Chem. Soc.*, 1927, 999; (*c*) J. March, *Advanced Organic Chemistry*, John Wiley and Sons, Inc., New York, USA, 4th edn., 1992.
51 M. Zanger, C. A. VanderWerf and W. E. McEwen, *J. Am. Chem. Soc.*, 1959, **81**, 3806.
52 J. B. Campbell, *US Pat.*, 3,639,493, 1972 (DuPont).
53 We note that *dynamic* thermal stabilities normally reported for ionic liquids are typically much higher than *static* thermal stabilities. Thus, most ionic liquids are not stable for extended periods of time at, or even well below, the 'onset of decomposition' temperature typically measured by TGA. We are currently in the process of investigating static stabilities of several phosphonium ionic liquids, and will report the results on these investigations in due course.
54 Viscosity measurements from −20 to 100 °C at 10° intervals were obtained using a TA Instruments AR1000N Rheometer. Geometry: cone and plate; cone: 40-mm diameter., 2° angle and 62 μm truncation, stainless steel; mode: peak hold at various selected stresses, *i.e.* steady shear rates; temp. gap compensation: 0.4 μm °C^{-1}; temp. control: Peltier plate (±1 °C).
55 (*a*) K. R. Seddon, A. Stark and M. J. Torres, *Pure Appl. Chem.*, 2000, **72**, 2275; (*b*) K. R. Seddon, A. Stark and M. J. Torres, in *Clean Solvents: Alternative Media for Chemical Reactions and Processing, ACS Symp. Ser. 819*, ed. M. Abraham and L. Moens, American Chemical Society, Washington, DC, 2002, vol. 819.
56 Samples at a concentration of 1% by weight of toluene were prepared at room temperature according to the following protocol: 57.8 μl of Baker Analyzed® A.C.S Reagent toluene were transferred by syringe (100 μl) to 4.95 g of the ionic liquids contained in 1 oz. vials (room temperature was 22–23 °C; the density of toluene in this range is ~0.86 g ml^{-1}). Each vial was immediately tightly capped then shaken for 1 h using a moderate speed wrist-shaker. A spatula was used to give a final gentle mixing before making the viscosity measurements. Samples containing other solvents were prepared similarly.
57 A. G. Avent, P. A. Chaloner, M. P. Day, K. R. Seddon and T. Welton, *J. Chem. Soc., Dalton Trans.*, 1994, 3405.

58 (*a*) D. Jerchel, *Chem. Ber.*, 1943, **76B**, 600; (*b*) D. Jerchel and J. Kimmig, *Chem. Ber.*, 1950, **83**, 277; (*c*) K. P. Davis and R. E. Talbot, *US Pat.*, 4,673,509 (Albright and Wilson, Ltd.); (*d*) R. E. Talbot, *Eur. Pat.*, EP 275207A2 (Albright and Wilson, Ltd.) (*e*) *Tolcide PS 72A Product Brochure*, Albright and Wilson Biocides, Oldbury, Worley, West Midlands, UK; (*f*) W. Wehner and R. Grade, Eur. Pat., EU0549006, 1993 (FMC Corp. (UK) Ltd.).

59 (*a*) W. A. Rickelton and D. Nucciarone, *The Treatment of Cobalt/Nickel Solutions Using CYANEX Extractants*, in *Proceedings of the Nickel-Cobalt 97 International Symposium—Hydrometallurgy and Refining of Nickel and Cobalt*, ed. W.C. Cooper and I. Mihaylov, Canadian Institute of Mining, Metallurgy and Petroleum, Montreal, 1997, pp. 275–292; (*b*) P. R. Danesi, L. Reichley-Yinger, G. Mason, L. Kaplan, E. P. Horwitz and H. Diamond, *Solvent Extr. Ion Exch.*, 1985, **4**, 435.

60 (*a*) W. A. Rickelton and A. J. Robertson, *US Pat.*, 4,353,883, 1982 (Cytec Technology Corp.); (*b*) A. J. Roberston, *US Pat.*, 4,374,780, 1983 (Cytec Technology Corp.); (*c*) W. A. Rickelton, D. S. Flett and D. W. West, *Solv. Extr. Ion. Exch.*, 1984, **2**, 815.

61 A. J. Carmichael, M. J. Earle, J. D. Holbrey, P. B. McCormac and K. R. Seddon, *Org. Lett.*, 1999, **1**, 997.

62 For proprietary reasons, quantities of reagents in this section have been scaled.

63 Sodium tetrafluoroborate can be extremely toxic and corrosive (due to liberated HF) in the presence of moisture. It should be handled with extreme care, and special safety considerations should be reviewed before its use. In particular, it is recommended that calcium gluconate gel be kept on hand when working with this reagent.

64 H. Bayer, W. Fischer, W. Hekele and E. Wipfelder, *US Pat.*, 6,160,077, 2000 (A. G. Siemens).

65 M. Yokoyama, J. Takano, M. Hasegawa and Y. Tatsukawa, *US Pat.*, 5,578,694, 1996 (Mitsubishi).

66 S. Mori, K. Ida and M. Ue, *US Pat.*, 4,892,944, 1990 (Mitsubishi).

67 *Chem. Eng. News*, 2002 (April 22), 32.

68 I. Hechenbleikner and K. R. Molt, *US Pat.*, 3,652,735, 1972 (Carlisle Chemical Works, Inc.).

69 Searches for this information can be conducted using free resources available on the Internet. For example, see: (a) http://ep.espacenet.com/; (b) http://www.uspto.gov/. Reflecting the use of these methods, the survey presented here is intended to be informal and representative rather than exhaustive.

70 K. R. Seddon, A. J. Carmichael and M. J. Earle, *World Pat.*, WO 01/40146 A1, 2000.

71 J. A. King, Jr., *US Pat.*, 5,705,696, 1998 (General Electric Company).

72 T. Kitazume, *US Pat.*, 2,001,0031,875A1 2001 (Crowell & Moring LLP Intellectual Property Group).

73 W. Keim, A. Boesmann and P. Wasserscheid, *World Pat.*, WO 01/55060, DE10003708, 2001 (Solvent Innovation GmbH).

74 W. Keim, W. Korth and P. Wasserscheid, *World Pat.*, WO 00/16902, 2000 (BP Chemicals Ltd., Akzo Nobel NV, Elementis UK Ltd.).

75 B. Ellis, *World Pat.*, WO 96/18459, 1996 (BP Chemicals Ltd.).

76 A. A. K. Abdul-Sada, K. R. Seddon and N. J. Stewart, *World Pat.*, WO 95/21872, 1995 (BP Chemicals Ltd.).

77 H. Bahrmann and M. Schulte, *US Pat.*, 6,103,908, 2000 (Celanese GmbH).

78 H. Bohnen and H. Bahrmann, *World Pat.*,, WO 00/66597, DE19919494, 2000 (Celanese GmbH).

79 (*a*) W. R. Pitner, D. W. Rooney and K. R. Seddon, *World Pat.*, WO 99/41752, 1999 (British Nuclear Fuels Plc) (*b*) C. G. Mackintosh, M. Fields, G. V. Hutson and K. R. Seddon, TW420809, 2001 (British Nuclear Fuels Plc) (*c*) R. C. Thied, A. J. Jeapes, W. R. Pitner, D. W. Rooney, T. Welton, J. E. Hatter and K. R. Seddon, *World Pat.*, WO 01/15175, 2001 (British Nuclear Fuels Plc) (*d*) W. R. Pitner, D. Hebditch, J. Hatter D. W. Rooney, K. R. Seddon and R. C. Thied, *World Pat.*, WO 01/13379, 2001 (British Nuclear Fuels Plc) (*e*) C. G. McIntosh, M. Fields, G. V. Hutson and K. R. Seddon, *World Pat.*, WO 98/06106, 1988 (British Nuclear Fuels Plc).

80 W. M. Schwarz, *US Pat.*, 6,048,388, 2000 (Xerox).

81 B. J. Palmer, D. Fu, R. J. Card and M. J. Miller, *World Pat.*, WO 01/77486A1, 2001 (Schlumberger).

82 Y. Chauvin, D. Commereuc, I. Guibard, A. Hirschauer, H. Olivier and L. Saussine, *US Pat.*, 5,104,840, 1992 (Institut Français du Petrole).

83 B. Ellis, F. Hubert and P.Wasserscheid, *World Pat.*, WO 00/41809, 2000 (BP Chemicals Ltd.).

Selective palladium-catalysed dimerisation of methyl acrylate in ionic liquids: towards a continuous process†

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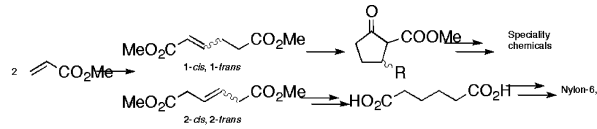
Received 3rd December 2002
First published as an Advance Article on the web 27th March 2003

The activity and stability of cationic palladium complexes $[Pd(PBu_3)_2S_2]^{2+}$ used for the selective tail-to-tail dimerisation of methyl acrylate are significantly improved with the utilisation of ionic liquids like $[BMIM][BF_4]$ or the protonated *N*-butyl-imidazole, $[HBIM][BF_4]$. Problems related to product inhibition and catalyst recycling are overcome by running the reaction in a two-phase mode, toluene being used as extractant. Catalyst stabilisation is further improved by trapping the ancillary ligand into the ionic liquid with an ionic tail: with the use of 1-dibutylphosphino-2-dimethylaminoethane, the catalyst is stable for more than 100 h, therefore demonstrating the feasibility of a continuous process for methyl acrylate dimerisation.

Introduction

The dimerisation of methyl acrylate (MA) to dimethyl Δ^2-, **1**, and Δ^3-, **2**, dihydromuconate (DHM) leads to a highly interesting intermediate which can be transformed to both speciality chemicals (such as cyclopentenones) and nylon-6,6 *via* adipic acid (Scheme 1). The latter reaction is of general interest since it allows the production of adipic acid from propene rather than from benzene,[1] 1,3-butadiene or 1,4-dimethoxybut-2-ene *via* stepwise carbonylation.[2,3]



Scheme 1

This reaction has been the subject of many investigations in the past forty years. Nickel,[4] ruthenium,[5] rhodium[6,7] and palladium[8,9] complexes, generally in association with various additives, have been reported. The catalysts described are almost not selective enough for the formation of the linear isomers **1** and **2**: in fact the head-to-tail dimer, **3**, which is also formed leads to poor mechanical properties of nylon-6,6. Apart from the example of cationic rhodium(III) species stabilised with $B(Ar_F)_4$ counter anions,[7] the most interesting catalyst systems are based on palladium, though the main drawback lies on catalyst deactivation by formation of metallic palladium. The highest rates are observed when silver salts with non-

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Green Context

The combination of clean technologies is increasingly recognised as being necessary to achieve significant improvements in chemical processes. This paper demonstrates how the combination of catalysis and a biphase solvent system brings an efficient and environmentally sound route to methyl acrylate dimerisation closer to technical reality. Potentially interesting is the stabilisation of the catalyst through clever ligand design to make it compatible with the non-volatile (ionic liquid) phase. Long catalyst lifetime makes a continuous process feasible. ***JHC***

† This work was presented at the Green Solvents for Catalysis Meeting, held in Bruchsal, Germany, 13–16th October 2002.
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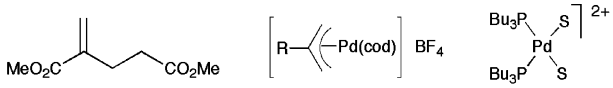
complexing anions are used as co-catalysts, therefore suggesting that ionic species may be implied.



3 **4**, R = H, Me, Ph **5**

We reported briefly on the use of cationic allylpalladium complexes, **4**,[10] which are prepared by the reaction of allyloxyphosphonium salts with zerovalent palladium complexes such as $Pd(dba)_2$.[11] The resulting species are selective catalysts for the dimerisation of methyl acrylate in the presence of basic phosphines like PBu_3 or PCy_3. We also reported on specific catalytic species arising from protonation of $Pd(acac)_2$, albeit with poor activity due to reduction of the dicationic active species to metallic palladium.[11] A clear improvement of catalyst activity and stability makes use of phosphine-stabilised palladium complexes arising from the reaction of Pd(II) salts or Pd(0) complexes with an excess of $[HOEt_2][BF_4]$ in the presence of phosphines.[12] In pure MA, these catalysts convert MA to DHMs in over 96% selectivity. Again, some catalyst reduction to metallic palladium was observed which required a complicated regeneration of the Pd after the catalytic reaction. Studies on the nature of the active species which are produced in the protonation process, have shown that solvated dicationic *cis*-bis(phosphine)palladium species, **5**, are involved.[13] Catalyst deactivation is probably related to the build-up of dimethyl muconate resulting from consecutive β-elimination processes in the coordination sphere of the $[Pd(II)]^{2+}$ species which is no more stabilised.[14] It was expected that these ionic species could be sequestered and stabilised in ionic liquids (ILs), thus providing new opportunities for a continuous process with technical feasibility. In fact, the initial idea to use ILs as solvent for catalysis improvement came to us with regard to the well-known rate enhancing effect of $Li[BF_4]$ addition,[9] and the observation that catalysis in presence of an excess of $[HPBu_3][BF_4]$, which is liquid under the reaction conditions used (T = 80 °C), leads to better TOFs and TONs.[13]

In the few last years, several Pd-catalysed reactions have been investigated in ILs. The rate of dimerisation of butadiene is significantly increased by switching from organic solvents like THF to $[BMIM][BF_4]$.[15] Heck reactions in ILs demonstrated the *in situ* formation of Pd-carbene complexes.[16] The selectivity of some Heck reactions with aryl bromides and electron rich olefins was found to be enhanced by the use of $[BMIM][BF_4]$ as solvent.[17] Moreover, Pd-catalysed allylation reactions[18] and Tsuji–Trost-coupling reactions[19] have been carried out in a biphasic reaction mode using an IL as catalyst carrier: no catalyst leaching into the product layer was observed using the ionic ligand Na_3TPPTS.

We describe here our achievements towards the first continuous, biphasic, Pd-catalysed dimerisation of MA using a tetrafluoroborate IL as catalyst immobilising solvent. A preliminary account of this work has been published.[20]

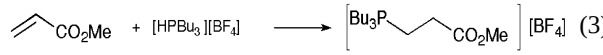
Results and discussion

Catalysts

The preparation of the catalyst, made up of three components, is critical for the realisation of good performances. As reported elsewhere,[13] in addition to the generation of the palladium active species [eqn. (1)], the phosphine may be protonated [eqn. (2)] and involved in the formation of the Michael-type adduct (AMP^+) with methyl acrylate [eqn. (3)]. In order to avoid the Michael-type reaction, the protocol we have retained was to add methyl acrylate to a mixture of tributylphosphine (P) and tetrafluoroboric acid etherate (H^+) in the appropriate ratio, then palladium bis(acetylacetonate) (Pd). The combination is stirred for 15 min before running the reaction at 80 °C which was reported to be the optimum temperature.[13] Under these conditions, and for Pd : P : H^+ : MA = 1 : 10 : 16 : 2500, a turnover frequency (TOF) of 58 h^{-1} and a turnover number (TON) of 229 after 24 h are registered.

$$[Pd] + 2[HOEt_2][BF_4] + 2PBu_3 \longrightarrow \mathbf{5} + 2\{H\} + 2Et_2O \quad (1)$$

$$PBu_3 + [HOEt_2][BF_4] \longrightarrow [HPBu_3][BF_4]\} + Et_2O \quad (2)$$



(3)

Ionic liquids

Different types of ionic liquids have been examined, namely phosphonium, pyridinium and imidazolium derivatives. The methyltributylphosphonium salts are prepared in good yields by alkylation of tributylphosphine with the appropriate reagent, *i.e.* trimethyloxonium tetrafluoroborate (preparation of $[MePBu_3][BF_4]$, mp 125–127 °C) and methyl *p*-toluene sulfonate (formation of $[MePBu_3][OTs]$, mp 78–79 °C). The methylpyridinium salts are obtained by reaction of the appropriate substituted pyridine with trimethyloxonium tetrafluoroborate. Finally, hydrogenoimidazolium salts were obtained by protonation of the corresponding alkylimidazole (*N*-methylimidazole, MIM, *N*-butylimidazole, BIM) with tetrafluoroboric acid etherate ($[HMIM][BF_4]$, mp 54 °C, $[HBIM][BF_4]$, mp 40 °C).[21]

Catalytic experiments

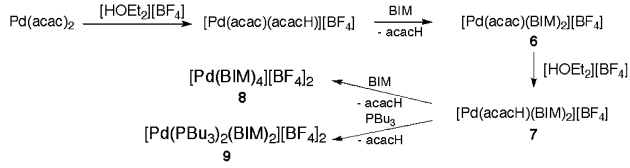
A mass ratio of 50% IL with respect to MA was used for this screening; under the reaction conditions used, a monophasic system is obtained, except in the case of $[HMIM][BF_4]$ where a biphasic system is observed at RT as well as at the temperature used for the dimerisation reaction. Table 1 shows that only the tetrafluoroborate salts lead to dimerisation with activities and selectivities comparable to those observed with neat substrate. This confirms the specificity of the tetrafluoroborate anion which has been already reported for methyl acrylate dimerisation and co-dimerisation with dienes.[10,14] In fact coordinating anions like tosylate, acetate and, to a lesser extent triflate, are occupying the sites available in **5**, therefore inhibiting coordination of MA. This inhibition is of course stronger with halides, so that trace amounts of chloride anion in $[BMIM][BF_4]$ prepared *via* metathetical exchange of Cl^- and BF_4^-, will reduce the catalyst performances (Table 1, entries 11, 12 and 13). In fact, addition of [BMIM]Cl to the reaction mixture efficiently terminates MA conversion. The nature of the cation has no strong effect within the same family: the introduction of an electron-donating (methyl-(2-methoxy)pyridinium tetrafluoroborate, Table 1, entry 5) or electron-withdrawing group (methyl-(2-fluoro)pyridinium tetrafluoroborate, Table 1, entry 6) does not change both activity and selectivity. Moreover, the same rate enhancing effect in pyridinium salts ILs as in imidazolium salts ILs indicates that there is no significant influence by *in situ* formed palladium carbene complexes (see for example refs. 22, 23), since this formation is unlikely under the acidic reaction conditions used.

The lower rate observed for $[HMIM][BF_4]$ is explained by the biphasic nature of the reaction medium leading to unfavourable mass transfer of the substrate to the ionic phase: no attemps (*i.e.* increase of the speed of agitation) have been made to overcome this phenomenon. The higher rate observed for $[HBIM][BF_4]$ may reflect the lack of residual chloride as well as specific interactions [eqn. (1–3) and *vide infra*] due to the Brønsted character of this IL. However, this IL should be prepared *ex situ*.

Table 1 Influence of the nature of the ionic liquid on the catalytic conversion of methyl acrylate (reaction conditions: Pd : HP^+ : H^+ : MA = 1 : 10 : 6 : 300; 50 mass% of IL; 80 °C, 1 h)

Entry	Ionic liquid	TOF/h^{-1}	Selectivity **1** + **2** (%)	Remarks
1	—	78	97.1	
2	$[MePBu_3][BF_4]$	100	96.8	
3	$[MePBu_3][OTs]$	0		
4	[4-Me-Bupyridinium][BF_4]	134	96.5	
5	[4-Me-Bupyridinium][BF_4]/[Me(2MeO)pyridinium][BF_4]	136	96.9	80 : 20 ratio
6	[4-Me-Bupyridinium][BF_4]/[Me(2-F)pyridinium][BF_4]	129	97.2	80 : 20 ratio
7	[HMIM][BF_4]	35	97.5	two phases
8	[HBIM][BF_4]	220	98.0	*ex situ* preparation
9	[HBIM][BF_4]	44	97.8	*in situ* preparation
10	[EMIM][BF_4]	130	96.8	
11	[BMIM][BF_4]	126	97.4	
12	[BMIM][BF_4]	72	97.8	[Cl^-] = 3.6 mol%
13	[BMIM][BF_4]	100	98.0	[Cl^-] = 0.5 mol%

We have shown that under the acidic conditions used, the palladium precursor, $Pd(acac)_2$, gives rise to ionic palladium species due to protonation and dissociation of the acac ligands as acetylacetone.[14] In the present case, the ^1H NMR spectrum of a solution of $Pd(acac)_2$ in acetone-d_6 treated with $[HBIM]BF_4$ (Pd : $[HBIM]BF_4$ = 1:10) kept at RT for 28 h shows the formation of $[Pd(acac)(BIM)_2][BF_4]$, **6**, and $[Pd(BIM)_4][BF_4]_2$, **8**. Comparison with authentic samples prepared *via* stepwise protonation of $Pd(acac)_2$ and interaction with BIM (Scheme 2),



Scheme 2

allows the assignment of signals at δ 0.92, 1.33, 1.82, 2.07, 4.20, 5.74, 7.01, 7.43, and 8.08 ppm to **6**, and at δ 0.88, 1.20, 1.72, 4.12, 7.15, 7.33, and 8.16 ppm to **8**. Trace amounts of these species could be observed even after 30 min of reaction at RT. It is worthy to note that $[HPBu_3]BF_4$ cannot promote the protonation of $Pd(acac)_2$ to $[Pd(acac)(acacH)]BF_4$.[24] ^{31}P NMR monitoring of the reaction medium indicates, in addition to the signals expected for HP^+, AMP^+, and $[Pd(acac)(PBu_3)_2][BF_4]$, the appearance of a new signal at δ 22.3 ppm. Indeed, $[Pd(PBu_3)_2(BIM)_2][BF_4]_2$, **9**, prepared from **7** by displacement of acetylacetone with PBu_3 (Scheme 2) exhibits a signal at δ 20.2 ppm. However, none of these complexes are really active in MA dimerisation (*i.e.* under standard conditions, TOF = 1 h^{-1} with the use of **6**, 7 h^{-1} with **8** and 9 h^{-1} with **9**). This should imply that the TOF observed with the use of $[HBIM][BF_4]$ represents a lower limit, since part of the palladium is quenched as inactive species.

Optimisation

As already mentioned, the concentration in acid of the catalyst system is a key parameter influencing its activity and stability [eqn. (1–3)]. An optimum, which depends on the amount of HP^+ added, has been already found when the reaction is run in pure MA.[13,14] It is therefore expected that the addition of ionic liquid will influence these equilibria as well as the strength of added tetrafluoroboric acid etherate. If the IL is a substitute of the acid, an increase of its amount will induce an increase in activity for the dimerisation of MA and a decrease in stability of the catalyst system. Studies on variation of H^+ concentration combined with variation of IL mass content with respect to the MA engaged have been performed with the 1-butyl-2-methylpyridinium tetrafluoroborate [4-MBP][BF_4] which cannot produce a palladium-carbene complex. Fig. 1 shows the relative activities

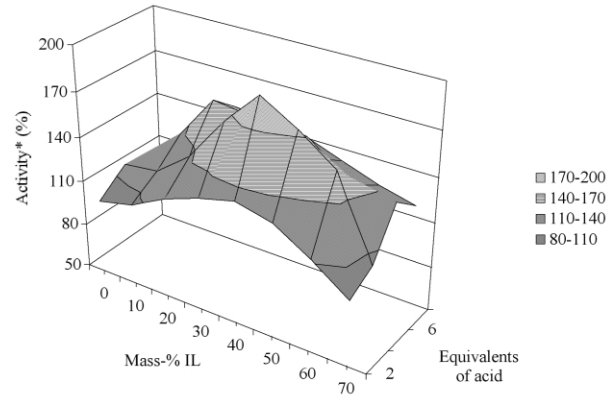


Fig. 1 Effect of tetrafluoroboric acid etherate and IL concentration on the activity for MA dimerisation (activity is defined as the % ratio of TOF found for a reaction without IL and with 2 equiv. of H^+ and TOF found for any IL mass% with respect to MA and *n* equiv. H^+; catalyst system: Pd : HP^+ : MA = 1 : 10 : 1000; 80 °C, 1 h).

observed on the basis of a standard assay without IL and 2 equiv. of H^+. A maximum is observed for 40 mass% of IL and 4 equiv. of H^+. An increase in the H^+ concentration leads to catalyst destabilisation, which is indicated by a rapid decomposition of the catalyst system leading to the formation of palladium black. This process is not accelerated by a simultaneous increase of IL concentration so that the decrease of activity observed at higher IL concentrations presumably reflects a dilution effect. These results indicate that a change in acidity of the reaction medium by addition of IL is not observed.

The same trends are observed with the use of $[BMIM][BF_4]$, except that the optimum is reached for 50 mass% of IL and 6–10 equiv. of H^+. We finally chose this IL for its ready availability, good performances and comparisons with the corresponding $[HBIM][BF_4]$ which seems to be a promising medium.[25] Table 1 and Fig. 1 indicate only the catalytic performances after 1 h of reaction. On a longer basis, as shown in Fig. 2, it is obvious that the addition of $[BMIM][BF_4]$ to the reaction medium leads to a clear improvement, despite the dilution of MA in the IL. After 176 h, the TON registered for the reaction run in IL is 3910. However, in both cases catalyst decomposition is observed after 50 h and becomes more pronounced with time.

Catalyst recycling

In all dimerisation reactions of MA, the substrate conversion is practically limited to about 80%, even if the integrity of the

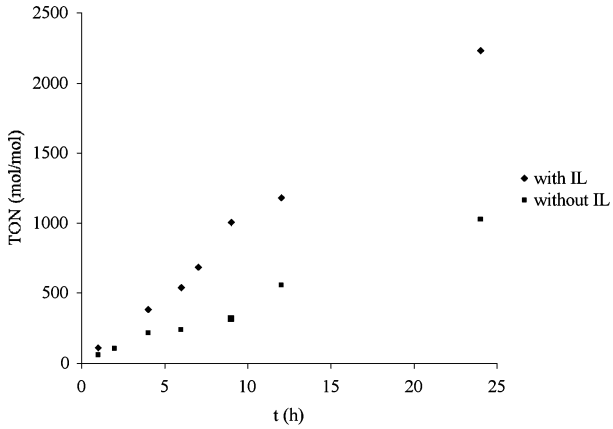


Fig. 2 Comparison of catalyst productivity in the presence or not of [BMIM][BF_4] (reaction conditions: Pd : HP^+ : H^+ : MA = 1 : 10 : 6 : 5000; 50 mass% IL; 80 °C; 1.4 equiv. of H^+ added after 6 and 12 h).

catalyst system is maintained. One possible explanation is an inhibition effect by the reaction products which compete with MA for coordination on the cationic palladium centre. In fact, by addition of MA, the reaction starts again, albeit with a lower activity due to the dilution of the catalyst system. The occurrence of an inhibition effect is further supported by the fact that addition at the beginning of the reaction of a mixture of the dimers **1**, **2** and **3**[14] or of methyl adipate, leads to a lower activity of the catalyst system (Fig. 3).

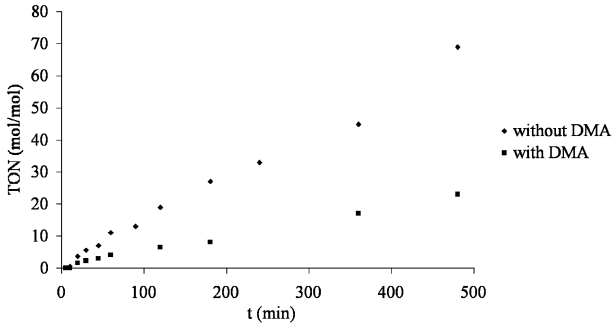


Fig. 3 Product inhibition of the catalyst system by addition of the reaction products or methyl adipate, DMA (reaction conditions: Pd : HP^+ : H^+ : MA = 1 : 10 : 5.7 : 5000; 70 °C).

In order to overcome this occurrence, a continuous process was outlined requiring the development of a biphasic reaction mixture. Toluene has an appropriate miscibility gap with [BMIM][BF_4], dissolves the reaction products and is inert against the catalytic conditions. However, first recycling experiments revealed a dramatic loss in activity during the recycling if tributylphosphine is used as the ancillary ligand. A TOF of 80 h^{-1} is achieved for the original run, but only 25 h^{-1} are reached in the fourth recycle (Fig. 4); the overall TON of eight runs is 265. Obviously this result is related to heavy leaching of the catalyst system into the organic layer and its decomposition as indicated by the coloration of the toluene phase. According to the reactions outlined in eqn. 1–3, it is possible that tetrafluoroboric acid etherate is consumed in order to maintain the palladium centre at the Pd(II) stage by a re-oxidation process [eqn. (4)][24] therefore facilitating the release of tributylphosphine and the fate of the catalyst system.

$$[Pd(PBu_3)_2S_2] + 2[HOEt_w][BF_4] \rightarrow \mathbf{5} + H_2 + 2Et_2O \quad (4)$$

Repeated additions of [$HOEt_2$][BF_4] to the catalyst system overcomes this problem to some extent, since a TON of 700 is achieved after eight runs.

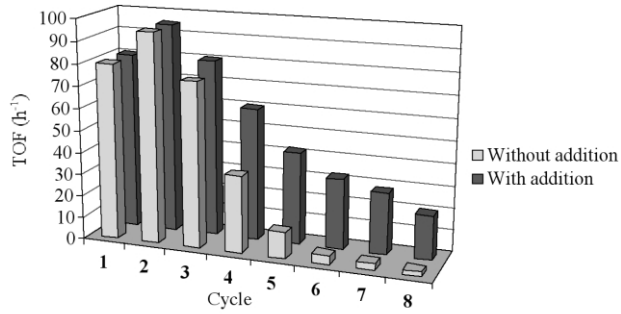
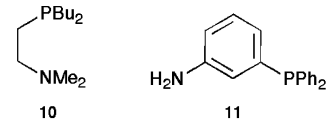


Fig. 4 Recycling of the catalyst system with toluene as extractant in the absence (light gray bars) and in the presence (dark gray bars) of tetrafluoroboric acid etherate (reaction conditions: Pd : HP^+ : H^+ : MA = 1 : 10 : 8 : 300; 80 °C; addition of 4 equiv. H^+ after run 2, 4, and 6).

Ionic ligands

In order to trap efficiently the ligand into the IL phase, we expect that an ionic ligand should provide this retention effect. The catalyst system will remain in the IL due to the charges carried *both* by the palladium centre and the ancillary ligand. Since even weakly coordinating anions have a detrimental effect on the cationic Pd-catalyst (Table 1, entry 3), the use of the anionic ligand TPPMSNa was not a promising alternative to solve this problem: in fact a TOF of only 42 h^{-1} is observed (Pd : TPPTS : H : MA = 1 : 5 : 11 : 2500, 50 mass% nitromethane, 80 °C). Therefore phosphine derivatives bearing a positive charge were examined. As reported elsewhere,[25] examination of a series of bidentate aminophosphine ligands clearly shows that the 1-dibutylphosphino-2-dimethylamino-ethane **10** provides the best results for the selective dimerisation of methyl acrylate under acidic conditions ([$HOEt_2$][BF_4]) in nitromethane).



10 **11**

Indeed, controlled protonation of **10** provides a very suitable combination of properties for the biphasic, Pd-catalysed methyl acrylate dimerisation in ILs: protonation at the dimethylamino arm, good donating character of the dibutylphosphino arm, strong retention of the ligand in the IL. Moreover, with the same Pd : ligand ratio it stabilises the catalyst much better than in case of PBu_3. Under the set of reaction conditions used, the catalyst system with **10** has been recycled four times, following extraction of the reaction products with toluene, without noticeable loss of activity (Fig. 5). During these cycles, no

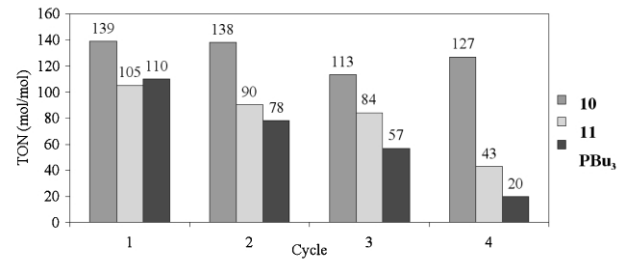


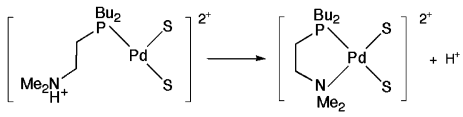
Fig. 5 Recycling of the catalyst system with toluene in the presence of different ancillary ligands (reaction conditions: Pd : HP^+ : H^+ : MA = 1 : 10 (PBu_3 and **11**) or 5 (**10**) : 6 : 2500; 50 mass% [BMIM][BF_4]; 20 ml toluene; 80 °C, 1 h. After each cycle, addition of 6 equiv. H^+, 2500 equiv. MA and 20 ml toluene).

coloration of the organic phase is observed, nor formation of palladium black. It is noteworthy that the ligand **11** provides a

better effect than PBu_3 even though the ligand to palladium ratio is 5 instead of 10. No coloration of the organic phase is observed; however palladium black is noticed at the third cycle, indicating, as expected, a weaker stabilisation of the palladium ionic centre leading to catalyst deactivation.[13,25] These results could certainly be amended by the optimisation of the palladium : ligand : proton ratios which are critical for the performances of the catalyst system.[13]

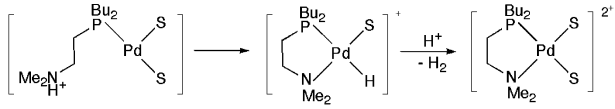
Possible explanations for the improvement of the catalyst system with **10**/**10H**$^+$ may be:

• the stabilisation of the active species in its resting state *via* a chelating effect (Scheme 3),



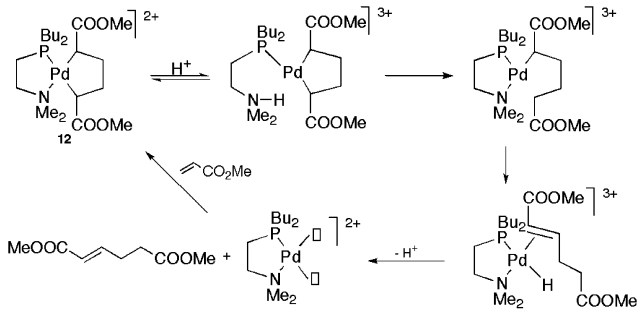
Scheme 3

• the reoxidation of Pd(0) species resulting from catalyst deactivation, according to eqn. (4), by bringing the N–H proton close to the catalytic centre, which facilitates the oxidative addition reaction (Scheme 4),



Scheme 4

• the opening of the metallacycle **12** *via* σ-bond metathesis involving the acidic N–H bond and a Pd–C bond of **12** rather than a β-elimination process, which is not sterically favourable. This reaction will readily occur in the next step where no sterical constraints are imposed, leading to Δ-2-DMHs and the active species (Scheme 5).



Scheme 5

Continuous process

On the basis of these encouraging results, a continuous process could be anticipated. To test this possibility a simple device has been used, based on extraction of the organic products with toluene (Fig. 6). The reactor is filled with glass beads (2 mm Ø)

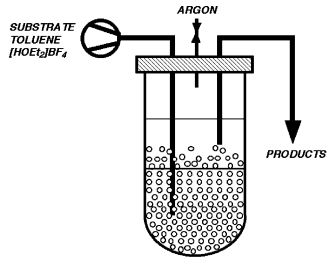


Fig. 6 Schematic drawing of the flow reactor.

in order to facilitate the mass transfer between the heavier ionic liquid phase and the organic phase, and is heated in a regulated oil bath. The organic phase, comprising toluene, methyl acrylate and tetrafluoroboric acid etherate, is pumped to the bottom of the glass reactor with the help of a pump syringe. The phase separation is made easy by the presence of the glass beads and the organic phase could be readily removed in the presence of a slight pressure of argon. With a flow rate of 3.3 ml h^{-1}, a residence time of 2 h 39 min is determined for dimethyl Δ^2-dihydromuconates **1**.

The reaction occurs with a high selectivity for DMHs. The TON measured every hour up to 10 h indicates a steady activity for this catalyst system (Fig. 7). The flow reactor was also used

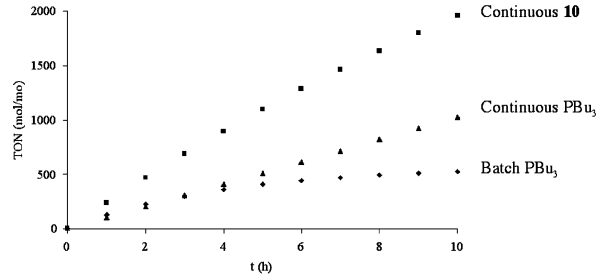


Fig. 7 Continuous flow reaction with **10** (■), PBu_3 (▲) and comparison with the batchwise reaction with PBu_3 (◆) (reaction conditions: Pd : ligand : H^+ : MA = 1 : 10 : 6 : 1750; 50 mass% $[BMIM][BF_4]$; 80 °C; feed rate = 3.3 ml h^{-1} of a mixture of toluene (60 ml), methyl acrylate (40 ml), $[HOEt_2][BF_4]$ (2.4 ml)).

for a catalytic run with the use of PBu_3. Comparison of both systems clearly shows a much lower activity for the PBu_3-based system, which constantly decreases with the reaction time due to the extraction of the catalyst components by the organic phase and its decomposition as indicated by the appearance of metallic palladium. The continuous reaction with the catalyst system using **10**/**10**H$^+$ is surprisingly stable and maintains the higher activity observed in batch reactions (*vide supra*). No deactivation can be observed over the first 10 h; after 43 h of continuous reaction, an overall TON of 3800 is achieved. This value is observed in batchwise reactions after 100 h.

Conclusions

This work clearly demonstrates the potential of a biphasic ionic liquid system to bring the Pd-catalysed MA dimerisation closer to a technical realisation. This can be achieved by avoiding the leaching of the components of the catalyst system, especially by trapping the phosphine ligand into the IL liquid phase *via* the introduction of a polar head generated *in situ* by the protonation of an amino group. The sequestration of the different constituents of the catalyst system allows higher reaction rate and catalyst recycling, therefore leading to lower catalyst consumption. Several aspects connected to the reaction engineering require further studies on the reactor design and the possibility of using other solvents like supercritical carbon dioxide.[26]

Moreover, it is obvious that the concept of 'protonated, hemilabile ligands' can be extended to others ligands and/or reactions. Work is in progress along this line.

Experimental

General

All the air or water sensitive reactions were run under argon in Schlenk glassware or in a glovebox. Solvents were distilled and kept under argon.

Chemicals: methyl acrylate, di-n-butylether, dimethyl glutarate, tetrafluoroboric acid (~54% in ether), tributyl- and

triphenylphosphine, butylchloride and Meerwein reagent were purchased from Fluka. Methyl acrylate was dried and distilled under argon.

GC: GC analyses were performed with a Siemens Sichromat 3 (Column: 50 m Pona HP-FS; carrier gas: helium, 1.5 bar, oven temperature programmation: 30–230 °C: 5 min isothermal, then 8 °C min^{-1}; inlet temperature: 250 °C; FID detection, detector temperature: 250 °C) coupled to a Hewlett Packard 3359 LAS-System or with a Shimadzu GC14-A (Column: 15 m Megabore Carbowax/BTR; carrier gas: He, 7.2 ml min^{-1}; oven temperature programmation: 45 °C (3 min), 12 °C min^{-1} up to 120 °C, 3 °C min^{-1} up to 200 °C, and 20 min at 200 °C; inlet temperature: 200 °C; FID detection, detector temperature: 200 °C).

GC/MS: GC/MS analyses were performed with a Varian 3700/MAT 112S (Column: 50 m Pona HP-FS; carrier gas: helium, 1.5 bar, temperature programmation: 30–230 °C, 15 min isotherm, then 25 °C min^{-1}; inlet temperature: 300 °C; ionisation source temperature: 210 °C, pressure: 2 Torr, ion current: 0.7 mA, ion energy: 70 eV) coupled with Varian MAT SS 200 data treatment system.

NMR: the NMR spectra were recorded on Bruker DPX-300 (Aachen), Bruker Avance 300 (Dijon) (^{1}H: 300 MHz; ^{13}C: 75 MHz; ^{31}P: 121 MHz; ^{19}F: 282 MHz), or Bruker DRX-500 (Dijon) (^{1}H: 500 MHz; ^{13}C: 125 MHz; ^{31}P: 202 MHz) FT-spectrometers. Tetramethylsilane is used as internal standard for ^{1}H and ^{13}C NMR; for {^{1}H}^{31}P and {^{1}H}^{19}F NMR, 85% phosphoric acid and trifluorochloromethane are respectively used as external standards.

Abbreviations utilised: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad signal.

Melting points: melting points are only measured for crystalline compounds. Air-sensitive samples are prepared in a glove box and sealed before determination with a Büchi SMP-20 or an Electrothermal 9100 equipment and are uncorrected.

Solvents: acetonitrile; 2 h reflux on calcium hydride and distillation under argon. Diethyl ether; 4 h reflux on sodium sand–benzophenone and distillation under argon. Dichloromethane; 2 h reflux of pure dichloromethane on calcium hydride and distillation under argon. Methanol; 3 h reflux on magnesium–magnesium methylate and distillation under argon. Nitromethane; 2 h reflux on calcium hydride and distillation under argon. Pentane; 2 h reflux on calcium hydride and distillation under argon. Toluene; 4 h reflux on sodium sand–benzophenone and distillation under argon.

Syntheses and analytical data

Syntheses of the phosphonium salts.

Hydrogenotributylphosphonium tetrafluoroborate. In a 250 ml Schlenk flask, tributylphosphine is dissolved (110 mmol, 22.3 g) in CH_2Cl_2 (50 ml). $[HOEt_2]BF_4$ (100 mol, *ca.* 54%, 13.7 ml) is added dropwise *via* a septum at 0 °C and the mixture is stirred for 1 h at RT. The ionic phase is diluted with 150 ml Et_2O, then cooled to −20 °C. Under vigorous stirring, the phosphonium salt precipitates as a white flocculent product. The liquid phase is removed by inverse filtration. The crude product is washed with *ca.* 400 ml Et_2O, dried *in vacuo* and kept in a glove box in a tight-sealed Schlenk flask. Total amount of product recovered: 27.6 g (95 mmol, 95% yield). mp: 52–54 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.89 (t, $^3J_{H–H}$ = 7.5 Hz, 9H, P–$CH_2CH_2CH_2CH_3$), 1.39–1.60 (m, 12H, P–$CH_2CH_2CH_2CH_3$), 2.21 (m, 6H, P–$CH_2CH_2CH_2CH_3$), 5.92 (dm, 1H, $^1J_{P–H}$ = 477.6 Hz, *H*–P) ppm.

{^{1}H}^{13}C NMR (75 MHz, $CDCl_3$): δ 11.2 (s, P–$CH_2CH_2CH_2CH_3$), 14.3 (d, $^1J_{C–P}$ = 39.4 Hz, P–$CH_2CH_2CH_2CH_3$), 21.5 (d, $^2J_{C–P}$ = 15.6 Hz, P–$CH_2CH_2CH_2CH_3$), 22.6 (d, $^3J_{C–P}$ = 4.5 Hz, P–$CH_2CH_2CH_2CH_3$) ppm.

{^{1}H}^{31}P NMR (121 MHz, $CDCl_3$): δ 15.1 (s) ppm.

{^{1}H}^{19}F NMR (282 MHz, $CDCl_3$): δ −150.8 (s) ppm.

Methyltributylphosphonium tetrafluoroborate. In a 250 ml Schlenk flask, fresh Meerwein reagent is suspended ($[OMe_3]BF_4$, 14.8 g, 100 mmol) in CH_2Cl_2 (100 ml). Tributylphosphine (22.3 g, 110 mmol) is added dropwise through a septum at −20 °C . The mixture is stirred for 10 h at RT. The solution is reduced to half its volume then diluted with Et_2O (150 ml) and cooled to −20 °C. Under vigorous stirring, the phosphonium salt precipitates as a white flocculent product. The liquid phase is removed by inverse filtration. The crude product is washed with pentane (*ca.* 400 ml), dried *in vacuo* and kept in a glove box in a tight-sealed Schlenk flask. Total amount of product recovered: 30.9 g (85 mmol, 85% yield based on Merweein reagent). mp: 125–127 °C

Analysis: C 51.14, H 9.72%; Calc. for $C_{13}H_{30}PBF_4$: C 51.34, H 9.94%.

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.89 (t, $^3J_{H–H}$ = 6.9 Hz, 9H, P–$CH_2CH_2CH_2CH_3$), 1.41–1.50 (m, 12H, P–$CH_2CH_2CH_2CH_3$), 1.72 (d, $^2J_{P–H}$ = 13.2 Hz, 3H, P–CH_3), 2.09–2.15 (m, 6H, P–$CH_2CH_2CH_2CH_3$) ppm.

{^{1}H}^{13}C NMR (75 MHz, $CDCl_3$): δ 2.1 (d, $^1J_{C–P}$ = 50.0 Hz, P–CH_3), 11.8 (s, P–$CH_2CH_2CH_2CH_3$), 18.1 (d, $^1J_{C–P}$ = 49.4 Hz, P–$CH_2CH_2CH_2CH_3$), 21.8 (d, $^3J_{C–P}$ = 4.4 Hz, P–$CH_2CH_2CH_2CH_3$), 22.2 (d, $^2J_{C–P}$ = 15.8 Hz, P–$CH_2CH_2CH_2CH_3$) ppm.

{^{1}H}^{31}P NMR (121 MHz, $CDCl_3$): δ 32.8 (s) ppm.

{^{1}H}^{19}F NMR (282 MHz, $CDCl_3$): δ −150.9 (s) ppm.

Methyltributylphosphonium tosylate. Methyl tosylate (18.6 g, 100 mmol) and tributylphosphine (22.3 g, 110 mmol) are placed in a 250 ml Schlenk flask at RT. The mixture is stirred for 5 h at 80 °C. The solution is diluted with CH_2Cl_2 (50 ml), then Et_2O (150 ml) and cooled to −20 °C. Under vigorous stirring, the phosphonium salt precipitates as a white flocculent product. The liquid phase is removed by inverse filtration. The crude product is washed with Et_2O (*ca.* 400 ml), dried *in vacuo* and kept in glove box in a tight-sealed Schlenk flask. Total amount of product recovered: 37.7 g (97 mmol, 97% yield based on methyl tosylate). mp: 78–79 °C

Analysis: C 61.97, H 9.51 %; Calc. for $C_{20}H_{37}PSO_3$: C 61.83, H 9.60%.

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.89 (t, $^3J_{H–H}$ = 6.9 Hz, 9H, P–$CH_2CH_2CH_2CH_3$), 1.41–1.50 (m, 12H, P–$CH_2CH_2CH_2CH_3$), 1.72 (d, $^2J_{P–H}$ = 13.2 Hz, 3H, P–CH_3), 1.90 (s, 3H, C(4)–CH_3), 2.09–2.15 (m, 6H, P–$CH_2CH_2CH_2CH_3$), 6.68 (d, $^3J_{H–H}$ = 7.8 Hz, 2H, C(3)*H*), 7.29 (d, $^3J_{H–H}$ = 8.1 Hz, 2H, C(2)H) ppm.

{^{1}H}^{13}C NMR (75 MHz, $CDCl_3$): δ 2.1 (d, $^1J_{C–P}$ = 50.0 Hz, P–CH_3), 11.8 (s, P–$CH_2CH_2CH_2CH_3$), 18.1 (d, $^1J_{C–P}$ = 49.4 Hz, P–$CH_2CH_2CH_2CH_3$), 18.8 (s, C(4)–CH_3), 21.8 (d, $^3J_{C–P}$ = 4.4 Hz, P–$CH_2CH_2CH_2CH_3$), 22.2 (d, $^2J_{C–P}$ = 15.8 Hz, P–$CH_2CH_2CH_2CH_3$), 123.5 (s, *C*(3)), 126.0 (s, *C*(2)), 136.4 (s, C(4)), 142.5 (s, C(1)) ppm.

{^{1}H}^{31}P NMR (121 MHz, $CDCl_3$): δ 32.8 (s, 1P) ppm.

Syntheses of pyridinium salts.

N-butyl-4-methylpyridinium tetrafluoroborate. The salt is commercially available (Solvent Innovation) and is made free of water and remaining chloride by, (i) drying a solution of the molten salt in CH_2Cl_2 with molecular sieves, (ii) treating with enough silver tetrafluoroborate until a chloride test with an aqueous solution of silver nitrate is negative. The solution is evaporated, the residue put on a column of dry Kieselgel and eluted with dry methylene chloride.

N-methyl-2-methoxypyridinium tetrafluoroborate. To a suspension of Meerwein reagent (4.955 g, 33.5 mmol) in CH_2Cl_2 (20 ml) is added 2-methoxypyridine (3.32 g, 30.4 mmol) at 0 °C under argon. The mixture is stirred for 16 h during which most of the N-methylated product precipitates as a white solid. After solvent evaporation, the salt is recrystallised at −20 °C in CH_2Cl_2 (20 ml). Total amount of product recovered: 5.28 g (25 mmol, 82% yield) as a white, crystalline compound. mp: 74–76 °C

Analysis: C 39.69, H 4.67, N 6.60%; Calc. for $C_7H_{10}NOBF_4$: C 39.85, H 4.78, N 6.64%.

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.86 (s, 3H, N–C*H*$_3$), 4.13 (s, 3H, O–C*H*$_3$), 7.33 (m, 1H, C(5)*H*), 7.41 (d, $^3J_{H–H}$ = 9.0 Hz, 1H, C(3)*H*), 8.19 (d, $^3J_{H–H}$ = 6.3 Hz, 1H, C(6)*H*), 8.27 (m, 1H, C(4)*H*) ppm.

{^{1}H}^{13}C NMR (75 MHz, $CDCl_3$): δ 41.1 (s, N–*C*H$_3$), 58.8 (s, O–*C*H$_3$), 110.8 (s, *C*(3)–*H* and *C*(5)–*H*), 118.3 (s, *C*(4)–*H*), 143.2 (s, *C*(6)–*H*), 147.6 (s, *C*(2)) ppm.

{^{1}H}^{19}F NMR (282 MHz, $CDCl_3$): δ −152.5 (s) ppm.

N-methyl-2-fluoropyridinium tetrafluoroborate. To a suspension of Meerwein reagent (4.955 g, 33.5 mmol) in CH_2Cl_2 (20 ml), 2-fluoropyridine (4.74 g, 48.8 mmol) is added at 0 °C under argon. The mixture is stirred for 16 h during which most of the N-methylated product precipitates as a white solid. After solvent evaporation, the salt is recrystallised at RT in a mixture of acetic acid (10 ml) and CH_2Cl_2 (30 ml). Total amount of product recovered: 7.69 g (38.7 mmol, 79% yield) as a white, crystalline compound. mp: 105–107 °C

Analysis: C 36.20, H 3.47, N 7.07%; Calc. for $C_6H_7NBF_4$: C 36.23, H 3.55, N 7.04%.

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.96 (s, 3H, N–C*H*$_3$), 7.66–7.57 (m, 2H, C(5)*H* and C(3)*H*), 8.31 (m, 1H, C(6)*H*), 8.41 (m, 1H, C(4)*H*) ppm.

{^{1}H}^{13}C NMR (75 MHz, $CDCl_3$): δ 41.4 (s, N–*C*H$_3$), 114.1 (s, *C*(3)H), 114.3 (s, C(5)H), 123.9 (s, C(4)H), 144.2 (s, C(6)H), 151.0 (d, $^2J_{F–C}$ = 11.5 Hz, C(2)) ppm.

{1H}^{19}F NMR (282 MHz, $CDCl_3$): δ −152.5 (s, 4F) ppm.

Preparation of ionic liquids.

Purification of 1-butyl-3-methylimidazolium tetrafluoroborate. The imidazolium salt is prepared according to the literature.[27] The removal of the residual chloride coming from metathetical exchange is carried out by (i) drying the IL *in vacuo*, (ii) dissolving it in dry dichloromethane, (iii) treating with enough silver tetrafluoroborate until a chloride test with an aqueous solution of silver nitrate is negative. The solution is evaporated, the residue put on a column of dry Kieselgel and eluted with dry methylene chloride.

Preparation of 1-hydrogeno-3-methylimidazolium tetrafluoroborate. In a Schlenk tube cooled to 0 °C with an ice–water bath, methylimidazole (14.432 g, 175.7 mmol) and, dropwise, tetrafluoroboric acid etherate (54%; 24 ml, 175.9 mmol) are introduced under argon . After stirring for 10 min at room temperature the solution is evaporated *in vacuo*. The dense oil obtained is worked up with dry Et_2O (50 ml) and the mixture cooled in liquid nitrogen.

After immersion of the Schlenk tube at −80 °C, Et_2O is removed by inverse filtration. The crystallisation process is repeated once using the same amount of dry Et_2O. The white solid is dried *in vacuo* overnight (29.156 g, 171 mmol; yield: 97%). mp: 54 °C.

Analysis: C 28.41, H 4.42, N 16.39%; Calc. for $C_4H_7BF_4N_2$: C 28.27, H 4.15, N 16.49%.

IR (nujol/NaCl): 3323, (br $\nu_{N–H}$) cm^{-1}.

^{1}H NMR (500 MHz, acetone-d_6): δ 4.02 (s, 3H, N–C*H*$_3$), 7.61 (s, 1H, C(5)–*H*), 7.63 (s, 1H, C(4)–*H*), 8.85 (s, 1H, C(2)–*H*), 12.18 (broad singlet, 1H, N–*H*) ppm.

{^{1}H}^{13}C NMR (125 MHz, acetone-d_6): δ 35.34 (N–*C*H$_3$), 119.85 (*C*(4)), 123.34 (*C*(5)), 135.81 (*C*(2)) ppm.

Preparation of 1-hydrogeno-3-butyl imidazolium tetrafluoroborate. In a Schlenk tube cooled to 0 °C with an ice–water bath, butylimidazole (20.218 g, 162.8 mmol) and, dropwise, tetrafluoroboric acid etherate (54%; 22.3 ml, 163.1 mmol) are introduced under argon . After stirring for 10 min at room temperature the solution is evaporated *in vacuo*. The dense oil obtained is worked up with dry Et_2O (50 ml) and the mixture cooled in liquid nitrogen.

After immersion of the Schlenk tube at −80 °C, Et_2O is removed by inverse filtration. The crystallisation process is repeated once using the same amount of dry Et_2O. The white solid is dried *in vacuo* overnight (34.088 g, 161 mmol, yield: 99%). mp: 40 °C.

Analysis: C 39.54, H 6.24, N 13.17%; Calc. for $C_7H_{13}BF_4N_2$: C 39.66, H 6.18, N 13.21%.

IR (Nujol/NaCl): 3334 (br, $\nu_{N–H}$) cm^{-1}.

^{1}H NMR (300 MHz, acetone-d_6): δ 0.89 (t, 3H, $^3J_{H–H}$ = 7.3 Hz, N–$CH_2CH_2CH_2CH_3$), 1.32 (m, 2H, $^3J_{H–H}$ = 7.1 Hz, N–$CH_2CH_2CH_2CH_3$), 1.88 (m, 2H, $^3J_{H–H}$ = 7.2 Hz, N–$CH_2CH_2CH_2CH_3$), 4.36 (m, 2H, $^3J_{H–H}$ = 6.9 Hz, N–$CH_2CH_2CH_2CH_3$), 7.65 (s, 1 H, C(5)–*H*), 7.74 (s, 1 H, C(4)–*H*), 8.94 (s, 1 H, C(2)–*H*), 12.41 (broad, 1 H, N–*H*) ppm.

{^{1}H}^{13}C NMR (125 MHz, acetone-d_6): δ 12.67 (s, N–$CH_2CH_2CH_2CH_3$), 18.96 (s, N–$CH_2CH_2CH_2CH_3$), 31.81 (s, N–$CH_2CH_2CH_2CH_3$), 48.95 (s, N–$CH_2CH_2CH_2CH_3$), 120.14 (s, *C*-(5)), 122.10 (s, *C*-(4)), 135.13 (s, *C*-(2)) ppm.

Ligand syntheses.

1-Dibutylphosphino-2-(dimethylamino)ethane **10**. To a solution of dibutylphosphine (2.31 g, 15.8 mmol) in THF (30 ml), a 1.6 M solution of BuLi in hexane (10.0 ml, 16 mmol) is added under argon at 0 °C. After 1 h, 1-dimethylamino-2-chloroethane (2.00 g, 18.59 mmol) is added dropwise at 0 °C under stirring: the mixture turns from orange–yellow to colourless. The reaction mixture is stirred for an additional hour, then the solvent is evaporated. The residue is treated with pentane, the solution filtrated over Celite, and evaporated. The crude product is distilled under vacuum (2.5 mbar): in the boiling range up to 60 °C, dibutylphosphine is recovered; the aminophosphine is collected at 80 °C as a colourless oil in 79% yield (2.71 g, 12.47 mmol).

Analysis: C 65.84, H 12.53, N 6.75%; Calc. for $C_{12}H_{28}NP$: C 66.32, H 12.99, N 6.45%.

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.88 (t, $^3J_{H–H}$ = 6.9 Hz, 9H, P–$CH_2CH_2CH_2CH_3$), 1.45 (br, 12H, P–$CH_2CH_2CH_2CH_3$), 1.54 (m, 2H, P–CH_2–CH_2–N), 2.22 (s, 6H, N–C*H*$_3$), 2.36 (m, 2H, P–CH_2–CH_2–N) ppm.

{^{1}H}^{13}C NMR (75 MHz, $CDCl_3$): δ 14.2 (s, P–$CH_2CH_2CH_2CH_3$), 24.9 (d, $^3J_{C–P}$ = 10.9 Hz, P–$CH_2CH_2CH_2CH_3$), 25.9 (d, $^1J_{C–P}$ = 12.8 Hz, P–CH_2–CH_2–N), 27.2 (d, $^2J_{C–P}$ = 11.6 Hz, P–$CH_2CH_2CH_2CH_3$), 28.4 (d, $^1J_{C–P}$ = 12.1 Hz, P–$CH_2CH_2CH_2CH_3$), 45.6 (s, N–*C*H$_3$), 57.0 (d, $^2J_{C–P}$ = 19.6 Hz, P–CH_2–CH_2–N) ppm.

{^{1}H}^{31}P NMR (121 MHz, $CDCl_3$): δ −32.1 (s) ppm.

3-Diphenylphosphinoaniline **11**. The ligand was prepared according to the literature.[28]

Analysis: C 77.45, H 5.91, N 5.06%; Calc. for $C_{18}H_{16}NP$: C 77.96, H 5.82, N 5.05%.

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.38 (br, 2H, N*H*$_2$), 6.51–6.64 (br, m, 3H, aryl), 7.02 (m, 1H, aryl), 7.24 (br, m, 10H, aryl) ppm.

{^{1}H}^{13}C NMR (75 MHz, $CDCl_3$): δ 116.0 (s, P–C–CH–CH–*C*H–C–NH_2), 120.4 (d, $^2J_{C–P}$ = 20.19 Hz, P–C–CH–*C*H–C–NH_2), 124.5 (d, $^2J_{C–P}$ = 20.0 Hz, P–C–*C*H–CH–CH–C–NH_2), 128.9 (d, $^3J_{C–P}$ = 7.1 Hz, P–C–CH–*C*H–CH), 129.1 (s, P–C–

CH–CH–*C*H), 129.8 (d, $^3J_{C-P}$ = 8.8 Hz, P–C–CH–*C*H–CH–C–NH_2), 134.2 (d, $^2J_{C-P}$ = 19.7 Hz, P–C–*C*H–CH–CH),), 137.7 (d, $^1J_{C-P}$ = 10.7 Hz, P–*C*–CH–CH–CH–C–NH_2), 138.5 (d, $^1J_{C-P}$ = 10.4 Hz, P–*C*–CH–CH–CH), 146.8 (d, $^3J_{C-P}$ = 8.1 Hz, P–C–CH–*C*H–CH–C–NH_2) ppm.

{^{1}H}^{31}P NMR (121 MHz, $CDCl_3$): δ −3.6 (s) ppm.

Synthesis of other organic compounds.

1-Dimethylamino-2-chloroethane. In a beaker are successively placed (1-chloro-2-ethyl)dimethylammonium chloride (20.00 g, 138.85 mmol), ice (100 g) and potassium hydroxide (7.00 g, 175 mmol). The mixture is stirred for 5 min, then CH_2Cl_2 (100 ml) is added. The organic phase is washed in a separating funnel with water (3 × 30 ml), then dried with magnesium sulfate. The solution is evaporated and the residue subjected to short-path distillation under vacuum (5.4 mbar). Collection at −78 °C gives the expected product (13.97 g, 130 mmol) as a colourless liquid in 93.5% yield.

Analysis: C 44.52, H 9.34, N 12.89%; Calc. for $C_4H_{10}NCl$: C 44.66, H 9.37, N 13.02%.

^{1}H NMR (300 MHz, $CDCl_3$): δ 2.10 (s, 6H, N–CH_3), 2.45 (t, $^3J_{H-H}$ = 6.8 Hz, 2H, Cl–CH_2–CH_2–N), 3.37 (t, $^3J_{H-H}$ = 6.8 Hz, 2H, Cl–CH_2–CH_2–N) ppm.

{^{1}H}^{13}C NMR (75 MHz, $CDCl_3$): δ 41.7 (s, 1C, Cl–CH_2–*C*H_2–N), 45.5 (s, 2C, N–*C*H_3), 61.1 (s, 1C, Cl–*C*H_2–CH_2–N) ppm.

Synthesis of organometallic compounds.

Palladium bis(acetylacetonate). $Pd(acac)_2$ is prepared according to the literature.[29]

^{1}H NMR (300 MHz, $CDCl_3$): δ 2.01 (s, 12H, CH_3–C(O)–CH_2–C(O)–CH_3); 5.36 (s, 2H, CH_3–C(O)–CH_2–C(O)–CH_3) ppm.

{^{1}H}^{13}C NMR (75 MHz, $CDCl_3$): δ 23.5 (s, 4C, *C*H_3–C(O)–CH_2–C(O)–CH_3); 99.7 (s, 2C, CH_3–C(O)–*C*H_2–C(O)–CH_3) ppm.

Synthesis of [Pd(acac)(BIM)$_2$][BF$_4$] **6**. [Pd(acac)-$(CH_3CN)_2$]BF_4 (0.287 g, 0.76 mmol) prepared according to refs. 12 and 24 and CH_2Cl_2 (12 ml) are placed in a Schlenk tube under argon. After addition of 1-butylimidazole (0.201 ml, 0.190 g, 1.53 mmol), a pale-yellow solution was obtained which is stirred at RT for 15 min. The solution is evaporated *in vacuo* to approximately 1 ml. By addition of dry Et_2O (5 ml), a solid precipitates, which is isolated by inverse filtration. The powder is washed with Et_2O (2 × 10 ml) and dried *in vacuo* (0.368 g, 0.68 mmol, 90% yield).

Analysis: C 41.9, H 5.81, N 10.98%; Calc. for $C_{19}H_{31}BF_4N_4O_2Pd$: C 42.21, H 5.78, N 10.36%.

IR (Nujol/NaCl): 3139 (s, ν_{C-H}), 1567 (s), 1525 (s), 1276 (w), 1248 (w), 1113 (s), 1061 (s), 966 (w), 970 (w), 855 (w), 810 (w), 751 (m), 722 (w), 664 (w) cm^{-1}.

^{1}H NMR (500 MHz, acetone-d_6): δ 0.89 (t, 6H, $^3J_{H-H}$ = 7.4 Hz, N–$CH_2CH_2CH_2CH_3$), 1.29 (m, 4H, $^3J_{H-H}$ = 7.3 Hz, N–$CH_2CH_2CH_2CH_3$), 1.79 (m, 4H, $^3J_{H-H}$ = 7.6 Hz, N–$CH_2CH_2CH_2CH_3$), 2.02 (s, 6H, CH_3C(O)–), 4.16 (t, 4H, $^3J_{H-H}$ = 7.2 Hz, N–$CH_2CH_2CH_2CH_3$), 5.67 (s, 1H, −C(O)–C*H*–), 6.97 (s, 2H, C(5)–*H*), 7.39 ppm (s, 2H, C(4)–*H*), 8.05 (s, 2H, C(2)–*H*) ppm.

{^{1}H}^{13}C NMR (125 MHz, acetone-d_6): δ 12.69 (N–$CH_2CH_2CH_2CH_3$), 19.09 (N–$CH_2CH_2CH_2CH_3$), 24.57 (s, CH_3C(O)–), 32.30 (s, N–$CH_2CH_2CH_2CH_3$), 47.81 (N–$CH_2CH_2CH_2CH_3$), 100.89 (–C(O)–CH–), 120.77 (s, *C*(5)), 127.68 (*C*(4)), 138.27 (*C*(2)), 186.89 (–*C*(O)–CH–) ppm.

Synthesis of [Pd(BIM)$_4$][BF$_4$]$_2$ **8**. $Pd(acac)_2$ (0.966 g, 3.17 mmol) and CH_2Cl_2 (12 ml) are placed in a Schlenk tube under argon. After addition of tetrafluoroboric acid etherate (54%, 0.866 ml, 6.34 mmol), an orange solid precipitates. Addition of 1-butyl imidazole (1.667 ml, 1.577 g, 12.7 mmol) immediately affords a colourless solution which is stirred at RT for 1 h. Evaporation of the solvent provides an off-white powder which is washed with Et_2O (2 × 10 ml) and dried *in vacuo* (2.2 g, 3.4 mmol, 92% yield).

Analysis: C 43.25, H 6.21, N 14.35%; Calc. for $C_{28}H_{48}B_2F_8N_8Pd$: C 43.30, H 6.23, N 14.43%.

IR (Nujol/NaCl): 3137 (s, ν_{C-H}), 1623 (w), 1534 (s), 1286 (m), 1256 (m), 1119 (s), 1051 (s), 948 (m), 844 (m), 759 (s), 737 (w), 661 (s), 635 (w) cm^{-1}.

^{1}H NMR (500 MHz, acetone-d_6): δ 0.88 (t, 3H, $^3J_{H-H}$ = 7.3 Hz, N–$CH_2CH_2CH_2CH_3$), 1.22 (m, 2H, $^3J_{H-H}$ = 7.1 Hz, N–$CH_2CH_2CH_2CH_3$), 1.74 (m, 2*H*, $^3J_{H-H}$ = 7.2 Hz, N–$CH_2CH_2CH_2CH_3$), 4.12 (m, 2H, $^3J_{H-H}$ = 7.1 Hz, N–$CH_2CH_2CH_2CH_3$), 7.17 (s, *1*H, C(5)–*H*), 7.34 ppm (s, 1H, C(4)–*H*), 8.18 (s, 1H, C(2)–H) ppm.

{^{1}H}^{13}C NMR (125 MHz, acetone-d_6): δ 12.65 (N–$CH_2CH_2CH_2CH_3$), 18.94 (N–$CH_2CH_2CH_2CH_3$), 32.15 (s, N–$CH_2CH_2CH_2CH_3$), 47.69 (N–$CH_2CH_2CH_2CH_3$), 121.02 (s, *C*(5)), 127.96 (s, *C*(4)), 138.49 (*C*(2)) ppm.

Synthesis of [Pd(BIM)$_2$(PBu$_3$)$_2$][BF$_4$]$_2$ **9**. [Pd(acac)(P-Bu_3)$_2$][BF_4] (0.316 g, 0.45 mmol) and CH_2Cl_2 (7 ml) are placed in a Schlenk tube under argon. To the pale yellow solution are added tetrafluoroboric acid etherate (54%, 0.063 ml, 0.45 mmol) and 1-butylimidazole (0.121 ml, 0.92 mmol). The colourless solution obtained is evaporated, dried *in vacuo* and affords an oily product which is washed with Et_2O (2 × 10 ml) and dried *in vacuo* (0.369 g, 0.4 mmol, 88% yield).

IR (Nujol/NaCl): 1248 (m), 1104 (m), 822 (m), 798 (s), 651 (m) cm^{-1}.

^{1}H NMR (500 MHz, acetone-d_6): as the ^{31}P NMR spectrum did not show the presence of free PBu_3 ligand, ^{1}H integrals have been calculated assuming the presence of two PBu_3 ligands per Pd. δ 0.88 (t, 6 H, $^3J_{H-H}$ = 7.5 Hz, N–$CH_2CH_2CH_2CH_3$), 0.97 (t, 18 H, $^3J_{H-H}$ = 7.4 Hz, P–$CH_2CH_2CH_2CH_3$), 1.47 (m, 12 H, $^3J_{H-H}$ = 7.3 Hz, P–$CH_2CH_2CH_2CH_3$), 1.56 (m, 4 H, $^3J_{H-H}$ = 7.5 Hz, N–$CH_2CH_2CH_2CH_3$), 1.76 (m, 16 H, N–$CH_2CH_2CH_2CH_3$ and P–$CH_2CH_2CH_2CH_3$), 1.93 (m, 12 H, P–$CH_2CH_2CH_2CH_3$), 4.10 (t, 4 H, $^2J_{H-H}$ = 6.8 Hz, N–$CH_2CH_2CH_2CH_3$), 7.33 (s, 2 H, C(5)–*H*), 7.36 (s, 1.75 H, C(4)–*H*), 8.39 (s, 2 H, C(2)–*H*) ppm.

{^{1}H}^{13}C NMR (125 MHz, acetone-d_6): δ 12.75 (N–$CH_2CH_2CH_2CH_3$ and P–$CH_2CH_2CH_2CH_3$), 18.90 (N–$CH_2CH_2CH_2CH_3$), 22.78 (m, $^1J_{C-P}$ = 15.2 Hz, P–$CH_2CH_2CH_2CH_3$), 22.84 (t, $^3J_{C-P}$ = 7.2 Hz, P–$CH_2CH_2CH_2CH_3$), 25.63 (s, P–$CH_2CH_2CH_2CH_3$), 32.28 (s, N–$CH_2CH_2CH_2CH_3$), 47.48 (N–$CH_2CH_2CH_2CH_3$), 121.29 (s, *C*(5)), 127.43 (s, *C*(4)), 138.54 (*C*(2)) ppm.

{^{1}H}^{31}P NMR (202 MHz, acetone-d_6): δ 20.07 ppm.

Catalytic reactions

One-phase assays. In a Schlenk tube (ST1), the relevant amounts of ligand, tetrafluoroboric acid etherate and eventually ionic salt are successively added under argon. The mixture is diluted with methyl acrylate and transferred into a Schlenk tube (ST2) containing the appropriate amount of $Pd(acac)_2$ in methyl acrylate. ST1 is rinsed three times with methyl acrylate. Depending on the catalytic test, the total amount of ester corresponds to 4.6 ml (4.3 g, 50 mmol) or 9.2 ml (8.6 g, 100 mmol). The mixture is stirred at RT for 15 min (starting from the beginning of the addition).

ST2 is heated in an oil bath maintained at 80°C under controlled stirring for the required time. The reaction is blocked by cooling at −78 °C (acetone-dry ice). The reaction mixture is neutralised with an aqueous solution of Na_2CO_3. n-Bu_2O (*ca.* 1

ml) or methyl benzoate (*ca.* 1 ml) is added as an internal GC standard and the mixture is diluted with Et_2O before GC analysis.

One-phase assay with follow-up. In a Schlenk tube (ST1), the relevant amounts of tributylphosphine (0.2 mmol), tetrafluoroboric acid etherate (0.32 mmol) and [BMIM][BF_4] (8.6 g) are successively added under argon. The mixture is diluted with methyl acrylate and transferred into a Schlenk tube (ST2) containing $Pd(acac)_2$ (0.0061 g, 0.02 mmol) and dimethyl glutarate as internal standard (0.8 g) in methyl acrylate. ST1 is rinsed three times with methyl acrylate. The total amount of ester corresponds to 9.2 ml (8.6 g, 100 mmol). The mixture is stirred at RT for 15 min (starting from the beginning of the addition).

ST2 is heated in an oil bath maintained at 80 °C under controlled stirring for the required time. Further additions of tetrafluoroboric acid etherate are made after 6, 12, 24, 81 and 103 h. After that time, 4.6 ml methyl acrylate (4.3 g, 50 mmol) are added again. Samples are withdrawn with a syringe through a septum and neutralised with an aqueous solution of Na_2CO_3. The organic layer is recovered by addition of Et_2O and immediately analysed by GC or kept at −20 °C until analysis.

Product inhibition test. In a Schlenk tube (ST1), tributylphosphine (0.071 g, 0.35 mmol) and tetrafluoroboric acid etherate (0.089 g, 0.55 mmol) are successively added under argon. The mixture is diluted with methyl acrylate and transferred into a Schlenk tube (ST2) containing $Pd(acac)_2$ (0.0107 g, 0.035 mmol) and *n*-Bu_2O as internal standard (*ca.* 1 ml) in methyl acrylate. ST1 is rinsed three times with methyl acrylate. The total amount of ester corresponds to 16.7 ml (15.1 g, 175 mmol). The mixture is stirred at RT for 15 min (starting from the beginning of the addition).

One half of the reaction mixture is placed in another Schlenk tube (ST3) where methyl adipate is added (3.1 g, 18 mmol). Both ST2 and ST3 are placed in an oil bath maintained at 70 °C under controlled stirring for the required time. Samples are withdrawn with a syringe through a septum and neutralised with an aqueous solution of Na_2CO_3. The organic layer is recovered by addition of Et_2O and immediately analysed by GC or kept at −20 °C until the analysis.

One-phase reactions with catalyst recycling.

(a) without addition of acid. In a Schlenk tube (ST1), hydrogenotributylphosphonium tetrafluoroborate (0.285 g, 0.098 mmol), tetrafluoroboric acid etherate (54%, 0.060 ml, 0.808 mmol) and [BMIM][BF_4] (8.6 g) are successively added under argon. The mixture is diluted with methyl acrylate and transferred into a Schlenk tube (ST2) containing $Pd(acac)_2$ (0.0284 g, 0.1 mmol) in methyl acrylate. ST1 is rinsed three times with methyl acrylate. The total amount of ester corresponds to 2.7 ml (2.588 g, 30 mmol). The mixture is stirred at RT for 15 min (starting from the beginning of the addition).

ST2 is heated in an oil bath maintained at 80°C under controlled stirring for 1 h, then rapidly cooled down to −20°C. Toluene (20 ml) is added and the two-phase system vigorously stirred for 15 min. The toluene phase is removed and neutralised with an aqueous solution of Na_2CO_3. The organic layer is recovered by further addition of Et_2O and methyl benzoate added as internal standard for GC analysis. The mixture is immediately analysed by GC or kept at −20 °C until analysis.

To the ionic phase remaining in ST2 is added again methyl acrylate (2.588 g, 30 mmol) and toluene (20 ml). The reaction mixture is placed again in the oil bath maintained at 80 °C under controlled stirring for 1 h, then cooled down to −20 °C and extracted with toluene as above.

The whole process is repeated six additional times.

(b) with addition of acid. The same protocol is operated with further addition of tetrafluoroboric acid etherate (54%, 0.030 ml, 0.404 mmol) every two runs.

Two-phase reaction with catalyst recycling. In a Schlenk tube (ST1), the appropriate amount of ligand (PBu_3: 0.20 mmol, **10**: 0.20 mmol, **11**: 0.10 mmol) and tetrafluoroboric acid etherate (PBu_3: 0.32 mmol, **10**: 0.52 mmol, **11**: 0.22 mmol) and [BMIM][BF_4] (4.3 g) are successively added under argon . The mixture is diluted with methyl acrylate and transferred into a Schlenk tube (ST2) containing $Pd(acac)_2$ (0.0061 g, 0.02 mmol) in methyl acrylate. ST1 is rinsed three times with methyl acrylate. The total amount of ester corresponds to 4.6 ml (4.3 g, 50 mmol). The mixture is stirred at RT for 15 min (starting from the beginning of the addition), then toluene is added (20 ml).

ST2 is heated in an oil bath maintained at 80 °C under controlled stirring for 1 h, then blocked by cooling at −78 °C (acetone-dry ice). The organic phase recovered and neutralised with an aqueous solution of Na_2CO_3. *n*-Bu_2O (*ca.* 1 ml) is added as an internal GC standard and the mixture is analysed by GC.

To the ionic phase remaining in ST2 are added once more methyl acrylate (4.3 g, 50 mmol), tetrafluoroboric acid etherate (0.12 mmol) and toluene (20 ml). The reaction mixture is placed again in the oil bath maintained at 80 °C under controlled stirring for 1 h, then cooled down for another separation and analysis.

A total of four cycles are performed in this way.

Continuous two-phase reactions. In a Schlenk tube (ST1), ligand **10** (0.0435 g, 0.20 mmol), tetrafluoroboric acid etherate (0.0842 g, 0.52 mmol) and [BMIM][BF_4] (3.0 g) are successively added under argon. The mixture is diluted with methyl acrylate (1 ml) and transferred into a Schlenk tube (ST2) containing $Pd(acac)_2$ (0.0061 g, 0.02 mmol) in methyl acrylate. ST1 is rinsed three times with methyl acrylate (total amount: 3.2 ml, 3.0 g, 35 mmol). The Schlenk tube (ST2) is filled with glass beads (ø 2 mm, 20 g) left for 45 min at RT, then heated in an oil bath maintained at 80 °C. A solution of methyl acrylate (80 ml, 827.1 mmol) and *n*-Bu_2O as internal standard (8 ml) in toluene (120 ml) is pumped throughout the reactor with a flow rate of 3.3 ml h^{-1} during 50 h. Samples of the organic phase are taken every 0.5 h, and treated as above for GC analysis.

Acknowledgements

We thank Professor Willi Keim for his continuous support and interest in this research. We thank CNRS and Université de Bourgogne for support. S. Stutzmann and I. Tommasi gratefully acknowledge, respectively, CNRS and Région Bourgogne for post-doctoral fellowships.

References

1 (*a*) U. Onken and A. Behr, *Lehrbuch der Technischen Chemie, Band 3: Chemische Prozeßkunde*, Thieme, Stuttgart, 1996; (*b*) *Ullmann's Encyclopedia of Industrial Chemistry*, 6th edn. on CD–ROM, Wiley–VCH, Weinheim, 1998.

2 R. Platz, R. Kummer and H. W. Schneider, *Ger. Offen.*, 2 836 518, BASF, 1978; R. Kummer, H. W. Schneider, F. J. Weiss and C. L. Lemann, *Ger. Offen.*, 2 837 815, BASF, 1979; N. Isogai, M.

Hosokawa, T. Okawa, N. Watui and T. Watanabe, *Ger. Offen.*, 3 146 313, Mitsubishi Gas Chemical Co., 1981; Rhône–Poulenc Industrie, Eur. Pat. EU 60 734, 1981.
3 A. S. C. Chan and D. E. Morris, US Pat. 4 611 082, Monsanto Co., 1986.
4 G. Wilke, K. Sperling and L. Stehling, *Ger. Offen.*, 3 336 691, Studiengesellschaft Kohle, 1985.
5 T. Alderson, E. L. Jenner and R. V. Lindsey Jr., *J. Am. Chem. Soc.*, 1965, **87**, 5638; R. J. McKinney, *Organometallics*, 1986, **5**, 1080; R. J. McKinney, *Organometallics*, 1986, **5**, 1752.
6 W. A. Nugent and R. J. McKinney, *J. Mol. Catal.*, 1985, **29**, 65.
7 M. Brookhart and S. Sabo–Etienne, *J. Am. Chem. Soc.*, 1991, **113**, 2777–2779; M. Brookhart and E. Hauptman, *J. Am. Chem. Soc.*, 1992, **113**, 4437.
8 M. G. Barlow, M. J. Bryant, R. N. Haszeldine and A. G. Mackie, *J. Organomet. Chem.*, 1970, **21**, 215; G. Oehme and H. Pracejus, *Tetrahedron Lett.*, 1979, 343; H. Pracejus and G. Oehme, *Z. Chem.*, 1980, **20**, 24; W. A. Nugent, *US Pat.* 4 451 665, DuPont, 1984; G. Oehme, *J. Prakt. Chem.*, 1984, **326**, 779; E. Drent, *US Pat.* 4 559 476, Shell Research, 1986.
9 W. A. Nugent and F. W. Hobbs, *J. Org. Chem.*, 1983, **48**, 5364.
10 P. Grenouillet, D. Neibecker and I. Tkatchenko, *Organometallics*, 1984, **3**, 1130.
11 P. Grenouillet, D. Neibecker and I. Tkatchenko, *Inorg. Chem.*, 1980, **19**, 3189.
12 P. Grenouillet, D. Neibecker and I. Tkatchenko, *French Pat.* 2 596 390, Rhône–Poulenc, 1987; P. Grenouillet, D. Neibecker and I. Tkatchenko, *US Pat.* 4 889 949, Rhône–Poulenc, 1989.
13 M. Bonnet, L. Carmona, P. Grenouillet, I. Guibert, D. Neibecker and I. Tkatchenko, *J. Mol. Catal. A: Chem.*, submitted.
14 I. Guibert, D. Neibecker and I. Tkatchenko, *J. Chem. Soc., Chem. Commun.*, 1989, 1850.
15 S. M. Silvana, P. A. Z. Suarez, R. F. de Souza and J. Dupont, *Polym. Bull.*, 1998, **40**, 401.
16 L. Xu, W. Chen and J. Xiao, *Organometallics*, 2000, **19**, 1123.
17 L. Xu, W. Chen, J. Ross and J. Xiao, *Org. Lett.*, 2001, **3**, 295.
18 W. Chen, L. Xu, C. Chatterton and J. Xiao, *Chem. Commun.*, 1999, 1247.
19 C. de Bellefon, E. Pollet and P. Grenouillet, *J. Mol. Catal. A: Chem.*, 1999, **145**, 121.
20 J. Zimmermann, P. Wasserscheid, I. Tkatchenko and S. Stutzmann, *Chem. Commun.*, 2002, 760.
21 M. Picquet, I. Tkatchenko, I. Tommasi, P. Wasserscheid and J. Zimmermann, *Adv. Synth. Catal.*, 2003, in press.
22 D. S. McGuiness , K. J. Cavell, B. F. Yates, B. W. Skelton and A. H. White, *J. Am. Chem. Soc.*, 2001, **123**, 8317.
23 S. Gründemann, M. Albrecht, A. Kovacevic, J. W. Faller and R. H. Crabtree, *J. Chem. Soc., Dalton Trans.*, 2002, 2163.
24 I. Guibert, *Thèse de doctorat de l'Université Paul Sabatier*, Toulouse, 1986.
25 J. Zimmermann, I. Tkatchenko and P. Wasserscheid, *Adv. Synth. Catal.*, in press.
26 A. Bösmann, G. Franciò, E. Jansenn, M. Solinas, W. Leitner and P. Wasserscheid, *Angew. Chem., Int. Ed.*, 2001, **40**, 2697; M. F. Sellin, P. B. Webb and D. J. Cole-Hamilton, *Chem. Commun.*, 2001, 781.
27 P. A. Z. Suarez, S. Einloft, J. E. L. Dullius, R. F. de Souza and J. Dupont, *Polyhedron*, 1996, **15**, 1217.
28 A. Hessler, O. Stelzer, H. Dibowski, K. Worm and F. P. Schmidtchen, *J. Org. Chem.*, 1997, **62**, 2362.
29 D. A. White, *J. Chem. Soc. A*, 1971, 143.

3-Methylimidazolium bromohydrogenates(I): a room-temperature ionic liquid for ether cleavage†

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Received 22nd November 2002
First published as an Advance Article on the web 21st February 2003

^{1}H- and ^{13}C{^{1}H}-NMR indicate that the liquid formed at room temperature from 1 mole of 1-methylimidazole and 2 moles of anhydrous HBr contains the 3-methylimidazolium cation ($Hmim^+$) and an equilibrium anionic mixture of Br^-, HBr_2^-, and $H_2Br_3^-$. This liquid cleaves ethers efficiently, producing the corresponding bromides and alcohols from cyclic and straight-chain dialkyl ethers and phenols and alkyl bromides from aryl alkyl ethers. During the course of the reaction, the single anion proton signal moves several ppm downfield as the $[HBr_2]/[H_2Br_3^-]$ ratio increases. The nitrogenic proton of $Hmim^+$ is unaffected, confirming that it is not labile and nor is it involved in the reaction, in accord with the large proton affinity of 1-methylimidazole.

Introduction

Ionic liquids (ILs) containing the 3-methylimidazolium cation are characterized for the first time. The only reference found in the literature for any liquid containing this cation was a European patent application[1] made in the year 2000 which described the formation of a liquid at 100 °C by combination of aluminium chloride with 1-methylimidazole under a dry hydrogen chloride atmosphere. That systems containing the $Hmim^+$ cation have not been studied is likely due to the fact that initially, ILs were largely prepared for their excellent electrochemical uses. The choice of a protic cation for these purposes would have quickly become unpopular due to the unavoidable hydrogen ion reduction potential. Additionally, systems of this type are often highly associated from hydrogen bonding. The main interest in this work was to explore the nature of the pure liquid so as to allow for confident use of it as a reaction medium. All too often ILs are used with the emphasis placed on the reaction products and not on the reaction medium. Additionally, reports in the literature, have often over-emphasized the chemistry of the anion and understated that of the cation, when in general, changing the cation is what distinguishes the chemical properties of one liquid to another.[2] The combination of 1-methylimidazole with anhydrous hydrogen bromide, in a 1 : 2 mole ratio, produced the 3-methylimidazolium bromohydrogenates(I) ionic liquid (HmimBr–HBr) at room temperature. Preliminary results indicate that this liquid cleaves ethers efficiently at room temperature. Interest in this reaction has arisen from the need for an economical and environmentally friendly process for the cracking of the polymeric ether linkages found in lignin. In this way, lignin could potentially serve as a natural source of fuel additives for the petroleum industry.[3a,b] It will be shown from ^{1}H- and ^{13}C{^{1}H}-NMR studies that the title room-temperature ionic liquid contains the fused 'onium' cation, 3-methylimidazolium ($Hmim^+$). Nitrogenic protons of fused 'onium' cations are typically considered to be acidic[4–6] but evidence found in this work indicates that the nitrogenic proton of the 3-methylimidazolium cation ($Hmim^+$) was neither the source of the acidic proton nor labile to any observable extent. Further characterization of the IL by IR spectrophotometry and cyclic voltammetry have been included in this report, along with the results some physico-chemical measurements.

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† This work was presented at the Green Solvents for Catalysis Meeting, held in Bruchsal, Germany, 13–16th October 2002.

Experimental

Techniques and equipment

All reactions were carried out either using standard Schlenk tube techniques under inert conditions or in an M-Braun

Green Context

The use of ionic liquids is ever-increasing. This paper deals with a novel aspect of these liquids. Instead of forming the quaternary centre with an alkyl group, the ionic liquids here are formed by reaction of alkyl imidazoles with HBr. The resultant liquid is a potent Brønsted acid, and is very active in the cleavage of ethers. In particular, the cleavage of anisole takes place under very mild conditions, and is unusually selective. ***DJM***

Labmaster 100 glove box with a dry N_2 atmosphere. NMR spectra were obtained with a Bruker AC-200 spectrometer. Both ^{1}H- and ^{13}C{^{1}H}-NMR spectra were obtained from samples containing a DMSO-d_6 capillary as locking solvent with the chemical shift δ (ppm) reported downfield relative to internal tetramethylsilane (TMS). Density was measured using a 2.00 mL volumetric flask calibrated with water. Conductivity measurements were made at 1000 Hz with a YSI-Model 31 (Yellow Springs Instrument Company) conductivity bridge using a glass cell containing two fixed platinum electrodes with mercury junction reservoirs. The Pt electrodes were replatinized according to published procedures.[7] The cell was then calibrated under standard conditions using 0.01 and 0.1 M KCl solutions to give a cell constant of 0.184 cm^{-1} ± 1%. The cell was placed in a moderately heated glycol bath during the measurements. The temperature was controlled by adding cold quantities of glycol to the bath. Viscosity was measured using a size 150 Cannon-Fenske viscometer that was calibrated with aqueous glycerol standards using known methods.[8a,b] IR spectra were obtained with a Perkin-Elmer 1600 FT-IR spectrophotometer. The samples were sandwiched between a folded piece of polyethylene plastic that was pressed between two sodium chloride salt plates held in place with a sample holder. Cyclic voltammograms were obtained with a BAS-100 W electrochemical analyzer using Pt working and auxiliary electrodes and a Pt pseudo-reference electrode. Measurements were made at a scan rate of 50 mV s^{-1} at room temperature.

Preparation of 3-methylimidazolium bromohydrogenates(I)

1-Methylimidazole (Aldrich) was dried over potassium hydroxide for 24 h and then doubly distilled from activated 3 Å molecular sieves into a two-necked round bottom flask containing activated 3 Å molecular sieves and fitted with a purge valve. Typically 5–10 g of 1-methylimidazole was added *via* an airless syringe to a pre-weighed, evacuated, septum capped, 20 mL glass vial. Under slight pressure, two equivalents of anhydrous hydrogen bromide gas (Aldrich) ($HBr_{(g)}$) were admitted to the vial *via* Teflon tubing from a gas trap, over the period of 30–40 min. The HmimBr–HBr ionic liquid was then stored in a capped vial in the glove box. The liquid loses HBr gas if not sealed.

The ether cleavage reactions

All liquid ethers were purified according to known procedures[9] and stored over magnesium sulfate in capped vials in the glove box. Solid ethers were used directly from the bottle. The general method was to place 0.5000 g of IL in an NMR tube where approximately 0.1000 g of ether was admitted. Reactions were then monitored by ^{1}H- and ^{13}C{^{1}H}-NMR analysis. For the ethers where yields are reported, the reactions were scaled up and stirred. Products were isolated *via* direct distillation from the IL. In those cases, a IL/ether mole ratio of approximately 2:1 was employed. All products, with the exception of methyl bromide, were confirmed by ^{1}H- and ^{13}C{^{1}H}-NMR analysis of the authentic sample in 3-methylimidazolium bromohydrogenates(I). Methyl bromide was not confirmed by spectral analysis of an authentic sample but evidence for its presence was indicated with both the proton and carbon NMR spectra where signals were observed in positions expected for methyl bromide as indicated from the literature values of the authentic, reference sample.[10,11]

Results

Characterization of the 3-methylimidazolium bromohydrogenates(I) ionic liquid

The HmimBr–HBr product was a clear light yellow liquid that exhibited the characteristics shown in Table 1. All measurements were made at room temperature unless otherwise indicated. 3-Methylimidazolium bromohydrogenates(I) is a dense and viscous ionic liquid that conducts well. The liquidus range spans from the glass transition temperature to approximately 100 °C as observed during the boiling point determination. The liquid evolved HBr immediately upon heating and by 100 °C it boiled vigorously. Heating through to 370 °C resulted in the loss of one molar equivalent of HBr from the system leaving behind the liquid 3-methylimidazolium bromide (HmimBr) salt that was clear but brown in colour. It was also noted that the HBr vapour temperature in the still head reached a maximum of 58 °C over 1 h of heating. Cyclic voltammetric analysis indicated a narrow electrochemical window, as expected. The ^{1}H-NMR spectrum shown in Fig. 1 yielded the following signals (ppm): δ 11.76 (1H, broad singlet, NH^+); 7.91 (1H, singlet, 2C-H); 6.47 (2H, singlet, 4,5C-H); 5.53 (1H, singlet, bromohydrogenate(I) species); 2.88 (3H, singlet, N-CH_3). The results from a variable temperature (VT) ^{1}H-NMR experiment are shown in Fig. 2(a) and (b). Temperatures increase from the bottom to the top, starting at 24 °C and increasing with 10 degree increments. The VT spectra indicate that the ionic protic species in the HmimBr–HBr ionic liquid are not chemically exchanging over the entire temperature range studied. The ^{13}C{^{1}H}-NMR analysis yielded the following signals in ppm: δ 133.57 (C-2); 122.22 (C-4); 118.15 (C-5); 35.96 (N-CH_3). The IR spectrum of neat 3-methylimidazolium bromohydrogenates(I) showed a broad band at 3131 cm^{-1} due to the stretching frequencies of the N–H^+ functionality. Upon comparison with the analogous 3-methylimidazolium bromide system it was noted that the number of N–H^+ stretching frequencies due to hydrogen bonding was reduced for HmimBr–HBr as was indicated by the relative narrowness of the band.

Table 1 Properties of 3-methylimidazolium bromohydrogenates(I)

Glass transition (T_g)/°C	~17–20
Boiling point (bp)/°C	~100
Density (ρ)/g mL^{-1}	1.75 ± 0.01
Molarity/M	7.17
Molar volume (V_m)/M^{-1}	0.139
Viscosity (η) @ 25 °C/cP	17.0
Conductivity (κ) @ 25 °C/mS cm^{-1}	40.6
Electrochemical window/V	0.426

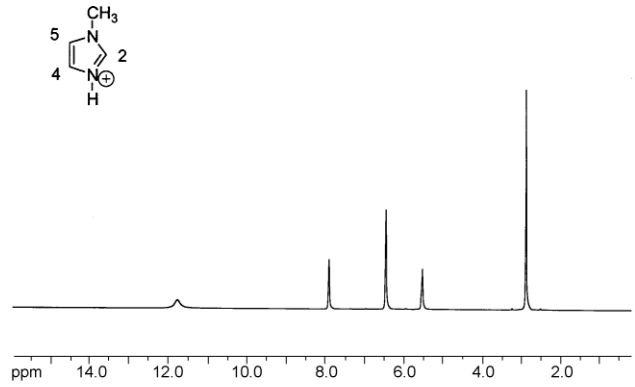


Fig. 1

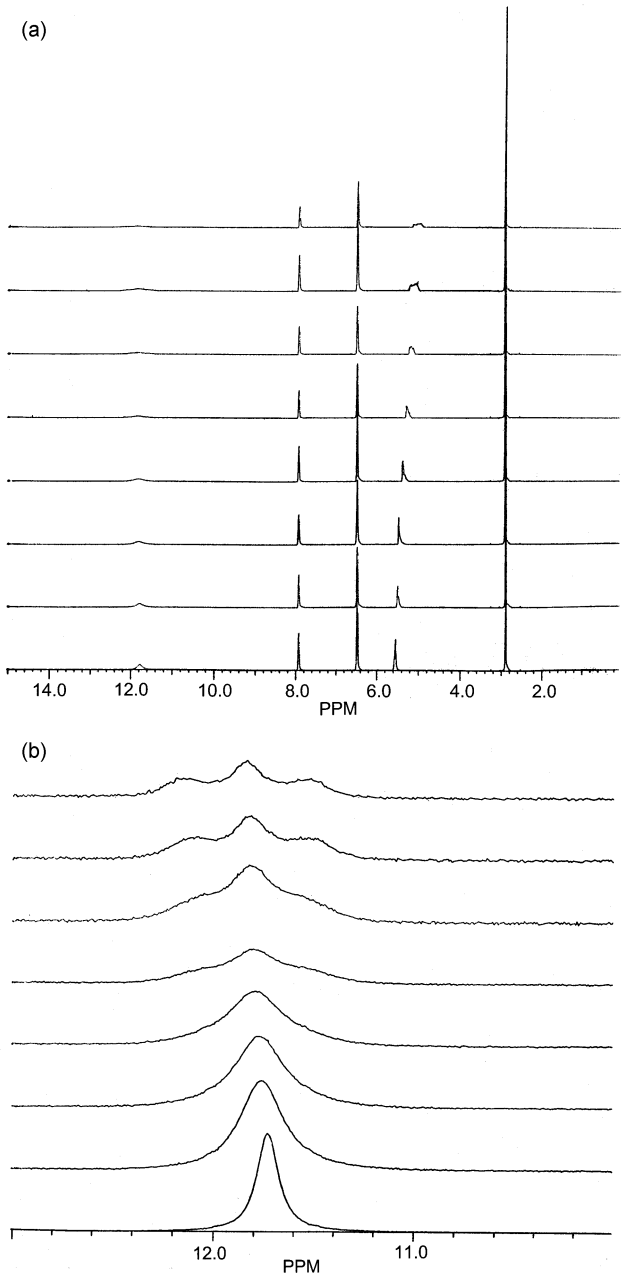
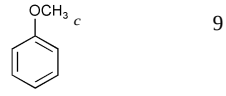
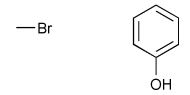
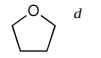
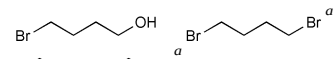
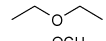
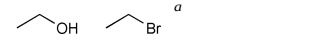
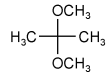
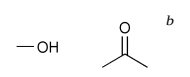
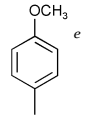
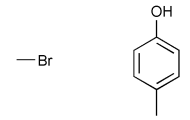
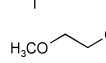
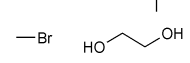
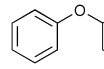
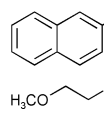
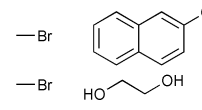


Fig. 2

The ether cleavage reactions

Simple reaction conditions were chosen to gain an indication of the inherent potency of the ionic liquid in the cleavage of ethers. At present, no attempt has been made to optimize the reaction conditions since in this primary study the main interest has been in the nature of the solvent and its suitability for ether cleavage reactions. Straight-chain and cyclic dialkyl and aryl-alkyl methyl ethers have been cleaved at room temperature in this system with ease. Alkyl aryl methyl ethers have been cleaved to produce the corresponding phenol and methylbromide while the straight-chain and cyclic dialkyl ethers produce both the alcohols and alkylbromides. Depending on the alkyl ether cleaved, a mixture of alcohol and bromide is produced but isolation *via* distillation promotes the formation of more bromide when excess acid is present. Phenolic products are stable under these conditions. It is likely that the acid content of the IL could be adjusted to avoid loss of alcohol or a quench and extraction sequence could be developed if desired. Many of the cleavage reactions were quite fast and did not require stirring at room temperature other than initial mixing. All ether cleavage reactions were followed by $^{13}C\{^{1}H\}$-NMR analysis and were considered to be complete (to 95%) once the carbon signals due to the ether were completely absent from the spectrum and only product carbon signals were observed. All products and yields of some products obtained (characterized by $^{13}C\{^{1}H\}$- and ^{1}H-NMR) are given in Table 2. Table 3 shows the $^{13}C\{^{1}H\}$-NMR data for each of the reactions and was included to emphasize the solvent shift of the signals observed in the IL when compared to literature values. Simple matching of the product chemical shifts observed in the IL, with known literature values for that product, will not provide sufficient evidence for its presence since solvent shifts of up to 5 ppm have been observed.

Table 2 Some ethers cleaved by HmimBr–HBr at room temperature

Ether	Time/h	Products	Yield (%)
	9		61.6
	< 1		91.3
	6		63.8
	< < 1		—
	< 24		65.2
	< 1		—
	—	no reaction	—
	< 24		—
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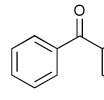
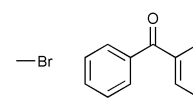
	< 24		—

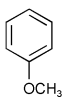
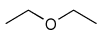
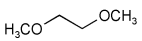
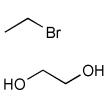
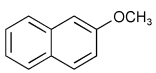
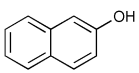
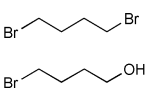
All reactions were run to 95% conversion.[a] Yield given for isolated product. [b] Decomposes, products were not characterized. [c] Fisher Scientific. [d] BDH. [e] Aldrich. [f] Eastman Kodak.

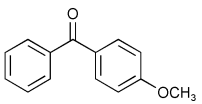
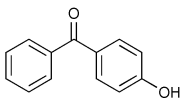
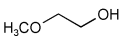
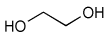
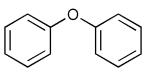
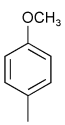
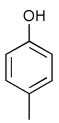
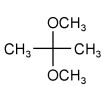
Discussion

The 3-methylimidazolium bromohydrogenates(I) ionic liquid

The production of the dibromohydrogenate(I) anion (HBr_2^-) was expected from the 1 : 2 melt stoichiometry. HX_2^- anions (X = Cl, Br) have been known since 1903 and the higher order polymers of $H_2X_3^-$ and $H_3X_4^-$ since 1909.[12] Mixed halide species, such as $HClBr^-$, were prepared at least as early as 1963.[13] The halohydrogenate(I) anions can have linear or bent symmetry and have bridged hydrogen structures with bond energies comparable to those of normal covalent bonds.[14,15a–c] ^{1}H-NMR analysis of freshly prepared ionic liquid indicated the chemical shift of the acidic proton signal (δ 5.44 ppm) to be several ppm upfield of the chemical shift expected from the literature value for HBr_2^- (δ 10.2 ppm)[16] and closer to the chemical shift expected for $H_2Br_3^-$ (δ 3.69 ppm).[17] The proton signal observed for the bromohydrogenates(I) system is likely an average for both the HBr_2^- and the $H_2Br_3^-$ protons. The $[HBr_2^-]/[H_2Br_3^-]$ ratio is then less than unity in the pure liquid since the averaged proton signal is *upfield* of the average signal position expected.

Table 3 $^{13}C\{^{1}H\}$-NMR study of ether cleavage with HmimBr–HBr (δ (ppm) reported relative to TMS)

Ether	δ Ether in IL	Product	δ Product in IL	Reference in IL	Lit.[a]
	157.57 128.36 118.86 112.58 54.58		154.71 128.43 119.42 114.24	154.59 128.51 119.40 114.33	155.6 130.5 120.8 116.1
	67.40 13.41		11.24 60.48 14.33	— 60.91 14.36	10.2 57.3 17.9
	69.04 57.70		29.00 18.48 61.63	28.88 18.60 61.72	28.3 20.3 63.4
			11.68	—	10.2
	155.57 132.63 127.99 126.79 126.15 125.28 124.89 122.48 117.22 104.79 54.86		152.60 132.70 128.21 126.50 126.21 125.18 124.75 121.90 117.16 108.04	152.53 132.70 128.23 126.66 126.23 125.22 124.78 121.97 117.21 108.12	[b]155.26 134.61 129.01 127.78 127.36 126.01 125.84 122.43 118.54 108.73
			11.37	—	10.2
	66.45 24.34		33.50 29.87 60.14 34.17 28.74 27.87	33.34 29.77 63.99 33.46 27.26 26.29	33.6 31.8 [c]62.0 32.9 31.6 30.1

Ether	δ Ether in IL	Product	δ Product in IL	Reference in IL	Lit.[a]
	198.74 167.59 137.75 135.39 132.39 129.93 127.76 114.67 56.54		197.81 166.01 137.68 134.70 131.96 130.54 129.68 127.60 116.00	198.09 166.27 138.05 134.92 132.14 130.70 130.26 127.69 116.16	[b]197.39 161.30 137.83 133.22 132.28 129.83 129.02 128.24 115.47
			11.60	—	10.2
	69.13 62.45 57.82		61.43	61.72	63.4
			11.72	—	10.2
	155.11 128.82 122.23 117.40	no reaction	—	—	—
	155.63 128.79 128.73 112.39 54.43 19.21		152.62 128.69 127.48 114.13 19.13	152.08 128.71 127.61 114.10 19.32	[c]154.3 130.6 130.3 115.6 20.9
			10.84	—	10.2
	110.40 51.02 29.97		48.14	48.33	49.3
			— 11.51	— —	205.1 24.9 10.2

[a] See ref. 10. [b] See the Aldrich Library of NMR data. [c] Approximate values calculated using ChemDraw Ultra© Version 5.0.

Evidence that the acidic proton in this system was not provided by the protic cation has been indicated by ^{1}H-NMR analysis where the nitrogenic proton chemical shift has been observed to be unaffected throughout the entire course of the reaction and well after complete consumption of the bromohydrogenates(I) species. The results from the variable-temperature run are significant because they have strongly indicated that the chemical exchange phenomenon is not active in the system. These results are in accord with the large proton affinity of 1-methylimidazole in the gas phase, P.A. = 958 kJ mol^{-1}.[18] In this work, gas phase proton affinities are considered to be the best reference for the relative order of acid/base strength, since in the absence of any 'solvent effect', the intrinsic acidity/basicity of the species is revealed.[19,20] The chemical shift of the N–H$^+$ proton was observed slightly downfield ($\Delta\delta \cong 0.1$ ppm) and that of the acidic species was observed slightly upfield ($\Delta\delta \cong 0.5$ ppm) over the 70 °C range. The resonance signal of the nitrogenic proton showed a transition from a broad singlet to a broad triplet at a temperature of 64 °C which remained through to 94 °C. In this case, the low temperature broad singlet was observed to further broaden from room temperature to 64 °C. Above this temperature, a broad triplet resonance was observed and sharpened slightly through to 94 °C (the upper limit of the variable temperature unit). The initial broadness of the triplet in the pure liquid is not due to intermediate rates of exchange since the signal width decreases with raised temperatures. This is opposite to the behaviour expected for the exchange phenomenon which has a positive temperature coefficient.[21] Furthermore, any slow exchange process would have been rapidly increased with an increase in temperature where the triplet would broaden into a singlet and eventual signal coalescence would have been observed.

The observation of the triplet arises from spin–spin coupling between the nitrogenic proton and the ^{14}N nucleus ($I = 1$) where the proton experiences coupling with all three spin states of the nitrogen ($m_I = +1, 0, -1$, for the low-field, center-field and high-field signals, respectively). The ^{14}N quadrupole moment couples the nuclear spin with rotational molecular motion *via* the quadrupole moment–electric field gradient interaction.[22] A triplet resonance is not observed at lower temperatures because the quadrupole moment–electric field gradient interaction undergoes more efficient relaxation, due to the slow molecular motion, which induces reduced fluctuations of the electric field gradient. The more efficient relaxation reduces the ^{14}N spin state lifetimes. The net result is that the proton attached to the nitrogen experiences an average spin state from ^{14}N and the signal is broadened. Broadening here is caused by the nitrogenic proton experiencing different spin states not through mobile chemical exchange but by means of rapid spin state change of the ^{14}N nucleus to which it is attached.[23] As the temperature is increased, the relaxation of the quadrupole moment–electric field gradient interaction becomes much less efficient since the increased rotational/tumbling motion of the cation increases the fluctuation of the electric field gradient. The lifetimes of each of the three ^{14}N spin states are increased as a result of the less efficient relaxation of the quadrupole moment-electric field gradient interaction and become sufficient enough to cause splitting of the nitrogenic proton signal where a triplet is observed.[24] It was also observed that the results from the V T ^{1}H-NMR experiment indicate that both the N-methyl and aromatic ring protons are not extremely temperature sensitive with $\Delta\delta$ N-CH$_3$ = 0.04 ppm, $\Delta\delta$ 2C-H = 0.01 ppm and $\Delta\delta$ 4,5C-H = 0.02 ppm, over a 70 °C range.

The non-exchanging behaviour found for this system has been observed for other highly acidified protic 'onium' salts in several earlier reports. For example, it has been demonstrated that an acidified aqueous solution of methylammonium chloride (pH = 0.86) gave no indication of chemical exchange and the methyl group proton signal was split by the three nitrogenic protons to a sharp quartet.[25] In another study, an acidified aqueous solution of pyrrolidinium chloride also indicated N–H coupling as well as α-hydrogen splitting.[26] The systems studied in the above reports were observed to chemically exchange in the presence of excess parent base. In this work, detectable α-hydrogen splitting was not observed for the Hmim$^+$ cation which would suggest exchange but evidence obtained from the VT ^{1}H-NMR and ether cleavage experiments does not support any view that the nitrogenic proton is labile in this system.

The results of the IR analysis indicate the system is less hydrogen bonded than the 3-methylimidazolium bromide salt. This is likely due to the fact that the interaction between the nitrogenic proton and the intense force field associated with the smaller bromide ion would be weakened as the bromide becomes sequestered by HBr to form the larger higher order polymeric bromohydrogenate(I) species.[27] This result is consistent with the IR spectrum of liquid pyridinium dichlorohydrogenate(I) in which hydrogen-bonding bands were completely absent in relation to the pyridinium chloride system.[28]

Emphasis on the chemistry of the nitrogenic proton in this work was warranted by the notion that 'onium' cations are generally acidic. This has been the case since the work of Audrieth, Long and Edwards[4] where in 1936 the investigation of the 'acidic' nature of fused pyridinium chloride was undertaken with a variety of metals, oxides and chloride, nitrate and carbonate salts. In the summary, they concluded that fused pyridinium chloride possessed the 'typical' 'onium' salt acidic character. Results in this laboratory on the nature of fused pyridinium chloride also support the notion that it can be acidic but there is evidence that the pyridinium cation is not the active species. As with 3-methylimidazolium bromohydrogenates(I) ionic liquid, the acidic species is more likely the dichlorohydrogenate(I) anion, which is generated *in situ* at high temperatures in fused pyridinium chloride.

The ether cleavage reactions

The acidic cleavage of simple straight-chain and cyclic dialkyl and aryl alkyl ethers has been successful in the 3-methylimidazolium bromohydrogenates(I) ionic liquid system. ^{1}H-NMR studies of the reactions in HmimBr–HBr indicated a shift of the acidic proton signal. The resonance was observed downfield ($\Delta\delta \cong 3$–5 ppm in general) from that obtained in the pure liquid and closer to the signal position expected for the dibromohydrogenate(I) proton. The dynamic nature of the acidic proton observed from the ^{1}H-NMR spectra may be explained in terms of the equilibrium

$$Br^- + H_2Br_3^- \leftrightarrow 2\ HBr_2^- \quad (1)$$

In the fresh sample of the 1:2 ionic liquid the anionic equilibrium mixture at hand favours the formation of the higher-order acidic polymer, $H_2Br_3^-$. The bromide concentration increases during an ether cleavage reaction and thereby increases the $[HBr_2^-]/[H_2Br_3^-]$ ratio as more bromide becomes available to combine with the $H_2Br_3^-$ species. The equilibrium shifts to increase the concentration of HBr_2^-, which is reflected, by the downfield shift of the proton signal towards the value expected for the HBr_2^- anion.

The reactions occur efficiently at room temperature with a variety of ethers that in other systems require harsh conditions. For example, 1.990 g (18 mmol) of anisole is cleaved in less than 9 h with 2 molar equivalents of the title liquid to 95% completion at room temperature. Phenol was distilled directly from the reaction flask in a yield of 61.6%. Similarly *p*-methylanisole (5.6981 g, 47 mmol) was cleaved using the above conditions to 95% completion in under 24 h with an isolated yield of *p*-cresol of 65.2%. A literature survey of several systems capable of cleaving anisole reveals that the 3-methylimidazolium bromohydrogenates(I) liquid is superior on several counts. Various and assorted Lewis acid mixtures are efficient but generally require higher temperatures, give side reactions,

require increased molar equivalents of reagent and finally, quenching with extensive aqueous work up to remove the Lewis acid adduct and isolate the product.[29a–d,30] Brønsted acid mixtures in various solvents can also cleave anisole but require even higher temperatures, longer reaction times and product work up while giving poorer yields.[31a–d] Since the molarities of HmimBr–HBr (7.17 M) and the 48% HBr solution (8.68 M) are similar, the difference in reactivity is likely due to a change in the Hammett acidity, to more negative values in the ionic liquid from the value of $H_o = -3.414$ in the aqueous system.[32] The reaction time for the cleavage of anisole in the aqueous HBr system can be cut from 22 h to 5 h (with a high isolated yield of phenol), only with the use of a catalyst.[31c] Even with the boron tribromide–methyl sulfide complex (4 : 1 complex/anisole mole ratio) in 1,2-dichloroethane the reaction takes 12 h at 83.5 °C (86% complete by VPC, products not isolated).[33] Reaction of *p*-methylanisole under the same conditions resulted in a 77.7% isolated yield of *p*-cresol.

The cleavage of diethyl ether produced ethyl bromide and ethanol. A 2 : 1 IL : diethyl ether mole ratio was employed using 4.0132 g (54 mmol) of diethyl ether, going to 95% completion in 6 h. Only ethyl bromide was isolated *via* distillation since excess acid was present during the heating of the solution. In one method for the cleavage of diethyl ether, a low boiling petroleum ether solution of boron bromide was employed, which was more efficient and yielded ethanol but required a temperature of 100 °C and the usual work-up sequence.[34] In another report, deuterated chloroform solutions of trimethylsilyl iodide cleaved diethyl ether at 25 °C completely, to ethyl iodide, over 70 h (product not isolated).[29c]

The cleavage of 3.5744 g (50 mmol) of tetrahydrofuran (THF) was complete in less than 1 h with 2 molar equivalents of HmimBr–HBr. During the reaction a small quantity of 4-bromobutanol was converted to dibromobutane. Distillation of the product in the presence of excess acid, resulted in the quantitative formation of the alcohol to dibromobutane in a yield of 91.3%. THF has also been cleaved efficiently using dimethylboron bromide in methylene chloride, to 4-bromobutanol, with a high isolated yield.[35] One drawback of this method is that dimethylboron bromide is pyrophoric upon exposure to moist air which could be problematic upon product isolation. In another report, THF was cleaved over 8 h to dichlorobutane in high isolated yields, using catalytic quantities of cetyltrimethylammonium bromide or cetylpyridinium chloride, in refluxing aqueous HCl solutions.[36]

The method developed in this work for the cleavage of ethers is efficient but suffers from the further reactions of the alcohol. This could likely be avoided by cooling the reaction mixture or by decreasing the quantity of HBr in the ionic liquid. Since the reaction of the alcohol is promoted *via* distillation, isolation of the product using vacuum distillation may lower the temperature sufficiently to suppress the second reaction. If the bromide is desired then heating the reaction mixture and/or increasing the IL : ether mole ratio would shorten reaction times. The recycling of the post-distillation HmimBr ionic liquid to HmimBr–HBr with subsequent addition of HBr gas is also very possible since the ^{1}H-NMR spectrum of the remaining liquid does not indicate decomposition. This was also noted visually where the solvent remaining was light yellow and clear.

Conclusions

The novel 3-methylimidazolium bromohydrogenates(I) ionic liquid containing the stable fused $Hmim^+$ cation and the bromohydrogenate(I) anions has been prepared. The liquid is conducting, viscous and dense with an electrochemical window of less than 0.5 V. The ^{1}H-NMR signal for the mixture of the bromohydrogenate(I) species exhibits dynamic behaviour in the presence of the ether indicating it is acidic. All other protons in the system show little temperature dependence from room temperature to 94 °C. This room-temperature ionic liquid system cleaves ethers efficiently. Some advantages over other ether cleaving systems are: it is simple to prepare, reacts with stable ethers at room temperature, with low molar equivalents, gives no side reactions and does not require a catalyst or an extensive work up scheme to obtain products of high purity. Results from this work indicate the HmimBr–HBr RTIL to be a good candidate as an alternate solvent for the cracking of the polyphenolic ether linkages found in lignin, to value-increased products. The $Hmim^+$ cation has also been prepared with the following anions to form stable room-temperature ionic liquids: $HClBr^-$, HCl_2^- and basic/acidic liquid haloaluminates with large liquidus regions. Further work with ionic liquids containing the $Hmim^+$ cation is warranted and will likely provide new stable reaction media with applications in many areas of chemistry.

Acknowledgements

We thank the Natural Sciences and Engineering Research Council of Canada for partial support of this work.

References

1 C. P. M. Lacroix, F. H. M. Dekker, A. G. Talma and J. W. F. Seetz, *Eur. Pat. Appl.* 2000, 9 pp.
2 K. E. Johnson, L. Xiao and G. Driver, *Significance of cations in ionic liquids chemistry: Applications for Green Chemistry*, ed. R. D. Rogers and K. R. Seddon, ACS Symposium 818 2002, pp. 230–240.
3 (*a*) J. Shabtai, W. Zmierczak, S. Kadangode, E. Chornet and D. K. Johnson, *Lignin conversion to high- octane fuel additives*, Biomass: A Growth Opportunity in Green Energy and Value-Added Products, Proceedings of the Biomass Conference of the Americas, 4th, Oakland, California, Aug. 29–Sept. 2, 1999; (*b*) J. Shabtai, W. Zmierczak, E. Chornet and D. K. Johnson, *Conversion of lignin. 2. Production of high-octane fuel additives*, Preprints of Symposia—Am. Chem. Soc.; Division of Fuel Chemistry, 1999, vol. 44(2), 267–272.
4 L. F. Audrieth, A. Long and R. E. Edwards, *J. Am. Chem. Soc.*, 1936, **58**, 428–429.
5 R. L. Burwell, *Chem. Rev.*, 1954, **54**, 615–685.
6 R. M. Pagni, *Adv. Molten Salt Chem.*, 1987, **6**, 211–346.
7 D. F. Evans and Sister M. A. Matesich, *Techniques of Electrochemistry*, ed. E. Yeager and A. J. Salkind, John Wiley & Sons, New York, 1973, vol. 2, p. 49.
8 (*a*) M. L. Sheely, *Ind. Eng. Chem.*, 1932, **24**, 1060–1064; (*b*) J. B. Segur and H. E. Oberstar, *Ind. Eng. Chem.*, 1951, **43**, 2117–2120.
9 D. D. Perrin and W. L. F. Armarego, *Purification of Laboratory Chemicals*, Pergamon Press, New York, 1988.
10 J. B. Stothers, *Carbon-13 NMR Spectroscopy*, ed. A. T. Blomquist and H. Wasserman, Academic Press Inc., New York, 1972, vol. 24, p. 128.
11 J. W. Emsley, J. Feeney and L. H. Sutcliffe, *High Resolution Nuclear Magnetic Resonance Spectroscopy*, Pergamon Press, New York, 1966, vol. 2, p. 667.
12 D. G. Tuck, *Progress in Inorganic Chemistry*, ed. F. A. Cotton, John Wiley & Sons, New York, 1968, vol. 9, pp. 161–194.
13 D. H. McDaniel and R. E. Valleé, *Inorg. Chem.*, 1963, **2**, 996–1001.
14 F. Y. Fujiwara and J. S. Martin, *J. Chem. Phys.*, 1972, **56**, 4091–4097.
15 (*a*) W. D. Chandler, K. E. Johnson, B. D. Fahlman and J. L. E. Campbell, *Inorg. Chem.*, 1997, **36**, 776–781; (*b*) W. D. Chandler, K. E. Johnson and J. L. E. Campbell, *Inorg. Chem.*, 1995, **34**, 4943–4949; (*c*) K. N. Rankin, W. D. Chandler and K. E. Johnson, *Can. J. Chem.*, 1999, **77**, 1599–1607.
16 J. S. Martin and F. Y. Fujiwara, *J. Chem. Phys.*, 1972, **56**, 4098–4102.

17 M. Ma and K. E. Johnson, *Can. J. Chem.*, 1995, **73**, 593–598.
18 S. G. Lias, J. F. Liebman and R. D. Levin, *J. Phys. Chem. Ref. Data*, 1984, **13**, 718–727.
19 It has become obvious through the course of this work that perhaps a cautionary comment regarding the 'solvent' effect on relative orders of acid or base strength is warranted. It seems as though the relative order of acid or base strength determined from aqueous studies has become generalized to a point where it has replaced the order determined from gas phase studies. That 1-methylimidazole could possibly retain its nitrogenic proton as the 3-methylimidazolium cation in the melt is not precluded by the fact that it does not do so in water or any other solvent because 1-methylimidazole is intrinsically a strong base.
20 M. B. Smith and J. March, *Advanced Organic Chemistry*, John Wiley & Sons, New York, 5th edn., 2001, pp. 327–351.
21 J. D. Roberts, *J. Am. Chem. Soc.*, 1956, **78**, 4495–4496.
22 A. Carrington and A. D. McLachlan, *Introduction to Magnetic Resonance With Applications to Chemistry and Chemical Physics*, Harper & Row Publishers, New York, 1967, p. 63.
23 See ref. 11, p. 818.
24 R. S. Drago, *Physical Methods For Chemists*, Saunders College Publishing, New York, 2nd edn., 1992, p. 270.
25 E. Grunwald, A. Loewenstein and S. Meiboom, *J. Chem. Phys.*, 1957, **27**, 630–640.
26 J. D. Roberts, *Nuclear Magnetic Resonance*, McGraw-Hill Book Co., New York, 1959, p. 85.
27 D. Cook, *Can. J. Chem.*, 1961, **39**, 2009–2024.
28 M. Goffman and G. W. Harrington, *J. Phys. Chem.*, 1963, **67**, 1877–1880.
29 (*a*) E. C. Friedrich and G. J. Delucca, *Org. Chem.*, 1983, **48**, 1678–1682; (*b*) M. O. V. Bendetti, E. S. Monteagudo and G. Burton, *J. Chem. Res. (S)*, 1990, 248–249; (*c*) M. E. Jung and M. A. Lyster, *J. Org. Chem.*, 1977, **42**, 3761–3764; (*d*) see ref. 5.
30 Certain high melting alcohols may require a work up scheme if they can not be distilled or sublimed out of solution.
31 (*a*) C. A. Smith and J. B. Grutzner, *J. Org. Chem.*, 1976, **41**, 367–370; (*b*) S. P. Walvekar and A. B. Halgeri, *Tet. Lett.*, 1971, **28**, 2663–2666; (*c*) D. Landini, F. Montanari and F. Rolla, *Synthesis*, 1978, 771–773; (*d*) see ref. 5.
32 Y. Marcus, E. Pross and N. Soffer, *J. Phys. Chem.*, 1980, **84**, 1725–1729.
33 P. G. Willard and C. B. Fryhle, *Tetrahedron Lett.*, 1980, **21**, 3731–3734.
34 F. L. Benton and T. E. Dillon, *J. Am. Chem. Soc.*, 1942, **64**, 1128–1129.
35 Y. Guindon, M. Therein, Y. Girard and C. Yoakim, *J. Org. Chem.*, 1987, **52**, 1680–1686.
36 B. Juršic, *J. Chem. Res. (S)*, 1989, 284–285.

A green protocol for the silylation of alcohols using bonded fluorous phase catalysis†

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Received 7th November 2002
First published as an Advance Article on the web 27th January 2003

The surface of a solid silica support has been functionalized with long perfluoroalkyl chains. The resulting surface layer readily adsorbs fluorous molecules from organic solutions. In this way, dirhodium(II) perfluorocarboxylate catalysts can be conveniently immobilized on a solid support. The resulting Bonded Fluorous Phase (BFP) catalysts display a high activity in the silane alcoholysis reaction using a solventless procedure and are easily recycled.

Introduction

Among the routinely employed methodologies for the protection of hydroxyl groups in organic synthesis, silylation undoubtedly plays a major role.[1] The reaction is usually accomplished utilising a chlorosilane to introduce the silyl group (eqn. (1)). However, this invariably requires the presence of a base in order to neutralize the hydrochloric acid formed as byproduct, which implies the production of one equivalent of salt per equivalent of product. A much more atom economical silylation protocol is represented by silane alcoholysis (eqn. (2)), where H_2 is the only byproduct.

$$R'OH + ClSiR_3 + B \rightarrow R'OSiR_3 + BH^+Cl^- \quad (1)$$

$$R'OH + HSiR_3 \rightarrow R'OSiR_3 + H_2 \quad (2)$$

A catalyst is needed in order for silane alcoholysis to proceed at a synthetically useful rate. Over the years, quite a number of catalysts have been proposed in the literature, ranging from heterogeneous metal catalysts[2] to organic compounds[3] and transition metal complexes.[4] The latter, most notably those of ruthenium, rhodium, iridium, manganese and platinum appear to be currently the most productive and versatile catalysts. However, they usually tolerate only a limited range of reaction solvents, *i.e.* nonpolar, noncoordinating solvents such as benzene or dichloromethane, which are of concern for the environment and health. Furthermore, in most cases they require strictly anhydrous reaction conditions and the exclusion of atmospheric oxygen. Finally, they present the problem of the separation of the catalyst from the reaction products and of its recycling. In this contribution, we wish to report how these disadvantages can be overcome using dirhodium(II) perfluorocarboxylate catalysts.

Results and discussion

The application of a dirhodium(II) perfluorocarboxylate as catalyst for silane alcoholysis was originally reported by Doyle *et al.*,[4h] who utilized 1 mol% dirhodium(II) perfluorobutyrate in dichloromethane at room temperature. The selectivity of this catalyst for the alcoholysis reaction product is very good even with unsaturated alcohols, which easily undergo metal-catalyzed hydrogenation along with silane alcoholysis. However, the amount of catalyst which has to be employed is untolerably high for commercial applications. Therefore, it is mandatory to increase the productivity of this catalytic system. In a previous publication,[5] we have introduced dirhodium(II) perfluorocarboxylates bearing long perfluoroalkyl chains (*i.e.* from 7 to 13 carbon atoms long, Fig. 1) as catalysts for this reaction.

Such highly fluorous dirhodium(II) complexes can be easily prepared in one step from common commercial precursors and are air-stable, easy to handle solid compounds. Since they are preferentially soluble in fluorinated solvents, they can be employed as catalysts in a dichloromethane/Fluorinert® FC-77 fluorous biphasic system, which ensures the easy recovery and recycling of the catalyst. However, their catalytic activity in the

Green Context

Many strategies exist for the immobilisation of catalysts onto a solid phase. Here, a new protocol, termed Bonded Fluorous Phase Catalysis is put forward. the key concept is the affinity of a catalyst containing fluorous chains to partition into a silica-supported perfluoroalkyl surface layer. The catalyst was demonstrated in the silylation of alcohols, and was found to be very active and recoverable, working in the absence of solvent. ***DJM***

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† This work was presented at the Green Solvents for Catalysis Meeting, held in Bruchsal, Germany, 13–16th October 2002.

 DOI: 10.1039/b210992a

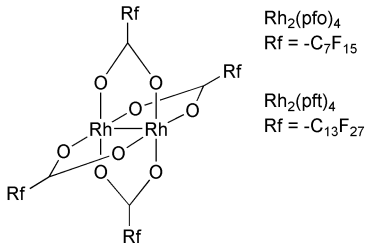

Fig. 1

fluorous biphasic system was found to be lower than in the related homogeneous system, which was most probably due to mass transport limitations between the two liquid phases.

In the search for a more efficient way to run the reaction while maintaining the possibility of an easy recovery and recycling of the catalyst, we have envisaged the possibility of increasing the surface area of the interphase between the fluorous phase and the organic phase. A fruitful strategy for reaching such a goal is the one commonly referred to as 'Supported Liquid Phase Catalysis' (SLPC) in which a liquid phase containing the catalyst (usually made out of a polar protic solvent such as water or ethylene glycol) is adsorbed as a thin film on a hydrophilic solid support with a high surface area such as porous silica beads.[6] This supported catalyst is then contacted with a second liquid phase, immiscible with the first, which contains the reagents, so that the reaction takes place at the interphase between the two liquids.

Since there is no conventional solid support able to adsorb a fluorous solvent on its surface, we decided to investigate a variation of this approach, in which a fluorous film is built on a solid support by covalently binding perfluoroalkyl chains on its surface. Such materials are not entirely new: they have been used for long time as stationary phases for liquid chromatography (Bonded Phase Chromatography) and have recently enjoyed a considerable revival of interest due to their application in the extraction of fluorous tagged molecules from complex mixtures.[7] Since in this case the fluorous phase containing the catalyst is covalently bound to the support, we propose the name 'Bonded Fluorous Phase Catalysis' (BFPC) for our approach (Fig. 2).

A related approach was recently proposed by Neumann and Cohen,[8] who prepared 'solvent-anchored supported liquid phase catalysts' by synthesising a silica functionalized with poly(ethyleneglycol) chains by sol–gel methods. The resulting poly(ethyleneglycol) layer was then utilized to embed polyoxometalate catalysts. In this case, however, the poly(ethyleneglycol) tails actually act as true ligands for the catalyst molecules rather then being simply a 'solvent' for them. Very recently, Pozzi *et al.* tried to apply the same BFPC strategy for supporting fluorous chiral Co(salen) catalysts for the hydrolytic kinetic resolution of terminal epoxides.[9] However, the supported catalyst turned out to be completely inactive.

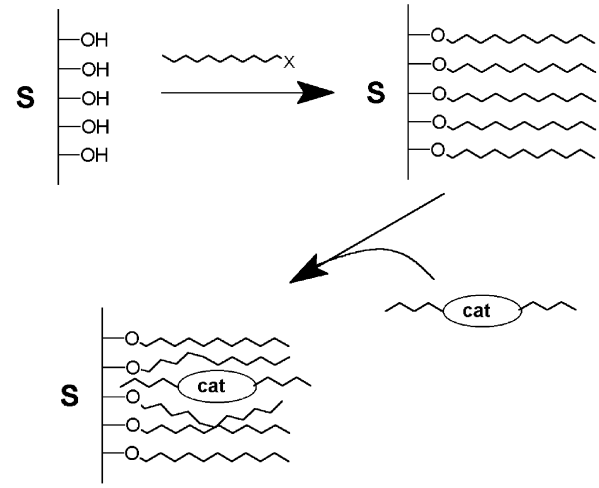

Fig. 2 The 'Bonded Fluorous Phase Catalysis' (BFPC) approach. The surface of a solid support **S** is derivatized with molecules bearing long fluorous chains; in this way, a surface layer is created in which a fluorous catalyst can be embedded.

We have prepared our own support by derivatization of silica gel following a procedure originally reported by Curran *et al.*[10] Functionalization of the silica surface with 1*H*,1*H*,2*H*,2*H*-perfluorodecyldimethylchlorosilane results in a material with high affinity for fluorous compounds. Such derivatized silica can be conveniently loaded with dirhodium(II) perfluorocarboxylate complexes by contacting it with a solution of the complex of choice; adsorption of the complex on the fluorous layer covering the silica surface takes place in good yields and the resulting product can be easily isolated by simple filtration. The adsorption process is reversible, and the metal complex can be washed off the support by treating the supported catalyst with diethyl ether, which strongly binds the free apical positions of the rhodium compound. Control experiments performed with underivatized silica resulted in no significant adsorption of metal complex. Consequently, adsorption of the dirhodium(II) perfluorocarboxylate by direct interaction of the complex with residual hydroxyl groups on the silica surface can be ruled out. In this way, BFP catalysts with metal complex loadings of 22 μmol g^{-1} fluorous silica for $Rh_2(pfo)_4$ and of 12 μmol g^{-1} fluorous silica for $Rh_2(pft)_4$ could be prepared.

The BFP catalysts were tested in a model reaction such as the triethylsilane alcoholysis with 1-octanol. Initial experiments were performed using dichloromethane as a solvent for the reagents, in analogy to the reaction protocol developed by Doyle *et al.* (Table 1, first two entries). The BFP catalysts did exhibit catalytic activity under these conditions. However, the BFP catalysts apparently also underwent rapid deactivation; they changed their colour from light green to brown and after the first few hours of reaction silane alcoholysis did not proceed further to a significant extent. A similar, although slower, deactivation of these catalysts was already observed by us in

Table 1 Triethylsilane alcoholysis with 1-octanol using BFPC

Entry	Catalyst	Mol% catalyst	Solvent	Yield after 24 h[a] (%)	TON	TOF/h^{-1}
1	BFP–$Rh_2(pft)_4$	1	Dichloromethane	45	45	1.9
2	BFP–$Rh_2(pfo)_4$	0.2	Dichloromethane	37	185	7.7
3	BFP–$Rh_2(pfo)_4$	0.1	—	100	1000	42
4	BFP–$Rh_2(pfo)_4$[b]	0.1	—	92	920	38
5	BFP–$Rh_2(pfo)_4$[c]	0.1	—	72	720	30
6	BFP–$Rh_2(pfo)_4$	0.01	—	39	3900	162
7	BFP–$Rh_2(pfo)_4$	0.01	—	70 (72 h)	7000	97
8	Fluorous silica	—	—	4	—	—
9	$Rh_2(pfb)_4$[d]	1	Dichloromethane	96 (3 h)	96	32

Reaction conditions: see the Experimental section;[a] GC yield. [b] Recycle of entry 3. [c] Recycle of entry 4. [d] Dirhodium(II) perfluorobutyrate catalyst: literature data from ref. 4(*h*).

fluorous biphasic systems and interpreted in terms of catalyst decomposition.[5]

Very recently, we have discovered that dirhodium(II) perfluorocarboxylate complexes can be employed as homogeneous catalysts for silane alcoholysis in a *solventless* system, which leads to significantly increased catalyst productivities.[11] For example, using 0.1 mol% $Rh_2(pfo)_4$ as a homogeneous catalyst for the solventless triethylsilane alcoholysis of 1-octanol, 73% yield is reached in 24 h. Therefore, we set out to evaluate if we could improve the performance of our BFP catalysts by using the solventless reaction protocol. Experiments were run with catalyst BFP–$Rh_2(pfo)_4$, which gave the best results in the initial tests in dichloromethane solution. It turned out that the BFP catalyst is extremely efficient under solventless conditions (Table 1, entry 3). Quantitative yields are reached within 24 h with only 0.1% catalyst. This implies an overall productivity of the BFP catalyst, expressed by the turnover number (TON), one order of magnitude higher than that of a closely related homogeneous catalyst in dichloromethane solution, as reported by Doyle *et al.* (entry 9).[4h] Furthermore, experiments performed using 0.01% catalyst (Table 1, entry 6) clearly reveal that also the activity of the BFP catalyst is much higher than in Doyle's system, as indicated by the turnover frequancy (TOF) values. Actually, the activity of the BFP catalyst slowly decreases as the reaction proceeds (compare entries 6 and 7 in Table 1). In our opinion, this is mostly due to catalyst decomposition, which also takes place in the solventless system as evidenced from the progressive colour change of the catalyst from green to brown. An additional contribution to catalyst deactivation may stem from poisoning by the reaction product, which contains a triethylsilylether moiety that may compete with the reagents for coordination to the free apical positions of the rhodium complex. Experiments are planned in order to confirm this hypothesis.

The BFP catalyst can be most conveniently recovered from the reaction mixture by simple filtration and subsequently recycled. Analysis of the filtrate indicates that only 2.6% of the supported rhodium is lost in the liquid phase after the first cycle. A slight reduction in catalytic activity is found in the recycled catalyst (Table 1, entry 4), while the recorded metal leaching remains almost constant at 2.5%. Given the catalytic activity of the $Rh_2(pfo)_4$ homogeneous catalyst under identical reaction conditions (see above),[11] it is clear that such a low level of metal leaching cannot account for the high catalytic activity observed, which has to be ascribed to the supported metal complex. An activity comparable to that reported by Doyle is preserved also in a third reaction cycle (Table 1, entry 5).

Finally, a blank experiment was performed in order to rule out the possibility of catalytic activity stemming from the support. A test was run using 300 mg fluorous silica as catalyst (entry 8). Only a trace of silane alcoholysis product was formed after 24 h.

In conclusion, we have been able to show that the utilization of long-chain dirhodium(II) perfluorocarboxylates in a BFPC approach to silane alcoholysis results in a catalytic system with clearly superior productivity. It is also important to remark that no strictly anhydrous conditions are required in order to operate with these catalysts: reagents can be used as received, without any further purification. These advantages, combined with the ease of catalyst recovery and recycling and with the absence of *any* solvent in the reaction protocol makes this a very simple and green procedure for the silylation of alcohols. Further work is currently in progress in order to assess the selectivity of these catalysts and to extend their applications to other synthetically useful alcohols and silanes. Furthermore, in order to reduce the extent of metal leaching we plan to optimize the nature of the silica-bound fluorous phase. For example, changing from perfluoroalkyl chains to perfluoropolyether chains should result in a less ordered fluorous layer, which should more efficiently adsorb the catalyst molecules.

Experimental

Solvents (Carlo Erba), fluorinated solvents and reagents (ABCR) and common reagents (Aldrich) were used as received unless otherwise stated. The preparation of dirhodium(II) perfluorocarboxylates has been previously described.[5,12]

Preparation of fluorous silica

The fluorous silica was prepared starting from high purity silica gel 60 (Fluka) and 1*H*,1*H*,2*H*,2*H*-perfluorodecyldimethylchlorosilane following a procedure fully analogous to that reported by Curran *et al.*[10]

Preparation of BFP catalysts

BFP–$Rh_2(pfo)_4$: 25 mg (13 μmol) $Rh_2(pfo)_4$ were suspended in 5 mL toluene. 500 mg fluorous silica were then added and the resulting mixture was briefly heated at reflux with efficient stirring, upon which the metal complex quantitatively dissolved. The mixture was allowed to cool to room temperature while stirring was continued, after which the green solid was filtered off, thoroughly washed with toluene and dried *in vacuo* to constant weight. The mother-liquor and the solution from the washings were collected and the solvent was removed at reduced pressure. The residue was dissolved in 6 mL hot *aqua regia* and the resulting solution was diluted to 100 mL with water. The Rh content in the solution was quantitatively estimated by ICP-AAS, and from this datum the Rh content in the BFP catalyst was determined by difference. The yield in supported complex turned out to be 22 μmol g^{-1} fluorous silica (86% with respect to the initial amount of complex).

BFP–$Rh_2(pft)_4$: 25 mg (8.2 μmol) $Rh_2(pft)_4$ were dissolved in 2 ml THF. 500 mg fluorous silica were then added and the resulting mixture was stirred at room temperature for 4 h, after which the supported catalyst was filtered off, thoroughly washed with THF and dried *in vacuo* to constant weight. The Rh content in the resulting BFP catalyst was determined as described above for BFP–$Rh_2(pfo)_4$. The yield in supported complex turned out to be 12 μmol g^{-1} fluorous silica (78% with respect to the initial amount of complex).

Catalytic tests

Reactions in dichloromethane: catalytic tests were run in a Schlenk tube equipped with a magnetic stirring bar. The Schlenk tube was charged with the required quantity of catalyst, evacuated and filled with argon. 5 mL anhydrous dichloromethane were then added under argon, followed by 162 μL (1 mmol) 1-octanol and 173 μL (1.05 equivalents) triethylsilane. The resulting suspension was vigorously stirred at room temperature for 24 h. 0.5 mL samples were taken after 2 and 24 h reaction time and analyzed by GC following the previously established procedure.[5]

Solventless reactions: catalytic tests were run in a Schlenk tube equipped with a magnetic stirring bar. The Schlenk tube was charged with the required quantity of catalyst, evacuated and filled with argon. 1 mL (6.17 mmol) 1-octanol and 1.1 mL (1.05 equivalents) triethylsilane were then added, and the resulting suspension was vigorously stirred at room temperature for 24 h. 0.1 mL samples were withdrawn after this period, diluted with 1 mL dichloromethane and analyzed by GC following the previously established procedure.[5] Catalyst recycling was performed by filtering off the catalyst under air, washing with dichloromethane and drying *in vacuo* before starting the new run. Rhodium leaching was determined by ICP-AAS on an aliquot of the filtrate (0.5 mL), which was treated

with 6 mL hot *aqua regia* and diluted to 100 mL with water before the measurement.

Acknowledgments

Financial support from MURST-PRIN 1999 (Project nr. 9903153427) and from the University of Padova—'Progetti giovani ricercatori 1999' is gratefully acknowledged. We wish to thank Dr Giulia Zanmarchi, University of Padova, for the ICP-AAS measurements.

References

1 T. W. Greene and P. G. Wuts, *Protective Groups in Organic Synthesis*, Wiley, New York, , 2nd edn., 1991.
2 (*a*) K. Yamamoto and M. Takemae, *Bull. Chem. Soc. Jpn.*, 1989, **62**, 2111; (*b*) L. H. Sommer and J. E. Lyons, *J. Am. Chem. Soc.*, 1969, **91**, 7061.
3 (*a*) F. Le Bideau, T. Coradin, J. Henique and E. Samuel, *Chem. Commun.*, 2001, 1408; (*b*) J. M. Blackwell, K. L. Foster, V. H. Beck and W. E. Piers, *J. Org. Chem.*, 1999, **64**, 4887; (*c*) Y. Tanabe, H. Okumura, A. Maeda and M. Murakami, *Tetrahedron Lett.*, 1994, **35**, 8413.
4 Selected recent examples: (*a*) M.-K. Chung, G. Ferguson, V. Robertson and M. Schlaf, *Can. J. Chem.*, 2001, **79**, 949; (*b*) S. Chang, E. Scharrer and M. Brookhart, *J. Mol. Catal. A: Chem.*, 1998, **130**, 107; (*c*) X. Wang, W. W. Ellis and B. Bosnich, *Chem. Commun.*, 1996, 2561; (*d*) C. Lorenz and U. Schubert, *Chem. Ber.*, 1995, **128**, 1267; (*e*) B. T. Gregg and A. R. Cutler, *Organometallics*, 1994, **13**, 1039; (*f*) T. C. Bedard and J. Y. Corey, *J. Organomet. Chem.*, 1992, **428**, 315; (*g*) D. H. Barton and M. J. Kelly, *Tetrahedron Lett.*, 1992, **33**, 5041; (*h*) M. P. Doyle, K. G. High, V. Bagheri, R. J. Pieters, P. J. Lewis and M. W. Pearson, *J. Org. Chem.*, 1990, **55**, 6082; (*i*) X.-L. Luo and R. H. Crabtree, *J. Am. Chem. Soc.*, 1989, **111**, 2527; (*j*) W. Caseri and P. S. Pregosin, *Organometallics*, 1988, **7**, 1373.
5 A. Biffis, E. Castello, M. Zecca and M. Basato, *Tetrahedron*, 2001, **57**, 10391.
6 For a review, see for example: M. S. Anson, M. P. Leese, L. Tonks and J. M. J. Williams, *J. Chem. Soc., Dalton Trans.*, 1998, 3529.
7 D. P. Curran, *Synlett*, 2001, 1488.
8 R. Neumann and M. Cohen, *Angew. Chem., Int. Ed.*, 1997, **36**, 1738.
9 M. Cavazzini, S. Quici and G. Pozzi, *Tetrahedron*, 2002, **58**, 3943.
10 D. P. Curran, S. Hadida and H. Mu, *J. Org. Chem.*, 1997, **62**, 6714.
11 A. Biffis, M. Zecca and M. Basato, manuscript in preparation.
12 A. Endres and G. Maas, *Tetrahedron Lett.*, 1999, **40**, 6365.

Green heterocycle synthesis, isochromenones and artemidin†

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Received 4th December 2002
First published as an Advance Article on the web 13th February 2003

Organic transformations in near critical water, generated in heated stainless steel pressure reactors or microwave irradiated Teflon or glass pressure reactors, yield a green synthesis of isochromen-1-ones or isocourmarins.[1] A synthesis of the isochromen-1-one artemidin using a combination of synthetic microwave and commercial microwave equipment is presented.

Introduction

Near critical water (NCW) is a useful green media for organic transformations.[2] The extreme variation in properties of NCW could, in principle, be tuned to selectively promote one of several possible reaction products. Unfortunately, NCW is infrequently applied for synthesis of materials, drugs and other general preparations due to the limited history of C–C bond forming reactions using compounds with multiple functional groups. Our objective is to formulate C–C bond forming processes in hot pressurized water[3] directed towards preparing pharmaceutical intermediates and natural products. One group of compounds that we have targeted is the isochromenones. The 3-substituted isochromenone system is the core of mitocidal (insecticidal) natural products and medicinal agents.[4]

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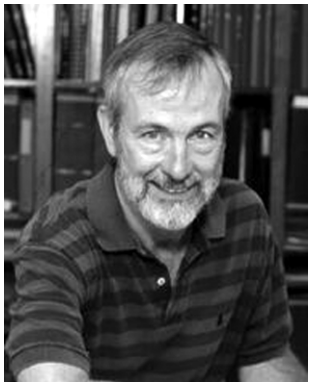
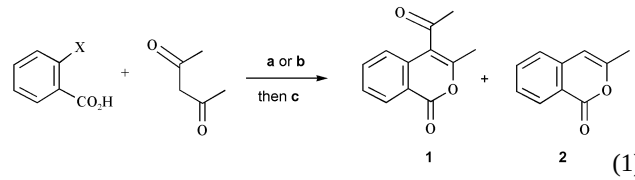


† This work was presented at the Green Solvents for Catalysis Meeting, held in Bruchsal, Germany, 13–16th October 2002.

Results and discussion

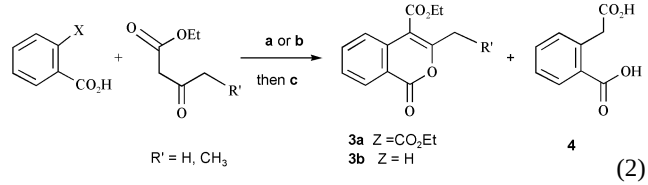
Aromatic substitution using activated methylene compounds in organic solvent with base[5] and stoichiometric amounts of copper catalyst can be an effective route to the isochromenone system [step a, eqn. (1)].[6] Hot pressurized water can be equally effective in forming isochromenones [step b, eqn. (1)] with the advantage of providing product selectivity (**1** or **2**) based on temperature, pressure and the nature of the activating methylene groups. For example substitution product **1** [50–60%, step a then c; eqn. (1)] formed by standard reflux techniques is the minor product from employing near critical water [step b then c; eqn. (1)].



(1)

a. NaH, Cu^+, THF; b. KOH, Cu^+, NCW; c. dil. HCl.

In a heated Parr pressure reactor (p-NCW, 200 °C, ~400 psi)[7] or under microwave irradiation in a pressure flask (m-NCW, 100–150 °C, 40–200 psi)[8a] isochromenone **2** is the major product (55–70%) after acidification.[9] Cleavage of an acyl group in the aggressive water media accounts for the formation of **2**.[10]



(2)

a. NaH, Cu^+, THF; **b**. KOH, Cu^+, p-NCW or m-NCW; **c**. dil. HCl.

Green Context

The extreme changes in the properties of water over a range of temperatures and pressures provides an excellent and environmentally benign way of tuning organic reactions towards different outcomes. Here this is nicely illustrated through the synthesis of isochromenones and artemidin in near critical water. Reactions are carried out using a microwave reactor. ***JHC***

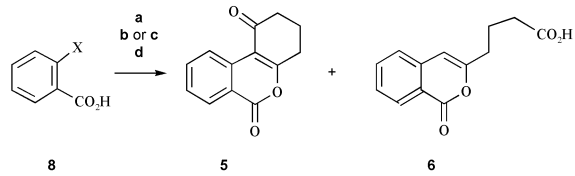
 DOI: 10.1039/b211966h

Table 1 Substitution techniques

Entry	Acid	Technique	Yield (%) 5	6
1	**8**, X = I or Br	Reflux/dioxane	60	Trace[a]
2	**8**, X = I	Parr/200 °C	Trace	55[b]
3	**8**, X = I	Synthetic microwave/150 °C/80 psi	5[b]	65
4	**8**, X = I	Commercial microwave/100 °C	60	8[b]
5	**8**, X = Br	Parr/200 °C (CuBr cat.)	< 5	50

[a] NaH as the base. [b] GC yield.

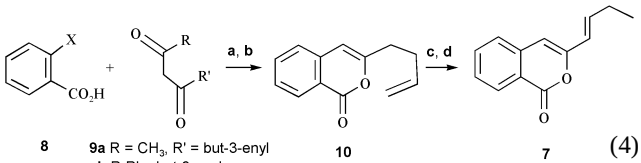
Similarly, β-ketoesters give the reflux product **3a** [steps a, c; eqn. (2)] or diacid **4** [steps b, c; eqn. (2)][11] in NCW. What attracted attention was that 1,3-cyclohexanedione could afford either 3,4-dihydro-2*H*-benzo[*c*]chromen-1,6-dione (**5**) or 4-(1-oxo-1*H*-isochromen-3-yl)butyric acid (**6**) *in water* with the same reagents using different energy input [eqn. (3), Table 1]. Chromendione **5** has been investigated as a natural product and drug synthon and **6** has the same carbon skeleton as artemidin [**7**, eqn. (4)], an active natural product.[12] Structure **6** could be converted to artemidin and this is currently being pursued.[13] However, a two-step proof of principle preparation of **7** has been completed to exploit the diversity of hot pressurized water in this substitution process.



8 5 6 (3)

a. 1,3-cyclohexanedione, base, CuX; **b**. dioxane/Δ; **c**. NCW; **d**. dil. HCl aq.

Synthesis of artemidin: *o*-Iodobenzoic acid (**8**), in a Parr or microwave pressure reactor, was treated with **9a** [step a then b; eqn. (4)] yielding a mixture of mainly **2** [eqn. (1), above] and minor amounts of desired structure **10**. It was errantly anticipated that the acyl group of **9a** would be more susceptible to *retro*-Claisen reaction than the pentenoyl group. To avoid this unfavorable cleavage symmetrical dione **9b** was used. The potassium salts of **9b** and acid **8** with cuprous iodide in water at 150 °C in a synthetic microwave pressure reactor[8a] (80 psi) for an hour affords 3-but-3-enylisochromen-1-one (**10**) as a distillable oil.[14–16]



8 **9a** R = CH_3, R' = but-3-enyl; **b** R,R' = but-3-enyl 10 7 (4)

a. KOH, Cu^+, NCW; b. dil. HCl; **c**. m-NCW; **d**. m-NCW/ethylene glycol.

The terminal olefin of **10** is induced to migrate *via* irradiation (10 one minute bursts on full power)[8b] in a commercial microwave with palladium on carbon in water–ethylene glycol, giving a mixture of isomeric structures, 45% of which is artemidin (**7**).[17] Additional irradiation (15 one minute bursts on full power), drives isomerization to predominately artemidin with less than 10% of the isomers of **7** by GC.[18]

Water washing of organic reaction products is often the first step of purification and water–alcohol mixtures are frequently employed for crystallization of materials. Thus in addition to the role of being a green reaction media, water has the potential of being the first step of a greener purification protocol. The above NCW reaction [eqn. (4)] on cooling and neutralization gives an oil [**6**, steps a, c, d; eqn. (4)] or solid [**5**, steps a, b, d; eqn. (4)] separable from the aqueous phase in larger scale preparations. Initial studies have employed classical organic (ethyl acetate) aqueous extractions and minimal chromatography.

Conclusion

The extreme changes in properties of water[19] over a range of temperatures and pressures provide the potential to 'tune' reactions towards different outcomes. Formation of **1a** or **2b** by varying heating and pressure in water illustrates this potential. Further aspects of this process and the effects of catalyst efficiency are being investigated.

Acknowledgements

The University of South Carolina (The South Carolina EPA/EPSCoR Program, R826399-01-0), Wingate University, and SDR Pharmaceuticals are gratefully acknowledged for support of this work. J. J. S. is the 1998 Ken Hancock Memorial Green Chemistry Scholar.

References

1 Isochromen-1-one and isocoumarin refer to the same fused ring system.
2 For examples of organic reactions in water, see: A. R. Katritzky and S. M. Allin, *Acc. Chem. Res.*, 1996, **29**, 399–406; J. An, L. Bagnell, T. Cablewski, C. R. Strauss and R. W. Trainor, *J. Org. Chem.*, 1997, **62**, 2505–11; P. E. Savage, *Chem. Rev.*, 1999, **99**, 603–21; M. Siskin and A. R. Katritzky, *Chem. Rev.*, 2001, **101**, 825–835; N. Akiya and P. E. Savage, *Chem. Rev.*, 2002, **102**, 2725–2750.
3 The general range of temperatures and pressures used in pressure reactors: 100–275 °C and 40–800 psi.
4 F. Bellina, D. Ciucci, P. Vergamini and R. Rossi, *Tetrahedron*, 2000, **56**, 2533–2545(*a*) R. D. Barry, *Chem. Rev.*, 1964, **64**, 229–259; (*b*) F. Bohlmann and C. Zdero, *Chem. Ber.*, 1970, **103**, 2856–2859; (*c*) F. Bohlmann and C. Zdero, *Phytochemistry*, 1976, **15**, 1318–1319; (*d*) G. Qabaja, E. M. Perchellet, J.-P. Perchellet and G. B. Jones, *Tetrahedron Lett.*, 2000, **41**, 3007–3010; (*e*) W. B. Turner, *Fungal Metabolites*, Academic Press, London, 1971, ch. 5; (*f*) R. A. Hill, *Progress in the Chemistry of Organic Natural Products*, Wein-Springer-Verlag, New York, 1986, vol. 49; (*g*) S. Ohta, Y. Kamata, T. Inagaki, Y. Masuda, S. Yamamoto, M. Yamashita and I. Kawasaki, *Chem. Pharm. Bull.*, 1993, **41**, 1188–1190.
5 Base generally refers to KOH. For convenience alkoxides were also used to form salts of carboxylic acids and β-dicarbonyl compounds.
6 Examples: A. McKillop and D. P. Rao, *Synthesis*, 1977, 759–760; A. McKillop and D. P. Rao, *Synthesis*, 1977, 760–761; A. Bruggink and A. McKillop, *Tetrahedron*, 1975, **31**, 2607–2619; G. Chang, seminar USC, 2001, MTP inhibitor made by the analogous *o*-haloacid substitution and converted to a tetrahydroisoquinoline.

7 p-NCW refers to near critical water generated in a Parr pressure reactor; m-NCW refers to near critical water generated with microwaves.
8 (*a*) MARS5 synthetic microwave (*b*) Goldstar 300 watt microwave oven.
9 Without acidification isochromenone formation is incomplete.
10 Retro-Claisen reaction (*e.g.* formation of **2**) must occur before isochromenone formation; treating isochromenone **1** with NCW (Parr, 200–250 °C) affords no **2** with good recovery of **1**.
11 Isochromenone **3b** is a minor product from organic solvent reflux or near critical water procedures.
12 Synthesis of artemidin: G. Batu and R. Stevenson, *J. Org. Chem.*, 1980, **45**, 1532–1534.
13 As of the present we have no green way of reducing acid **6** to an alcohol.
14 (*a*) Synthon **10**: (110–130 °C, 0.02 mm, bulb-to-bulb), IR (cm^{-1}): 1731, 1658; ^1H NMR (ppm): signals of isochromen-1-one plus 5.77 (m, 1H), 5.04 (m, 2H), 2.55 (m, 2H), 2.40 (m, 2H); MS (*m*/*z*): 200 (M), 159 (M − 41 (allyl)), 131 (B) (*b*) artemidin (**7**): IR (cm^{-1}): 1728, 1606; ^1H NMR (ppm): signals of isochromen-1-one plus 6.68 (dt, 1H), 6.01 (dt, 1H), 2.25 (m, 2H), 1.09 (t, 3H); MS (*m*/*z*): 200 (M, B).
15 For convenience the preformed potassium salts of acid **8** and the β-dicarbonyl or β-ketoester were prepared and mixed together.
16 For this study dione **9b** was prepared by dianion alkylation of acetylacetone and allyl bromide (2×); 4-pentenoyl chloride is commercially available for a malonic ester synthesis of **9b**. 4-Pentenoic acid is recovered from the reaction of **8** and **9b**.
17 Ethylene glycol is added to enhance energy absorption. A heat sink of water was used around a glass pressure reactor. The glass pressure reactor was briefly air-cooled by shaking between bursts. See: B. Hayes, *Microwave Synthesis, Chemistry at the Speed of Light*, CEM Publishing, Matthews, NC, USA, 2002, ch. 2, p. 70.
18 The minor components consist mainly of the *cis* isomer of **7**. Long-term commercial microwave irradiation of **10** at very low power settings led to only minor amounts of olefin isomerization to **7** and 3-(but-2-enyl)isochromen-1-one.
19 As the temperature and pressure increase, the dielectric constant and hydrogen bonding decrease, and the water ionization and organic solubility increases.

Synthesis of quinolines, pyridine ligands and biological probes in green media†

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Received 4th December 2002
First published as an Advance Article on the web 13th February 2003

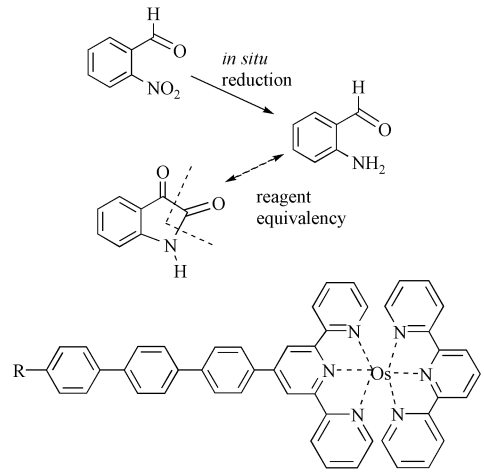
Nitrogen heterocycles are prepared using hot pressurized water under microwave and thermal conditions. Selective reduction, cyclodehydrations (Friedländer and Pfitzinger syntheses), Suzuki coupling, and ligand exchange have been effected in water or water–protic solvent media.

Introduction

Pyridines and quinolines of relevance to metal complexes and natural product, drug, and materials synthesis are generally readily prepared from condensation and cyclodehydration reactions. These preparations frequently employ environmentally unfavorable techniques such as acid catalyzed azeotropic removal of water using aromatic solvents. We have sought to address some typical organic preparations[1] and synthetic applications in water[2] or alternative environmentally friendly protic media, using pressure reactors and microwave techniques.

The cyclodehydration of *o*-aminobenzaldehyde and α-methylene ketones, the Friedländer synthesis, in organic media is one such preparation.[3] The use of this reaction has been limited because of the availability of *o*-aminocarbonyl compounds.[4] Described is an *in situ* green preparation of *o*-aminobenzaldehyde.

Biological probe **1**[5] has been assembled by following literature precedence for terpyridine synthesis[6] and a Suzuki



1 R = H, acetyl, 1-hydroxyethyl

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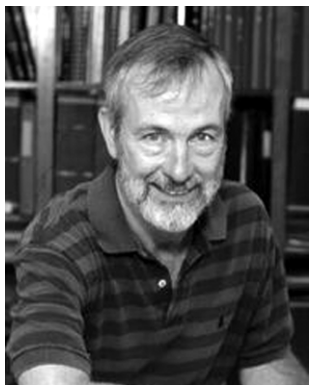


† This work was presented at the Green Solvents for Catalysis Meeting, held in Bruchsal, Germany, 13–16th October 2002.

Green Context

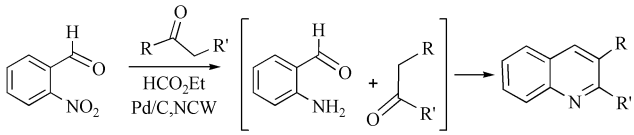
Water has many obvious attractions as a reaction solvent for organic synthesis but the poor solubility of many organic compounds in water restricts such applications under normal conditions. Water under high temperatures and pressures however, undergoes quite dramatic changes in its properties and it becomes a generally good solvent for organic compounds. While this has been exploited in remediation type processes it has been little used in synthesis. Here the use of near critical water as a medium for the organic synthesis of nitrogen heterocycles is demonstrated. The potential for solvent recycling is also demonstrated. The authors go on to use combined clean technologies—catalysis in near critical water, and microwave activated water systems to further demonstrate the clean synthesis potential for these interesting systems. ***JHC***

coupling.[7] However the terpyridine synthesis and the generally dependable Suzuki coupling, which can become problematic with high molecular weight materials, demonstrated to us the opportunities for improvements based on green chemistry.

Disclosed is a greener preparation of biological probe **1** of possible interest for photoinjection[5] studies.

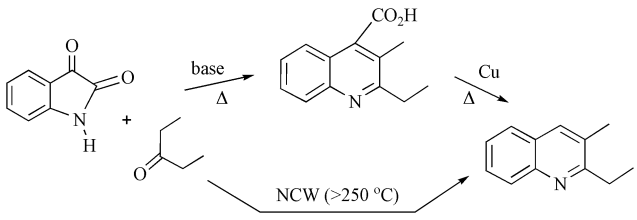
Results and discussion

Quinoline chemistry. One of the most used preparations of *o*-aminobenzaldehyde is the ferrous sulfate reduction of *o*-nitrobenzaldehyde which is done in water but is waste prone in reducing reagent and energy.[8] Other excellent preparations of *o*-aminobenzaldehyde are not environmentally benign.[9] An alternative is to reduce the nitro group *in situ* for imine formation with carbonyl compounds using ethyl formate and palladium on carbon in near critical water (NCW) as illustrated in eqn. (1). Ethyl formate in hot pressurized water has been shown to be an effective green reducing system for olefins, acetylenes and aldehydes.[10] However the nitro group can be selectively reduced in the presence of aldehydes and ketones in a pressure reactor at 170–200 °C yielding the Friedländer quinoline product in good to modest yields (Table 1, method A).[11,12] The yields of this combined one-step quinoline preparation is generally close to the overall yield of a two-step procedure from *o*-nitrobenzaldehyde.[13] The equivalents of formate, carbonyl substrate, reaction time and temperature have not been varied. These variables will be reviewed to optimize a green preparation of these heterocyclic products.

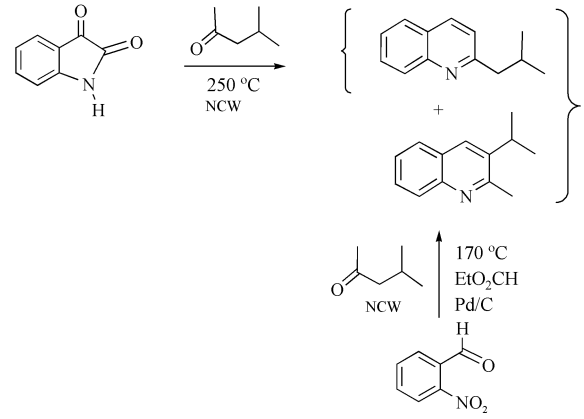


(1)

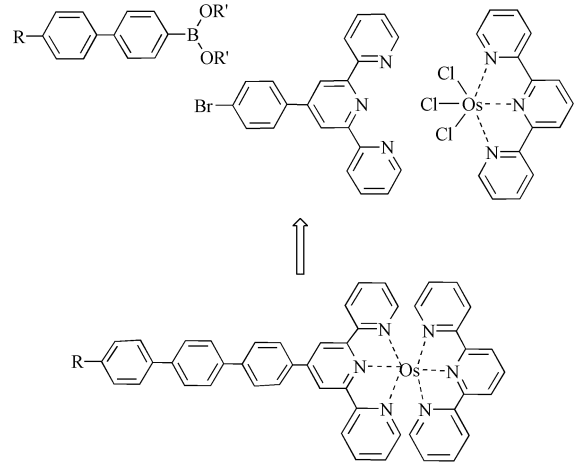
The use of isatin is a classical alternative to the *o*-aminobenzaldehyde-Friedländer synthesis. Isatin in heated aqueous base, opens and condenses on methylene ketones, to give quinoline carboxylic acids.[14] Although these acids are troublesome to isolate, they do decarboxylate under forcing conditions to 2- or 2,3-substituted quinolines. The same carbonyl compounds with isatin in NCW (> 250 °C, 1 h) form the substituted quinoline systems with *in situ* decarboxylation (Table 1, method B). Hot pressurized water (NCW) is more ionized and it is a dehydrating media well suited for isatin opening, condensation and cyclodehydration with carbonyls.[15,16] 4-Quinoline carboxylic acids can be found for reaction temperatures below 250 °C and these acids decarboxylate on cycling with a higher temperature (> 250 °C) water treatment. In the few comparative reactions the yields of quinolines from isatin are generally about the same as using *o*-nitrobenzaldehyde (*e.g.* entries 3 and 4, Table 1) but in the case of methyl isopropyl ketone with isatin, no regioisomer is formed (entries 6 and 7, Table 1). This is presumably due to steric hindrance at C-3 of the forming quinoline carboxylic acid.



Pyridine-ligand chemistry. Biphenylboronic acids (or esters), bromophenylterpyridine and a suitable osmium complex

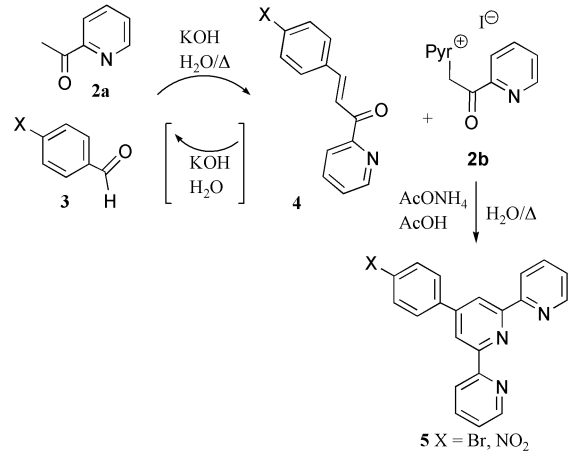


are the rational building blocks for biological probe **1**. However without microwave assistance **1** could not have been prepared for potential use as a biological probe.



1 R = H, acetyl, 1-hydroxymethyl

The published procedures for making terpyridines are quite good, but the preparation of the necessary terpyridine **5** was reformulated to greener techniques without a reduction in yield.



5 X = Br, NO_2

General procedure. Acetylpyridine (**2a**) and *para*-substituted benzaldehydes **3** (X = Br, NO_2)[17] with one equivalent of KOH in water were heated using 10 min low power bursts (total of 50 min) over a 3 h period with a commercial microwave oven, resulting in the formation of azachalcone **4**. As the organics begin to solidify, the solid was removed by filtration and, in the case of bromide **4**, the aqueous base was recharged

Table 1 Quinolines from *in situ* formation of *o*-aminobenzaldehyde (A) or isatin (B)

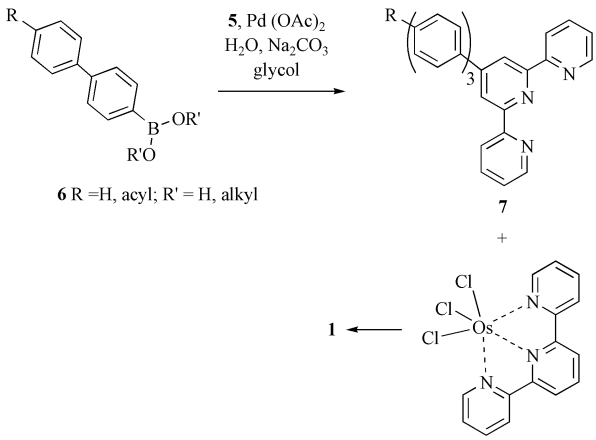
Entry	Method	Carbonyl	Product(s)	Yield (%)
1	A	Diethyl ketone	2-Ethyl-3-methylquinoline	60
2	B	Diethyl ketone	2-Ethyl-3-methylquinoline	43
3	A	Cyclohexanone	1,2,3,4-Tetrahydroacridine	45
4	B	Cyclohexanone	1,2,3,4-Tetrahydroacridine	45
5	A	Valeraldehyde	3-Propylquinoline	55
6	A	4-Methyl-2-pentanone	2-Isobutyl- and 3-isopropyl-2-methylquinoline	46 (4/1)
7	B	4-Methyl-2-pentanone	2-Isobutylquinoline	48
8	A	Dipropyl ketone	3-Ethyl-2-propylquinoline	25
9	B	Dipropyl ketone	3-Ethyl-2-propylquinoline	40
10	A	1-Indanone	11*H*-Indeno[1,2-*b*]quinoline	20
11	B	1-Indanone	11*H*-Indeno[1,2-*b*]quinoline	22
12	B	5-Benzyloxyvaleraldehyde	3-(3-Benzyloxypropyl)quinoiline	30[a]

[a] Ether cleavage reduced yields of 3-benzyloxypropylquinoline.

with benzaldehyde (**3**, X = Br) and acetylpryidine (**2**) for additional preparation of the azachalcone **4**.[18] After a couple of cycles the aqueous layer began to color but the yield of azachalcone (**4**, X = Br) remained nearly quantitative.

The azachalcone **4** (X = Br) was recrystallized from ethanol[19] and mixed with ammonium acetate and iodopyridylacetylpyridine (**2b**) in water–acetic acid (25 : 75). The heterogeneous mixture was irradiated[20] in a commercial microwave oven, affording bromophenylterpyridine **5**. Alternatively the same reaction mixture in a stainless steel pressure reactor (filled to less than 30% capacity) was heated between 140–190 °C for 2 h yielding terpyridine **5** (X = Br).

Normal Suzuki coupling of **5** to biphenylboronic acids **6** was confirmed by mass spectra but only in low yield and long periods of heating under reflux in high boiling solvents.[7]



6 R =H, acyl; R' = H, alkyl

Based on literature precedence[21] intense microwave radiation (200 °C, 200 psi max, 1 h) rapidly forms the desired terpyridine ligand **7** in high yield after an acid–base extractive purification. Similarly a sluggish ligand exchange **7** to **1** (R = H)[22] is best accomplished using microwave assistance (200 °C, 75 psi max, 1 h).[23] The PF_6 salt of **1** is separated from a mixture of two other osmium compounds on Al_2O_3 in acetonitrile–sat. aq. KNO_3–water (14 : 2 : 1).[24]

Conclusion

Preliminary results further demonstrate the potential of near critical water as a green medium for heterocyclic synthesis and in some procedures water with reaction catalyst can be easily recycled. Microwave techniques and pressure vessels can alter long-term low yielding processes to short term, more efficient reactions. The combination of these techniques yields green preparation of quinolines and photoinjection tools.

Acknowledgements

The University of South Carolina, NSF (REU CHE-0139143), NIH (funding in support of J. H. D. and H. V.), Wingate University, and SDR Pharmaceuticals are gratefully acknowledged for support of this work. J. Jennings Stewart is the 1998 Ken Hancock Memorial Green Chemistry Scholar.

References

1 A number of organic transformations have been effected in water.[2] This group's long range goal is to effect multistep synthesis replacing various organic solvents and exotic or environmentally unfriendly reagents with water and green catalysts and reagents.
2 For examples of organic reactions done in water, see: A. R. Katritzky and S. M. Allin, *Acc. Chem. Res.*, 1996, **29**, 399–406; P. E. Savage, *Chem. Rev.*, 1999, **99**, 603–621; J. An, L. Bagnell, T. Cablewski, C. R. Strauss and R. W. Trainor, *J. Org. Chem.*, 1997, **62**, 2505–2511.
3 C.-C. Cheng and Y.-S. Yan, *Org. React.*, 1982, **28**, 37–201.
4 B. Mundy and M. Ellerd, *Name Reactions and Reagents in Organic Synthesis*, Wiley, New York, 1988, p. 86–87.
5 I. J. Dmochowski, J. R. Winkler and H. B. Gray, *J. Inorg. Biochem.*, 2000, **81**, 221–228.
6 P. Korall, A. Borje, P. Norrby and B. Akermark, *Acta Chem. Scand.*, 1997, **51**, 760–766.
7 A. Suzuki, *Metal-Catalyzed Cross-Coupling Reactions*, ed. F. Diederich and P.J. Stang, Wiley-VCH, Weinheim, Germany, 1998, ch. 2.
8 L. I. Smith and J. W. Opie, *Org. Synth.*, 1948, **28**, 11; this procedure produces good quality product but requires a laborious steam distillation limiting the amounts of *o*-aminobenzaldehyde and the scope of *ortho*-amino carbonyl compounds that can be prepared by this reduction; *ortho*-amino carbonyl compounds do not store well due to intermolecular imine formation.
9 S. Murata, M. Miura and M. Nomura, *Chem. Lett.*, 1998, **2**, 361–362.
10 J. M. Jennings, T. A. Bryson and J. M. Gibson, *Green Chem.*, 2000, 87–88; T. A. Bryson, J. M. Jennings and J. M. Gibson, *Tetrahedron Lett.*, 2000, **41**, 3523–3526.
11 *General procedure*: the amounts of liquid (primarily water) and solids used were adjusted to less than 40% of the reactor volume. A stainless steel pressure reactor containing a mix of degassed water, ethyl formate (3 to 4 eq.), Pd/C (~0.02 eq. of Pd), *o*-nitrobenzaldehyde (1 eq.) and reagent ketone or aldehyde (1.5+ eq) was heated at 170–200 °C for 2 h; the quinoline product was isolated using acid–base chemistry.
12 Mixed formate systems (ethyl formate/formic acid and ethyl formate/sodium formate) also afford the same quinolines adding to the variables that must be reviewed to optimize a green preparation of these heterocyclic products.
13 Using the best yield for ferrous sulfate reduction of *o*-nitrobenzaldehyde, the two-step conversion to 2-ethyl-3-methylquinoline is 61%.
14 For a typical example of an isatin-Pfitzinger synthesis, see: C. Koelsch, *J. Org. Chem.*, 1951, **16**, 1362.
15 C. Eckert, *Chem. Eng. News*, 2000, **3**, 26–27.
16 *General procedure*: isatin (1 eq.), ketone or aldehyde (>1 eq.), degassed water (total volume less than 40% of the pressure reactor)

were brought to 250–275 °C for 0.5 h. The product was purified using minimal ether extraction or acid–base chemistry.
17 The nitrobenzaldehyde substrate was used to provide an alternate (diazonium ion) coupling route.
18 The nitro azachalcone **4** formed in excellent yield but both the product and aqueous layer were highly colored. This aqueous layer was not recycled.
19 Recrystalization was done for aesthetics and is not necessary.
20 Irradiation: in a glass pressure reactor with a water heat sink, 7–10 min bursts were administered on low power in a commercial microwave totaling approximately 1 h of irradiation. Each burst was followed by a cooling period of from 5 to 35 min.
21 G. C. Blettner, W. A. König, W. Stenzel and T. Schotten, *J. Org. Chem.*, 1999, **64**, 3885–3890; general reference: B. Hayes, *Microwave Synthesis, Chemistry at the Speed of Light*, CEM Publishing, Matthews, NC, USA, 2002, ch. 4 (MARS5 system was used for this coupling).
22 E. C. Constable and A. M. Cargill Thompson, *J. Chem. Soc., Dalton Trans.*, 1995, 1615–1627.
23 T. Matsumura-Inoue, M. Tanabe, T. Minami and T. Ohashi, *Chem. Lett.*, 1994, 2443–2446.
24 The mass spectra of the complex has a predominant 443 double charged ion. The remarkable chromatographic separation of **1** is the procedure of Constable and Cargill Thompson, ref. 22.

Improved preparations of ionic liquids using microwave irradiation†

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Received 3rd January 2003
First published as an Advance Article on the web 27th March 2003

Controlled, multimode microwave irradiation has been employed in a generic solvent-free process to prepare a wide range of ionic liquids based on nitrogen-containing heterocycles. The developed method offers a flexible, small to large-scale approach to prepare ionic liquids, in either sealed or open vessels, in a faster and greener process than any previously described.

Introduction

Ionic liquids based on nitrogen-containing heterocycles continue to receive much attention as green solvents, with many excellent reviews available summarising their preparation, use, and advantages compared to traditional solvents.[1–3] However, despite ionic liquids being promoted as environmentally benign reaction media, their own purification is a flawed process, often requiring large volumes of organic solvents to extract impurities.[4] An obstacle that therefore exists in the quest to make ionic liquids even 'greener' is the minimisation or, even better, elimination of waste generation during their synthesis. The main sources of ionic liquid contamination are the result of synthesis, and include unreacted starting materials and reaction by-products (Fig. 1). The general syntheses of ionic liquids based on nitrogen-containing heterocycles involve a consecutive quaternisation-metathetic/acid–base procedure. The first step affords an alkylated halide precursor, which upon metathesis with a metal salt or acid–base neutralisation reaction gives an ionic liquid with a different anion (Fig. 1). Using conventional heating methods, the first step in ionic liquid synthesis is time-consuming and usually requires a large molar excess of haloalkane (10–400%)[5] to achieve good yields.

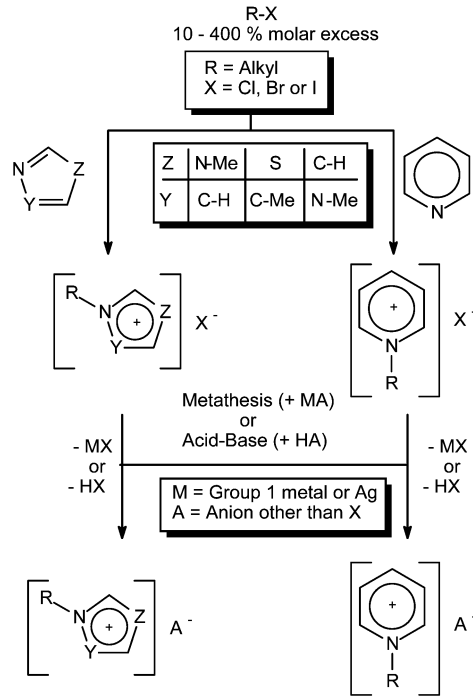

Fig. 1 General syntheses of ionic liquids.

Together, these make the first step in ionic liquid syntheses both dirty and expensive.

The second step in ionic liquid syntheses (Fig. 1) produces a stoicheiometric amount of halide waste (MX or HX) and is a problem that has been dealt with in separate papers from our

Green Context

The extraordinary volume of research on ionic liquids is yet to come to fruition through commercial exploitation. This, at least in part, can be attributed to the very large quantities of waste that can be produced in the preparation of the ionic liquids. Here we see described a novel, low waste, quick and efficient methodology for their synthesis. Imidazolium, pyrazolium and thiazolium ionic liquids are prepared in a commercial microwave reaction. Other advantages of the method include flexibility of scale and high purity products.

JHC

Dr. Maggel Deetlefs was born in Klerksdorp, South Africa in 1973. She studied at the University of the Orange Free State from 1992 to 1994, completed her Masters degree at the Rand Afrikaans University in 1997, and obtained her PhD from the University of Stellenbosch under the supervision of Prof. Helgard G. Raubenheimer in 2001. She has been working at the QUILL Centre in Belfast since August 2001. Her research focuses on syntheses of ionic liquids and their physical properties, as well as inorganic chemistry in ionic liquids.

† This work was presented at the Green Solvents for Catalysis Meeting held in Bruchsal, Germany, 13–16th October 2002.

group[4,6] as well as others.[7] The foci of the current paper are procedures to both minimise waste generation and to accelerate the first step in the ionic liquid syntheses, *viz.* quaternisation of a nitrogen-containing heterocycle. Varma *et al.*[8] were the first to recognise microwave (mw) irradiation as a potential solution to this problem.

The use of microwave ovens as tools for synthetic chemistry is a fast growing area of research.[9,10] Since the first reports of microwave-assisted synthesis in 1986,[11,12] the technique has been accepted as a method for dramatically reducing reaction times[13,14] and for increasing isolated yields of products compared to conventional methods.[15,16] The transfer of energy from microwaves to the substance being heated is governed by two fundamental mechanisms:[17] (i) dipole rotation, where a reaction medium or reactant with a high dielectric constant tries to align itself to the oscillating electric field of the microwave, generating heat; and (ii) ionic conduction, where the electric field of the microwave generates ionic motion of free ions present in a reactant or reaction medium, resulting in rapid heating. Ionic liquids are clearly ideal candidates for the exploitation of microwave heating *via* mechanism (ii) and, in this manuscript, their utilisation in the preparation of ionic liquids is described. At present, the application prospects of using ionic liquids coupled with microwave heating is evidenced by the growing number of papers detailing transformations using such a methodology.[18–20]

Most early microwave-enhanced syntheses were performed using domestic microwave ovens where effective control of reaction conditions is very limited. Indeed, we explored the use of microwaves in the early 90s for the dissolution of kerogen, but abandoned the work because of the lack of available control at the time.[21] However, with the advent of modern multimode microwave systems, reaction conditions are controlled very specifically, with direct monitoring of temperature, pressure, and reaction times.[22] Although multimode microwave systems do not focus microwave energy as effectively as their monomode counterparts, they have been used successfully to process multiple samples and have found specific application in large-scale preparations.[23]

Our interests in utilising microwave radiation are diverse, but the first step in ionic liquid syntheses (*viz.* quaternisation of a nitrogen-containing heterocycle) was selected as a preliminary study in order to address and rectify the time-consuming and dirty nature of these syntheses, which was damaging their green image. Although the majority of heterocycle-based ionic liquids have required the syntheses of imidazolium and pyridinium derivatives, the same general synthetic strategy applies to pyrazolium- and thiazolium-based ionic liquids, and these compounds were also included in our study.

Experimental

1-Haloalkanes, pyridine, 1-methylimidazole, and 4-methylthiazole were purchased from Aldrich and distilled before use. 1-Methylpyrazole was purchased from Lancaster and used as received. All the ionic liquid precursors were stored over 4 Å molecular sieves. A multimode microwave reactor, Mars 5,[22] purchased from CEM Corporation, was used. NMR spectra were recorded on a Bruker Avance DPX300 NMR spectrometer. The general preparative procedures for the ionic liquid syntheses are illustrated by four examples.

Medium-scale preparation of 1-butyl-3-methylimidazolium chloride (150–300 mmol)

The medium-scale 1-alkyl-3-methylimidazolium and 1-alkylpyridinium halide salts preparations were performed on reaction scales of 150, 200, 250, and 300 mmol using the general procedure described below and employing the reaction conditions given in Table 1. Reactions were monitored at regular intervals (*ca.* 4–6 min) by ^{1}H NMR spectroscopy, until 1-methylimidazole or pyridine was no longer detected. ^{1}H NMR spectroscopy detection limits for the imidazolium and pyridinium ionic liquid preparations were determined as described below.

A mixture of 1-methylimidazole (150 mmol) and 1-chlorobutane (153 mmol) was placed in a quartz reaction vessel equipped with a magnetic stirrer and fitted with temperature and pressure probes. The mixture was irradiated at 300 W, programmed to ramp to 150 °C over 2 min, and irradiation continued for a total of 18 min. (every 4 min, microwave irradiation was stopped, the sample allowed to cool to 70 °C, and an NMR spectroscopy sample taken to monitor the reaction progress). Upon completion of the reaction (1-methylimidazole no longer evident in ^{1}H NMR spectrum), ethanenitrile (*ca.* 25 cm^3) was added to the pale yellow, viscous oil and this phase was washed twice with ethyl ethanoate (*ca.* 15 cm^3). The lower (ethanenitrile) phase was collected, the solvent removed *in vacuo*, and the ionic liquid dried under continuous evacuation (1 mm Hg) at 80 °C for 16 h. Upon cooling to room temperature, the product was obtained as a white or pale yellow, crystalline solid in 96% yield, which was stored under dry conditions. The

Table 1 Preparation of [C$_n$mim]X and [C$_n$py]X salts on a medium scale (150–300 mmol)

Heterocycle	n = 4	n = 6	n = 8	n = 10	n = 4	n = 6	n = 8	n = 10	n = 4	n = 6	n = 8	n = 10
[C$_n$mim]X	**Cl**	**Cl**	**Cl**	**Cl**	**Br**	**Br**	**Br**	**Br**	**I**	**I**	**I**	**I**
Power/W	300	300	300	300	240	240	240	240	200	200	200	200
Temperature/°C	150	150	180	120	80	80	110	120	165	190	210	165
Microwave irradiation time/min	20	20	20	10	6	8	8	10	4	7	9	11
Conventional heating time/min	1440	1440	1440	1080	840	960	960	1080	640	720	720	720
Conversion (%)[a]	99.95	99.95	99.95	99.95	99.95	99.95	99.95	99.95	99.95	99.95	99.95	99.95
Work-up yield (%)[a]	95	95	90	95	87	91	95	95	93	90	95	94
Conversion (%)[b]	99.95	99.95	99.95	99.95	99.95	99.95	99.95	99.95	99.95	99.95	99.95	99.95
Work-up yield (%)[b]	96	93	91	92	93	90	97	95	92	94	97	94
[C$_n$py]X	**Cl**	**Cl**	**Cl**	**Cl**	**Br**	**Br**	**Br**	**Br**	**I**	**I**	**I**	**I**
Power/W	300	300	300	300	240	240	240	240	200	200	200	200
Temperature/°C	120	120	150	180	130	130	130	130	165	190	210	165
Microwave irradiation time/min	40	60	60	60	30	30	30	20	10	12	15	15
Conventional heating time/min	3360	3360	3360	2880	2880	2880	2880	2880	960	960	1080	1140
Conversion (%)[a]	99.9	99.9	99.9	99.9	99.9	99.9	99.9	99.9	99.9	99.9	99.9	99.9
Work-up yield (%)[a]	87	94	94	93	98	100	98	93	95	97	97	93
Conversion (%)[b]	99.9	99.9	99.9	99.9	99.9	99.9	99.9	99.9	99.9	99.9	99.9	99.9
Work-up yield (%)[b]	90	93	94	94	95	98	99	95	95	91	97	95

[a] Employing a 10% molar excess of haloalkane. [b] Employing a 1–2% molar excess of haloalkane.

used ethanenitrile and ethyl ethanoate were both recycled by fractional distillation. The product was characterised by ^{1}H and ^{13}C NMR spectroscopy, as well as by its melting point. Mp/°C: 66.5 (65)[5]; ^{1}H NMR (300 MHz; CD_3CN; 25 °C): δ (ppm) = 0.92 (3H, t, J = 7.2 Hz, N-$(CH_2)_3$-CH_3), 1.36 (2H, m, N-CH_2-CH_2-CH_2-CH_3), 1.83 (2H, m, N-CH_2-CH_2-CH_2-CH_3), 3.72 (3H, s, NCH_3), 4.13 (2H, t, J = 7.3 Hz, N-CH_2-$(CH_2)_2$-CH_3), 7.47 (1H, s, H-4), 7.53 (1H, s, H-5), 9.24 (1H, s, H-2); ^{13}C NMR (75.4 MHz; CD_3CN; 25 °C): δ (ppm) = 13.55 (N-$(CH_2)_3$-CH_3), 19.04 (N-CH_2-CH_2-CH_2-CH_3), 31.78 (N-CH_2-CH_2-CH_2-CH_3), 35.98 (NCH_3), 48.60 (N-CH_2-$(CH_2)_2$-CH_3), 122.64 (C-4) and 123.83 (C-5), 137.15 (C-2).

Large-scale preparation of 1-butyl-3-methylimidazolium chloride (0.3–2 mol)

The large-scale preparations of imidazolium, [$C_n$mim]X, and pyridinium, [$C_n$py]X, halide salts (n = 4 or 6, X = Cl, Br, or I) were performed on reaction scales of 0.5, 1, 1, 1.5 and 2 mol at the boiling point of the appropriate haloalkane using the general procedure described below. Reactions were monitored at regular intervals (*ca.* 30–40 min) using ^{1}H NMR spectroscopy, until either 1-methylimidazole or pyridine was no longer detected. Reaction monitoring was performed as described under medium-scale preparation of 1-butyl-3-methylimidazolium chloride and the ^{1}H NMR spectroscopy detection limits were determined as described below.

A mixture of 1-methylimidazole (1.5 mol) and 1-chlorobutane (1.65 mol) was placed in a round-bottomed flask (1 l) fitted with a 'glass finger' temperature probe housing and a magnetic stirrer. A reflux condenser, protruding through an aperture in the reactor roof and fitted with a drying tube, was connected to the flask. The mixture was irradiated at 1200 W, programmed to ramp to 80 °C over 5 min, and then irradiation was continued for a total of 5.5 h (NMR spectroscopy samples were taken at intervals of *ca.* 30–40 min to monitor the reaction). Upon completion of the reaction, ethanenitrile (*ca.* 50 cm^3) was added to the pale yellow, viscous oil and this phase washed with ethyl ethanoate (*ca.* 30 cm^3 in five portions). The lower (ethanenitrile) phase was collected, the solvent removed *in vacuo*, and the ionic liquid dried under continuous evacuation (1 mm Hg) at 80 °C for 24 h. Upon cooling to room temperature, the product was obtained as a white to pale yellow crystalline solid in 85% yield. The product was characterised as described for the medium-scale synthesis of 1-butyl-3-methylimidazolium chloride.

Small-scale preparation of 3-butyl-4-methylthiazolium bromide (50 mmol)

The small-scale preparation of 3-alkyl-4-methylthiazolium bromide and iodide salts were performed using the general procedure described below and employing the reaction conditions given in Table 2. Reactions were monitored at regular intervals (*ca.* 10 min) by ^{1}H NMR spectroscopy until 4-methylthiazole was no longer detected. ^{1}H NMR spectroscopy detection limits were determined as described below, and reaction monitoring (reaction mixture samples taken at 80 °C) was performed as described for the medium-scale preparation of 1-butyl-3-methylimidazolium chloride.

A mixture of 4-methylthiazole (50 mmol) and 1-bromobutane (51 mmol) was placed in a quartz reaction vessel equipped with a magnetic stirrer and fitted with temperature and pressure probes. The mixture was irradiated at 300 W, programmed to ramp to 135 °C over 5 min, and irradiation continued for a total of 1 h (NMR spectroscopy samples were taken at intervals of *ca.* 10 min to monitor the reaction). Upon completion of the reaction, the yellow reaction mixture was dissolved in ethanenitrile (*ca.* 20 cm^3) and this phase washed twice with ethyl ethanoate (*ca.* 10 cm^3). The lower (ethanenitrile) phase was collected, the solvent removed *in vacuo*, and the ionic liquid dried under continuous evacuation (1 mm Hg) at 70 °C for 18 h. Upon cooling to room temperature, the product was obtained as a yellow crystalline solid in 94% yield. The product was characterised by ^{1}H and ^{13}C NMR spectroscopy. Mp/°C: 74.6; ^{1}H NMR (300 MHz; CD_3CN; 25 °C): δ (ppm) = 0.91 (3H, t, J = 7.1 Hz, N-$(CH_2)_3$-CH_3), 1.37 (2H, m, N-CH_2-CH_2-CH_2-CH_3), 1.87 (2H, m, N-CH_2-CH_2-CH_2-CH_3), 2.65 (3H, s, CCH_3), 4.45 (1H, t, J = 7.2 Hz, N-CH_2-$(CH_2)_2$-CH_3), 7.94 (1H, s, H-5), 10.24 (1H, s, H-2); ^{13}C NMR (75.4 MHz; CD_3CN; 25 °C): δ (ppm) = 13.55 (N-$(CH_2)_3$-CH_3), 12.86 (N-CH_2-CH_2-CH_2-CH_3), 21.74 (C-CH_3), 30.42 (N-CH_2-CH_2-CH_2-CH_3), 52.59 (N-CH_2-$(CH_2)_2$-CH_3), 121.31 (C-5), 146.17 (C-4), 158.06 (C-2).

Small-scale preparation of 1-hexyl-2-methylpyrazolium iodide (50 mmol)

The small-scale preparation of 1-alkyl-2-methylpyrazolium bromide and iodide salts were performed using the general procedure described below, and employing the reaction conditions given in Table 2. Reactions were monitored at regular intervals (*ca.* 10 min) by ^{1}H NMR spectroscopy until 1-methylpyrazole was no longer detected. ^{1}H NMR spectroscopy detection limits and reaction monitoring (reaction mixture samples taken at 100 °C) were performed as described above.

A mixture of 1-methylpyrazole (50 mmol) and 1-iodohexane (51 mmol) was placed in a quartz reaction vessel equipped with a magnetic stirrer and fitted with temperature and pressure probes. The mixture was irradiated at 300 W, programmed to ramp to 130 °C over 5 min, and irradiation continued for a total of 80 min (NMR spectroscopy samples were taken at intervals of *ca.* 10 min. to monitor the reaction). Upon completion of the reaction, the resulting dark yellow viscous oil was washed with diethyl ether (3 × 10 cm^3) followed by hexane (3 × 10 cm^3), and dried under continuous evacuation (1 mm Hg) at 65 °C for 24 h to give a product yield of 93%. The product was

Table 2 Preparation of [$C_n$mpz]X and [$C_n$mtz]X salts (50 mmol)

	[$C_n$mpz]X						[$C_n$mtz]X					
	n = 4	n = 6	n = 8	n = 4	n = 6	n = 8	n = 4	n = 6	n = 8	n = 4	n = 6	n = 8
X	Br	Br	Br	I	I	I	Br	Br	Br	I	I	I
Power/W	300	300	300	300	300	300	300	300	300	300	300	300
Temperature/°C	130	150	220	130	180	220	135	150	170	130	150	220
Microwave irradiation time/min	85	85	75	35	35	20	65	60	35	35	35	20
Conventional heating time/min	—	—	—	1020	1440	1440	2880	2160	2160	1080	720	720
Conversion (%)[a]	99.95	99.95	99.95	99.95	99.95	99.95	99.95	99.95	99.95	99.95	99.95	99.95
Work-up yield (%)[a]	90	89	92	98	96	98	93	94	95	96	91	98
Conversion (%)[b]	99.95	99.95	99.95	99.95	99.95	99.95	99.95	99.95	99.95	99.95	99.95	99.95
Work-up yield (%)[b]	95	93	97	98	94	97	94	93	96	96	94	97

[a] Employing a 10 % molar excess of haloalkane. [b] Employing a 1–2% molar excess of haloalkane.

characterised by ^{1}H and ^{13}C NMR spectroscopy and its melting point. Mp/°C: −60 (−59)[24]; ^{1}H NMR (300 MHz; D_2O; 25 °C): δ (ppm) = 0.71 (3H, t, J = 7.2 Hz, N-$(CH_2)_5$-CH_3), 1.15 and 1.79 (8H, 2 × m, N- CH_2-$(CH_2)_4$-CH_3), 4.07 (3H, s, N-CH_3) 4.25 (2H, t, J = 7.4 Hz, N-CH_2-$(CH_2)_4$-CH_3), 6.64 (1H, t, J = 7.0 Hz, H-4), 8.05 (1H, s, H-3 or H-5), 8.37 (1H, s, H-2 or H-4); ^{13}C NMR (75.4 MHz; D_2O; 25 °C): δ (ppm) = 13.56 (N-$(CH_2)_5$-CH_3), 22.09 (N-$(CH_2)_4$-CH_2-CH_3), 25.33 (N-$(CH_2)_3$-CH_2-CH_2-CH_3), 28.26 (N-$(CH_2)_2$-CH_2-$(CH_2)_2$-CH_3), 30.66 (N-CH_2-CH_2-$(CH_2)_3$-CH_3), 32.61 (N-CH_2-$(CH_2)_4$-CH_3), 39.52 (N-CH_3), 50.33 (N-CH_2-$(CH_2)_4$-CH_3), 107.491 (C-4), 136.94 and 138.15 (C-3 and C-5).

Results and discussion

Although previous reports have shown that domestic microwave ovens can be used to prepare imidazolium halide[8] and tetrafluoroborate[25] salts (Fig. 2), realistic power control cannot

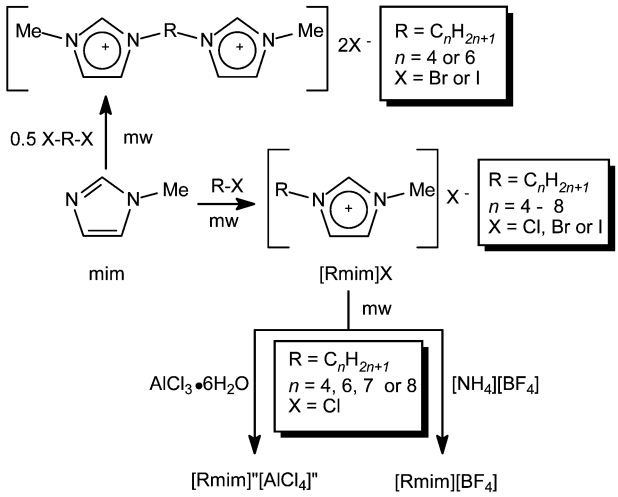

Fig. 2 Previously reported ionic liquid syntheses using mw irradiation.

be achieved. Due to power control restrictions and reaction container limitations, all the aforementioned preparations could only be performed on a small scale (3 mmol; 0.2 g) in open vessels, which necessitates a haloalkane molar excess of up to 100%, due to evaporative loss. It should also be noted that the reported preparation of tetrachloroaluminate compounds by Varma *et al.*[26] must be incorrect, as employing $AlCl_3 \cdot 6H_2O$ (Fig. 2) would result in irreversible formation of hydroxoaluminate species *via* hydrolysis of the anion.

Further restrictions associated with the use of domestic microwave ovens include problems encountered when attempting to reproduce reactions, as well as product charring due to superheating. Indeed, our group, as well as another,[27] experienced difficulty in repeating Varma's previously reported imidazolium halide preparations.[8] Meticulous reaction supervision was required to successfully reproduce the reactions and avoid product scorching. Chan and coworkers[27] attempted to moderate the heat of these 1-methylimidazole quaternisation reactions, and thereby improve reaction reproducibility, by placing reaction flasks in a water bath in a domestic microwave oven, but this procedure still does not provide convincing control of reaction conditions. Furthermore, haloalkane molar excesses between 10 and 300% were required to obtain good product yields, again making these syntheses dirty. It is of interest to note that Varma and co-worker[8,25,26] used intermittent vortex mixing during their microwave syntheses of ionic liquids. In this way a domestic microwave oven can be successfully employed to prepare ionic liquids on a small scale in a reproducible fashion, although commercial microwave reactors incorporating reaction condition control mechanisms offers a more flexible and convenient route to ionic liquids.

The ionic liquids prepared in the current investigation are shown in Fig. 3 (showing NMR numbering schemes). The

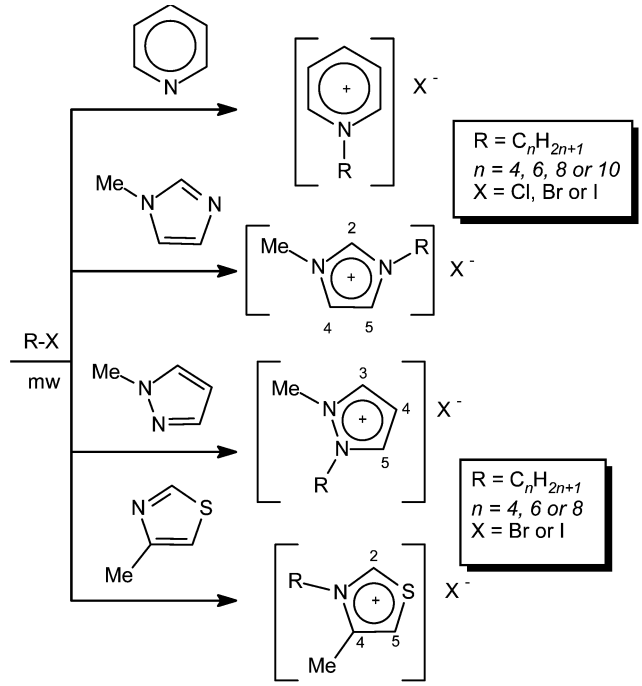

Fig. 3 Ionic liquids prepared using microwave irradiation.

1-alkylpyridinium and 1-alkyl-3-methylimidazolium halide salts were initially prepared using a 10% haloalkane molar excess, but this value was later reduced (*vide infra*). The reactions were performed on a 150–300 mmol scale in a sealed quartz reaction vessel, fitted with temperature and pressure probes. The former regulates the selected temperature by adjusting the microwave power input and the latter monitors the autogenous pressure. The optimum reaction conditions determined for the medium-scale, sealed vessel syntheses of [$C_n$mim]X and [$C_n$py]X salts are shown in Table 1. A reaction programme was created for each of the preparations and consisted of a two-minute ramp to reach the desired temperature and thereafter maintaining the reaction at this temperature. The microwave irradiation times given in Table 1 include the two-minute ramping period.

Due to evaporative loss, the preparation of 1-alkyl-3-methylimidazolium and 1-alkylpyridinium halide salts in open vessels often requires a large molar excess of the haloalkane to obtain good yields. For example, a 100% molar excess of 1-chlorobutane or 2-bromobutane has previously been used[8] to respectively prepare [C_4mim]Cl (76% yield) and [C_4mim]Br (61% yield). In contrast, all the sealed vessel preparations in the current study required only 10% molar excess of the appropriate haloalkane to obtain ≥87% work-up yields. Furthermore, conversions (based on ^{1}H NMR spectroscopy) of 99.95% for 1-methylimidazole and 99.9% conversion of pyridine (Table 1) were obtained, making the current synthetic route more cost and reagent efficient, and hence greener.

It is important to note that the reported conversions are probably close to 100%, but possible experimental error factors were included when the ^{1}H NMR spectroscopy detection limits for the four heterocycles were determined, making the conversion numbers slightly conservative. The ^{1}H NMR spectroscopy detection limits for all the ionic liquid preparations were determined by firstly recording the ^{1}H NMR spectrum of the pure ionic liquid sample. Thereafter, 2% by mass of the appropriate heterocycle was added to the solution, the ^{1}H NMR

spectrum recorded again, and the ratio of ionic liquid to heterocycle determined from the product to heterocycle signal integral ratio. A well-resolved and unobscured azole ^{1}H NMR signal was selected in the ionic liquid–heterocycle sample spectrum and its height measured. Finally, from the integral values and the heterocycle peak heights, the NMR spectrometer detection limit was visually determined by carefully discriminating whether the heterocycle signal would be clearly discernable above the noise of the baseline at levels of 0.01–0.05%. The reported conversion values for pyridine (99.9%) are lower than those for the azolium compounds (99.95%), since the ^{1}H NMR signals for unreacted pyridine are not as well resolved as those of the various azoles, making them more difficult to measure and hence, making their detection limit determination less reliable.

The rate at which the quaternisation of 1-methylimidazole or pyridine proceeds follows the conventional order: R–I > R–Br > R–Cl. Using microwave, as opposed to conductive, heating, this reactivity order remains the same, but reaction times are significantly decreased. For example, compared to conductive heating, microwave irradiation accelerates the formation of [C_4mim]Cl, [C_6mim]Cl and [C_8mim]Cl by a factor of *ca.* 70, and [C_{10}mim]Cl is generated *ca.*110 times faster. [$C_n$mim]X and [$C_n$py]X (X = Br or I) salts show a similar trend. A further result of haloalkane reactivity differences is that the chloride preparations require higher power levels (300 W) than the bromides (240 W), which in turn require greater levels than the iodides (200 W) to achieve similar conversions. In addition, shorter irradiation times are required for bromide and iodide preparations than for the chlorides. Despite the high temperatures of > 150 °C employed in some of the syntheses (Table 1), no imidazolium-based disproportionation products were observed. However, if irradiation is continued at these temperatures for extended periods of time, the 1-alkyl-3-methylimidazolium halides decompose according to the known route,[28,29] giving the corresponding halomethane and alkylimidazole as the major products. The pyridinium-based salts also visibly decompose with extensive heating, but the decomposition products were not identified.

Following the initial syntheses of 1-alkylpyridinium and 1-alkyl-3-methylimidazolium halide salts, the haloalkane molar excesses were reduced even further to determine whether this would affect product purity. It was found that the product yields obtained in the original study (Table 1; haloalkane molar excesses of 10%) did not change significantly when employing between 0.1–2% molar excess of haloalkane. While our study was underway, Rebeiro and coworker[30] published a stoicheiometric procedure to prepare imidazolium and pyridinium halides, which is analogous to the route we have developed, and provides a truly green route to ionic liquids. However, although the current results resemble Rebeiro's findings,[30] and despite a range of stoicheiometric ionic liquids having been prepared in our laboratories in excellent conversions and yields, it was found that in practice, and also in general, that a slight molar excess of haloalkane (1–2%) is advantageous, since it ensures complete conversion of 1-methylimidazole or pyridine, which are extremely difficult to remove from reaction mixtures. Due to the difficulty in removing these heterocycles from reaction mixtures, the small haloalkane excess also minimises the generation of waste in the form of solvent washings.

In our laboratories, the general purification of both azolium- and pyridinium-based ionic liquids involves dissolution of the crude product in ethanenitrile followed by washing of the ethanenitrile phase with ethyl ethanoate until unreacted starting materials are no longer detected by ^{1}H NMR spectroscopy after *in vacuo* removal of ethanenitrile (for reuse). In this way, azolium- and pyridinium-based ionic liquids that are either solid or liquid at room temperature are easily purified. Although recrystallisation of the halide salts that are solid at room temperature is also a purification option, it is neither convenient nor energy efficient, often requiring large volumes of recrystallisation solvent. In addition, azolium and pyridinium halide salts are very hygroscopic, deliquescing in the presence of atmospheric moisture, thereby eliminating recrystallisation as a purification option, and rendering the aforementioned ethanenitrile/ethyl ethanoate method most suitable in all cases.

Having established an efficient route to produce imidazolium and pyridinium halides rapidly on a medium-scale, the scale-up of these reactions was attempted. Our efforts were, however, restricted by the current lack of availability of sealed vessels capable of withstanding high pressures and with capacities greater than 250 cm^3. Therefore, ionic liquid syntheses using an open vessel and microwave irradiation were attempted. The large scale [$C_n$mim]X and [$C_n$py]X salt preparations (n = 4 or 6, X = Cl, Br, or I; 0.3–2.0 mol) were performed using a conventional reflux arrangement. A one-litre round-bottomed flask, equipped with a temperature-probe housing, was placed inside the microwave reactor cavity, with a reflux condenser protruding through an aperture in the reactor roof. All reactions gave conversions ≥99.95% (based on ^{1}H NMR spectroscopy) and isolated yields ≥85% with a 10% excess of haloalkane and at the boiling point of the appropriate haloalkane. On these scales, the reaction times were between 20–400 times shorter compared to conventional heating. Despite the 10% haloalkane excess used in the large-scale preparations, this method represents the cleanest current method to produce imidazolium and pyridinium halide salts on a large scale. For example, Chan and coworkers[27] carried out large-scale imidazolium halide syntheses (0.5–1.0 mol) in open vessels in a domestic microwave oven, but required up to 300% molar excess of haloalkane to achieve good product yields, making their procedure non-green and uneconomic.

Although the vast majority of ionic liquid chemistry based on nitrogen-containing heterocycles focuses on the use of 1-alkyl-3-methylimidazolium and 1-alkylpyridinium cations,[1–3] many heterocycles exist that can potentially serve as ionic liquid precursors. In an effort to extend the current repertoire of ionic liquids, derivatives of 3-alkyl-4-methylthiazolium and 1-alkyl-2-methylpyrazolium were prepared using microwave irradiation (Table 2). The synthesis of these compounds was selected since their preparation using conductive heating had proved extremely time-consuming, especially for the chloride and bromide derivatives.[24] The 1-alkyl-2-methylpyrazolium, [$C_n$mpz], and 3-alkyl-4-methylthiazolium, [$C_n$mtz], bromide and iodide salts (Fig. 3) were prepared in sealed quartz vessels by mixing the appropriate haloalkane (52.5 mmol) with either 1-methylpyrazole or 4-methylthiazole (50 mmol). Although the reactions were initially performed using a molar excess of the appropriate haloalkane (10%), this was later reduced (*vide infra*). As ascertained for their imidazolium and pyridinium analogues, the most effective reaction temperature, giving the best conversions and work-up yields, was established to be the approximate average boiling point of the employed haloalkane and the heterocycle (Table 2). Using microwave irradiation, the 3-alkyl-4-methylthiazolium bromide and iodide salts form between 36 and 61 times faster, 1-methyl-2-butylpyrazolium iodide forms 29 times faster, 1-methyl-2-hexylpyrazolium 41 times faster, and 1-methyl-2-octylpyrazolium iodide forms 72 times faster, compared to conventional heating.

Despite repeated attempts and extensive microwave irradiation, pyrazolium and thiazolium chloride salts did not form to any significant extent. Preliminary computational work from our group suggests that this is due to the lower nucleophilicity of the available pyrazole and thiazole nitrogen atoms compared to those of pyridine and imidazole.[31] These computational results will be published in a separate paper.

The bromide and iodide salt syntheses of 1-alkyl-2-methylpyrazolium and 3-alkyl-4-methylthiazolium required longer microwave irradiation times (Table 2) than their imidazolium

and pyridinium analogues (Table 1) to achieve 99.95% conversion. Once again, this is probably due to the lower nucleophilicity of the imine nitrogen atoms of 1-methylpyrazole and 4-methylthiazole compared to those of 1-methylimidazole and pyridine.[31] As already discussed for the imidazolium and pyridinium syntheses, the conversion values of 99.95% are conservative and in reality are probably close to 100%. As expected, the more reactive 1-iodoalkanes required shorter microwave irradiation times than the 1-bromoalkanes, although power levels of 300 W gave the best conversion figures for both the bromide and iodide preparations.

In our laboratories, 1-alkyl-2-methylpyrazolium iodide salts have been synthesised by charging an autoclave with the reactants, pressurising to *ca.* 4 bar, and heating to *ca.* 130 °C for 1824 h, to give product yields of between 40 and 60%.[24] The microwave approach, on the other hand, involves simple mixing of the reagents followed by microwave irradiation to give excellent conversions. Until now, we have concentrated on the preparation of pyrazolium iodides since they give the best yields using conventional reaction conditions. It should, therefore, be noted that preparation times under reflux are not available for the pyrazolium bromide salts, and thus comparison with microwave irradiation times is not possible (Table 2).

In a recent study, we have reduced haloalkane excesses in pyrazolium and thiazolium preparations from 10% to between 1 and 2% without significant changes in the conversions and yields (Table 2), providing an even cleaner route to these ionic liquids. However, as found in the imidazolium and pyridinium syntheses, a slight molar excess of haloalkane ensures complete heterocycle quaternisation, which diminishes solvent washings and gives an overall cleaner method to prepare 1-alkyl-2-methylpyrazolium and 3-alkyl-4-methylthiazolium bromides and iodides. Although the scale up of these reactions is possible in principle, we did not include this in our study due to the cost of 4-methylthiazole and the limited availability of 1-methylpyrazole.

Decomposition of 1-alkyl-2-methylpyrazolium bromides and iodides was observed upon heating for long periods. The decomposition products have not been characterised, but NMR spectroscopic evidence suggests that a disproportionation process, analogous to that of imidazolium salts,[29] occurs.

Conclusion

Simple synthetic methods to prepare 1-alkylpyridinium, 1-alkyl-3-methylimidazolium, 1-alkyl-2-methylpyrazolium and 3-alkyl-4-methylthiazolium ionic liquids using a commercial multimode microwave reactor[22] have been developed. These methods display dramatically reduced reaction times compared to conventional methods, minimise the generation of organic waste, and also afford the ionic liquid products in excellent yields and purity. The syntheses can be performed on flexible reaction scales (50 mmol–2 mol) in either sealed or open vessels, with the large molar excess of haloalkane (often required in conventional ionic liquid syntheses) significantly reduced. Only a small molar excess of haloalkane was found to be necessary to ensure excellent conversion of heterocycle to product, which in turn, minimises the generation of solvent waste for purification. We see no reason why this methodology should not be generally applicable to the alkylation of any neutral molecule containing a nitrogen atom with a reasonable nucleophilicity and steric accessibility (or, indeed, any other nucleophilic centre). This microwave technique makes the syntheses of ionic liquids not only faster but also ‘greener’, and much more convenient.

Acknowledgements

We would like to thank QUILL for funding this work, and Suzanne Johnson and Jan-Albert van den Berg for their invaluable assistance.

References

1 (*a*) R. Sheldon, *Chem. Commun.*, 2001, 2399–2407; (*b*) C. M. Gordon, *Appl. Catal. A.*, 2001, **222**, 101–117; (*c*) D. Zhao, M. Wu, Y. Kou and E. Min, *Catal. Today*, 2002, **2654**, 1–33; (*d*) H. Olivier-Bourbigou and H. Magna, *J. Mol. Catal. A*, 2002, **164**, 1–19.
2 (*a*) T. Welton, *Chem. Rev.*, 1999, **99**, 2071–2083; (*b*) J. D. Holbrey and K. R. Seddon, *Clean Prod. Proc.*, 1999, **1**, 223–236; (*c*) P. Wasserscheid and W. Keim, *Angew. Chem., Int. Ed. Engl.*, 2000, **39**, 3772–3789.
3 *Synthesis in Ionic Liquids*, ed. P. Wasserscheid and T. Welton, Wiley-VCH, Weinheim, 2002.
4 K. R. Seddon, A. Stark and M.-J. Torres, *Pure Appl. Chem.*, 2000, **72**, 2275–2287.
5 J. S. Wilkes, J. A. Levinsky, R. A. Wilson and C. L. Hussey, *Inorg. Chem.*, 1982, **21**, 1263–1264.
6 (*a*) K. R. Seddon, A. J. Carmichael and M. J. Earle, World Patent, WO 0140146, 2001; (*b*) M. J. Earle and K. R. Seddon, World Patent Patent, WO 0177081, 2001.
7 P. Bonhôte, A.-P. Dias, N. Papergeorgiou, N. Kalyanasundaram and M. Grätzel, *Inorg. Chem.*, 1996, **35**, 1168–1172.
8 R. S. Varma and V. V. Namboodiri, *Chem. Commun.*, 2001, 643–645.
9 P. Lindström, J. Tierney, B. Wathey and J. Westman, *Tetrahedron*, 2001, **57**, 9225–9283.
10 R. S. Varma, *Green Chem.*, 1999, **1**, 43–55.
11 R. Gedye, F. Smith, K. Westaway, A. Humera, L. Baldisera, L. Laberge and L. Rousell, *Tetrahedron Lett.*, 1986, **27**, 279–282.
12 R. Giguere, T. L. Bray, S. M. Duncan and G. Majetich, *Tetrahedron Lett.*, 1986, **27**, 4945–4948.
13 S. Deshayes, M. Liagre, A. Loupy, J.-L. Luche and A. Petit, *Tetrahedron*, 1999, **55**, 10851–10870.
14 A. Loupy, A. Petit, J. Hamelin, F. Texier-Boullet, P. Jacquault and D. Mathe, *Synthesis*, 1998, **9**, 1213–1234.
15 (*a*) J. Westman, *Org. Lett.*, 2001, **3**, 3745–3747; (*b*) N. Kuhnert and T. N. Danks, *Green Chem.*, 2001, **3**, 68–70.
16 (*a*) A. Loupy and S. Regnier, *Tetrahedron Lett.*, 1999, **40**, 6221–6224; (*b*) A. Loupy, L. Perreux, M. Liagre, K. Burle and M. Moneuse, *Pure Appl. Chem.*, 2001, **73**, 161–166.
17 A. G. Whittaker, *New Scientist*, 1998, **157**, 34.
18 K. S. A. Vallin, P. Emilsson, M. Larhed and A. Hallberg, *J. Org. Chem.*, 2002, **67**, 4340–4343.
19 N. E. Leadbeater and M. Marco, *Org. Lett.*, 2002, **4**, 2973–2976.
20 K. Selvakumar, A. Zapf and M. Beller, *Org. Lett.*, 2002, **4**, 3031–3033.
21 Y. Patell, MPhil Thesis, University of Sussex, 1994; L. Dutta, MPhil Thesis, University of Sussex, 1995; Y. Patell, K. R. Seddon, L. Dutta and A. Fleet, in *Green Industrial Applications of Ionic Liquids*, ed. R. D. Rogers, K. R. Seddon and S. Volkov, Kluwer, Dordrecht, 2003, 499–510.
22 Mars Synthesis System: http://www.cem.com/products/MARS5.html.
23 E. D. Neas and M. J. Collins, in *Introduction to Microwave Sample Preparation Theory and Practice*, ed. H. M. Kingston and L. B. Jassie, American Chemical Society, Washington, DC, 1988, pp. 7–32.
24 S. Johnston, unpublished results, 1999–2002.
25 R. S. Varma and V. V. Namboodiri, *Tetrahedron Lett.*, 2002, **43**, 5381–5383.
26 V. V. Namboodiri and R. S. Varma, *Chem. Commun.*, 2002, 342–343.
27 M. C. Law, K.-Y. Wong and T. K. Chan, *Green Chem.*, 2002, **4,** , 328–330.
28 C. G. Begg, M. R. Grimmet and P. D. Wethey, *Aust. J. Chem.*, 1973, **26**, 2435–2438.
29 A. J. Jeapes, R. C. Thied, K. R. Seddon, W. Pitner, D. W. Rooney, J. E. Hatter and T. Welton, World Patent, WO 0115175, 2001.
30 B. M. Khadilkar and G. L. Rebeiro, *Org. Process Res. Dev.*, 2002, **6**, 826–828.
31 J.-A. van den Berg, unpublished results, 2002.

Synthesis of benzimidazoles in high-temperature water†‡

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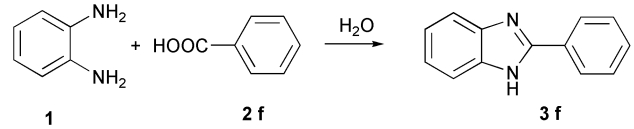
Received 17th December 2002
First published as an Advance Article on the web 12th March 2003

The objective of this research was to conduct constructive organic chemistry in water and to achieve yields that were comparable to, or better than, those in conventional media. The synthesis of 2-phenylbenzimidazole from 1,2-phenylenediamine and benzoic acid was chosen as a benchmark reaction. The reaction parameters, such as temperature, density and reaction time, have been systematically studied to understand whether the solvent properties of high-temperature water can have a positive effect on the chemistry. The reaction was performed in a new design of batch-type autoclave and was also monitored *in situ* by UV-vis spectroscopy. By tuning the parameters, the yield has been optimised to around 90%. The optimised conditions were then applied to related benzimidazoles, some of which crystallised from solution *in situ* to yield single crystals that were sufficiently pure to be analysed directly by X-ray diffraction, without any further purification.

Introduction

The benzimidazole moiety is an important heterocyclic nucleus which has been used extensively in medicinal chemistry. Current clinical examples include the antihistamine Astemizole,[1] the anti-ulcerative Esomeprazole[2] and Albendazole,[3] which is used to treat parasitic diseases. Benzimidazoles are a component of vitamin B_{12} and are related to the DNA base purine and the stimulant caffeine. Bisbenzimidazoles are being developed as DNA minor-groove binding agents with antitumor activity[4] and can act as ligands to transition metals for modelling biological systems.[5]

Conventional synthesis of benzimidazoles involves heating the reactants in refluxing aqueous hydrochloric acid for 30 minutes[6] or in a slurry of the dehydrating agent polyphosphoric acid at 250 °C for 4 hours.[7] The reaction mixture must then be neutralised with a base, such as aqueous ammonia, thereby generating aqueous waste. The pure product is obtained after recrystallisation from an organic solvent. Clearly, there is a strong opportunity for devising a cleaner route to benzimidazoles. Solid phase synthesis[8] and microwave irradiation using silica gel as a solid acid,[9] are two approaches that have been reported. This work describes the preparation of 2-phenylbenzimidazole (**3f**) from 1,2-phenylenediamine (**1**) and benzoic acid (**2f**) (Scheme 1) using near and supercritical water as an alternative, environmentally benign solvent.



1 2 f 3 f

Scheme 1 Double dehydration and intramolecular cyclisation reaction between 1,2-phenylenediamine and benzoic acid to yield 2-phenylbenzimidazole.

Water is an abundant and cheap solvent, the use of which is limited by its high polarity and consequent poor solubility of organic molecules. As water approaches its critical point (T_c =

Four of the authors (from left to right): Lucinda Dudd, Dr. Peter Licence, Dr. Eduardo Garcia-Verdugo and Eleni Venardou. L. M. D. and E. V. are final year PhD students. E. G. V. is a Marie Curie Fellow and P. L. is a CRYSTAL Faraday Associate.

† This work was presented at the Green Solvents for Catalysis Meeting held in Bruchsal, Germany, 13–16th October 2002.
‡ Electronic supplementary information (ESI) available: analytical data for compounds **3a–f** and **5g–j**. See http://www.rsc.org/suppdata/gc/b2/b212394k/

Green Context

Water is an obvious candidate as an environmentally benign replacement for VOC solvents. However the incompatibility of many organics with water restrict its use as a solvent for organic synthesis. Here we see how high temperature water can help overcome this limitation by being better able to solvate organic molecules and by enabling their reaction chemistry. Thus 2-phenylbenzimidazole, a useful compound in medicinal chemistry, can be synthesised effectively in high temperature water. Careful control of the reaction parameters enables high product yields to be obtained. The change in solvation properties of water can be further exploited by allowing the product to crystallise out from the water on cooling. ***JHC***

374 °C, P_c = 22.1 MPa, ρ_c = 0.317 g cm^{-3}), the physical and chemical properties of the fluid change.[10] As the temperature is increased, at a fixed pressure of 20.0 MPa, the dielectric constant (ε) decreases from 80 (25 °C) to 36 (200 °C), 21 (300 °C), 14 (350 °C) and 2 (400 °C).[11] These dielectric constants are comparable to those for methanol (33), ethanol (24), acetone (14), and hexane (2) at ambient temperature and pressure.[12] A further change occurs as a result of the breakdown in hydrogen bonding as the temperature is increased; the ionic product (K_w) increases with increased local concentration of H_3O^+ and OH^- ions, which reaches a maximum at around 250 °C and 25 MPa and then decreases sharply at the critical temperature.[13] This property has allowed acid- and base-catalysed reactions to be performed at this near-critical temperature without adding an acid or base, *e.g.* in the acid-catalysed Beckmann and pinacol rearrangements[14] and dehydration of alcohols[15,16] and in the base-catalysed aldehyde disproportionation[17] and ester hydrolysis.[18]

The majority of constructive organic chemistry in hot water has been conducted at near-critical temperatures[19] where the ionic product is favourable, the dielectric constant comparable to organic solvents and the rate of decomposition of organic molecules less than at even harsher conditions. Our group has reported the hydrolysis of esters,[20] the reduction of nitroarenes[21] and subsequent cyclisation to quinolines,[22] the partial oxidation of *p*-xylene to terephthalic acid[23] and the use of water as a reactant in hydrogen exchange reactions.[24]

Experimental

Safety warning: these reactions involve high pressures and must only be carried out in an apparatus with the appropriate pressure rating at the reaction temperature. A trip switch must be used to stop the heating when the pressure nears the limit of the reaction vessel. The maximum amount of water which could be safely loaded without over pressure was calculated from steam tables.[25] A drawing and description of the mini autoclave, which was built in Nottingham, is given in Fig. 1. The vessel was leak tested using CO_2 and hydrostatically tested before commissioning. All chemicals were used as received (Aldrich) and water used was HPLC grade triply distilled (BDH). Water (typically 5.4 mL) and a 1 : 2 molar ratio of 1,2-phenylenediamine (typically 0.20 g, 1.8 mmol) and benzoic acid (typically 0.44 g, 3.6 mmol) were charged to the 10 mL high-pressure mini autoclave. The water density was defined as the mass of water (g) in the vessel (cm^3) to ± 0.01 g cm^{-3}. The concentration of 1,2-phenylenediamine in water was constant to within experimental error (±0.03 M). Reaction times did not include the time taken to heat the contents. When the vessel had been cooled, the shut-off valve was opened to allow excess pressure to be released. The vessel was opened and the contents, including the water, were dissolved in methanol and transferred to a 50 mL volumetric flask and analysed by HPLC.[26]

Results and discussion

A systematic study of the reaction parameters in the synthesis of 2-phenylbenzimidazole (**3f**) was conducted in order to tune the solvent properties of water and optimise the yield. Such a study should provide some understanding of the rôle of water as solvent and possible catalyst. Obviously such a route would be impracticable if the product were unstable under the reaction conditions. Therefore, a commercial sample of **3f** was heated in H_2O for 4 hours at 350 °C in the mini autoclave. The HPLC analysis showed that **3f** was highly stable; 99% of the initial sample was recovered. Regarding the stability of the reactants, **1** gave 70% recovery while only 10% of **2f** was recovered.[27]

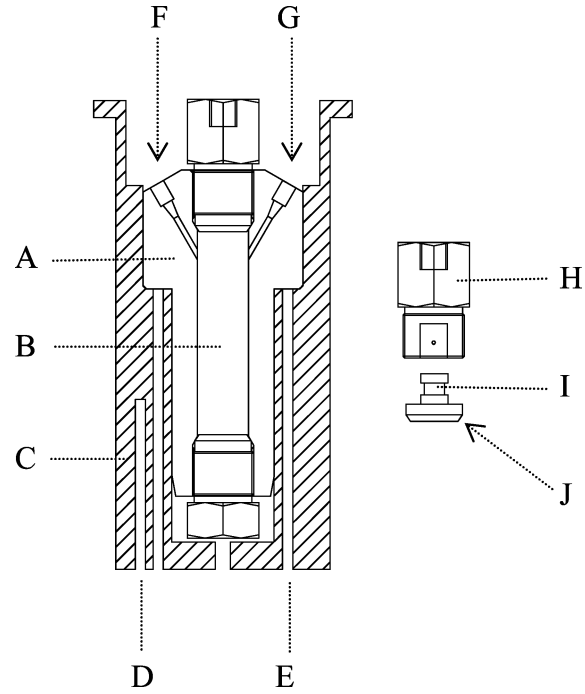


Fig. 1 Drawing of the 10 mL high-pressure mini autoclave (316 SS) in an aluminium holder, showing detail of cap and sealing face. (A) stainless steel autoclave; (B) autoclave cavity of 10 mL volume; (C) aluminium holder surrounded by heating jacket or cooling pipe; (D) well for thermocouple controlling heating jacket; (E) vents to release air during heat-up; (F) high-pressure fitting for tubing to pressure transducer and shut-off valve; (G) high-pressure fitting for securing thermocouple into autoclave cavity; (H) top cap with screw-thread for tool to transfer from hot to cold holder; (I) rotating insert held into top cap by screw; (J) sealing face of cap. The maximum pressure rating is 60 MPa at 400 °C. The autoclave is closed with caps at both ends (sealed to a torque of 50 Nm). 1/16 inch tubing (Swagelok, maximum pressure rating 67 MPa) is held in place by SSI fittings in the top of the autoclave and links a pressure transducer (RDP Electronics, maximum pressure rating 68 MPa) and shut-off valve (HIP) in series. A chromal/alumel thermocouple is positioned at the centre of the autoclave and sealed in place using SSI fittings. The apparatus consisted of two similar aluminium holders for the autoclave, one surrounded by a heating jacket (850 W, Watlow) and the other surrounded by a copper tubing coil for cooling water. Heat up time is between 5 and 10 min and cooling down takes 15 min, though the temperature is halved in the first two minutes.

Thus, for the reaction to be successful, the rate of formation of product must be faster than the rate of decomposition of the reagents.

A set of experiments was performed to assess the effect of temperature over the range 100 to 400 °C. The yields were calculated from HPLC analysis by comparison with standards of commercially available **3f**.[26] As it is shown in Table 1, the yield increased with increasing temperature from 0% at 100 °C (entry 1) to 71% at 350 °C (entry 5). The highest yield of 89%

Table 1 Yield of **3f** at different temperatures and pressures

Entry	Time/h	Temp/°C	Pressure/MPa	Yield (%)[a]
1	2	100[b]	0.1	0
2	2	200	1.7	18
3	2	250	4.5	28
4	2	300	8.5	43
5[c]	2	350	17.8	71
6	4	350	21.7	89
7	14	350	20.9	91
8	2	400	57.4	74

[a] Yield based on HPLC analysis. [b] Reaction was carried out in a round-bottomed flask with reflux condenser. [c] The experiment was repeated to assess the reproducibility of the reaction. The yield was reproducible to ±1% and the pressure was accurate to ±0.6%. *Reaction conditions*: concentration = 0.3 ± 0.03 M; water density = 0.54 ± 0.01 g cm^{-3}.

was seen at 350 °C after 4 hours and remained constant after 14 hours (Entries 6 and 7 respectively). A further increase in temperature did not lead to any significant improvement in yield *e.g.* 74% at 400 °C (entry 8). The pressure observed in the vessel was almost identical to the vapour pressure of pure water at the same temperature, and increased greatly around the critical temperature as the liquid water was compressed in the vessel. Using the temperature and pressure measured in our reactions, the dielectric constant of water can be estimated to be 35 (200 °C), 27 (250 °C), 20 (300 °C), 14 (350 °C) and 13 (400 °C).[11] The water becomes less polar with increasing temperature, becoming comparable to room temperature dichloromethane.[12] The high pressure observed for the reaction at 400 °C gives rise to high densities, thus the dielectric constants of the water at 350 and 400 °C are similar; this may be an explanation for the similar yields recorded at the two temperatures.

As stated above, high-temperature water can act as both an acid and base catalyst due to the increased ionic product from around −14 to −11 (log K_w) at 25 and 300 °C, respectively (at 400 °C, log K_w is around −20).[13] A one-fold molar excess of **2f** was used in all experiments. The dissociation constant of **2f** decreases at high temperatures from around −4 to −7 (log K) at 25 and 400 °C, respectively,[28] in a similar way to β-naphthoic acid.[29]

The effect of the temperature on the initial rate of the reaction was also investigated (Fig. 2). The concentration profiles can be

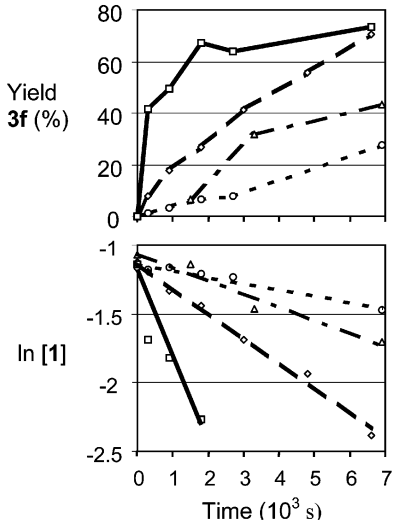


Fig. 2 Plots of the yield of **3f** (upper) and logarithm of concentration of **1** (lower) against reaction time for temperatures of 250 (dotted line), 300 (dot-dash line), 350 (dashed line) and 400 °C (solid line). Pressures obtained were approximately 4 MPa (250 °C), 9 MPa (300 °C), 17 MPa (350 °C) and from 34 to 57 MPa (400 °C).

approximated, within experimental error, to pseudo-first-order reaction kinetics with reference to 1,2-phenylenediamine (**1**). The reaction rates were strongly influenced by temperature, showing a two-fold increase between 250 and 300 °C and a four-fold increase between 250 and 350 °C. The most dramatic change occurred under supercritical conditions, at 400 °C, where the increase was 12-fold. At 400 °C, the yield increased sharply with reaction time and reached 67% after 1800 s and a further increase in time did not lead to a substantial improvement in yield, *e.g.* 74% after 6600 s. Therefore, the initial rate for the reaction at 400 °C was calculated using data from the first 1800 s of the reaction, while the rates for the lower temperatures were calculated from the first 6900 s of the reaction. The limiting factor in the reaction at 400 °C was likely to be the decomposition of reactants. Indeed the pressure was seen to increase over the 2 hour reaction time, which may have been due to such decomposition. At 400 °C, a small residual pressure of 0.4 MPa was seen on cooling the vessel and the gas was analysed by GC and found to contain 3.5% carbon monoxide in air for the reaction after 2700 s at 50 MPa. It is likely that carbon dioxide evolved reacts with the H_2O to form carbonic acid, which may play a part in catalysing the reaction.

This rate effect is also reflected in the *in situ* UV-vis spectra of the reactions at 350 °C, see Fig. 3. The band at around 300 nm

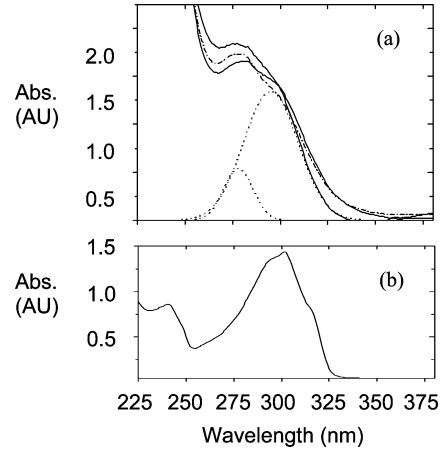


Fig. 3 (a) UV-vis spectrum of reaction forming **3f** recorded after 120 s (top solid line), 1200 s (dot-dash line) and 8880 s (bottom solid line). The deconvolution procedure was applied to the spectrum at 8880 s; the contour was approximated to the sum of n Gaussian peaks, where n is the number of inflection points. The experimental conditions were 350 °C, 25.0 MPa, 0.534×10^{-3} M of **1** and 1.064×10^{-3} M of **2f**. (b) Absorption spectrum of a pure sample of **3f**.

corresponds to **3f**. Clearly, the band at 280 nm decreased with time while the band at 300 nm increased with time. By contrast, the spectrum recorded at 300 °C showed no band at 300 nm being formed over a similar period of time. The concentration of reactants was necessarily very low because of the low solubility of the reactants at lower temperatures and this is the likely explanation for the reaction rate, which is slow compared to the batch experiments. The experiments were carried out in a stopped flow mode in a new high-pressure, high-temperature UV-vis cell.[30]

Table 2 Yield of **3f** at different solution concentrations

Entry	Concentration/M[a]	Pressure/MPa	Yield (%)[b]
1	0.003	—[c]	4
2	0.030	14.0	5
3	0.096	15.3	19
4	0.158	15.1	35
5	0.312	17.8	71
6	0.766	16.4	82

[a] Concentration of **1** ± 0.009 M. [b] Yield based on HPLC analysis. [c] Pressure not recorded. *Reaction conditions*: temperature = 350 °C; reaction time = 2 h (chosen as the yield at 4 h had already been found around 89%, hence a change in yield should be more pronounced at 2 h); water density = 0.60 − 0.47 ± 0.01 g cm^{-3}.

Table 2 summarizes the effect of the concentration of **1** on the yield of **3f**. The yield increased linearly with concentration from 0.003 to 0.31 M (4–71% yield). Further increase in the concentration did not lead to a significant increase in the yield (0.77 M, 82% yield). These concentrations were equivalent to 0.1 to 27% weight/volume of reactants in the vessel. This increase is consistent with a bimolecular reaction.

Under supercritical conditions, increased density has been shown to increase the product yields of cyclohexanol dehydration due to the increased ionic product.[16] The reaction mechanism to form **3f** is also an acid catalysed dehydration so

the effect of density was investigated at 410 °C, well above the critical point of water. However, we did not find a strong variation in yield (45–67%) over a five-fold increase in density (Table 3). The increase is likely to be due to the presence of more H_2O, which can dissociate to form H_3O^+ ions and catalyse the reaction.

Table 3 Yield of **3f** at different water densities

Entry	Water density/±0.01 g cm^{-3}	Pressure/MPa	Yield (%)[a]
1	0.09	20.9	45
2	0.18	29.3	55
3	0.36	30.5	56
4	0.54	45.1	67

[a] Yield based on HPLC analysis. *Reaction conditions*: temperature = 410 °C; reaction time = 4 h; concentration = 0.3 ± 0.03 M.

The effect of different solvents at near and supercritical conditions (Table 4) was studied to establish whether water with its favourable solvent properties (*e.g.* dielectic constant and ionic product) was playing a key role in the reaction or if the success of the reaction was largely due to the high temperature and pressure. Ethanol (T_c = 241 °C and P_c = 6.1 MPa)[31] and *i*-propanol (T_c = 235 °C and P_c = 4.8 MPa)[12] were chosen because they are polar, protic solvents; ethanol becomes nearly non-polar as its critical temperature is approached.[31] Acetone (T_c = 236 °C and P_c = 4.8 MPa) was chosen as a polar, aprotic solvent. By contrast, n-hexane (T_c = 234 °C and P_c = 3.0 MPa), and *p*-xylene (T_c = 345 °C and P_c = 3.4 MPa)[12] are non-polar solvents. In the event, ethanol (entry 1) appeared to react with the benzoic acid to form ethylbenzoate, and the only solvent where the yield was higher than in water was *p*-xylene (entry 7; *i.e.* 79%, 10% higher than that for H_2O). Combining *p*-xylene and water in a 1 : 1 ratio might be expected to give an intermediate result or even have a synergic effect. However, the mixed solvents gave a lower yield (entry 4) than for water alone (entry 6), possibly due to poor mixing in the vessel. For comparison, *p*-xylene was then used as the solvent for the reaction in a conventional reflux apparatus at 230 °C; even after 4 hours, the yield was only 3%. Although *p*-xylene is a more effective solvent than H_2O at high pressure and/or high temperature, it is obviously environmentally less benign. This result is surprising and warrants further study. Perhaps **2f** acts differently in water and *p*-xylene. When the reaction in H_2O was repeated with double the reaction time (entry 8), the yield exceeded that for *p*-xylene suggesting that although the reaction in H_2O is slower than in *p*-xylene, H_2O works quite as well as environmentally less acceptable solvents.

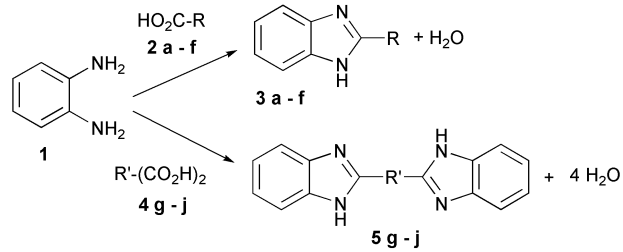
The yields for H_2O and *i*-propanol were better than for acetone and hexane; possibly the acidity of the dissociated solvent enhances the yield. A solid acid was added to the water to study the effect of acid on the reaction. We used 5% of the solid Brønsted acid catalyst, Deloxan® ASP II, a macroporous polysiloxane with alkylsulfonic acid groups, which has previously been used for reactions in supercritical water.[24] The conditions were identical to those given in Table 4. The yield was 70% as compared to 68% in water without catalyst. Therefore, additional acid is not catalysing the reaction significantly under these conditions.

Table 4 Yield of **3f** in different solvents

Entry	Solvent	Pressure/MPa	Yield (%)[a]
1	Ethanol	8.9	4
2	Acetone	8.0	8
3	Hexane	5.7	42
4	*p*-Xylene and water (1 : 1)	15.0	45
5	*i*-Propanol	10.7	64
6	Water	16.6	69
7	*p*-Xylene	8.1	79
8[b]	Water	16.4	82

[a] Yield based on HPLC analysis. [b] Reaction time = 4 h. *Reaction conditions*: temperature = 350 °C; reaction time = 2 h; concentration = 0.3 ± 0.03 M; water density = 0.18 ± 0.01g cm^{-3} (pressure generated by larger volumes of some organic solvents under these conditions exceeds the maximum pressure rating of our vessel).

Various substituted benzimidazole and bisbenzimidazole compounds were prepared (Scheme 2) to demonstrate that our method is not unique to the preparation of 2-phenylbenzimidazole. For compounds **3a**–**f**, the reaction conditions were those optimised in the study above except for **3a**, where the temperature was lowered to 210 °C because formic acid decomposed at higher temperatures.[32] The products were washed from the vessel with methanol; the methanol and water were then removed under vacuum and the product recrystallised and analysed by NMR (see ESI‡). Table 5 (entries 1–6) shows that good yields were obtained without further optimisation for a wide range of acids.



a. R = H **b**. R = CH_3 **c**. R = $CH(CH_3)_2$ **d**. R = $C(CH_3)_3$ **e**. R = C_6H_5
f. R = C_6H_5 **g**. R' = - **h**. R' = $(CH_2)_2$ **i**. R' = *p*-C_6H_4 **j**. R' = *o*-C_6H_4

Scheme 2 Synthesis of substituted benzimidazoles and bisbenzimidazoles.

Table 5 Results of substituted benzimidazoles and bisbenzimidazoles

Entry	Product number	Yield (%)[a]
1[b]	**3a**	79
2[c]	**3b**	42
3[c]	**3c**	72
4[c]	**3d**	31
5[c]	**3e**	92
6[c]	**3f**	90
7[d]	**5g**	30
8[e]	**5h**	68
9[e]	**5i**	70
10[e]	**5j**	62

[a] Yields obtained gravimetrically. [b] *Reaction conditions*: temperature = 210 °C; reaction time = 4 h; concentration = 0.3 ± 0.03 M; water density = 0.54 ± 0.01 g cm^{-3}. [c] Reaction temperature = 350 °C. [d] Temperature = 300 °C; reaction time = 1 h; concentration 0.4 ± 0.03 M. [e] Temperature = 350 °C; reaction time = 2 h; concentration = 0.8 ± 0.03 M.

In addition, various bisbenzimidazoles (Scheme 2) were prepared from diacids in a 2 : 1 molar ratio of 1,2-phenylenediamine to diacid (Table 5, entries 7–10). When the autoclave was allowed to cool slowly, crystals were formed which were used directly for single crystal X-ray diffraction studies[33] without any further purification. The unit cell parameters were determined for a single crystal of **5g** and matched those published.[34] The structure of **5h** obtained from collected diffraction data[35] is shown in Fig. 4. The unit cell[36] of **5i** (Fig. 5) is different from the previously published structure.[37] The structure reported here for **5j**[38] (Fig. 6) crystallises in a different form to that previously reported,[37] although the overall structure is very similar. Interestingly the previous sample was

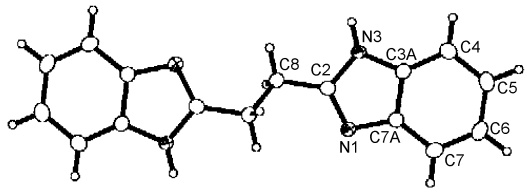


Fig. 4 Crystal structure of product **5h**, 2,2′-(1,2-ethanediyl)bis-1H-benzimidazole. **5h** crystallises around an inversion centre such that the asymmetric unit contains half the molecule with the other half inversion related. The two benzimidazole rings are coplanar and lie at an angle of ~133° to the central C–C bond.

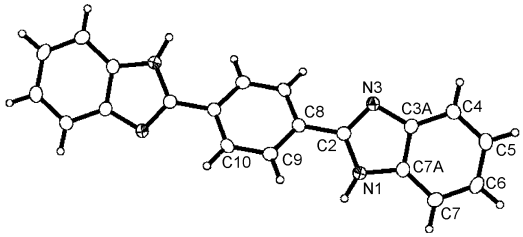


Fig. 5 Crystal structure of product **5i**, 2,2′-(1,4-phenylene)bis-1H-benzimidazole. **5i** also crystallises around an inversion centre, again with half the molecule in the asymmetric unit. The benzimidazole rings are planar, (mean deviation from planarity 0.033 Å), and lie at an angle of ~32° to the central phenyl ring. In both structures the molecules are linked by NH···N hydrogen bonds to form layers approximately perpendicular to the *a*-axis.

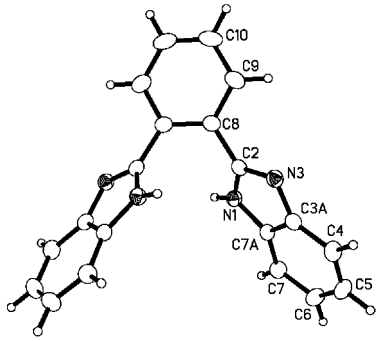


Fig. 6 Crystal structure of product **5j**, 2,2′-(1,2-phenylene)bis-1H-benzimidazole. **5j** crystallises with half the molecule in the asymmetric unit with the other half generated by a two-fold rotation. The angle between the benzimidazole rings and the central phenyl ring is 49° and in this case the two benzimidazole rings are not coplanar but lie at an angle of 67.2° to one another. The hydrogen bonding arrangement also differs for this compound with the NH···N hydrogen bonds forming a chain in the [001] direction.

red in colour whereas this current form is colourless. See ESI‡ for full details.

The yields for the above benzimidazoles are often comparable with those obtained using conventional synthetic methods, although in these forcing conditions, some functional groups are more susceptible to decomposition. Therefore less forcing conditions would be needed to optimise the yields.

Conclusions

This example of green chemistry includes replacement of volatile organic solvents with water and the elimination of acidic media and subsequent neutralisation. Some of the compounds have crystallised *in situ*, when the solvating power of water for organic compounds was lost on cooling, thereby eliminating the need to purify with environmentally less benign solvents. By varying the reaction parameters, such as temperature, reaction time and concentration, the yield of the desired benzimidazole compound has been successfully optimised. If we are to convince chemists to embrace new solvents, it is vital that we show how we can control the chemistry reproducibly. This work has begun to address this challenge.

Acknowledgements

We thank the EPSRC (Grant No. GR/NO6892), GlaxoSmith-Kline, The Marie Curie Program and DuPont Polyester Technology for funding. We thank Profs. Yu. E. Gorbaty and M. W. George and Mr. T. W. Ramsay for their help and advice. We are also grateful to Messrs P. Fields, R. Wilson, D. Lichfield and M. Guyler for their technical support.

References

1 H. Al Muhaimeed, *J. Int. Med. Res.*, 1997, **25**, 175.
2 L. J. Scott, C. J. Dunn, G. Mallarkey and M. Sharpe, *Drugs*, 2002, **62**, 1503.
3 P. Venkatesan, *J. Antimicrob. Chemother.*, 1998, **41**, 145.
4 J. Mann, A. Baron, Y. Opoku-Boahen, E. Johansson, G. Parkinson, L. R. Kelland and S. Neidle, *J. Med. Chem.*, 2001, **44**, 138.
5 E. Bouwman, W. L. Driessen and J. Reedijk, *Coord. Chem. Rev.*, 1990, **104**, 143; M. A. Pujar and T. D. Bharamgoudar, *Transition Metal Chem.*, 1988, **13**, 423.
6 M. A. Phillips, *J. Chem. Soc.*, 1928, 2393.
7 D. W. Hein, R. J. Alheim and J. J. Leavitt, *J. Am. Chem. Soc.*, 1957, **79**, 427.
8 B. Raju, N. Nguyen and G. W. Holland, *J. Comb. Chem.*, 2002, **4**, 320.
9 Y. Njoya, N. Boufatah, A. Gellis, P. Rathelot, M. P. Crozet and P. Vanelle, *Heterocycles*, 2002, **57**, 1423.
10 N. Akiya and P. E. Savage, *Chem. Rev.*, 2002, **102**, 2725.
11 M. Uematsu and E. U. Franck, *J. Phys. Chem. Ref. Data*, 1980, **9**, 1291.
12 R. C. Weast, *CRC Handbook of Chemistry and Physics: a ready reference book of chemical and physical data*, CRC Press, Ohio, 1972.
13 W. L. Marshall and E. U. Franck, *J. Phys. Chem. Ref. Data*, 1981, **10**, 295.
14 Y. Ikushima, K. Hatakeda, O. Sato, T. Yokoyama and M. Arai, *J. Am. Chem. Soc.*, 2000, **122**, 1908.
15 M. J. Antal, M. Carlsson, X. Xu and D. G. M. Anderson, *Ind. Eng. Chem. Res.*, 1998, **37**, 3820.
16 N. Akiya and P. E. Savage, *Ind. Eng. Chem. Res.*, 2001, **40**, 1822.
17 H. P. Lesutis, R. Gläser, C. L. Liotta and C. A. Eckert, *Chem. Commun.*, 1999, 2063.
18 H. Oka, S. Yamago, J. Yoshida and O. Kajimoto, *Angew. Chem., Int. Ed.*, 2002, **41**, 623.
19 P. E. Savage, *Chem. Rev.*, 1999, **99**, 603; D. Broll, C. Kaul, A. Krämer, P. Krammer, T. Richter, M. Jung, H. Vogel and P. Zehner, *Angew. Chem., Int. Ed.*, 1999, **38**, 2998; M. Siskin and A. R. Katritzky, *Chem. Rev.*, 2001, **101**, 825; A. R. Katritzky, D. A. Nichols, M. Siskin, R. Murugan and M. Balasubramanian, *Chem. Rev.*, 2001, **101**, 837.
20 P. A. Aleman, C. Boix and M. Poliakoff, *Green Chem.*, 1999, **1**, 65.
21 C. Boix and M. Poliakoff, *J. Chem. Soc., Perkin Trans. 1*, 1999, 1487.
22 C. Boix, J. M. de la Fuente and M. Poliakoff, *New J. Chem.*, 1999, **23**, 641.
23 P. A. Hamley, T. Ilkenhans, J. M. Webster, E. Garcia-Verdugo, E. Venardou, M. J. Clarke, R. Auerbach, W. B. Thomas, K. Whiston and M. Poliakoff, *Green Chem.*, 2002, **4**, 235.
24 C. Boix and M. Poliakoff, *Tetrahedron Lett.*, 1999, **40**, 4433.
25 E. Schmidt, *Properties of water and steam in SI-units*, Springer-Verlag, Berlin, 1969.
26 HPLC was used to determine the concentration of the 1,2-phenylenediamine, benzoic acid and 2-phenylbenzimidazole in the solution by comparison with calibrated standards of these compounds in CH_3OH. A gradient elution with solvents CH_3CN (16.7%) and buffer (83.3% to 60% and back to 83.3%) was used. The stock buffer solution was prepared by dissolving 15 g anhydrous CH_3CO_2Na in

250 mL deionised water, before adding CH_3CO_2H (50%, 100 mL). The pH was adjusted to 3.9 ± 0.01 with 5% CH_3CO_2H, before diluting to 500 mL. The dilute buffer was prepared by diluting 30 mL of the stock buffer solution to 500 mL with deionised water. The injection volume with needle wash was 1 μL. A Waters Xterra reverse phase C18 column, maintained at 40 °C was used (flow rate 0.7 mL min^{-1}, run time 14 min; UV detection at 254 nm). The retention times were 1.8 min (1,2-phenylenediamine), 4.5 min (benzoic acid) and 6.9 min (2-phenylbenzimidazole).

27 The apparent rate of decomposition of **2f** was faster than that very recently reported by Savage; J. B. Dunn, M. L. Burns, S. E. Hunter and P. E. Savage, *J. Supercrit. Fluids*, 2003, in press. The difference maybe due to the presence of **3f**.

28 E. L. Shock, *Am. J. Sci.*, 1995, **295**, 496.

29 T. Xiang and K. P. Johnston, *J. Solution Chem.*, 1997, **26**, 13.

30 Yu. E. Gorbaty, E. Venardou, E. Garcia-Verdugo and M. Poliakoff, *Rev. Sci. Instrum.*, submitted.

31 J. Lu, E. C. Boughner, C. L. Liotta and C. J. Eckert, *Fluid Phase Equilib.*, 2002, **198**, 1–37.

32 J. Yu and P. E. Savage, *Ind. Eng. Chem. Res.*, 1998, **37**, 2.

33 In all cases, diffraction data were collected at 150 K on a Bruker SMART1000 CCD area detector diffractometer equipped with an Oxford Cryosystem open-flow nitrogen cryostat. Data were corrected for Lorentz and polarization effects. The structures were solved by direct methods and the structure refined using full-matrix least squares refinement against F^2. Unless otherwise stated, all non-H atoms were refined with anisotropic atomic displacement parameters. All H atoms were placed in geometrically calculated positions, except the NH which was located from a difference Fourier synthesis. All H atoms refined as part of a riding model, with $U(H)_{iso} = 1.2U_{eq}(C)$.

34 J. Sakamoto, T. Nakagawa, N. Kanehisa, Y. Kai and M. Katsura, *Acta Crystallogr., Sect. C*, 2000, **56**, e596.

35 A colourless, plate-like crystal, 0.35 × 0.34 × 0.08 mm was mounted in perfluoropolyether oil. $C_{16}H_{14}N_4$, M = 262.31, orthorhombic, a = 8.5187(9), b = 9.8623(11), c = 14.8684(15) Å, U = 1249.2(4) $Å^3$, T = 150 K, space group *Pbca* (no. 61), Z = 4, μ(Mo-$K\alpha$) = 0.09 mm^{-1}, 5853 reflections measured, 1712 unique (R_{int} = 0.041). The final $wR(F^2)$ was 0.0999 for 1477 data, $R_1(F)$ was 0.0379 for 1012 observed data where $I > 2\sigma(I)$. CCDC reference number 200134.

36 A colourless, tablet crystal, 0.52 × 0.24 × 0.10 mm was mounted in perfluoropolyether oil. $C_{20}H_{14}N_4$, M = 310.35, monoclinic, a = 7.5866(11), b = 10.366(2), c = 9.728(2) Å, β = 107.895(2)°, U = 728.0(3) $Å^3$, T = 150 K, space group $P2_1/c$ (no. 14), Z = 2, μ(Mo-$K\alpha$) = 0.09 mm^{-1}, 5627 reflections measured, 1738 unique (R_{int} = 0.0407). The final $wR(F^2)$ was 0.0977 for 1642 data, $R_1(F)$ was 0.0419 for 1194 observed data where $I > 2\sigma(I)$. NH was refined freely. CCDC reference number 200135.

37 F. Bei, F. Jian, X. Yang, L. Lu, X. Wang, S. Shanmuga Sundara Raj and H.-K. Fun, *Acta Crystallogr., Sect. C*, 2000, **56**, 718.

38 A colourless, acicular crystal, 0.40 × 0.10 × 0.10 mm was mounted in perfluoropolyether oil. $C_{20}H_{14}N_4$, M = 310.35, orthorhombic, a = 17.712(2), b = 8.7976(8), c = 9.7375(9) Å, U = 1517.4(4) $Å^3$, T = 150 K, space group *Pbcn* (no. 60), Z = 4, μ(Mo-$K\alpha$) = 0.084 mm^{-1}, 13932 reflections measured, 1857 unique (R_{int} = 0.058). The final $wR(F^2)$ was 0.0974 for 1857 data, $R_1(F)$ was 0.0387 for 1305 observed data where $I > 2\sigma(I)$. The NH is statistically disordered being bonded to either N1 or N3 and has been placed geometrically, with 0.5 occupancy at both these positions. CCDC reference number 200136. See http://www.rsc.org/suppdata/gc/b2/b212394k/ for crystallographic data in .cif or other electronic format.

Direct mono-N-alkylation of amines in ionic liquids: chemoselectivity and reactivity†

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Received 15th November 2002
First published as an Advance Article on the web 25th February 2003

A simple method for the N-alkylation of primary amines was developed using ionic liquids as solvent in order to prepare secondary amines selectively. In ionic liquids overalkylation of the initially produced secondary amines is in general markedly reduced. Various amines, alkyl halides and sulfonates were examined. The observed selectivities between mono- and dialkylation are typically on the order of 9 : 1, or higher. Only in the cases of allyl or benzyl bromides does the reaction give the corresponding tertiary amines exclusively. The relative nucleofugality of chloride, bromide, iodide and tosylate with several primary amines was also evaluated, as well as the effect of caesium hydroxide.

Introduction

Amines and their derivatives are important functionalities in various natural products and unnatural synthetic targets. Because of their biological properties,[1] the synthesis of secondary amines has long been of interest and general methods for their preparation include direct N-alkylation,[2] amide reduction,[3] or reductive amination.[4] Although these methods are quite reliable, the possibility to control the concomitant overalkylations, when amine is employed as the limiting substrate, often reduces the application of these procedures. Direct N-alkylation is therefore generally used to convert primary and secondary amines to quaternary ammonium salts, although recently a novel method, using caesium bases in DMF, for the mono-N-alkylation of primary amines has been reported.[5] Room temperature ionic liquids (IL) are emerging as alternative recyclable, environmentally benign reaction media for various chemical transformations, due to their unique physical and chemical properties.[6] In continuation of our effort to explore new applications of ILs and in order to obtain information about the correlation between the physical properties of these solvents and the ability to affect reactivity, we have investigated the direct N-alkylation of amines in ionic liquids.

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† This work was presented at the Green Solvents for Catalysis Meeting, held in Bruschal, Germany, 13–16 October 2002.

Here we present a highly efficient method for the synthesis of secondary amines from alkyl tosylates or alkyl halides by a nucleophilic substitution reaction using primary amines in an ionic liquid. 1-Butyl-3-methylimidazolium hexafluorophosphate, [bmim][PF_6], 1-butyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide, [bmim][NTf_2], hexylpyridinium bis(trifluoromethylsulfonyl)imide, [hpyr][Tf_2N], and 1-butyl-2,3-dimethylimidazolium hexafluorophosphate, [bdmim][PF_6] have been used as solvents. In this method the ionic liquid plays an important role in enhancing reactivity as well as reducing overalkylation.

Results and discussion

To establish the potential of ionic liquids as solvents for direct N-alkylation of amines we began our investigation by screening a variety of different primary and secondary alkyl halides with benzylamine and 2-phenylethylamine. The reactions were carried out in [bmim][PF_6], at the temperatures reported in Table 1 and 2, under stirring.

Furthermore, since caesium hydroxide was found[5] to be the most successful base to increase chemoselectivity in molecular solvents, the reactions were also carried out in the presence of an equivalent of this base with the aim of improving the yield in the mono-N-alkylation product. Finally, CsOH in the presence of activated powdered molecular sieves (4 Å) was also probed since, at least in molecular solvents, the inclusion of a drying agent accelerates alkylation as well as improves the selectivity.

Green Context

Ionic liquids continue to be the focus of a large volume of research work. Their ultra-low volatility provides an obvious advantage over volatile organic solvents and their almost infinite flexibility in structure and anionic character enables their use in a wide range of reactions. Here they are applied as reaction media for the very selective mono-N-alkylation of amines. Overalkylation products are minimised. Mild reaction conditions enable the chemistry to be applied to complex subtrates with other labile functionalities. ***JHC***

Table 1 N-Alkylation of primary amines with variuos primary halogenides and tosylates at room temperature in [bmim][PF_6]

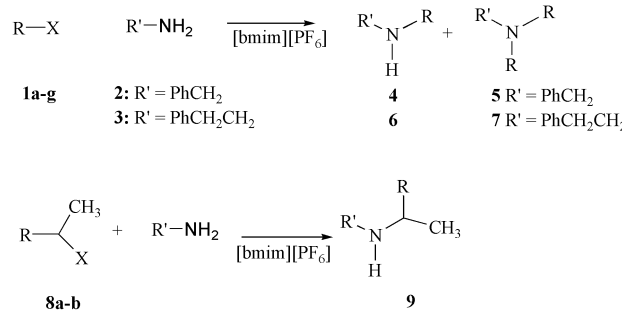
Substrate		Amine	$CsOH·H_2O$	Time/h	Conversion[a] (%)	Product ratio **4**	Product ratio **5**
$C_8H_{17}Cl$	**1a**	**2**	1 eq	24	0	n.d.	
$C_8H_{17}Br$	**1b**	**2**	—	24	49	100	0
$C_8H_{17}Br$	**1b**	**2**	1 eq	18	55	100	0
$C_8H_{17}Br$	**1b**	**2**	1 eq	24	70	100	0
$C_8H_{17}Br$	**1b**	**2**	1 eq + 4 Å MS	24	100	100	0
$C_8H_{17}I$	**1c**	**2**	—	18	40	87	13
$C_8H_{17}I$	**1c**	**2**	1 eq	18	50	80	20
$C_8H_{17}I$	**1c**	**2**	1 eq	24	60	84	16
$C_8H_{17}OTs$	**1d**	**2**	—	24	87	100	0
$C_8H_{17}OTs$	**1d**	**2**	1 eq	18	50	100	0
$C_8H_{17}OTs$	**1d**	**2**	1eq	24	100	100	0
$(CH_3)_3CCH_2Br$	**1e**	**2**	1 eq	24	0	n.d.	
$PhCH_2Br$	**1f**	**2**	—	4	100	0	100
$PhCH_2Br$	**1f**	**2**	0.1 eq	1	100	0	100
CH_2=$CHCH_2Br$	**1g**	**2**	—	4	100	0	100
CH_2=$CHCH_2Br$	**1g**	**2**	0.1 eq	1	100	0	100
						6	**7**
$C_8H_{17}Cl$	**1a**	**3**	—	24	0	n.d.	
$C_8H_{17}Cl$	**1a**	**3**	1 eq	24	0	n.d.	
$C_8H_{17}Br$	**1b**	**3**	—	24	40	88	12
$C_8H_{17}Br$	**1b**	**3**	1 eq	24	70	81	19
$C_8H_{17}I$	**1c**	**3**	—	18	48	82	18
$C_8H_{17}I$	**1c**	**3**	1 eq	24	64	66	34
$C_8H_{17}OTs$	**1d**	**3**	—	24	57	80	20
$C_8H_{17}OTs$	**1d**	**3**	1 eq	24	70	75	25
$PhCH_2Br$	**1f**	**3**	—	4	100	44	56
$PhCH_2Br$	**1f**	**3**	1 eq	1	100	27	73
CH_2=$CHCH_2Br$	**1g**	**3**	—	4	100	5	95
CH_2=$CHCH_2Br$	**1g**	**3**	1 eq	1	100	19	81

[a] The extraction yield was always > 85–90%. The remaining products were identified as the unreacted reagents. n.d. = not detected.

Table 2 N-Alkylation of amine **2** with secondary bromides and tosylates in [bmim][PF_6]

Substrate		$CsOH·H_2O$	Time/h	*T*/°C	Product **9** Yield (%)[a]
sec-$C_7H_{15}Br$	**8a**	1 eq	18	25	0
sec-$C_7H_{15}Br$	**8a**	1 eq	24	45	48
sec-$C_8H_{17}OTs$	**8b**	—	24	45	43
sec-$C_8H_{17}OTs$	**8b**	1 eq	18	25	50
sec-$C_8H_{17}OTs$	**8b**	1 eq	24	45	> 95

[a] The remaining products were identified as the unreacted reagents.



Reactions were typically carried out by addition of the alkyl halide or tosylate (0.7 M), under stirring, to the ionic liquid containing the amine (0.6 M). After 18–24 h at room temperature, or at 45 °C, the reactions were stopped by addition of a aqueous solution of $NaHCO_3$ followed by extraction of the products with Et_2O (extraction yields always > 85–90%). The reaction mixtures were analyzed by NMR and the products identified on the basis of the ^1H and ^{13}C NMR spectra. Generally, the residue IL was washed with water, dried and reused at least two times without any significant modification in yields and selectivity.

As shown by the data reported in Table 1 and 2 the conversion, *i.e.* the reaction rate, and the selectivity depend both on the nature of the reagents and on the type of leaving group, while the presence of caesium hydroxide, as well as of molecular sieves, only affects the reaction rate. Activate halides (allyl bromide, **1g**, and benzyl bromide, **1f**) react in relatively short times with benzylamine, a reactive amine, to give exclusively the tertiary amine **5**. 2-Phenylethylamine gives with the same bromides mixtures of tertiary and secondary amines. The addition of CsOH, even in a catalytic amount,[7] is not able to improve the selectivity. Primary alkyl chloride **1a** practically does not react with benzylamine or 2-phenylethylamine, also in the presence of CsOH. At variance, the primary bromide, iodide and tosylate, **1b–d**, undergo substitution easily to provide, after 24 h at room temperature, the expected secondary amine with high selectivity (ranging from 82 to 100%). The observed selectivity is similar (sometimes higher) to that recently reported for the reaction of primary and secondary bromides with 2-phenylethylamine or benzylamine in aprotic solvents (DMF, DMSO and DMAC) in the presence of CsOH, where the ratio between mono- and di-N-alkylation products ranges from 6:1 to 9:1.

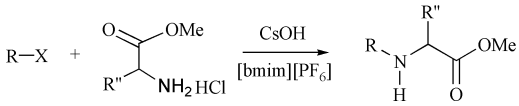
The reactivity scale of the leaving groups in [bmim][PF_6] is therefore the following: $TsO^- > I^- \cong Br^- >> Cl^-$. The addition of CsOH decreases the reaction times reducing the importance of the leaving group; similar conversions were obtained under comparable conditions.

Interestingly, the secondary, more demanding, bromide and tosylate **8a** and **8b** give exclusively the mono-N-alkylation product (Table 2). In this case, also with the more reactive tosylate, and in the presence of CsOH, slightly higher temperatures (around 45 °C) are necessary to obtain complete conversion in 24 h. These data suggest that the introduction of

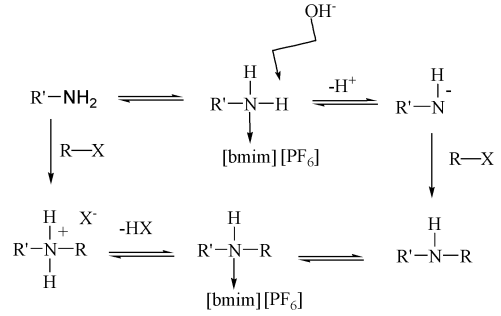
steric elements suppresses overalkylation. It is finally worthy of note that, as expected for a nucleophilic substitution, no reaction was observed when neopentyl bromide was used as substrate.

Based on these results, we maintain that the simple procedure, without addition of CsOH, is the most clean to obtain mono-N-alkylation products. Indeed caesium hydroxide is not able to affect chemoselectivity and the 2-H proton of the imidazolium cation is sufficiently acidic that in the presence of a strong base it might be deprotonated to form a carbene.

Encouraged by the generally good performance of this simple method, *i.e.* that only using an liquid ionic as reaction medium gives mono-N-alkylation products with yields and selectivities comparable to those obtained[5] in DMF, in the presence of caesium salts, the feasibility to use amino acid derivatives as substrates was also investigated. Alanine methyl ester hydrochloride was converted into the corresponding monoalkylated product (46% yield) by reaction with **1f** in [bmim][PF_6], at room temperature, in the presence of two equivalents of CsOH which was necessary in this case to transform the chlorohydrate into the corresponding free base and to increase the reaction rate.



Although, at variance with molecular solvents, only few data about nucleophilic displacement reactions have been reported in ionic liquids,[8] the results obtained in this work further confirm that ionic liquids are suitable solvents for this type of reaction and are able to affect positively the reaction chemoselectivity. Related to this latter feature, it is worthy of note that the product distribution obtained in [bmim][PF_6] seems to indicate that in this medium the reactivity of primary and secondary amines is opposite to that normally observed in molecular solvents. This behaviour may be rationalized, taking into account the explanation given[5] for the effect of CsOH in DMF, on the basis of a possible interaction between the amino group and the imidazolium ring. A stronger affinity of the secondary amine for [bmim][PF_6] over that of primary amine, which may be attributed to the higher basicity, may account for the observed selectivity. The interaction between the primary amine and the imidazolinium cation could give a weakly coordinated complex which, however, increases the acidity of the amine protons. They may become sufficiently acidic to be removed by the hydroxide anion when the reactions are carried out in the presence of CsOH. This feature may explain the shorter reaction times when CsOH was added. The reaction with the halide or tosylate gives the secondary amine, which should be more strongly coordinated to the imidazolium cation. The stronger interaction suppresses further alkylation by reducing the nucleophilicity of the secondary amine, thereby allowing complete transformation of the primary amine. Furthermore, the sterically more hindered complex of the secondary amine should be less prone to undergo proton abstraction by the eventually added base.



In agreement with this hypothesis recent NMR experiments and studies related to the selective transport of amines by using ionic liquids as supported liquid membranes have shown[9,10] a stronger interaction of the secondary amines, compared to primary and tertiary amines, with [bmim][PF_6]. In particular, on the basis of the ^{1}H NMR experiments the interactions of the imidazolium ring with the electron-donating group have been mainly attributed[9] to hydrogen bonding and ring stacking effects. To further investigate the nature of the interaction between amine and ionic liquid, alkyl bromide **1b** was added to benzylamine, **2**, in three different ILs; 1-butyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide, [bmim][NTf_2], hexylpyridinium bis(trifluoromethylsulfonyl)imide, [hpyr][Tf_2N], and 1-butyl-2,3-dimethylimidazolium hexafluorophosphate, [bdmim][PF_6]. It has been indeed recently shown[8c] that, for example, halide nucleophilicity depends on the used ionic liquid, being determined by a combination of cation and anion properties. Furthermore, it is well known that the anion structure plays an important role in the nature of the ionic liquids and on their interaction capabilities; the most dominant interaction constants are dipolarity/polarizability, hydrogen bond basicity and dispersion forces, although some ionic liquids also show hydrogen bond acidity.[11] The anion has a great influence on the overall hydrogen bond basicity of ionic liquids, but also affects the hydrogen bond acidity. It is well established[6] that ionic liquids having as the cation the [bmim] structure are able to take part in hydrogen bonding. More in particular, [bmim][Tf_2N] exhibits[11] the highest hydrogen bond acidity, therefore, under our reaction conditions [bmim][Tf_2N] should hydrogen bond more strongly to amines than [bmim][PF_6].[11] On the other hand, the introduction of a methyl group at the C-2 position of the imidazolium ring ([bdmim]) reduces this ability, as well as a reduced ability to undergo hydrogen bonding is generally attributed to pyridinium salts.

The data reported in Table 3 show that, although the natures of the cation and anion of the ionic liquid are able to affect significantly the reaction rate, they only moderately affects the chemoselectivity. In particular, although on going from [bmim][PF_6] to [bdmim][PF_6] the chemoselectivity decreases, in agreement with a possible role of the hydrogen bonding, this effect is very low and it is in contrast with the data related to the same reaction in [hpyr][Tf_2N], showing high chemoselectivity, and in [bmim][Tf_2N]. In this latter ionic liquid we find the lowest ratio between **4** and **5** although [bmim][Tf_2N] should be the more prone among the examined ionic liquids to give hydrogen bonding. Therefore, the data clearly show that the chemoselectivity is not dependent on the hydrogen bond acidity of the ionic liquid alone. Probably, factors and/or interaction(s) different from hydrogen bonding between the secondary amine and the solvent determine the apparently reduced nucleophilicity of the formed secondary amine.

Table 3 N-Alkylation of amine **2** with **1b** in ionic liquids at room temperature

IL	Time/h	Conversion[a] (%)	Product ratio **4**	**5**
[bmim][PF_6]	24	49	100	0
[bmim][Tf_2N]	24	66	94	6
[hpyr][Tf_2N]	24	30	99	1
[bdmim][PF_6]	24	90	96	4

[a] The remaining products were identified as the unreacted reagents.

In conclusion, we have demonstrated the possibility to perform the nucleophilic mono-N-alkylation of primary amines using simply alkyl halides or tosylates in an ionic liquid. The ionic liquid not only promotes N-alkylation but often also reduces or eliminates the formation of overalkylation products. High chemoselectivities involved in amine and amino acid derivative alkylations have been clearly shown. Furthermore,

the mild reaction conditions (room temperature or slightly higher, short reaction times, absence of caesium bases in the reaction medium) allow the application of this procedure even in the presence of labile functionalities. Further studies on the development of this protocol are in progress in our laboratory. Investigations on the nature of the interaction between amines and ionic liquids are also progressing.

Experimental

General remarks

^{1}H and ^{13}C NMR spectra were recorded with a Bruker AC 200 instrument. 1-Bromooctane (Fluka ≥98%), 1-iodooctane (Aldrich ≥98%), 1-chlorooctane (Janssen ≥99%), 1-bromo-2,2-dimethylpropane (Aldrich ≥98%), benzylbromide (Aldrich ≥98%), allylbromide (Aldrich ≥98%), 2-phenylethylamine (Aldrich 99+%), benzylamine (Aldrich ≥98%), caesium hydroxide monohydrate (Fluka), were used as supplied. 1-Butyl-3-methylimidazolium hexafluorophosphate and bis(trifluoromethylsulfonyl)imide, [bmim][PF_6] and [bmim][NTf_2], were prepared following the reported[12] procedures: attention was paid to the elimination of Cl^- present in the solvent as impurity. 1-Butyl-2,3-dimethylimidazolium hexafluorophosphate, [bdmim][PF_6], (Solvent Innovation, 98%) was used as supplied. Recycling of ILs was accomplished by washing with water. The uncoloured recovered ILs were dried, analyzed by NMR and reused at least two times.

Synthesis of [hpyr][Tf_2N]

To a sample of 1-hexylpyridinium chloride (15.85 g, 0.08 mol) in 30 ml of H_2O a solution of lithium bis((trifluoromethyl)sulfonyl)amide (Fluka puriss.) (22.78 g, 0.08 mol) in 30 ml of H_2O was added under stirring. The anion exchange was immediate, leading to the formation of a biphasic system, in which the lower phase was represented by the desired product. The ionic liquid was decanted in a separatory funnel and washed with water until no chloride was detectable. The organic layer was then dried over anhydrous $MgSO_4$, filtered and analyzed by NMR.

^{1}H NMR ($CDCl_3$, δ/ppm relative to TMS): 0.86 (t, 3H, J = 6.8 Hz, CH_3); 1.31 (br, 6H, 3 CH_2); 1.96 (m, 2H, CH_2); 4.58 (t, 2H, J = 7.5 Hz, N-CH_2); 8.05 (m, 2H, aromatic proton); 8.49 (m, 1H, aromatic proton); 8.83 (m, 2H, aromatic protons). ^{13}C NMR and DEPT ($CDCl_3$, δ/ppm): 13.62 (CH_3); 22.09 (CH_2); 25.41 (CH_2); 30.76 (CH_2); 31.35 (CH_2); 62.43 (N-CH_2); 128.55 (2 CH aromatic); 144.25 (2 CH aromatic); 145.43 (1 CH aromatic).

Synthesis of compound 1d

To a solution of *p*-toluenesulfonyl chloride (5.0 g, 0.027 mol) in 25 ml of dichloromethane, 1-octanol (2.3 g, 0.018 mol) was added. The reaction was performed using a catalytic amount of pyridine (0.5 ml). At the end of the reaction, the pyridinium chloride (visible as long white needles) was removed by filtration and the resulting filtrate was washed with 0.1 M HCl, then with $NaHCO_3$(aq) and finally with water until neutralisation. The organic layer was then dried ($MgSO_4$), filtered and the solvent was removed by distillation at reduced pressure. ^{1}H NMR ($CDCl_3$, δ/ppm relative to TMS): 0.79 (t, 3H, J = 6.8 Hz, CH_3); 1.14–1.30 (br, 10H, 5 CH_2); 1.55 (m, 2H, CH_2-CH_2O); 2.37 (s, 3H, Ph-CH_3); 3.94 (t, 2H, J = 6.8 Hz, CH_2OTs); 7.26 (m, 2H, aromatic protons); 7.71 (m, 2H, aromatic protons). ^{13}C NMR and DEPT ($CDCl_3$, δ/ppm): 14.00 (CH_3); 21.55 (CH_3); 22.53 (CH_2); 25.25 (CH_2); 28.79 (2 CH_2); 28.97 (CH_2); 31.62 (CH_2); 70.65 (CH_2OSO_2); 127.80 (2 =CH); 129.73 (2 =CH); 133.10 (> C <); 144.57 (> C <).

Synthesis of compound 8b

The procedure was the same as for **1d**. ^{1}H NMR ($CDCl_3$, δ/ppm relative to TMS): 0.85 (t, 3H, CH_3, J = 6.3 Hz); 1.15 (br, 8H, 4 CH_2); 1.25 (d, 3H, CH_3-CH, J = 6.2 Hz); 1.48–1.57 (m, 2H, CH_2); 2.43 (s, 3H, $PhCH_3$); 4.59 (m, 1H, CHOTs); 7.32 (m, 2H, aromatic protons); 7.79 (m, 2H, aromatic protons). ^{13}C NMR and DEPT ($CDCl_3$, δ/ppm): 13.93 (CH_3); 20.76 (CH_2); 21.48 (CH_3); 22.38 (CH_2); 24.73 (CH_2); 28.70 (CH_2); 31.49 (CH_2); 36.40 (CH_3); 80.58 (CH_2OSO_2); 127.62 (2 =CH); 129.59 (2 =CH); 134.60 (> C <); 144.57 (> C <).

General procedures for N-alkylation in ionic liquids

To a solution of amine (0.6 mmol) in the ionic liquid (1 ml), the required alkyl halide or tosylate (0.7 mmol) was added and the mixture was stirred at room temperature for 24 hours. The reaction mixture was washed with $NaHCO_3$(aq) and then extracted with Et_2O (1 ml × 5). The combined organic layers were dried over anhydrous $MgSO_4$ and filtered. The solvent was removed by distillation *in vacuo* and the crude mixture was analysed by NMR. The products were identified on the basis of NMR spectra (^{1}H, ^{13}C, DEPT), by comparison with data reported in literature.[5]

General procedures for N-alkylation in ionic liquids using caesium hydroxide

To a solution of amine (0.6 mmol) in [bmim][PF_6] (1.37 g, 1 ml) caesium hydroxide monohydrate (0.6 mmol) was added and the mixture was vigorously stirred for 30 minutes. During this period the suspension became yellow. The alkyl halide or tosylate (0.7 mmol) was then added to the suspension and the reaction was allowed to proceed at the temperature reported in Tables 1 and 2 for 24 hours. The reaction mixture was washed with $NaHCO_3$(aq) and then extracted with Et_2O (1 ml × 5). The combined organic layers were dried over anhydrous $MgSO_4$ and filtered. The solvent was removed by distillation *in vacuo* and the crude mixture was analysed by NMR.

From amine 2

Dialkylamine 4 (R = C_8H_{17}, R′ = $PhCH_2$). ^{1}H NMR ($CDCl_3$, δ/ppm relative to TMS): 0.88 (t, 3H, J = 7.0 Hz, CH_3); 1.25 (br, 10H, 5CH_2); 1.47–1.52 (m, 2H, CH_2); 1.68 (s, NH); 2.61 (t, 2H, J = 7.2 Hz, CH_2NH-); 3.78 (s, 2H, $PhCH_2$); 7.24–7.40 (m, 5H, aromatic protons). ^{13}C NMR and DEPT ($CDCl_3$, δ/ppm): 13.94 (CH_3); 22.50 (CH_2); 27.21 (CH_2); 29.13 (CH_2); 29.38 (2CH_2); 31.65 (CH_2); 48.52 (CH_2NH); 53.62 (CH_2NH); 127.39 (2 =CH); 127.92 (=CH); 128.41 (2 =CH); 137.68 (> C <).

Trialkylamine 5 (R = C_8H_{17}, R′ = $PhCH_2$). ^{1}H NMR ($CDCl_3$, δ/ppm relative to TMS): 0.88 (t, 6H, J = 6.8 Hz, 2CH_3); 1.25 (br, 20H, 10 CH_2); 1.43–1.47 (m, 4H, 2 CH_2); 2.41 (t, 4H, J = 7.2 Hz, CH_2NCH_2); 3.56 (s, 2H, $PhCH_2$); 7.24–7.40 (m, 5H, aromatic protons). ^{13}C NMR and DEPT ($CDCl_3$, δ/ppm): 14.07 (CH_3); 22.65 (CH_2); 27.01 (CH_2); 27.42 (CH_2); 29.32 (CH_2); 29.53 (CH_2); 31.86 (CH_2); 53.79 (CH_2N); 58.63 (CH_2N); 126.49-128.50 (5 =CH aromatic); 140.15 (> C <).

Trialkylamine 5 (R = benzyl, R′ = $PhCH_2$). ^{1}H NMR ($CDCl_3$, δ/ppm relative to TMS): 3.48 (s, 6H, 3 $PhCH_2$N); 7.11–7.41, (m, 15H, aromatic protons). ^{13}C NMR and DEPT ($CDCl_3$, δ/ppm): 57.86, (NCH_2); 126.86 (=CH); 128.20 (2 =CH); 128.75 (2 =CH); 139.44 (> C <).

Trialkylamine 5 (R = allyl, R′ = $PhCH_2$). ^{1}H NMR ($CDCl_3$, δ/ppm relative to TMS): 3.09 (d, 4H, J = 6.4 Hz, 2 =$CHCH_2$N); 3.54 (s, 2H, $PhCH_2$N); 5.12 (d, 2H, J = 10.3 Hz,

2 CH_2=); 5.18 (d, 2H, *J* = 17.2 Hz, 2 CH_2=); 5.76–5.95 (ddt, 2H, 2 =CH, *J* = 17.05 Hz, *J* = 10.3 Hz, *J* = 6.4 Hz); 7.17–7.40 (m, 5H, aromatic protons). ^{13}C NMR and DEPT ($CDCl_3$, *δ*/ppm): 56.30 (NCH_2); 57.45 ($PhCH_2$); 117.71 (2 =CH_2); 126.91 (=CH); 128.18 (2 =CH); 128.98 (2 =CH); 135.44 (2 =CH); 138.97 (> C <).

Dialkylamine 9a (R = C_5H_{11}, R′ = $PhCH_2$). ^{1}H NMR ($CDCl_3$, *δ*/ppm relative to TMS): 0.81 (t, 3H, *J* = 6.8 Hz, CH_3); 0.99 (d, 3H, *J* = 6.2 Hz, CH_3); 1.20–1.45 (br, 6H, 3CH_2); 1.73–1.85 (m, 2H, CH_2); 1.78 (s, NH); 2.55 (m, 1H, CHNH); 3.62 (d, 1H, *J* = 12.5 Hz, $PhCH_2$); 3.79 (d, 1H, *J* = 12.5 Hz, $PhCH_2$); 7.18–7.30 (m, 5H, aromatic protons). ^{13}C NMR and DEPT ($CDCl_3$, *δ*/ppm): 13.84 (CH_3); 20.06 (CH_3); 22.34 (CH_2); 27.27 (CH_2); 30.99 (CH_2); 36.82 (CH_2); 51.21 (CH_2N); 51.74 (CHNH); 126.91 (2 =CH); 128.21 (2 =CH); 128.36 (=CH); 139.80 (> C <).

Dialkylamine 9b (R = C_6H_{13}, R′ = $PhCH_2$). ^{1}H NMR ($CDCl_3$, *δ*/ppm relative to TMS): 0.89 (t, 3H, *J* = 6.8 Hz, CH_3); 1.09 (d, 3H, *J* = 6.3 Hz, CH_3); 1.17–1.40 (br, 8H, 4CH_2); 1.55 (m, 2H, CH_2); 2.14 (s, NH); 2.55 (m, 1H, CHNH); 3.75 (d, 1H, *J* = 12.5 Hz, $PhCH_2$); 3.89 (d, 1H, *J* = 12.5 Hz, $PhCH_2$); 7.27–7.82 (m, 5H, aromatic protons). ^{13}C NMR and DEPT ($CDCl_3$, *δ*/ppm): 13.80 (CH_3); 19.92 (CH_3); 22.36 (CH_2); 25.66 (CH_2); 29.23 (CH_2); 31.56 (CH_2); 36.73 (CH_2); 51.04 (CH_2N); 52.20 (CHNH); 126.91 (2 =CH); 128.21 (2 =CH); 128.36 (=CH); 139.80 (> C <).

From amine 3

Dialkylamine 6 (R = C_8H_{17}, R′ = $PhCH_2CH_2$). ^{1}H NMR ($CDCl_3$, *δ*/ppm relative to TMS): 0.80 (t, 3H, *J* = 6.7 Hz, CH_3); 1.18 (br, 10H, 5CH_2); 1.38 (m, 2H, CH_2); 1.94 (s, NH); 2.55, (t, 2H, *J* = 7.4 Hz, NCH_2); 2.65 (m, 2H, $PhCH_2$-); 2.84 (m, 2H, CH_2N); 7.07–7.20 (m, 5H, aromatic protons). ^{13}C NMR and DEPT ($CDCl_3$, *δ*/ppm): 13.84 (CH_3); 22.42 (CH_2); 27.11 (CH_2); 29.02 (CH_2); 29.26 (CH_2); 29.64 (CH_2); 31.60 (CH_2); 35.97 ($PhCH_2$); 49.56 (CH_2NH); 50.86 (CH_2NH); 125.90 (=CH); 128.20 (2 =CH); 128.45 (2 =CH); 139.75 (> C <).

Trialkylamine 7 (R = C_8H_{17}, R′ = $PhCH_2CH_2$). ^{1}H NMR ($CDCl_3$, *δ*/ppm relative to TMS): 0.80 (t, 6H, *J* = 6.8 Hz, 2CH_3); 1.18 (br, 20H, 10 CH_2); 1.38 (m, 4H, 2CH_2); 1.94 (s, NH); 2.45, (m, 4H, 2CH_2); 2.76 (m, 4H, $PhCH_2CH_2$N); 7.07–7.20 (m, 5H, aromatic protons). ^{13}C NMR and DEPT ($CDCl_3$, *δ*/ppm): 13.84 (CH_3); 22.42 (CH_2); 27.11 (CH_2); 29.02 (CH_2); 29.26 (CH_2); 29.64 (CH_2); 31.60 (CH_2); 35.97 ($PhCH_2$); 53.93 (CH_2N); 55.91 (CH_2NH); 125.90 (=CH); 128.20 (2 =CH); 128.45 (2 =CH); 139.75 (> C <).

Dialkylamine 6 (R = allyl, R′ = $PhCH_2CH_2$). ^{1}H NMR ($CDCl_3$, *δ*/ppm relative to TMS): 2.82–2.91 (m, 4H, $PhCH_2CH_2$); 3.27 (d, 2H, *J* = 5.9 Hz, CH_2N); 5.13 (m, 2H, CH_2=); 5.88 (m, 1H, =CH); 7.18–7.31 (m, 5H, aromatic protons). ^{13}C NMR and DEPT ($CDCl_3$, *δ*/ppm): 36.06 ($PhCH_2$); 50.29 (NCH_2); 52.08 (NCH_2); 116.19 (=CH_2); 126.16 (=CH); 128.26 (2 =CH); 128.43 (=CH); 135.51 (2 =CH); 139.80 (> C <).

Trialkylamine 7 (R = allyl, R′ = $PhCH_2CH_2$). ^{1}H NMR ($CDCl_3$, *δ*/ppm relative to TMS): 2.70–2.80 (m, 4H, $PhCH_2CH_2$); 3.17 (d, 2H, *J* = 6.5 Hz, CH_2N); 5.13 (d, 2H, *J* = 10.8 Hz, CH_2=); 5.18 (d, 2H, *J* = 17.2 Hz, CH_2=); 3.79 (d, 1H, *J* = 12.5 Hz, $PhCH_2$); 5.86 (ddt, 2H, *J* = 17.2, 10.8, 6.5 Hz, 2 =CH); 7.18–7.31 (m, 5H, aromatic protons). ^{13}C NMR and DEPT ($CDCl_3$, *δ*/ppm): 33.23 ($PhCH_2$); 55.04 (NCH_2); 56.76 (NCH_2); 117.44 (2 =CH_2); 125.86 (2 =CH); 128.26 (2 =CH); 128.66 (=CH); 135.51 (2 =CH); 140.49 (> C <).

Dialkylamine 6 (R = benzyl, R′ = $PhCH_2CH_2$). ^{1}H NMR ($CDCl_3$, *δ*/ppm relative to TMS): 1.87 (s, NH); 2.60–2.82 (m, 4H, $PhCH_2CH_2$); 3.68 (s, 2H, $PhCH_2$); 7.07–7.49 (m, 10H, aromatic protons). ^{13}C NMR and DEPT ($CDCl_3$, *δ*/ppm): 36.22 ($PhCH_2$); 50.40 (NCH_2); 53.71 (NCH_2); 126.06 (=CH); 126.84 (=CH); 128.07 (=CH); 128.36 (2 =CH); 128.60 (=CH); 139.61 (> C <).

Trialkylamine 7 (R = benzyl, R′ = $PhCH_2CH_2$). ^{1}H NMR ($CDCl_3$, *δ*/ppm relative to TMS): 2.60–2.82 (m, 4H, $PhCH_2CH_2$); 3.53 (s, 4H, $PhCH_2$); 7.07–7.49 (m, 15H, aromatic protons). ^{13}C NMR and DEPT ($CDCl_3$, *δ*/ppm): 33.43 (CH_2); 55.01 (NCH_2); 58.13 (NCH_2); 125.71 (=CH); 126.68; 126.84 (=CH); 128.07 (2 =CH); 128.60 (2 =CH); 128.72 (=CH); 140.06 (> C <).

From alanine methyl ester chlorohydrate

Dialkylamine (R = $PhCH_2$, R′ = $CH(CH_3)COOCH_3$). ^{1}H NMR ($CDCl_3$, *δ*/ppm relative to TMS): 1.14 (d, 3H, CH_3, *J* = 7.10 Hz); 3.39 (q, 1H, CHN, *J* = 7.05 Hz); 3.55 (d, 1H, CH(H)Ph, *J* = 14 Hz); 3.65 (s, 3H, OCH_3); 3.76 (d, 1H, CH(H)Ph, *J* = 14 Hz); 7.13–7.33 (m, 5H, aromatic protons). ^{13}C NMR and DEPT ($CDCl_3$, *δ*/ppm): 16.39 (CH_3); 52.65 (CHN); 55.80 (CH_2N); 57.47 (CH_3O); 126.90–128.23 (aromatic carbons); 139.95 (> C <); 173.88 (OC=O).

Acknowledgement

Financial support for this research was provided by MIUR and Università di Pisa.

References

1 I. S. Blagbrough, S. Carrington and A. J. Geall, *Pharm. Sci.*, 1997, **3**, 223; R. J. Bergeron, Y. Feng, W. R. Weimer, J. S. McManis, H. Dimova, C. Porter, B. Raisler and O. Phanstiel, *J. Med. Chem.*, 1997, **40**, 1475.

2 J. A. O'Meara, N. Gardee, M. Jung, R. N. Ben and T. Durst, *J. Org. Chem.*, 1998, **63**, 3117; F. Valot, F. Fache, R. Jacqot, M. Sagnol and M. Lemaire, *Tetrahedron Lett.*, 1999, **40**, 3689.

3 S. Salomaa, in *The Chemistry of Carbonyl Group*, ed. S. Patai, Wiley, New York, 1966, vol. 1, pp. 177–210.

4 A. K. Szardening, T. S. Burkoth, G. C. Look and D. A. Campbell, *J. Org. Chem.*, 1996, **61**, 6720; T. Rische, B. Kitsos-Rzychon and P. Eibracht, *Tetrahedron Lett.*, 1998, **54**, 2723.

5 R. N. Salvatore, A. S. Nagle and K. W. Jung, *J. Org. Chem.*, 2002, **67**, 674.

6 J. D. Holbrey and K. R. Seddon, *Clean Prod. Process.*, 1999, **1**, 223; M. J. Earle and K. R. Seddon, *Pure Appl. Chem.*, 2000, **72**, 1391; T. Welton, *Chem. Rev.*, 1999, **99**, 2071; P. Wasserscheid and M. Keim, *Angew. Chem., Int. Ed.*, 2000, **39**, 3773; J. Dupont, R. F. de Suaza and P. A. Z. Suarez, *Chem. Rev.*, 2002, **102**, 3667.

7 It has been reported (ref. 5) that, at least in molecular solvents, if more that a catalytic amount of CsOH is used with allyl and benzyl bromide overalkylation becomes more prominent due to the highly reactive nature of these electrophiles.

8 (*a*) C. Wheeler, K. N. West, C. L. Liotta and C. A. Eckert, *Chem. Commun.*, 2001, 887; (*b*) N. L. Lancaster, T. Welton and G. B. Young, *J. Chem. Soc. Perkin Trans. 2*, 2001, 2267; (*c*) N. L. Lancaster, P. A. Salter, T. Welton and G. B. Young, *J. Org. Chem.*, 2002, **67**, 8855; (*d*) D. W. Kim, C. E. Song and D. Y. Chi, *J. Am. Chem. Soc.*, 2002, **124**, 10278; (*e*) Z. M. A. Judeh, H.-Y. Shen, B. C. Chi, L.-C. Feng and S. Selvasothi, *Tetrahedron Lett.*, 2002, 9381.

9 L. C. Branco, J. G. Crespo and C. A. M. Afonso, *Chem. Eur. J.*, 2002, **8**, 17.

10 L. C. Branco, J. G. Crespo and C. A. M. Afonso, *Angew. Chem., Int. Ed.*, 2002, **41**, 2771.

11 J. L. Anderson, J. Ding, T. Welton and D. W. Armstrong, *J. Am. Chem. Soc.*, 2002, **124**, 14247.

12 J. Fuler, R. T. Carlin, H. C. De Long and D. Haworth, *J. Chem. Soc., Chem. Commun.*, 1994, 299.

Aqueous biphasic catalysis as a powerful tool for catalyst recycling in telomerization and hydrogenation chemistry†

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Received 27th November 2002
First published as an Advance Article on the web 28th February 2003

The synthesis of valuable ethers, carboxylic acids and alcohols has been achieved by telomerization and hydrogenation procedures using only butadiene, carbon dioxide, ethylene glycol and hydrogen as starting materials. High product selectivities and yields have been realized in all reaction steps and catalyst recycling has been achieved by liquid–liquid-two-phase techniques. This way, ecologically and economically favorable chemical syntheses have been demonstrated using the waste gas carbon dioxide and other cheap feedstocks.

1. Introduction

Although the use of carbon dioxide as a chemical building block and carbon source is abundant in nature by the unprecedented success of photosynthesis, only a few processes using CO_2 exist in the chemical industry, *e.g.* the production of urea, salicylic acid and its derivatives, cyclic carbonates and methanol.[1] Clearly this is because of its inert character. In view of its property as a greenhouse gas and the possibility of arising emission-taxes in the future, CO_2 is gaining interest as a carbon source for chemical synthesis but still has to be activated in a proper way. 1,3-Butadiene **(Bu)** is produced in huge amounts by steamcracking and finds applications in polymers and copolymers. In cases of oversupply however, it is hydrogenated to butene or butane and reused as steamcracker feed.[2] Therefore, the synthesis of valuable products from carbon dioxide, butadiene and other cheap feedstocks such as ethylene glycol **(EG)** and hydrogen is attractive. In this context, palladium catalyzed telomerization reactions are quite interesting although catalyst recycling problems are often encountered and follow-up chemistry of many products has not been developed to an advanced stage. In our workgroup, we have investigated a network of telomerization and downstream hydrogenation chemistry as shown in Scheme 1.

The telomerization of butadiene with ethylene glycol (Scheme 2) can yield the isomeric monotelomers 2-(2,7-octadienyloxy)ethanol **(1a)** and 2-(1-ethenyl-5-hexenyloxy)ethanol **(1b)** along with the ditelomers **(2)** and the butadiene dimers 1,3,7-octatriene and 4-vinyl-1-cyclohexene **(3)**. The product distribution strongly depends on the reaction conditions.

The monotelomers **(1)** are of high industrial interest as their saturated follow-up products can be used as plasticizer alcohols for polymers like PVC.[3] Further patents prove the industrial interest in these compounds for applications in surfactants and cosmetics.[4–6] However, the ditelomers **(2)** and butadiene dimers **(3)** are of lower interest. Therefore the control of selectivity is of great importance in order to produce the desired products **(1)** in an atom efficient way. This particular reaction has been described in the literature already in 1980 by Dzhemilev *et al.*[7] who obtained mixtures of **(1)**, **(2)** and **(3)** using a palladium catalyst activated by $AlEt_3$. Two other workgroups[8,9] have dealt with this subject, but highly effective procedures for the production of the monotelomers **(1)** also incorporating efficient catalyst recycling methods have not been achieved yet. In this paper, we describe the efficient and selective synthesis of the monotelomers **(1)** by aqueous biphasic catalysis employing a

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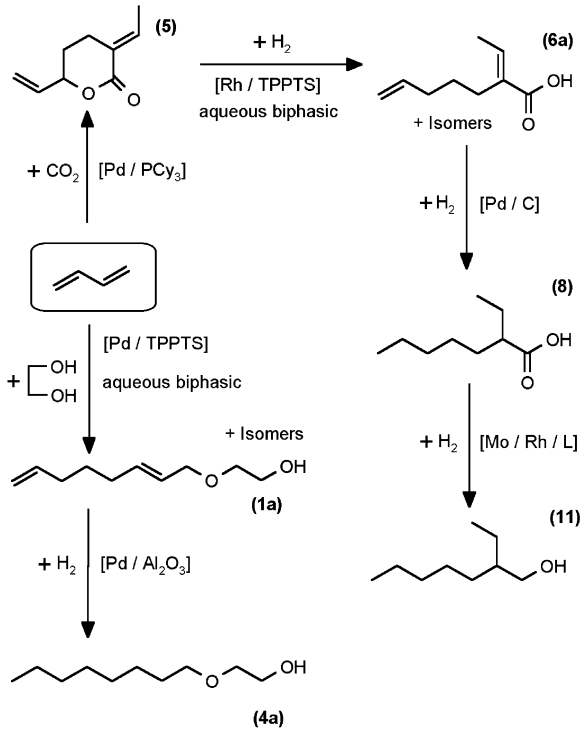
Green Context

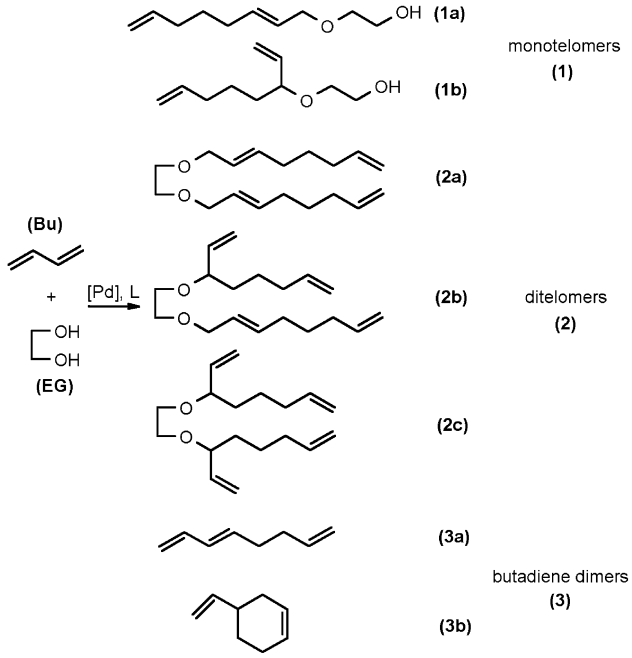
The efficient utilization of CO_2 and other small carbon feedstocks is still an important aspect of green chemistry. In particular, greater use of carbon dioxide would provide multiple benefits in terms of utilization of a cheap and readily available resource and help reduce the CO_2 waste we generate in todays society. Here, some interesting polyfunctional molecules are cleanly synthesized from CO_2 and other low-cost, available feedstocks, butadiene, ethylene glycol and hydrogen. Aqueous biphasic systems enable easy catalyst recycling and add to the green chemistry credentials. ***JHC***

† This work was presented at the Green Solvents for Catalysis Meeting held in Bruchsal, Germany 13–16th October 2002.

 DOI: 10.1039/b211815g



Scheme 1 Telomerization and hydrogenation chemistry of butadiene with CO_2, ethylene glycol and hydrogen (PCy_3: tricyclohexylphosphine, L: CO or acetylacetonate).



Scheme 2 Possible product range obtainable by telomerization of butadiene with ethylene glycol (L: phosphine or carbene ligand).

straightforward *in situ* palladium catalyst. Downstream hydrogenation to the saturated product **(4a)** is also described.

The telomerization of butadiene with CO_2 was discovered in 1976 by Inoue *et al.*[10] followed by first detection of the δ-lacone **(5)** in 1978.[11] Using a $Pd(acac)_2/PCy_3$ *in situ* catalyst, yields of 50% and selectivities exceeding 95% are possible.[12] Recycling concepts for the homogeneous catalyst system have been proposed by Behr *et al.*[13] and Pitter *et al.*[14] Surprisingly, the follow-up-chemistry of the interesting δ-lactone **(5)** has hardly been investigated yet. Behr *et al.* describe the synthesis of 2-ethylidene-5-hydroxy-6-heptenoic acid and some derivatives.[15] Dinjus *et al.* report the synthesis of polymers with an intact lactone ring structure in the main chain[16] based on **(5)**. Here, we describe efficient use of the δ-lactone **(5)** by several hydrogenation steps yielding 2-ethylheptanoic acid **(8)** and 2-ethylheptanol **(11)**. These products can find applications in alkyd resins, stabilizers for PVC, lubricants and as intermediates for the production of solvents and plasticizers.

Aqueous biphasic catalysis serves as an effective tool for selectivity control and catalyst recycling, both for the telomerization of butadiene with ethylene glycol and for the reductive cleavage of the δ-lactone (see Scheme 1). Consequently, attractive fine chemicals are available by telomerization and downstream hydrogenation chemistry in a more efficient and 'green' manner, making use of the greenhouse gas carbon dioxide and other cheap feedstocks.

2. Results and discussion

2.1 Aqueous biphasic telomerization of butadiene with ethylene glycol

Recently we established that this telomerization reaction yields a complex mixture of monotelomers **(1)**, ditelomers **(2)** and butadiene dimers **(3)** when performed in homogeneous liquid phases;[17] a result similar to those reported by Dzhemilev *et al.*[7] In this case, the standard catalyst system $Pd(acac)_2/PPh_3$ is used. The ratio of linear to branched products is typically 95 : 5. Yields of monotelomers higher than 60% can hardly be obtained this way. Typical product compositions and yields are shown in Fig. 1.

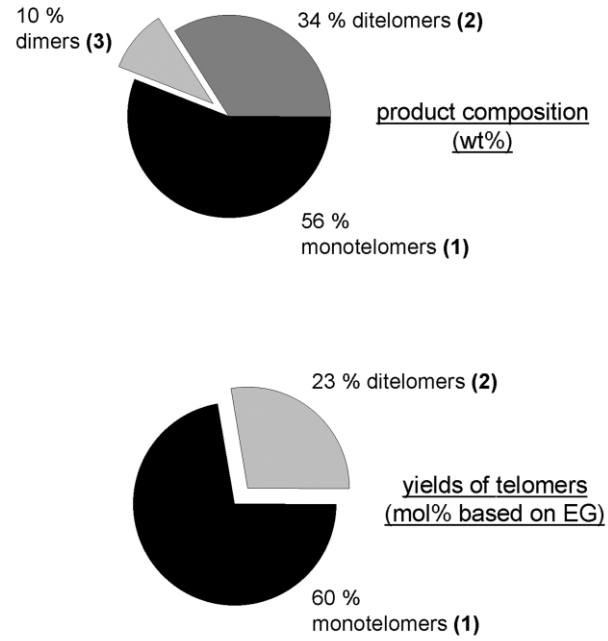


Fig. 1 Typical product composition (excluding unreacted EG) and yields obtained by telomerization of butadiene with ethylene glycol in homogeneous liquid phase. Conditions: Bu : EG = 2.5 : 1; Cat. 0.06 mol% (based on EG) $Pd(acac)_2$ + 2 equiv. PPh_3; 20 ml EG; 80 °C; 800 rpm; 2 h.

Turnover numbers (TON's) up to 1400 and average turnover frequencies (TOF's) up to 700 h^{-1} can be achieved. Yet, this process is not selective as rather high fractions of dimers **(3)** and ditelomers **(2)** are formed and catalyst recycling is not possible in the homogeneous system.

Using aqueous biphasic catalysis however, we found that the reaction can be carried out in a highly selective manner yielding about 75% monotelomers **(1)** along with only traces of ditelomers **(2)**, dimers **(3)** and octadienols. The ratio of linear to branched monotelomers is not altered compared to homoge-

neous liquid phase conditions. Here, the common triphenylphosphinetrisulfonate (TPPTS) ligand is used to make the catalyst system water-soluble. The product compositions and yields of telomers obtained are shown in Fig. 2.

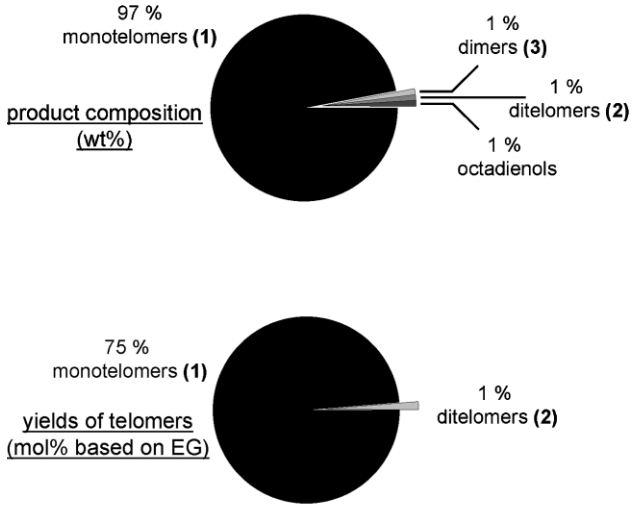


Fig. 2 Typical product composition (excluding unreacted EG) obtained by telomerization of butadiene with ethylene glycol in aqueous biphasic system. Conditions: Bu : EG = 2.5 : 1; Cat. 0.06 mol% (based on EG) $Pd(acac)_2$ + 5 equiv. NaTPPTS; 10 ml H_2O; 20 ml EG; 80 °C; 1200 rpm; 4 h.

The excellent selectivity can be explained by ligand- and *in situ* extraction effects as the product monotelomers **(1)** are only slightly soluble in the catalyst phase consisting of water, ethylene glycol and the catalyst components. The aqueous biphasic process is slower than the monophasic process (average TOF: 350 h^{-1}), but after longer reaction times the same TON of 1400 is achieved. Furthermore, the aqueous biphasic system permits effective catalyst recycling because after the reaction, the catalyst and product phases can be easily separated. Cyclohexane is added to improve phase separation and to remove traces of water from the product phase. The product phase can be readily worked up by distillative steps yielding the monotelomers **(1)** in purities greater than 95%. The catalyst phase still containing unreacted ethylene glycol can be recycled to the next run. Prior to each recycle run the catalyst phase has to be supplemented with an appropriate amount of fresh TPPTS ligand to compensate the loss by oxidation and decomposition. This way, the palladium catalyst can be recycled up to six times with only slight loss of activity. If the supplementation with fresh ligand is omitted, the catalyst activity rapidly decreases after the second run. Per run, about 1% of the initially used Pd is lost by leaching into the product phase, which can be explained by the residual water content (0.3 wt%) of the product phase. It should be possible to avoid this leaching by employing an additional extraction step. The results of a typical recycling experiment are shown in Fig. 3.

While the excellent selectivity is maintained throughout the complete series, the catalyst activity slowly decreases after the second recycle as a consequence of oxidation and decomposition processes. However, a total turnover number (TTN) of about 9000 can be achieved on a routine basis.

2.2 Heterogeneous hydrogenation of the monotelomers (1)

In order to increase the product stability against oxidation and unwanted decomposition reactions, the monotelomers have to be hydrogenated (Scheme 3).

Care has to be taken in the choice of the heterogeneous catalyst and reaction conditions as highly active catalysts (10 wt% Pd on charcoal powder) facilitate cleavage of the molecule,

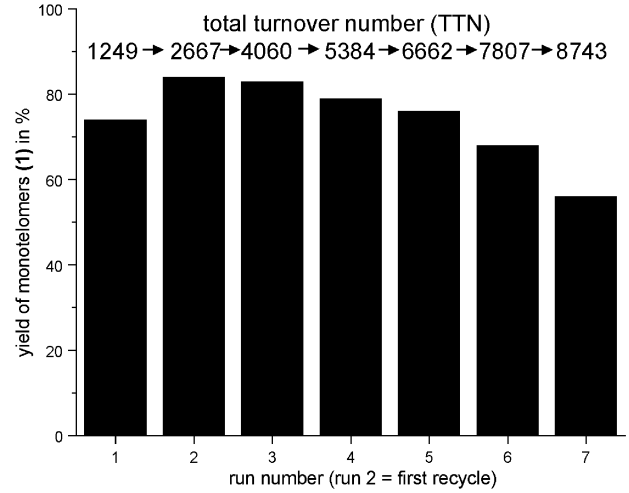
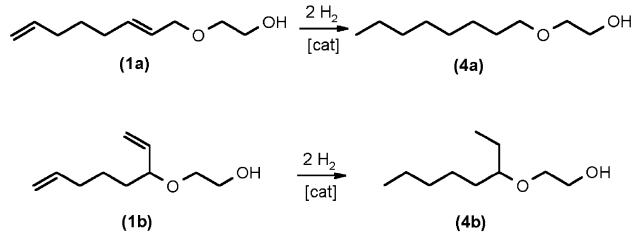


Fig. 3 Results of a typical recycling experiment for the telomerization of butadiene with ethylene glycol in aqueous biphasic system (yields based on EG). Conditions: Bu : EG = 2.5 : 1; Cat. 0.06 mol% (based on EG) $Pd(acac)_2$ + 5 equiv. NaTPPTS; ligand supplementation: 2.5 equiv. per recycle; 10 ml H_2O; 20 ml EG; 80 °C; 1200 rpm; 4 h.



Scheme 3 Heterogeneous hydrogenation of the monotelomers **(1)** to the corresponding saturated compounds **(4)**

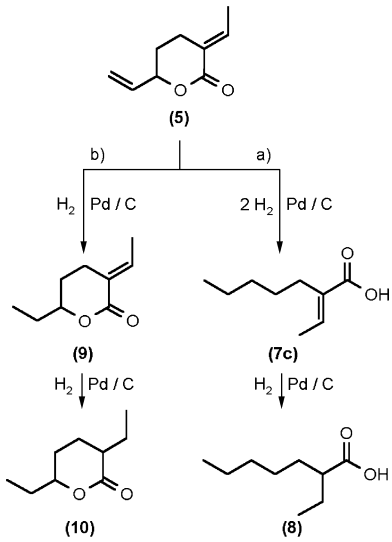
releasing octane and octanol as by-products in up to 15% combined yields. Using a less active catalyst however (1 wt% Pd on Al_2O_3 pellets) the hydrogenation reaction can be carried out with 100% selectivity, quantitatively yielding the hydrogenation products 2-octyloxyethanol **(4a)** and 2-(1-ethylhexyloxy)ethanol **(4b)** under mild conditions (70 °C; 10 bar H_2; 1 h). Both polar (THF) and nonpolar (cyclohexane) solvents can be used for this reaction step. The use of cyclohexane is very convenient as it can also be used as extractant in the telomerization as shown above, so that the same recyclable solvent can be used for two process steps in a potential plant. Different mixtures of linear and branched telomers can likewise be hydrogenated.

2.3 Heterogeneous hydrogenation of the δ-lactone (5)

At first, reductive cleavage of the δ-lactone **(5)** to the desired 2-ethylheptanoic acid **(8)** has been tried using standard heterogeneous catalysts (*e.g.* Pd/C or Pt/Al_2O_3).[18] Under these conditions the reaction is very fast but not selective as ring cleavage competes with double bond hydrogenation (Scheme 4). The mono-hydrogenated compounds **(7c)** and **(9)** have been identified as intermediate products.

The selectivity strongly depends on the solvent used. In methanol, 2-ethylheptanoic acid **(8)** can be obtained in up to 28% yield, while the fully hydrogenated δ-lactone **(10)** is obtained in up to 95% yield when THF is used. None of the products can be obtained in quantitative yields. A typical concentration plot with respect to time is shown in Fig. 4.

A further hydrogenation of the fully saturated δ-lactone **(10)** gives no more 2-ethylheptanoic acid **(8)**. Therefore, the desired product **(8)** cannot be conveniently and efficiently obtained this way.



Scheme 4 Parallel reaction: ring cleavage competing with double bond hydrogenation.

2.4 Aqueous biphasic hydrogenation of the δ-lactone (5)

Using aqueous biphasic catalysis the ring cleavage reaction can be performed with high selectivity, exclusively yielding a mixture of unsaturated isomeric C_9-carboxylic acids under mild conditions (Scheme 5).

For this reaction, a [Rh/TPPTS] catalyst is used, generating very high TOF's (up to 10000 h^{-1}). Complete conversion of the δ-lactone is achieved in only 30 minutes. A typical product composition is illustrated in Fig. 5.

The main product is 2-ethylidene-6-heptenoic acid **(6a)**. The product with the *cis*-double bond **(6c)** accounts for 26%, the *trans*-product **(6b)** only for 8%. Assumedly the distribution of the isomers is sterically founded. In a consecutive reaction 14% of 2-ethylideneheptanoic acid **(7c)** is already formed. The remaining percentages are due to single unsaturated C_9-carboxylic acids **(7a/b)**.

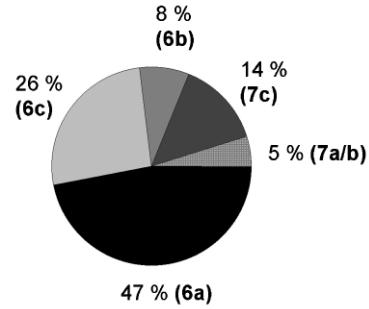


Fig. 5 Distribution of isomers obtained by biphasic hydrogenation of δ-lactone **(5)**. Conditions: *m*(δ-lactone) = 75 g, *m*(water) = 75 g; *m*(Rh) = 500 ppm; P : Rh = 20 : 1; 110 °C; 10 bar H_2; 1000 rpm.

Catalyst recycling is possible by simple phase separation. The catalyst phase could be recycled 10 times without considerable loss of activity. The results of a typical recycling experiment are shown in Fig. 6.

In each run, the δ-lactone **(5)** is quantitatively converted. A total turnover number of 14800 is possible demonstrating efficient use of the catalyst in this highly selective reaction. The loss of Rh by leaching into the product phase is about 1% of the initially used metal per run. Therefore an additional extraction step, analogous to the procedure outlined in section 2.1, using a non-polar solvent to reduce leaching is necessary. Due to its low boiling point the non toxic pentane is chosen to extract the product from the aqueous catalyst phase. After distilling off the pentane the product is obtained in pure form. The rhodium content is in the range of less than 0.2 ppm, which means the leaching is reduced by a factor of 45 by the extraction step.

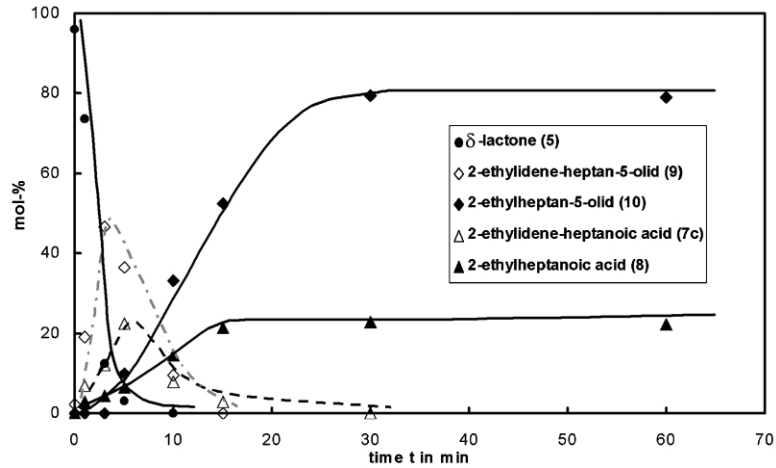
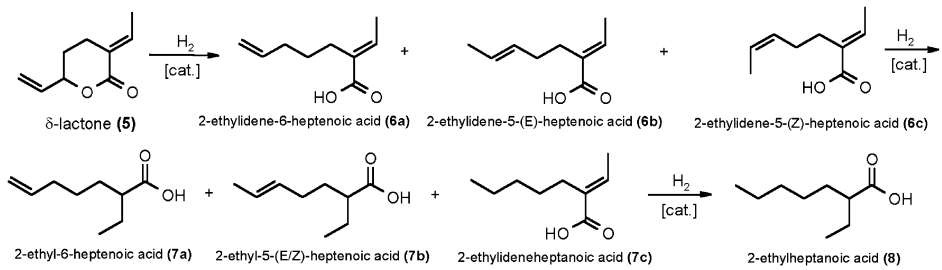


Fig. 4 Heterogeneous hydrogenation of δ-lactone **(5)**. Conditions: *m*(δ-lactone) = 20 g; *m*(THF) = 80 g; *m*(Pd/C, 10% Pd) = 0.25 g; 60 °C; 10 bar H_2; 700 rpm.



Scheme 5 Aqueous biphasic ring cleavage of the δ-lactone **(5)**.

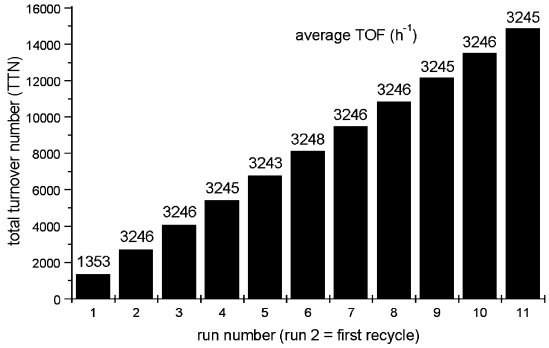
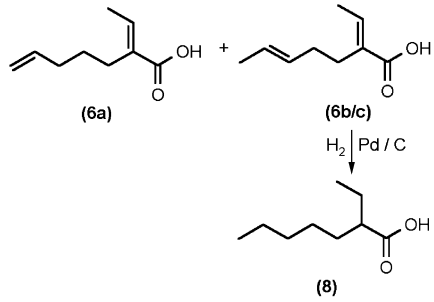


Fig. 6 Results of a typical recycling experiment for the ring cleavage of the δ-lactone **(5)** in an aqueous biphasic system. Conditions: *m*(δ-lactone **(5)**) = each run 75 g; *m*(Rh) = 500 ppm; P : Rh = 20 : 1; 110 °C; 10 bar H_2, 1000 rpm; 1st run 60 min; recycling runs 25 min.

2.5 Heterogeneous hydrogenation of the unsaturated C_9-carboxylic acids (6)

In order to obtain the desired product 2-ethylheptanoic acid **(8)**, the unsaturated isomeric C_9-carboxylic acids **(6)** have to be hydrogenated (Scheme 6).



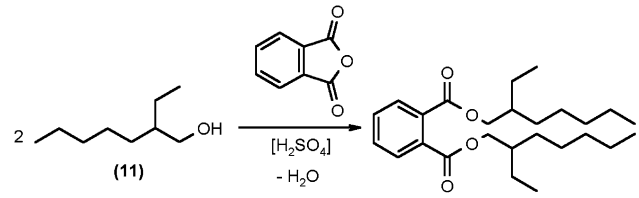
Scheme 6 Heterogeneous hydrogenation of the unsaturated isomeric C_9-carboxylic acids **(6)**.

This is conveniently achieved by employing a standard heterogeneous catalyst (Pd/C; 60 °C; $p(H_2)$ = 10 bar). The product **(8)** is obtained in quantitative yields after 5 to 30 minutes depending on the reaction conditions. Typical conversion curves are shown in Fig. 7.

This way, the desired product **(8)** is conveniently and efficiently synthesized in a two step procedure from the δ-lactone **(5)**.

2.6 Application of 2-ethylheptanoic acid (8) for the synthesis of plasticizers

As recently published,[19] 2-ethylheptanoic acid **(8)** can be efficiently hydrogenated to 2-ethylheptanol **(11)** using bimetallic catalytic routes. 2-Ethylheptanol **(11)** can then be esterified with phthalic acid anhydride as known in the literature[20] to obtain di(2-ethylheptyl)phthalate as potentially useful plasticizer (Scheme 7).



Scheme 7 Synthesis of di(2-ethylheptyl)phthalate from 2-ethylheptanol **(11)**.

Since the commercially available product di(2-ethylhexyl) phthalate (DEHP) is found to be one of the more toxic phthalates[21] the interest in alternative compounds increased.

2.7 Proposed processes for the production of fine chemicals from butadiene, CO_2, ethylene glycol and hydrogen

Based on the results presented in the previous sections, processes are proposed for the effective production of 2-octyloxyethanol **(4a)** from butadiene, ethylene glycol and hydrogen as well as for the production of 2-ethylheptanoic acid **(8)** from the δ-lactone **(5)** and hydrogen. The first process is shown in Fig. 8.

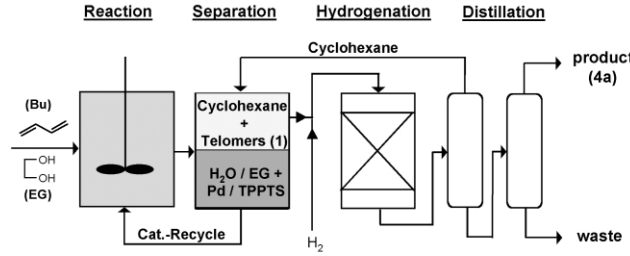


Fig. 8 Proposed process for the production of 2-octyloxyethanol **(4a)** from butadiene, ethylene glycol and hydrogen.

The reaction mixture obtained by telomerization of butadiene with ethylene glycol is subjected to phase separation under assistance of cyclohexane. While the aqueous catalyst phase also containing unreacted ethylene glycol is directly recycled to the reactor, the organic product phase is directly introduced into the heterogeneous hydrogenation step. After hydrogenation, the organic solvent is recycled to the separation unit while the

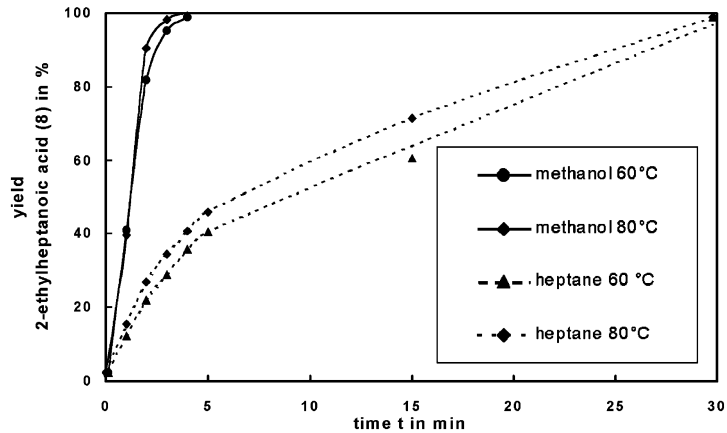


Fig. 7 Typical conversion curves for the heterogeneous hydrogenation of the unsaturated isomeric C_9-carboxylic acids **(6)** yielding 2-ethylheptanoic acid **(8)**. Conditions: *m*(**6**) = 10 g, *m*(Pd/C) = 0.25 g; 10 bar H_2; 700 rpm.

remaining residue is distilled to obtain 2-octyloxyethanol **(4a)** in high purities.

The second process is shown in Fig. 9.

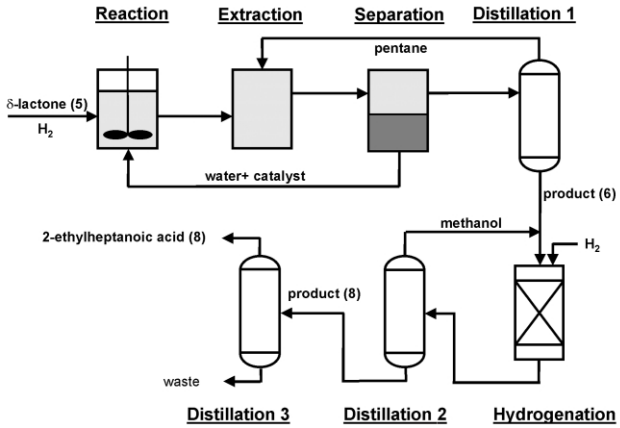


Fig. 9 Proposed process for the production of 2-ethylheptanoic acid **(8)** from the δ-lactone **(5)** and hydrogen.

This process starts with the δ-lactone **(5)** formed from butadiene and CO_2. In the first step a catalytic biphasic hydrogenation of the δ-lactone **(5)** with water-soluble rhodium catalysts is applied. After addition of pentane the phases are separated and the catalyst containing aqueous phase is reused. The pentane is distilled off the organic phase. In a second reaction step the remaining double bonds are hydrogenated using commercially available heterogeneous palladium catalysts in methanol. Then, the methanol is distilled off and after a second distillation the product 2-ethylheptanoic acid **(8)** is obtained in high purity.

In both processes, efficient use of the homogeneous catalysts is made by liquid–liquid-two-phase techniques. In the case of the telomerization reaction (Fig. 8) the biphasic mode of operation also serves to improve product selectivity significantly. All organic solvents used in the processes are completely recycled. Together with the closed recycling loops for the homogeneous catalysts, green processes result. These processes are currently under investigation using the established miniplant technology.[13]

2.8 Conclusions and outlook

Green catalytic processes for the production of fine chemicals from the greenhouse gas carbon dioxide, the steam cracker product butadiene and the cheap feedstocks ethylene glycol and hydrogen have been established. Aqueous biphasic catalysis serves as a powerful tool for catalyst recycling and selectivity control both in telomerization and downstream hydrogenation chemistry. The extension of the outlined telomerization procedures to other interesting polyfunctional nucleophiles is currently under investigation. The proposed processes are also studied using miniplant technology.

3. Experimental

3.1 Reagents, catalysts and handling

Ethylene glycol (99.5%), 1,3-butadiene (99.5%) and hydrogen (99.999%) were purchased from Fluka and Messer-Griessheim respectively and were used without further purification. The δ-lactone was synthesized according to the instructions in ref. 15. Dried argon (99.998%, Messer-Griessheim) was used as inert cover gas. Palladium bis(acetylacetonate)(II) $Pd(acac)_2$was synthesized according to the literature.[22] Triphenylphosphinetrisulfonate (TPPTS) was obtained from Celanese AG as a 25 wt% aqueous solution of the trisodium salt. $Mo(CO)_6$ (98%) was purchased from Alfa Aesar. $Rh(acac)(CO)_2$ (96.5%), $RhCl_3{\cdot}3H_2O$ (38% Rh), Pd/C and Pd/Al_2O_3 catalysts were supplied by the OMG group. All solvents were degasified and used saturated with argon. All reactions and handling were done under dry argon using standard Schlenk tube techniques.

3.2 Biphasic telomerization of butadiene with ethylene glycol

A typical experiment was conducted as follows: 63 mg (0.2 mmol) $Pd(acac)_2$ and 2.3 g (1 mmol) aqueous TPPTS-solution were dissolved in 10 ml of deionized water and mixed with 19.5 ml (0.35 mol) ethylene glycol, giving a clear bright yellow solution, which was transferred into an evacuated 300 ml stainless steel autoclave. 49 g (0.9 mol) butadiene were condensed into the autoclave. The vessel was heated to 80 °C and stirred at 1200 rpm for 4 h. Consumption of butadiene could be followed by a pressure drop from about 10 to about 5 bar. The vessel was cooled to ambient temperature and unreacted butadiene was burned through a safety-nozzle. The autoclave was opened and the biphasic content poured into a separating funnel. 100 ml cyclohexane were added, the mixture was shaken vigorously and the phases were allowed to separate over a period of 15 minutes. The lower phase consisting of the aqueous catalyst solution and unreacted ethylene glycol was separated and stored under argon. Cyclohexane was removed from the upper organic phase under reduced pressure (200 mbar, 50 °C) and recycled. The residue was analyzed by GC, Karl–Fischer titration and AAS-analysis. The remaining catalyst solution was supplemented with 1.15 g (0.5 mmol) aqueous TPPTS-solution and mixed in a Schlenk tube with 19.5 ml (0.35 mol) ethylene glycol, giving a clear yellow solution that was used for the telomerization reaction as described above.

3.3 Heterogeneous hydrogenation of monotelomer (1a)

In a typical experiment 5 g (29 mmol) **(1a)** were dissolved in 40 ml of THF or cyclohexane and transferred into a 300 ml stainless steel autoclave, which had been charged with 1 g palladium on aluminium oxide (1% Pd on Al_2O_3 pellets, Ø = 2–3 mm). A custom-made catalyst-cage was used to prevent grinding of the catalyst pellets by the stirrer. The vessel was closed, purged with argon and pressurized with hydrogen to 10 bar. The vessel was heated to 70 °C and stirred for 1 h at 800 rpm. Consumption of H_2 could be followed by a pressure drop to about 5 bar. Unconsumed hydrogen was vented and a sample of the reaction mixture filtered for GC-analysis.

3.4 Biphasic hydrogenation of δ-lactone (5)

In a typical experiment 38 mg (1.48×10^{-4} mol) $RhCl_3{\cdot}3H_2O$, 3.31 g (1.48×10^{-3} mol) aqueous solution of TPPTS, 12.17 g water and 15 g (0.1mol) of δ-lactone **(5)** were weighed in a Schlenk tube and transferred into an evacuated 67 ml stainless steel autoclave. The vessel was heated up to reaction temperature, pressurized with 10 bar hydrogen and the reaction started by accelerating the stirrer velocity to 1000 rpm. In regular intervals liquid samples were taken from the organic phase. For the sampling the stirrer was stopped for one minute to allow phase separation.

All recycling- and long-term-experiments were done in a 300 ml stainless steel autoclave with 75 g (0.49 mol) of δ-lactone and the appropriate other weighed portions.

3.5 Heterogeneous hydrogenation of δ-lactone (5)

A typical procedure for a heterogeneous hydrogenation of the δ-lactone is as follows: a 300 ml stainless steel autoclave was charged under argon with 10 g (0.066 mol) δ-lactone **(5)**, 0.25 g palladium on charcoal (5% Pd) and 90 ml methanol. The vessel was heated up to reaction temperature, pressurized with hydrogen and then the reaction started by accelerating the stirrer velocity to 700 rpm and held constant for 1 h. After cooling to ambient temperature, the remaining gas was vented from the reactor and the catalyst was removed by filtration of the reaction mixture.

3.6 Bimetallic reduction of 2-ethylheptanoic acid (8)

In a typical experiment 32.6 mg (1.26×10^{-4} mol) [Rh(acac)$(CO)_2$], 33.4 mg [$Mo(CO)_6$] (1.26×10^{-4} mol) and 2.00 g (12.6×10^{-3} mol) of 2-ethylheptanoic acid **(8)** were dissolved in 40 g 1,4-dioxane in a Schlenk tube and transferred into an evacuated 300 ml stainless steel autoclave. The vessel was pressurized with 120 bar hydrogen and heated up to 200 °C within 20 min leading to a hydrogen pressure of 150 bar at reaction temperature. The reaction time of 2 h was taken after accelerating the stirrer to 700 rpm. After the reaction mixture was cooled to room temperature the solvent was evaporated. The product was separated from the catalyst by vacuum distillation. A sample of the product mixture was taken and analyzed by gas chromatography with undecylacetate as internal standard and acetonitrile as solvent.

3.7 Analysis and product characterization

Routine gas chromatographic analyses were done on a HP 6890 instrument (Hewlett-Packard GmbH, Waldbronn, Germany) equipped with a FI-detector and a HP-INNOWax capillary column (30 m, coating polyethylene glycol, diameter 0.25 mm, film thickness 0.25 μm) in connection with an autosampler. GC/MS data were recorded on a HP 5973 instrument coupled with a HP 6890 (30 m HP 5-MS column, coating 5%-diphenyl-95%-dimethyl-polysiloxane, diameter 0.25 mm, film thickness 0.25 μm) in connection with an autosampler. FTIR-Spectra were recorded on a Nicolet Impact 400d FTIR-spectrometer using KBr-plates. NMR spectra were recorded on a DRX 400 spectrometer (Bruker Instruments Inc. Billerica, MA, USA) using $CHCl_3$ as internal standard. Water contents were determined by Karl–Fischer titration on a 652-KF-Coulometer (Metrohm, Herisau, Switzerland). Precious metal contents were measured by atomic absorption spectroscopy (AAS) using a UNICAM SOLAAR 989QZ instrument equipped with a GF90 Zeeman graphite tube oven. All reaction mixtures were analyzed by gas chromatography using calibration with pure compounds. The products were characterized by standard techniques (IR, ^{1}H-, ^{13}C- and ^{13}C-DEPT-NMR, GC and GC/MS).

4. Acknowledgements

We thank the OMG group for supply of catalysts and the Celanese AG for supply of TPPTS solution and AAS measurements. A scholarship from the 'Studienstiftung des deutschen Volkes' (M. U.) is gratefully acknowledged.

5. References

1 CD Römpp Chemie Lexikon–Version 1.0, Georg Thieme Verlag, Stuttgart/New York, 1995.
2 *Ullmann's Encyclopedia of Industrial Chemistry*, Wiley, New York, 6th edn., 2001, electronic release.
3 M. G. Romanelli, R. J. Kelly and N. J. Iselin, *Verfahren zur Herstellung von ungesättigten Alkoholen, Äthern und Ätheralkoholen*, US 2011163, 1970.
4 B. Gruber, K. J. Weese, S. M. Hoagland, H. P. Mueller, K. Hill and A. Behr, *Octadienyl ethers and a process for making octadienyl ethers*, WO 9013531, 1990.
5 B. Fabry, B. Gruber, *Octadienylethersulfate*, DE 4020973, 1992.
6 K. Hill, B. Gruber and K. J. Weese, *Tetrahedron Lett.*, 1994, **35**, 4541.
7 U. M. Dzhemilev, R. V. Kunakova, N. Z. Baibulatova, G. A. Tolstikov and A. A. Panasenko, *J. Org. Chem. USSR*, 1980, **16**, 999.
8 K. Kaneda, H. Kurosaki, M. Terasawa, T. Imanaka and S. Teranishi, *J. Org. Chem.*, 1981, **46**, 2356.
9 I. Inoue, S. Takeuchi, T. Yamauchi and H. Takita, *Method for recovering a catalyst from a homogenous catalytic reaction system*, GB 2054394, 1980.
10 Y. Inoue, Y. Sasaki and H. Hashimoto, *Bull. Chem. Soc. Jpn.*, 1978, **51**, 2375.
11 A. Musco, C. Perego and V. Tartiari, *Inorg. Chim. Acta*, 1978, **28**, L147–L148.
12 A. Behr, K. D. Juszak and W. Keim, *Synthesis*, 1983, **7**, 574.
13 A. Behr and M. Heite, *Chem. Ing. Tech.*, 2000, **72**, 58.
14 N. Holzhey and S. Pitter, *J. Mol. Catal.*, 1999, **146**, 25.
15 A. Behr, K. D. Juszak and W. Keim, *Synthesis*, 1983, **7**, 574.
16 V. Haack, E. Dinjus and S. Pitter, *Angew. Makromol. Chem.*, 1998, **257**, 19.
17 A. Behr and M. Urschey, *J. Mol. Catal. A*, in press.
18 A. Behr and V. A. Brehme, *J. Mol. Catal. A*, 2002, **187**, 69.
19 A. Behr and V. A. Brehme, *Adv. Synth. Catal.*, 2002, **344**, 525.
20 A. Musco, R. Santi and G. P. Chiusoli (Montedison S.p.A.), US Patent 4167513, 1979; A. Musco, R. Santi and G. P. Chiusoli, *Chem. Abstr.*, 1979, **90**, 186403.
21 (*a*) B. Hileman, *Chem. Eng. News*, 2000, **7**, 5–54; (*b*) B. Hileman, *Chem. Eng. News*, 2000, **3**, 8–9.
22 G. Künstle and H. Siegel, *Verfahren zur Herstellung von Palladium(II)acetylacetonat*, DE 2402383, 1975.

Platinum-containing polymeric catalysts in direct L-sorbose oxidation†

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Received 21st October 2002
First published as an Advance Article on the web 26th February 2003

Impregnation of hypercrosslinked polystyrene (HPS) with tetrahydrofuran (THF) or methanol solutions containing platinic acid resulted in the formation of Pt(II) complexes within the nanocavities of HPS. The highest selectivity (98% at 100% conversion) measured during the catalytic oxidation of L-sorbose in water was obtained with the HPS-Pt-THF complex. The structure of the catalyst isolated after the induction period was analyzed by transmission electron microscopy and X-ray photoelectron spectroscopy. Electron micrographs revealed enlarged Pt nanoclusters, which were most likely responsible for the high catalytic activity and selectivity observed.

Introduction

Catalytic selective oxidation of monosaccharides is widely used in pharmaceutical processes as the most technologically beneficial method. Existent technologies are carried out *via* protection of carbohydrate functional groups from oxidation and their subsequent recovery. This acetonation stage results in high losses of the end product and its pollution. Here, we propose direct catalytic oxidation of monosaccharides, avoiding the stage of acetonation. The monosaccharide studied was L-sorbose. The product of its oxidation is 2-keto-L-gulonic acid, which is the intermediate in vitamin C production (Fig. 1).

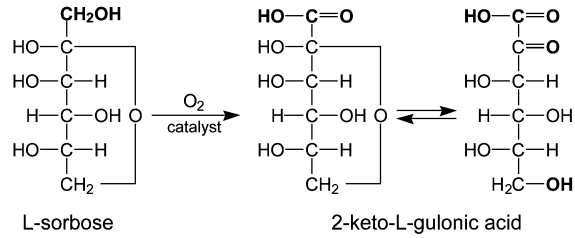

Fig. 1 Scheme of L-sorbose catalytic oxidation.

Using a Pt/C (5% Pt) catalyst, a 28–37% yield of 2-keto-L-gulonic acid was achieved at 100% L-sorbose conversion.[1] Such a catalyst did not provide high selectivity in L-sorbose oxidation. Lately attention has been focused on the synthesis and study of the catalytic properties of colloidal metal particles of nanometer size (nanoparticles), incorporated into a polymer matrix. The incorporation provides a stabilization of small particles with huge surface areas and high reactivity. The

Green Context

Heterogeneous catalysis is one of the key clean technologies for Green Chemistry. It is at its most effective in this context when it is used alongside the minimum number of auxiliaries. This is nicely illustrated in some heterogeneously catalysed oxidations using air as the consumable source of oxygen, and in the absence of solvent. Here we see an example of such a process which is close to the 'ideal synthesis' for an oxidation reaction. Furthermore, the target reaction—the oxidation of monosaccharides is often made more complex through a preliminary protection step which consumes resources and leads to waste. The process described here is direct, simple and effective. ***JHC***

Esther Sulman, born 1944 in the Primorski region (former USSR), studied chemistry at the Kalinin Polytechnic Institute. She received her PhD degree in 1972 at the Institute of Organic Catalysis and Electrochemistry (Kazakhstan) and Doctor of Science degree in 1989 at the Institute of Organic Chemistry, Russian Academy of Sciences (Moscow). Since 1989 E. Sulman has been a Full Professor, since 1992 she has been a Head of the Department of Biotechnology and Chemistry at the Tver Technical University (former Kalinin Polytechnic Institute) and Director of the Education-and-Research-and-Production Centre (TverTU). E. Sulman is an Honoured Inventor, Honoured Chemist and Honoured Teacher of High School of Russian Federation. She is a co-author of more than 160 research publications and 30 patents (Russia). Her research topics cover catalytic hydrogenation and oxidation of oxygen-containing organic compounds in the industrial syntheses of vitamins, pharmaceuticals and fragrant substances.

† This work was presented at the Green Solvents for Catalysis Meeting held in Bruchsal, Germany, 13–16th October 2002.

advantages of such catalysts are high selectivity in the absence of any added modifiers along with high activity, that strongly stimulates the search for more robust and inexpensive polymeric matrices exhibiting nanostructures that function in both aqueous and organic media. One such matrix is hyper-cross-linked polystyrene (HPS).[2] Due to its high cross-link density, which can exceed 100%, HPS consists of nanosized rigid cavities of comparable size in the 2–3 nm range. In the present study, we have used HPS with the following characteristics: (i) a formal degree of cross-linking of 200%, (ii) an apparent inner surface area of 833 $m^2\ g^{-1}$, (iii) a sharp pore size distribution maximum at about 2 nm in diameter, and (iv) particle sizes ranging from 0.2 to 0.4 mm in diameter. A unique feature of HPS is its ability to swell in a wide variety of different solvents, thus, access of reactant species to catalytic sites in a self-supporting substrate would be provided in virtually any reaction medium. The present work is devoted to a modifier-free catalyst based on Pt-containing HPS, which exhibits both high catalytic activity and selectivity in the oxidation of L-sorbose.

Result and discussion

Two different catalytic systems were studied in L-sorbose oxidation, namely, Pt nanoparticles formed in HPS after sorption of H_2PtCl_6 from tetrahydrofuran (THF) and methanol (ML) solutions. Platinum content was 3 wt%. According to XPS data collected from both HPS-Pt-THF and HPS-Pt-ML samples, the binding energy of Pt $4f_{7/2}$ in each material is virtually identical at 73.6 eV, which is measurably lower than that of Pt(IV). For comparison, the tabulated Pt $4f_{7/2}$ binding energy ranges for $K_2Pt(IV)Cl_6$, $K_2Pt(II)Cl_4$, and Pt(0) are 74.1–74.3, 72.8–73.4, and 71.0–71.3 eV, respectively. Probably, H_2PtCl_6 transformed chemically within the HPS matrix, resulting in the reduction of Pt(IV) to Pt(II). Deconvolution of the XPS spectra presented in Fig. 2 revealed that almost all the Pt(IV) was

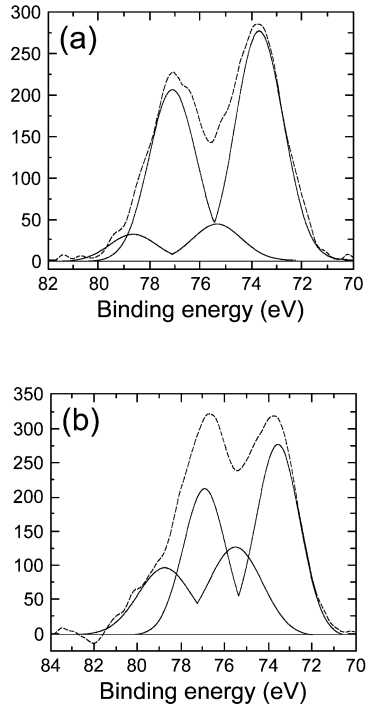

Fig. 2 X-Ray photoelectron spectra of (a) HPS-Pt-THF and (b) HPS-Pt-ML obtained with Mg KR radiation. The experimental data are displayed as dashed lines, whereas deconvolution fits are shown as solid lines.

reduced to Pt(II) in the HPS-Pt-THF sample, whereas a residual fraction of Pt(IV) remained in the HPS-Pt-ML sample.

The solid-state ^{13}C NMR spectrum of the HPS-Pt-THF material exhibited a new signal (relative to the metal-free HPS) at 69 ppm, which can be assigned to either ether or hydroxyl groups. We subjected the HPS-Pt-THF sample to THF extraction for 2 h under agitation, which yielded a THF solution that was subsequently evaporated and dried *in vacuo* (1 mbar) at ambient temperature. The FTIR spectrum of the resultant extract in the range 400–250 cm^{-1} revealed two signals at 330 and 305 cm^{-1}. They were assigned to the $[PtCl_3L]^-$ ion, where L denotes the ligand.[3] Similar signals were observed in the spectrum of HPS-Pt-THF. As the platinic acid used contains a small concentration of Pt(II) species, a mixture of Pt(IV) and Pt(II) compounds could catalyze THF oxidation in the presence of water (in our case, the source of water is $H_2PtCl_6{\cdot}6H_2O$).[4,5] Several side products could be obtained, such as γ-butyrolactone (GBL), γ-butyrolactol, and 4-hydroxybutyroaldehyde.[6] GBL could transform to the enole form, which was stabilized by coordination with $PtCl_3$ species.[5,6] In this scenario, Pt(IV) was reduced to Pt(II). In marked contrast, addition of $H_2PtCl_6{\cdot}6H_2O$ to ML, followed by 24 h of agitation and subsequent ML evaporation, did not yield any chemical changes, according to FTIR and XPS analyses. Both H_2PtCl_6 and ML remained unchanged.

According to TEM analysis, the HPS-Pt-THF and HPS-Pt-ML specimens contain no metal nanoparticles with a diameter exceeding 0.5 nm (the estimated resolution of the microscope).

Two samples were tested for L-sorbose oxidation. To ascertain the optimal conditions favoring L-sorbose oxidation with HPS-Pt-THF, the following reaction parameters were varied: catalyst concentration (C_c), L-sorbose concentration (C_0), $NaHCO_3$ concentration (C_{NaHCO3}), reaction temperature (T), reaction time (t), oxygen flow rate (V_O), and stirring rate (Table 1). The highest product selectivity (98%) at 100% L-sorbose conversion was achieved with the HPS-Pt-THF catalyst under the following set of reaction conditions: C_c = 0.021 M Pt, C_0 = 0.42 M, C_{NaHCO3} = 0.42 M, T = 70 °C, $V_O = 14 \times 10^{-6}$ $m^3\ s^{-1}$, stirring rate = 1000 rpm, and $NaHCO_3$ added continuously for 180 min. Gradual loading of the alkaline agent ensured higher selectivity than one-shot loading because it provided better control over the pH of the reaction medium. While the highest selectivity of the HPS-Pt-THF catalyst was 98%, the highest selectivity of the HPS-Pt-ML catalyst, on the other hand, did not exceed 40%. This significant difference in selectivity can be explained in terms of the different catalytic species present.

Since the oxidation rate was effectively limited by the rate of $NaHCO_3$ addition, continuous loading was not employed in the kinetic experiments. Fig. 3 presents the dependence of L-sorbose conversion on reaction time. These experiments were conducted with an O_2 flow rate of $V_O = 14 \times 10^{-6}$ $m^3\ s^{-1}$, stirring rate 1000 rpm, and at 70 °C. The kinetic curves reveal the existence of an induction period of about 100 min, during which time L-sorbose conversion is negligible.

On the basis of the experimental results at various temperatures we calculated the apparent activation energy using the reaction times yielding 10% L-sorbose conversion. The activation energies were found to be 39 kJ mol^{-1} (HPS-Pt-THF) and 41 kJ mol^{-1} (HPS-Pt-ML).

A sample of the HPS-Pt-THF catalyst collected after the induction period was isolated and subjected to examination by TEM and XPS. An electron micrograph of this sample (Fig. 4) showed the coexistence of small nanoparticles with a mean diameter approaching the resolution of the microscope (0.5 nm) and larger particles with a mean diameter of up to 6.0 nm. Formation of the enlarged nanoparticles in this catalyst can be explained by facilitated diffusion and, hence, aggregation of small Pt nanoclusters in water-swollen HPS during the oxidation reaction. This explanation is consistent with correspondingly lower activity, observed in the HPS-Pt-ML catalyst after its induction period (data not shown). According to the XPS data provided in Fig. 5, the Pt $4f_{7/2}$ binding energy changed

Table 1 Reaction activity and selectivity of HPS-Pt-THF in the direct oxidation of L-sorbose.[a]

Run[b]	C_c/M	C_0/M	C_{NaHCO3}/M	$V_O \times 10^6$/ $m^3\ s^{-1}$	T/°C	t/min	pH[c]	Conversion (%)	Yield (%)	Selectivity (%)
1	0.007	0.42	0.42	14.0	70	200	8.3	76	37	76.0
2	0.021	0.42	0.42	14.0	70	200	6.5	100	98	98
3	0.027	0.42	0.42	14.0	70	200	5.4	100	71	71.0
4	0.021	0.22	0.22	14.0	70	200	4.9	100	68	68.0
5	0.021	0.50	0.50	14.0	70	200	8.9	82	61	74.4
6	0.021	0.42	0.40	14.0	70	200	6.1	79	52	65.8
7	0.021	0.42	0.44	14.0	70	200	9.2	68	30	44.1
8	0.021	0.42	0.42	7.5	70	200	8.8	71	35	49.3
9	0.021	0.42	0.42	20.0	70	200	4.7	95	58	61.1
10	0.021	0.42	0.42	14.0	60	200	9.4	68	24	35.3
11	0.021	0.42	0.42	14.0	80	200	8.5	100	15	15.0
12[d]	0.021	0.42	0.42	14.0	70	200	9.2	74	41	55.4
13	0.021	0.42	0.42	14.0	70	180	7.7	85	83	97.7
14	0.021	0.42	0.42	14.0	70	220	5.9	100	70	70.0

[a] $NaHCO_3$ is loaded continuously over 180 min. [b] Stirring rate is 1000 rpm. [c] Final pH values. [d] Stirring rate is 200 rpm.

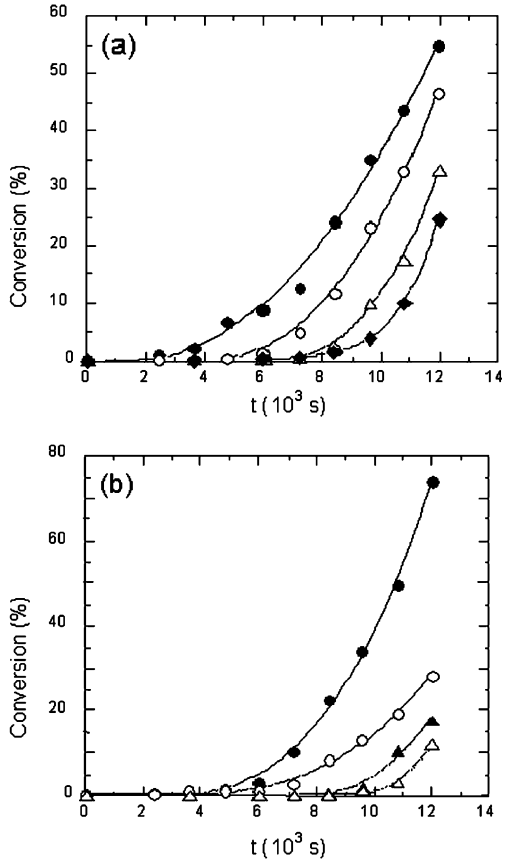

Fig. 3 Dependence of L-sorbose conversion on reaction time (t) in the presence of (a) HPS-Pt-THF and (b) HPS-Pt-ML at different L-sorbose concentrations (C_0, in M): 0.05 (●), 0.11 (○), 0.16 (▲), 0.22 (△), and 0.32 (◆).

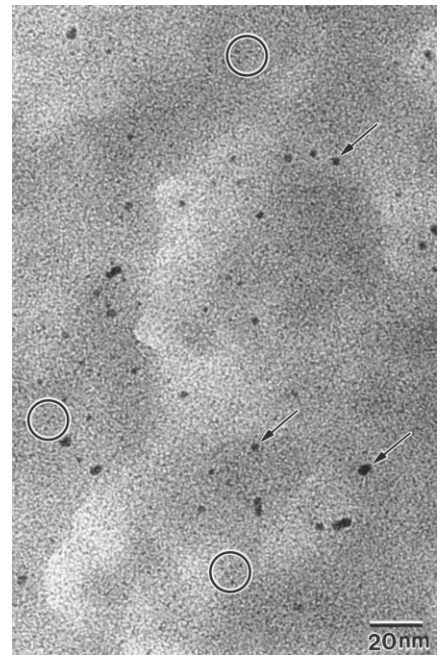

Fig. 4 TEM image of HPS-Pt-THF after the induction period during the direct oxidation of L-sorbose in aqueous medium. Groups of single Pt nanoparticles are highlighted by circles, whereas substantially enlarged nanoparticles are identified by arrows.

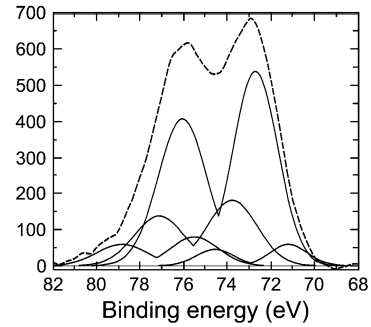

Fig. 5 XPS spectrum of HPS-Pt-THF after the induction period of the catalyst during the direct oxidation of L-sorbose in aqueous media. The experimental data are displayed as dashed lines, whereas deconvolution fits are shown as solid lines.

from 73.6 to 72.4 eV after the induction period in the HPS-Pt-THF catalyst. Deconvolution of this spectrum revealed four different species with different binding energies. While one of them possesses a Pt $4f_{7/2}$ binding energy of 71.3 eV and can be ascribed to Pt(0), additional species with higher binding energies also appear to exist. Probably, L-sorbose partially reduced Pt(II) to Pt(0), in which case mixed valence nanoparticles formed. Alternatively, the presence of 'oxidized' Pt species may reflect the strong chemical interaction between the surface atoms of the Pt nanoparticles and 2-keto-L-gulonic acid. Such interaction can strongly change the binding energy of Pt. In both scenarios, catalytic species were undoubtedly formed *in situ* during the induction period. Therefore, HPS appears to serve two crucial roles: one as a support for the Pt catalyst during L-sorbose oxidation and the other as the nanostructured matrix responsible for controlling nanoparticle growth.

In this regard, the nanostructured HPS matrix serves as both a nanoscale reactor and catalyst support to (i) restrict the growth

of the nanoparticles, (ii) prevent leaching of the nanoparticles and (iii) ensure a high degree of chemical interaction. Thus, high catalyst activity and selectivity are attributed both to nanometer scale of active metal and its chemical environment (polymer matrix and solvent).

Experimental

Materials

The HPS was synthesized according to the procedure described in detail elsewhere[7] whereas $H_2PtCl_6{\cdot}6H_2O$ and sodium hydrogencarbonate ($NaHCO_3$) were obtained from Reakhim, (Moscow, Russia). Reagent-grade tetrahydrofuran (THF) and methanol (ML) were purchased from Aldrich and used as received, as was the L-sorbose from Fluka. Water was purified with a Milli-Q water purification system.

HPS-Pt preparation

Particles of HPS were inserted into a Schlenk tube capped with a rubber septum. Following evacuation at 1.5 mbar, the tube was filled with Ar. In a typical synthesis, 0.4 g H_2PtCl_6 was dissolved in 4 ml THF or ML, which promoted complete swelling of 1 g HPS without excess solvent. The solution was subsequently added to the Schlenk tube by syringe through the rubber septum. After the HPS was allowed to swell for 30 min in the H_2PtCl_6 solution, it was evacuated for 3 days at 1.5 mbar.

L-sorbose oxidation

The reaction was conducted batchwise in a specially constructed apparatus that permits control over such parameters as the L-sorbose and $NaHCO_3$ concentrations, catalyst concentration, temperature, molecular oxygen feed rate and stirring rate. A solution of catalyst and L-sorbose (100 ml) prepared at a predetermined concentration was placed in the temperature-controlled apparatus equipped with a magnetic stir bar and reflux condenser. The rate of oxygen feed was controlled by a rotameter. An equimolar quantity of alkalizing agent ($NaHCO_3$) was fed to the apparatus in one shot or continuously over 180 min (to maintain a constant pH of 7.7) using an automatic dispenser. The high stirring rates employed here ensured good mixing without diffusion limitation. Samples of the reaction mixture were periodically removed for analysis. At the end of the experiment, the catalyst was separated by filtration, and the filtrate was analyzed for the presence of L-sorbose and 2-keto-L-gulonic acid. The amount of residual L-sorbose was discerned by gas chromatography (GC) through the use of a 'Chrom-5' chromatograph, operated isothermally with a flame-ionization detector and glass column filled with 5% SE-30 on Chromaton N-AW. The quantity of 2-keto-L-gulonic acid was measured by the classical iodometric method of Heyns.[8] For runs 2, 7 and 13 listed in Table 1, the quantity of 2-keto-L-gulonic acid was determined by direct isolation according to the criteria described elsewhere.[9] Each experiment reported here was repeated at least 3 (often 5) times to ensure reproducibility.

Material characterization

X-Ray photoelectron spectroscopy (XPS) was conducted with a two-chamber Kratos XSAM-800 spectrometer. Powdered samples were evacuated in the spectrometer for 12 h at 10^{-9}–10^{-10} mbar, and spectra were collected in the medium resolution regime at 25 °C. For photoelectron excitation, characteristic Mg K_α radiation ($h\nu$ = 1253.6 eV) was used. The power of the X-ray gun never exceeded 75 W (15 kV, 5 mA).

Transmission electron microscopy (TEM) was performed with a Zeiss EM902 electron spectroscopic microscope operated at 80 kV and an energy loss of 0 eV. Insoluble HPS-Pt powders were embedded in epoxy resin and subsequently microtomed at ambient temperature. Images of the resulting thin sections (*ca*. 50 nm thick) were collected on plate negatives, digitized at 600 dpi and analyzed with the Adobe Photoshop software package and the companion Image Processing Toolkit.

Fourier-transform infrared (FTIR) spectra were recorded with a Nicolet spectrometer in the spectral region ranging from 250 to 4000 cm^{-1} at a resolution of 2 cm^{-1}. Solid state ^{13}C magnetic resonance (NMR) spectra were collected with a 4.0 mm Bruker Magic Angle Spinning Probe in a Bruker Avame DSX spectrometer. Data were obtained by using cross polarization from protons (4 μs proton π/2 pulse, 500 μs contact time) under 12.000 kHz magic angle spinning. Two-pulse phase modulation (TPPM) decoupling was employed during acquisition.

Acknowledgement

Financial support was provided by NATO Science for Peace Programme (NATO SfP–Colloidal Catalysts [974173]) and Russian Foundation for Basic Research (grant 01-03-32937).

References

1 T. Mallat, C. Bronnimann and A. Baiker, *Appl. Catal.*, 1997, **1**, 103.
2 V. A. Davankov and M. P. Tsyurupa, *React. Polym.*, 1990, **13**, 27.
3 R. J. Goodfellow, P. L. Goggin and D. A. Duddell, *J. Chem. Soc.*, 1968, 504.
4 J. A. Labinger, A. M. Herring and J. E. Bercaw, *J. Chem. Soc.*, 1990, **112**, 5628.
5 A. Sen, M. R. Lin, L.-C. Kao and A. C. Hutson, *J. Chem. Soc.*, 1992, **114**, 6385.
6 M. J. Shi, *Chem. Res.– S*, 1998, 592.
7 M. P. Tsyurupa and V. A. Davankov, *J. Polym. Sci.: Polym. Chem. Ed.*, 1980, **18**, 1399.
8 K. Heyns, *Ann. Chem.*, 1947, **558**, 171, 177.
9 M. Schaper, *Ger. Offen.*, 1990, DE 3831070 A1.

Reforming of methane by CO_2 in presence of cobalt- based catalysts†

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Received 21st October 2002
First published as an Advance Article on the web 18th March 2003

Reforming of methane by CO_2 to syngas has been studied on cobalt-based catalysts. The catalysts have been characterised by BET, CO_2 adsorption and TG-DSC techniques. The catalytic activity and stability of catalysts are closely related to the basic character of the magnesium oxide additive. It has been observed that the catalytic activity increases with the MgO loading. The order of activity is the following: Co/SiO_2 < Co/5 wt% $MgO–SiO_2$ < Co/10 wt% $MgO–SiO_2$ < Co/35 wt% $MgO–SiO_2$. Moreover, the positive effect of MgO on the resistance to carbon deposition by adjustment of the acid–base function of the support has been evidenced. The basic function of the metal oxide promoter also seemed to increase H-abstraction of methane and CO_2 adsorption.

1 Introduction

Pollution has become a major concern on a global scale. Various factors contribute to make the protection of the environment a topic of fundamental importance to mankind. The climate perturbations caused by the greenhouse effect, the depletion of the ozone layer, acid rains… have brought industrialized countries as a whole, as well as developing ones, to establish national programs to fight against the various sources of pollution.

From this perspective, natural gas appears to be a clean and ecological energy, and is now viewed as an area of competitiveness and improved performance for the major oil companies.

One of the processes most commonly used in recent years is the dry reforming of methane.[1–3] Indeed, this process is of particular interest because it uses two greenhouse effect pollutant gases *via* the reaction:

$$CH_4 + CO_2 \rightarrow 2CO + 2H_2$$

This reaction is performed over a wide range of catalysts such as group VIII metals.[4–13] However, the major drawback of this reaction is coking, in particular when the reaction occurs over nickel-based catalysts.[4–7,10]

Cobalt-containing catalysts are also active for this reaction. However, in many cases, activity decreases over time. In the absence of impurities in the catalyst, this deactivation is caused by sintering of the metal phase or by coke deposition over the active surface.[14–17] Nonetheless, deactivation can be avoided by using noble metals[4,13,17] or by modifying the particle size.[14,18] However, the high cost of noble metals often limits their usability. One of the strategies that can be used to improve activity[9,10,19] and stability[10,14,18,20] is the association of a co-metal with the active phase. In the present study, we present more detailed results on the positive effect of an MgO additive on catalytic activity, stability and coking properties of a Co/SiO_2 catalyst.

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2 Experimental

The support materials xMgO–SiO_2, with x = 0, 5, 10 or 35%, were prepared by impregnating silica with solutions of nitrate magnesium salts. They were dried at 110 °C and calcined at 500 °C prior to impregnation with cobalt nitrate (5 wt% Co). These solids were again dried and calcined under air at 500 °C for 4 h.[14]

Inductively coupled plasma emission spectroscopy was used to determine cobalt and magnesium oxide contents in the catalysts after dissolving the samples in a mixture of hydrofluoric, nitric and sulfuric acids.

Green Context

Recently, there has been considerable effort put into the conversion of methane and CO_2 into the useful products CO and hydrogen, and highly selective catalysts are required for the reaction. This paper describes the effectiveness of Co–silica catalysts for the reaction, and indicates that MgO doping has a beneficial effect on the catalyst by reducing the rate of carbon deposition. ***DJM***

† This work was presented at the Green Solvents for Catalysis Meeting held in Bruchsal, Germany, 13–16th October 2002.

After pretreatment at 200 °C under vacuum, multipoint BET surface area measurements were performed using nitrogen as an adsorbate at −196 °C.

The basicity of the catalysts was studied by adsorption calorimetry of CO_2 as a probe molecule, after *in situ* activation at 600 °C under pure hydrogen. Successive small doses of CO_2 were sent over the catalyst. The adsorbed amount and the heat released were determined simultaneously at every coverage.

The CH_4 + CO_2 reaction was performed under a constant pressure of 1 atm and 600 °C in differential dynamic mode after *in situ* reduction in a hydrogen flow at 600 °C. The reactant mixture of CH_4 : CO_2 : He = 20 : 10 : 70% was introduced into the reactor at a total flow rate of 22 ml min^{-1}. The mixtures of reactant gases and products were periodically analysed on line using a TCD chromatograph which contained two 4 m carbosieve B columns (1/8 inch, 100 to 200 mesh). Prior to analysis, the effluent was passed through a water-trap at 0 °C in order to remove reaction water.[18]

The analysis of the carbonaceous residue was performed by DSC-TG (Setaram TG-DSC 111). Carbon combustion was monitored between 20 and 650 °C in an O_2–He mixture, using a flow rate of 23 ml min^{-1}. The weight loss and heat flow were collected and processed by microcomputer.

The chemical composition of the samples, their BET surface area and their basicity as determined by the amount of sorbed CO_2 under an equilibrium pressure of 0.5 torr are given in Table 1.

3 Results and discussion

BET surface measurement

The BET surface area of the modified catalysts and reference Co catalyst are shown in Table 1. The specific surface area increases when adding 10 wt% MgO. Surprisingly, this increase is not observed for the 35 wt% MgO sample, which tends to prove the formation of a solid solution between MgO and SiO_2 in this case.[14] Using the values of the BET surface area, the surface coverage of SiO_2 by MgO was tentatively calculated. The significance of this data is lower in the case of the high MgO loadings, which considerably exceeds the monolayer.

Adsorption microcalorimetry of CO_2

The basic properties of samples expressed in terms of CO_2 adsorbed amounts at an equilibrium pressure of 0.5 torr, are reported in Table 1 along with the data pertaining to the reference Co/SiO_2 catalyst. The initial heats of adsorption are relatively low, around 68 kJ mol^{-1} for Co/5 wt% MgO–SiO_2, Co/10 wt% MgO–SiO_2 and Co/35 wt% MgO–SiO_2 samples while the adsorbed amount is strongly dependent on the MgO content. The Co/35 wt% MgO–SiO_2 catalyst presents basic sites of intermediate strength and an amount of sorbed CO_2 of about 0.164 μmol m^{-2}. This result indicates the ability of catalysts with high MgO loadings to adsorb an acidic molecule such as CO_2.

Effect of MgO addition on catalytic activity

The results of MgO additive on the catalytic activity and stability of Co/SiO_2 are presented in Fig. 1 which displays the evolution of methane and carbon dioxide conversions with MgO content. The catalytic activity has been found to increase with the MgO concentration, to reach values limited by diffusion and thermodynamic WGS equilibrium in the case of Co/35 wt% MgO–SiO_2. Indeed, the activities of the catalysts after 24 h of reaction are in the following order: Co/SiO_2 < Co/5 wt% MgO–SiO_2 < Co/10 wt% MgO–SiO_2 << Co/35 wt% MgO–SiO_2. These results indicate that MgO significantly improved the catalytic performance of Co/SiO_2. Besides, the stability of the catalyst is enhanced in the presence of a higher content of MgO: almost no deactivation is observed for the 35 wt% MgO support composition. In contrast, strong deactivation occurs for the Co/5 wt% MgO–SiO_2 catalyst (initial CH_4 conversion decreased from 58% to near 0% after 24 h time reaction) see Fig. 2. This loss of activity and stability can be related to the formation of carbon on the metallic phase. Similar effects involving the presence of surface carbon are reported on Co/C and Co/SiO_2 systems.[21,22] Also, it has been proved that the addition of MgO to Co/C slows the deactivation of the cobalt catalysts by carbon deposition *via* the Boudouard reaction ($2CO \rightarrow CO_2 + C$).[21]

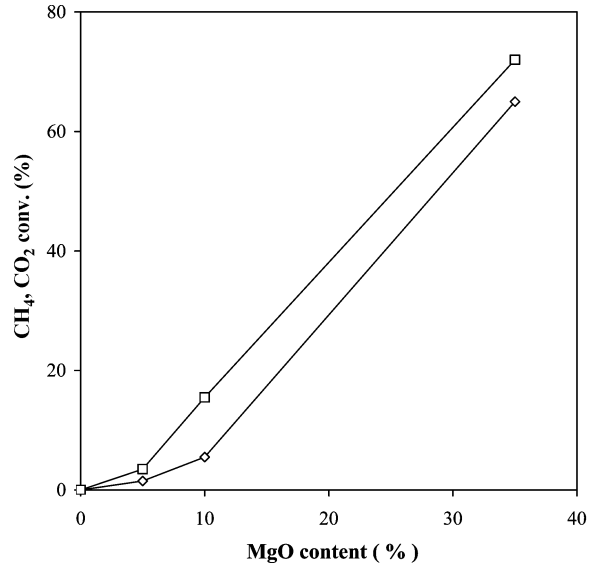

Fig. 1 Evolution of CH_4 and CO_2 conversions with MgO content: (□) CO_2 conversion; (◇) CH_4 conversion, after 24 h time reaction. CH_4 : CO_2 : He = 20 : 10 : 70%.

The presence of a carbon deposit on used catalysts was studied by TG-DSC (differential scanning calorimetry coupled with thermogravimetry) and XRD techniques. Results are shown in Table 2 and Fig. 3. In the case of the Co/5 wt% MgO–SiO_2 sample (Fig. 3a), the combustion of carbon in a flow of dilute oxygen in helium gave rise to two exothermic peaks of CO_2 outgassing, with a weight loss of 31%, accompanied by a dehydration endothermic peak which appeared at the beginning.

Table 1 Physicochemical properties of the catalysts

Catalyst	Composition/wt% Co	MgO	BET area/m^2 g^{-1}	Surface coverage[a]/ μmol_{MgO} m^{-2}	CO_2 adsorption[b]/ μmol m^{-2}
Co/SiO_2	4.7	0	185	—	~0
Co/5 wt% MgO–SiO_2	4.7	4.4	178	4.43	0.013
Co/10 wt% MgO–SiO_2	4.9	9.1	214	7.77	0.037
Co/35 wt% MgO–SiO_2	3.9	32.4	191	42.41	0.164

[a] (μmol MgO/g catalyst × BET surface). [b] Amount of sorbed CO_2 under an equilibrium pressure of 0.5 torr.

Table 2 Characteristics of used samples: coke amount and TPO experiments by TG-DSC

Catalyst	Coke[a]/wt%	Peak maxima/°C	ΔH/kJ g^{-1}	$\Delta m/m$ (%)
Co/SiO_2	nd[b]	—	—	—
Co/5 wt% MgO–SiO_2	43.6	475 560	6.19 1.36	30.9
Co/10 wt% MgO–SiO_2	3.3	447	0.57	5.7
Co/35 wt% MgO–SiO_2	traces	—	—	—

[a] From chemical analysis, determined after 24 h of reaction. [b] Not determined.

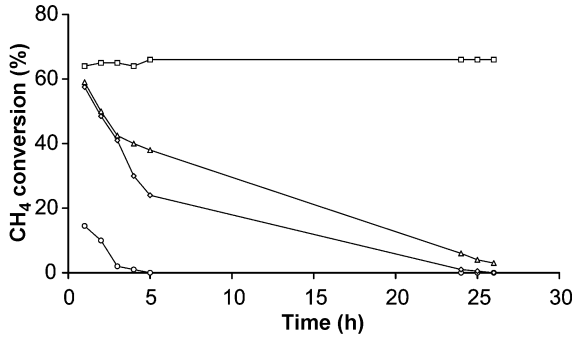

Fig. 2 Conversion of methane at 600 °C for : (□) Co/35 wt% MgO–SiO_2 ; (Δ) Co/10 wt% MgO–SiO_2, (◊) Co/5 wt% MgO–SiO_2 and (○) Co/SiO_2. CH_4 : CO_2 : He = 20 : 10 : 70%.

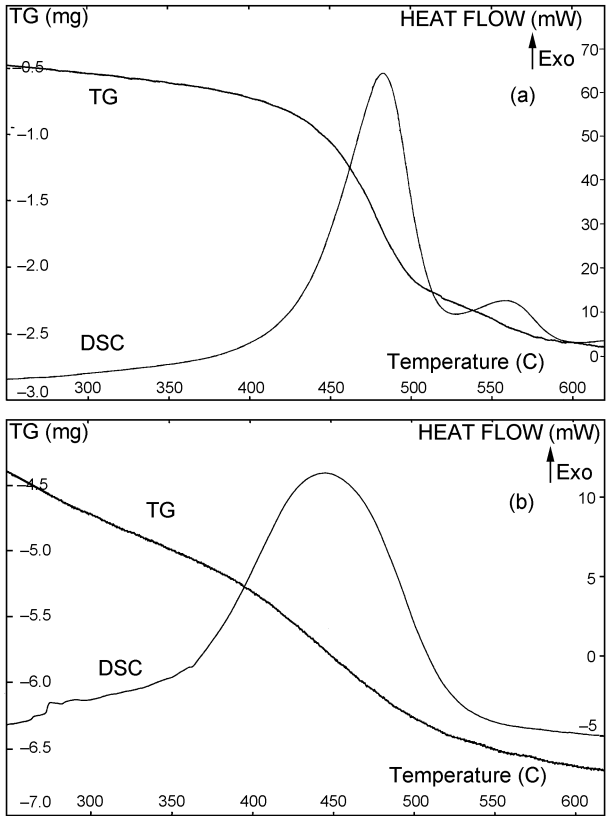

Fig. 3 Thermogravimetric and heat flow profiles of thermoprogrammed oxidation of used catalysts: (a) Co/5 wt% MgO–SiO_2 and (b) Co/10 wt% MgO–SiO_2.

Further, the peak which appears at 475 °C and tends to disappear for increasing MgO contents, could be assigned to the oxidation of the carbon deposit on the metallic phase. Note that the catalytic activity of this used catalyst was in part restored after treatment under oxygen around this temperature. The second peak at 560 °C is attributed to the reaction of the coke fixed over the acid sites. For the Co/10 wt% MgO–SiO_2 used catalyst (Fig. 3b), the peak at 447 °C became smaller and the second peak disappeared completely, which shows the beneficial effect of MgO on resistance to coking. It has to be noted that these enthalpic effects are not observed on the fresh catalysts. Our results are in agreement with those of Barbier *et al.*,[23] who observed on Pt/Al_2O_3 two distinct peaks both on the metal and on the support. Similarly, Beltramini *et al.*[24] have evidenced two peaks of CO_2 outgassing in the case of Pt/Al_2O_3 and only one peak for $Pt–Ir/Al_2O_3$.

The formation of carbon is confirmed by the X-ray diffraction peaks appearing in Fig. 4, which correspond to the

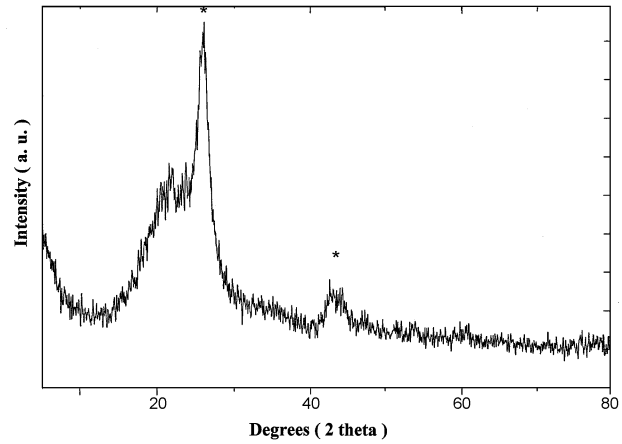

Fig. 4 XRD patterns of Co/5 wt% MgO–SiO_2 catalyst after reaction at 600 °C: (*) = carbon in graphite form.

used Co/5 wt% MgO–SiO_2 catalyst (after 24 h of reaction), at angles 2θ of 25 and 43.5°.

These results suggest that the basic ingredients increase the basicity of catalysts and their ability to adsorb an acidic molecule such as CO_2 over their surfaces.[22] This adsorbed CO_2 contributes to the stability of catalysts by speeding up coke gasification on catalyst surface and increases the life span of catalysts, with the following mechanism:

$$CH_{4\ (g)} + s_1 \rightarrow CH_4–s_1 \rightarrow C–s_1 + 2H_2 \quad (1)$$

$$CO_{2\ (g)} + s_2 \rightarrow CO_2–s_2 \quad (2)$$

$$CO_2–s_2 + s_1–C\ (-s_1) \rightarrow 2CO + s_2 \quad (3)$$

where s_1 = cobalt and s_2 = MgO–SiO_2.

4 Conclusion

Magnesium oxide-modified Co samples are good catalysts for the dry reforming of methane. Introduction of MgO significantly promotes the catalytic performance of the Co/SiO_2 reference catalyst. The promotion of activity is attributed to enhancement of H-abstraction of methane and increase of CO_2 adsorption. As to the stabilization of the catalytic activity, it may create acid sites neutralization or/and catalysts speeding up coke gasification by CO_2.

Acknowledgement

The authors are very grateful to Prof. M. M. Bettahar, University Nancy 1 – Henri Poincarré (France) for the critical reading of the manuscript and acknowledge the support of the Franco-Algerian CMEP grant number MDU 00459.

References

1 S. Teuner, *Hydrocarbon Process.*, 1985, **64**, 106.
2 S. Teuner, *Hydrocarbon Process.*, 1987, **66**, 52.
3 N. R. Udengoard, J. B. Hassen, D. C. Hanson and J. A. Stal, *Oil Gas J.*, 1992, **62**, 9.
4 J. R. Rostup-Nielsen and J. H. Bak Hansen, *J. Catal.*, 1993, **144**, 38.
5 Y. H. Hu and E. Ruckenstein, *Catal. Lett.*, 1996, **36**, 145.
6 Z. Zhang and X. E. Verykios, *Appl. Catal.*, 1996, **138**, 109.
7 V. C. H. Kroll, H. M. Swaan and C. Mirodatos, *J. Catal.*, 1996, **161**, 409.
8 M. C. J. Bradford and M. A. Vannice, *Appl. Catal.*, 1996, **142**, 73.
9 D. Halliche, R. Bouarab, O. Cherifi and M. M. Bettahar, *Catal. Today*, 1996, **29**, 373.
10 J. S. Choi, K. I. Moon, Y. G. Kim, J. S. Lee, C. H. Kim and D. L. Trimm, *Catal. Lett.*, 1998, **52**, 43.
11 R. Bouarab, S. Menad, D. Halliche, O. Cherifi and M. M. Bettahar, *Stud. Surf. Sci. Catal.*, 1998, **119**, 717.
12 M. Ito, T. Tagawa and S. Goto, *Appl. Catal.*, 1999, **177**, 15.
13 K. Bachari, R . Bouarab and O. Cherifi, *J. Alger. Chem. Soc.*, 1999, **9**, 99.
14 R. Bouarab, O. Akdim, A. Auroux, O. Cherifi and C. Mirodatos, in preparation.
15 J. R. Rostrup-Nielsen, *Stud. Surf. Sci. Catal.*, 1994, **81**, 25.
16 Z. L. Zhang, V. Tsipouriari, A. M. Efstathiou and X. E. Verykios, *J. Catal.*, 1996, **158**, 51.
17 J. T. Richardson and S. A. Paripatyadar, *Appl. Catal.*, 1990, **61**, 293.
18 R. Bouarab, A. Auroux and O. Cherifi, *J. Alger. Chem. Soc.*, 2001, **11**, 99.
19 S. M. Stagg, E. Romeo, C. Padro and D. E. Resasco, *J. Catal.*, 1998, **178**, 137.
20 T. Borowiecki and A. Golebiowski, *Catal. Lett.*, 1994, **25**, 309.
21 A. Guerrero-Ruiz, I. Rodriguez-Ramos and A. Sepulveda-Escribano, *J. Chem. Soc., Chem. Commun.*, 1993, 487.
22 A. Guerrero-Ruiz, A. Sepulveda-Escribano and I. Rodriguez-Ramos, *Catal. Today*, 1994, **21**, 545.
23 J. Barbier, G. Corro, Y. Zhang, J. P. Bournonville and J. P. Franck, *Appl. Catal.*, 1985, **13**, 245.
24 J. N. Beltramini and W. Trimm, *Erdöl Kohle*, 1987, **9**, 400.

Aqueous organometallic catalysis. Isotope exchange reactions in H_2–D_2O and D_2–H_2O systems catalyzed by water-soluble Rh- and Ru-phosphine complexes†

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Received 6th January 2003
First published as an Advance Article on the web 13th March 2003

The water-soluble complexes [{$RuCl_2$(*m*TPPMS)$_2$}$_2$], [$RuCl_2$(PTA)$_4$], [RhCl(*m*TPPMS)$_3$], [RhCl(*m*TPPTS)$_3$], and [RhCl(PTA)$_3$] (*m*TPPMS = sodium salt of *meta*-sulfonatophenyl-diphenylphosphine, *m*TPPTS = sodium salt of*tris*(*meta*-sulfonatophenyl)phosphine, and PTA = 1,3,5-triaza-7-phosphaadamantane) showed high catalytic activity (up to 1252 h^{-1}) in the H–D isotope exchange reactions between H_2 and D_2O or D_2 and H_2O. The reactions took place at 20–70 °C, 0.1–2 MPa H_2, and were strongly influenced by the pH. In the hydrogenation (with H_2) of unsaturated acids in D_2O, the relative rates of H–D exchange, hydrogenation and deuteration were determined by the individual substrates and catalysts: in the reaction of maleic acid catalyzed by [RhCl(*m*TPPMS)$_3$] only hydrogenation took place with no deuteration and H–D exchange, whereas a similar reaction of itaconic acid was accompanied by a fast H–D exchange and the product methylsuccinic acid was highly deuterated.

Introduction

The principles of green chemistry require – among others – the use of catalytic processes instead of stoichiometric reactions, and the replacement of hazardous organic solvents with environmentally more acceptable ones (or the application of solvent-free procedures).[1] Although some ambiguities can be raised,[2] water is the most environmental-friendly solvent, and its availability and relatively low price make its increasing use in synthesis[3] and catalysis[4] attractive. At present there are only a few large scale industrial processes based on aqueous–organic biphasic technology;[5] still the use of water as solvent may be worth considering in all those cases where the chemical nature of substrates, products and catalysts do not demand anhydrous reaction conditions. Nevertheless, water is not always innocuous, and may influence the rate and selectivity of a given catalytic reaction.[6] Aqueous solutions do always contain H^+ and OH^-; their concentration (usually expressed as the pH of the solution) can be changed by the addition of suitable acids or bases. In all those reactions in which transition metal hydrides play an important catalytic role (and homogeneous hydrogenations obviously belong to this class), one should be aware of the possible protonation–deprotonation equilibria of the hydride species as a function of pH, and the effect of these equilibria on the catalytic process.

Hydrogen–deuterium isotope exchange between D_2 and H_2O or H_2 and D_2O has often been observed during hydrogenations with transition metal complex catalysts in *organic solvents* containing only a small fraction (*e.g.*, 1%) of water.[7–10] In aqueous solutions, the study of the catalytic H–D exchange helped to clarify the properties of the enzyme hydrogenase.[4,11]

Water-soluble phosphine complexes are widely used in the hydrogenation of all the common reducible functionalities[4,5] and isotope labelling is one of the most powerful methods of the studies on the kinetics and mechanisms of such reactions. Catalytic deuteration of olefinic substrates, such as prochiral enamides or itaconic acid, in D_2O–H_2 or H_2O–D_2 systems has already been reported, however, in these cases the direct isotope (H–D) exchange between the catalytically active hydride species and the solvent was not investigated.[12–19] Halpern and James studied the isotope exchange between D_2 and H_2O catalyzed by Ru(III)- and Ru(II)-complexes in strongly acidic solutions by mass spectrometry.[20–22] The reactions were found to be very slow, with only a few turnovers of the catalyst per hour at 80 °C.

Green Context

Water is often cited as the 'ideal' solvent – it is readily available, inexpensive, non-toxic and totally environmentally compatible. However, it does suffer from some significant limitations including poor solubility of many organic compounds, and, as is demonstrated here, high reactivity in many systems. Water-soluble organometallic complexes of ruthenium and rhodium show high catalytic activity in the isotope exchange reactions between H_2 and D_2O and between D_2 and H_2O. It is also shown that the relative rates of H–D exchange and hydrogenation in catalytic aqueous hydrogenation systems are substrate and catalyst dependent. The authors show that water can indeed be a reactive solvent and that this should be kept in mind when designing organic-solvent free reactions. ***JHC***

† Part of this work was presented at the Green Solvents for Catalysis Meeting held in Bruchsal, Germany, 13–16th October 2002.

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Gábor Kovács

Levente Nádasdi

Gábor Laurenczy

Ferenc Joó

In the following, we report that certain water-soluble tertiary phosphine complexes of ruthenium(II) and rhodium(I) catalyze the H–D isotope exchange between H_2–D_2O and D_2–H_2O under mild conditions with unprecedented efficiency, and that the rate of this reaction is strongly influenced by the pH of the solutions. The ligands in these complexes (Fig. 1) are 1,3,5-triaza-7-phosphaadamantane (PTA), and the sodium salts of *meta*-sulfonatophenyl-diphenylphosphine (*m*TPPMS) and *tris*(*meta*-sulfonatophenyl)phosphine (*m*TPPTS). A water soluble chelating diphosphine ligand (DPPETS, Fig. 1) has also been studied. A preliminary communication of these findings has appeared.[23]

Experimental

All experiments were done under oxygen-free conditions using Schlenk-techniques. D_2O (99.9%) and d⁴-methanol were purchased from Cambridge Isotope Laboratories, whereas D_2 was the product of Linde. *m*TPPMS,[24] *m*TPPTS,[25] PTA,[26] DPPETS,[27] $[\{RuCl_2(m\text{TPPMS})_2\}_2]$,[24] $[RuCl_2(PTA)_4]$,[28] $[RhCl(m\text{TPPMS})_3]$,[24] $[RhCl(m\text{TPPTS})_3]$,[25] and $[RhCl(PTA)_3]$,[28] were prepared as described in the literature.

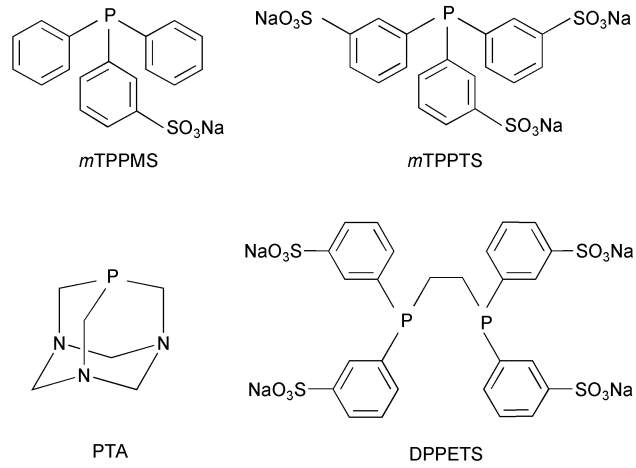


Fig. 1 The ligands used in the catalytic reactions.

$[RhCl(COD)]_2$ and TSPSA were purchased from Sigma-Aldrich.

H–D exchange experiments were carried out under both high and atmospheric pressures. In both kinds of experiments the concentration of the catalyst in the reaction mixture (in D_2O or

H_2O) was 2.61 mM. In the case of the *m*TPPMS-containing complexes a 3 equiv. ligand excess was used. The pH was set with HCl–DCl or NaOH–NaOD solutions.

Experiments under pressure were carried out in a 10 mm medium pressure sapphire NMR-tube[29] under 2 MPa of H_2. The tube was shaken in a thermostated chamber at 300 rpm, from which it was removed at timed intervals for *in situ* ^1H or ^2H NMR measurements. In the atmospheric pressure experiments, the reactions took place in a thermostated Schlenk-vessel connected to a large reservoir of hydrogen at constant (atmospheric) pressure. Samples were withdrawn periodically with a hypodermic syringe and were analyzed by NMR-spectroscopy. Spectra were collected on a Bruker AC 200 or an AM 360 instrument, the integrals were calculated using the WIN-NMR program and the ^1H chemical shifts were referenced to 3-trimethylsilyl-1-propanesulfonic acid Na-salt (TSPSANa). The latter and d^4-methanol served as internal standards for obtaining the concentration of HOD by integration.

The initial reaction rates were calculated from the integrals of the HOD peaks as a function of time using the first hour data giving a good linear fit. Reaction rates are given as turnover frequencies, TOFs (h^{-1}): TOF = moles of HDO formed (moles of catalyst × duration of the reaction)$^{-1}$. Each point reported in the figures is an average value of at least three measurements.

Results and discussion

Reactions at elevated H_2 pressures

All the investigated Ru(II)- and Rh(I)-complexes containing monodentate tertiary phosphine ligands were found to be active in the catalysis of the $H_2 + D_2O \rightleftharpoons HD + HOD$ reaction at 20–70 °C and 2 MPa H_2. The reactions were followed by recording ^1H NMR spectra over time. These were real *in situ* measurements, and, in fact, the higher pressure was only needed to maintain a sufficient amount of H_2 in the small gas space of the medium-pressure NMR tube. Over the time course of the reaction, a gradual increase is observed in the HOD signal intensity, as shown in Fig. 2. In such closed systems, an equilibrium distribution of deuterium between the gas and the liquid phase is reached eventually; then the [H]/[D] concentration ratio in the aqueous phase corresponds to the molar ratio of the total amounts of H and D introduced to the NMR tube. Representative rates for the various catalysts are summarized in Table 1.

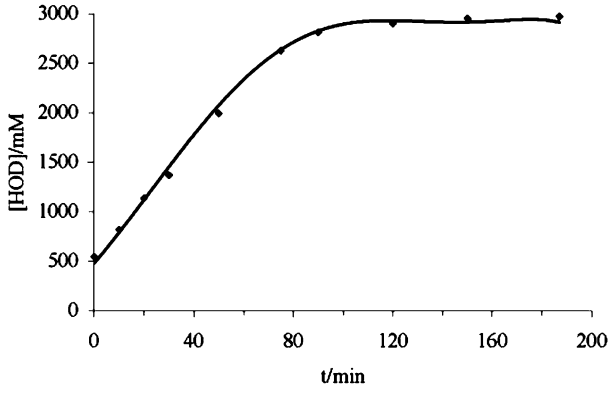


Fig. 2 Time course of an H–D exchange reaction catalyzed by [RhCl(*m*TPPMS)$_3$]. *c*(Rh) = 2.61 mM, *c*(*m*TPPMS) = 13.05 mM, *p*(H_2) = 2 MPa, pH = 3.2, *T* = 298 K.

It can be seen from the data in Table 1, that most of the catalysts show very high activity under mild conditions. These can be related to the catalytic activity of the same complexes in the hydrogenation of simple olefinic substrates in aqueous solutions. For example, under comparable conditions [{RuCl$_2$(*m*TPPMS)$_2$}$_2$] hydrogenated crotonic, maleic, fumaric and itaconic acids with TOFs in the range of 100–700 h^{-1}.[30] The results also show that the rhodium and ruthenium complexes containing aromatic sulfonated phosphine ligands are much more active (*ca.* 100 times) than the complexes with the aliphatic PTA ligand under the same conditions. This is, again, in line with the lower reactivity of PTA-containing Ru- and Rh-complexes in hydrogenation of olefins[18] and carbon dioxide.[31] However, in the case of the Rh-complex prepared *in situ* from [Rh(COD)Cl]$_2$ and a bidentate phosphine ligand (tetrasulfonated 1,2-diphenylphosphino-ethane, DPPETS), no reaction occurred even at elevated temperatures and long reaction times. This is not surprising if we consider that rhodium complexes of DPPE form active hydride species only in the presence of olefinic substrates,[32] and supports the key role of hydride species in the H–D exchange reaction.

Table 1 Specific rate of H–D exchange catalyzed by water-soluble Ru(II)- and Rh(I)-phosphine complexes in D_2O–H_2 system

Catalyst	pH	*T*/°C	TOF/h^{-1}
[RuCl$_2$(PTA)$_4$]	5.5	25	8.5
[RuCl$_2$(PTA)$_4$]	5.5	70	338
[RhCl(PTA)$_3$]	5.2	70	908
[{RuCl$_2$(*m*TPPMS)}$_2$]	2.0–5.0	25	1252
[RhCl(*m*TPPMS)$_3$]	2.0–7.0	25	806
[RhCl(*m*TPPTS)$_3$]	6.5	25	989

Conditions: *c*(cat.) = 2.61 mM; *p*(H_2) = 2 MPa.

It is now well documented that the reactivity and the catalytic activity of water-soluble phosphine complexes in hydrogenation reactions is largely influenced by the pH.[6,33] For example, in the hydrogenation of *trans*-cinnamaldehyde with a [{RuCl$_2$(*m*TPPMS)$_2$}$_2$] catalyst, the selective reduction of the C=C bond occurred at pH < 5, whereas at pH > 8 the C=O bond was hydrogenated selectively.[6] This phenomenon was explained by the formation of different hydride species at different pH values. Therefore we determined the catalytic activity of some of the above complexes in the H–D exchange reaction as a function of pH. The results are shown in Fig. 3 and 4.

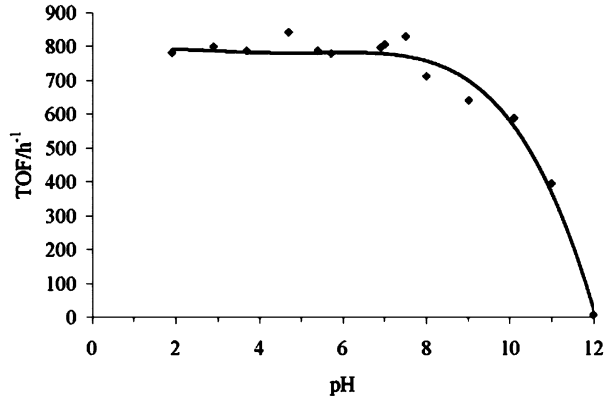


Fig. 3 The rate of H–D exchange, catalyzed by [RhCl(*m*TPPMS)$_3$], as a function of pH. *c*(Rh) = 2.61 mM, *c*(*m*TPPMS) = 13.05 mM, *p*(H_2) = 2 MPa, *T* = 298 K.

As seen in Fig. 3 and 4, there are noteworthy differences in the effect of the pH on the catalytic activity of the Rh-complexes with PTA and *m*TPPMS ligands. With both catalysts there is a drop in the activity in alkaline solutions, inasmuch that no isotope exchange is observed at pH > 12. This is the same phenomenon that was observed in the case of [{RuCl$_2$(*m*TPPMS)$_2$}$_2$].[23] It is conceivable that in the case of

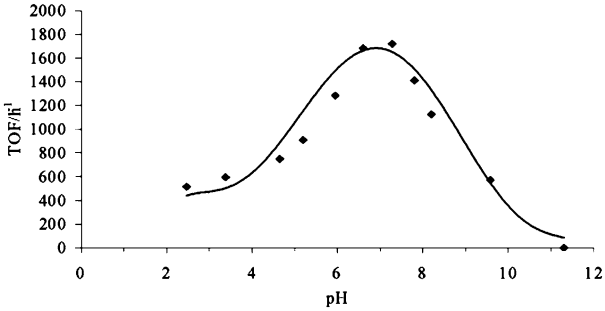


Fig. 4 The rate of H–D exchange, catalyzed by [RhCl(PTA)$_3$], as a function of pH. c(Rh) = 2.61 mM, p(H$_2$) = 20 bar, T = 343 K.

both catalysts the H–D exchange involves the protonation of an intermediate hydride species, which is preferable at lower pH-values but becomes negligible in strongly alkaline solutions. A possible general mechanism for [RhXP$_3$]-type complexes, involving the formation of a hydrido-dihydrogen complex, is depicted in Fig. 5. Although such complexes have not been

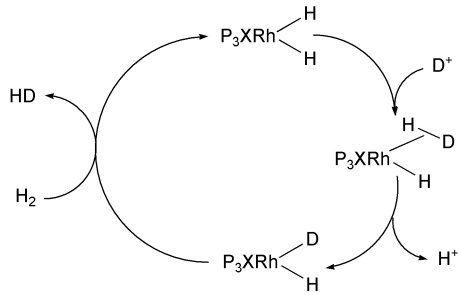


Fig. 5 Suggested mechanism of the H–D exchange catalyzed by [RhXP$_3$] complexes (P = *m*TPPMS, *m*TPPTS, or PTA).

isolated, reaction of a monohydrido intermediate with D$^+$ to yield [W(CO)$_3$(PR$_3$)$_2$(η^2-HD)] was assumed by Kubas *et al.* to account for the D–H exchange in the reaction of [W(CO)$_3$(PR$_3$)$_2$(η^2-D$_2$)] and H$_2$O.[9] However, in our case, the participation of monohydrido-rhodium complexes, [RhHP$_3$], in the H–D exchange is very unlikely, since only the well-known dihydrides, [Rh(H)$_2$ClP$_3$], were detected by ^{1}H and ^{31}P NMR spectroscopy in solutions of pH≤10.[33,34] As for the decrease in the activity showed by [RhCl(PTA)$_3$] at acidic pH values, presently we do not have a satisfactory explanation, although the protonation of the PTA ligand on one of its nitrogens might be a possible cause of the change in reactivity.

It is of interest to compare the rates of the H$_2$O + D$_2$ and the D$_2$O + H$_2$ exchange reactions using the same catalyst under the same conditions. The pH–TOF curves for the two reactions catalyzed by [RhCl(*m*TPPMS)$_3$] are shown in Fig. 6. As expected, the isotope effect is small (approximately 10%).

Measurements at atmospheric hydrogen pressure

Under otherwise identical conditions but at atmospheric hydrogen pressure, the reaction rate for the H–D exchange catalyzed by [{RuCl$_2$(*m*TPPMS)$_2$}$_2$] was about 20 times lower than at 2 MPa H$_2$. This suggests the rate is linearly proportional to the H$_2$ pressure in this pressure range. However, the effect of the pH on the reaction rate was very similar to that observed at 2 MPa.[23]

Since, with the same catalyst, both the H–D isotope exchange and the deuteration of olefins during catalytic hydrogenations involve the same metal hydride species, it was of interest to study how the presence of an olefinic substrate influenced the H–D exchange reactions. Therefore a series of H–D exchange experiments were run in the presence of itaconic acid (2-methylenesuccinic acid) (Scheme 1). This compound is highly soluble in water, and ^{13}C NMR experiments have shown, that its α-CH$_2$ (C-3) group remains unchanged during the hydrogenation reactions and can, therefore, serve as an internal reference in the integration of the ^{1}H NMR spectra.

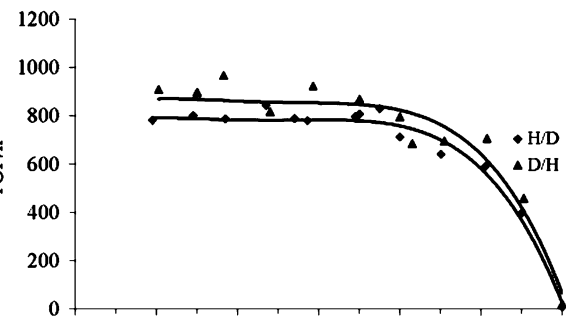
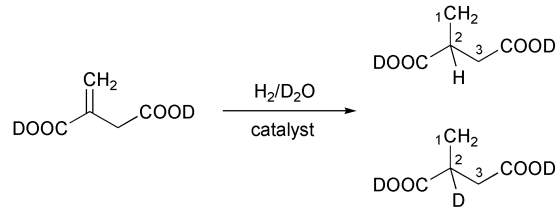


Fig. 6 Comparison of the rates of the H–D and D–H exchange catalyzed by [RhCl(*m*TPPMS)$_3$]. c(Rh) = 2.61 mM, c(*m*TPPMS) = 13.05 mM, p(H$_2$) = 2 MPa, T = 298 K.



Scheme 1 The reduction of itaconic acid in H$_2$–D$_2$O systems.

In the presence of [RhCl(*m*TPPMS)$_3$] and [RhCl(PTA)$_3$] both the H–D exchange and the reduction of the C=C double bond took place, and these reactions were competitive of each other. For example, [RhCl(PTA)$_3$] hydrogenated itaconic acid with TOFs in the range of 120–170 h^{-1}, with a fast concomitant H–D exchange (230–280 h^{-1}), depending on the pH of the solutions. Interestingly, only the C-2 carbon was deuterated, and the maximum deuteration (85%) was observed at pH 3.2.

With [RhCl(*m*TPPMS)$_3$] and maleic acid the picture is somewhat different. Addition of maleic acid to acidic aqueous solutions of this catalyst completely stops the H–D exchange, however, at the same time hydrogenation of maleic acid starts with *no deuterium incorporation*. Obviously, the hydride transfer from the intermediate [Rh(H)$_2$Cl(*m*TPPMS)$_3$] species to maleic acid is much faster than the H–D exchange on the rhodium.

In acidic solutions, [{RuCl$_2$(*m*TPPMS)$_2$}$_2$] appeared to be inactive in the hydrogenation of itaconic acid and this substrate also inhibited the H–D exchange between hydrogen and water due to the formation of a stable, catalytically inactive product. A striking example of this inhibition is shown in Fig. 7: a solution of itaconic acid was injected into a [{RuCl$_2$(TPPMS)$_2$}$_2$]–D$_2$O–H$_2$ reaction mixture resulting in an immediate stop of the fast H–D exchange.

Conclusion

The direct isotope exchange between the gas phase (H$_2$ or D$_2$) and the solvent (D$_2$O or H$_2$O) is efficiently catalyzed by several water-soluble Rh- and Ru-tertiary phosphine complexes.

Such an isotope exchange can be a rather important side-reaction in aqueous organometallic hydrogenations. It has also been shown that the pH of the aqueous reaction mixture has a

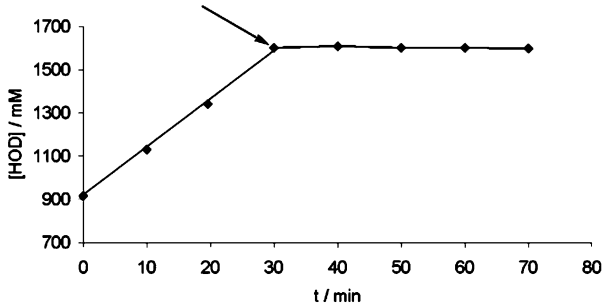


Fig. 7 The effect of itaconic acid (added at t = 30 min) on the H–D exchange catalyzed by [{$RuCl_2$(*m*TPPMS)$_2$}$_2$]. c(Ru) = 2.61 mM, c(*m*TPPMS) = 13.05 mM, p(H_2) = 0.1 MPa, T = 298 K.

strong effect on the reaction rate of the exchange process, which involves the protonation of intermediate hydride species.

The reduction of olefinic substrates in H_2–D_2O or D_2–H_2O modifies the rate of the H–D exchange and may result in isotope incorporation into the products. In some cases one of these reactions can proceed much faster than the other (*cf.* the [RhCl(*m*TPPMS)$_3$]-catalyzed hydrogenation of maleic acid with no deuterium incorporation and accompanying inhibition of the H–D exchange), in others hydrogenation, deuteration and H–D exchange may take place with comparable rates (*cf.* the [RhCl(PTA)$_3$]-catalyzed hydrogenation of itaconic acid). The above findings show that water may be a reactive solvent, which should be kept in mind when devising new green processes with water instead of organic solvents.

Acknowledgements

Financial support from FKFP, Hungary, A/K 13/0183 (L. N.), OTKA, Hungary, T043365 (F. J.) and NSF, Switzerland 2000-067976.02 (G. L.) is gratefully acknowledged. F. Joó thanks Johnson-Matthey Inc. for a loan of $RuCl_3$·aq and Albright and Wilson for a gift of [$P(CH_2OH)_4$]Cl.

References

1 P. T. Anastas and J. C. Warner, *Green Chemistry: Theory and Practice*, Oxford University Press, New York, 1998.
2 *Aqueous Organometallic Chemistry and Catalysis*, ed. I. T. Horváth and F. Joó, NATO ASI Ser. 3/5, Kluwer, Dordrecht, 1995.
3 *Organic Synthesis in Water*, ed. P. A. Grieco, Blackie, London, 1998.
4 F. Joó, *Aqueous Organometallic Catalysis*, Kluwer, Dordrecht, 2001.
5 *Aqueous Phase Organometallic Catalysis*, ed. B. Cornils and W. A. Herrmann, Wiley-VCH, Weinheim, 1998.
6 F. Joó, J. Kovács, A. C. Bényei and Á. Kathó, *Angew. Chem.*, 1998, **110**, 1024; F. Joó, J. Kovács, A. C. Bényei and Á. Kathó, *Angew. Chem., Int. Ed. Engl.*, 1998, **37**, 969.
7 R. R. Schrock and J. A. Osborn, *Chem. Commun.*, 1970, 567.
8 R. R. Schrock and J. A. Osborn, *J. Am. Chem. Soc.*, 1976, **98**, 2134.
9 G. J. Kubas, C. J. Burns, G. R. K. Khalsa, L. S. van der Sluys, G. Kiss and C. D. Hoff, *Organometallics*, 1992, **11**, 3390.
10 W. C. Chan, C. P. Lau, L. Cheng and Y. S. Leung, *J. Organomet. Chem.*, 1994, **464**, 103.
11 A. I. Krasna and D. Rittenberg, *J. Am. Chem. Soc.*, 1954, **76**, 3015.
12 E. G. Chepaikin and M. L. Khidekel', *J. Mol. Catal.*, 1978, **4**, 103.
13 T. Malström, O. F. Wendt and C. Andersson, *J. Chem. Soc., Dalton Trans.*, 1990, 2871.
14 M. Laghmari and D. Sinou, *J. Mol. Catal.*, 1991, **66**, L15.
15 J. Bakos, R. Karaivanov, M. Laghmari and D. Sinou, *Organometallics*, 1994, **13**, 2951.
16 Á. Bucsai, J. Bakos, M. Laghmari and D. Sinou, *J. Mol. Catal. A: Chem.*, 1997, **116**, 335.
17 F. Joó, P. Csiba and A. Cs. Bényei, *J. Chem. Soc., Chem. Commun.*, 1993, 1602.
18 F. Joó, L. Nádasdi, A. Cs. Bényei and D. J. Darensbourg, *J. Organomet. Chem.*, 1996, **512**, 45.
19 L. Nádasdi and F. Joó, *Inorg. Chim. Acta*, 1999, **293**, 218.
20 J. Halpern and B. R. James, *Can. J. Chem.*, 1966, **44**, 671.
21 J. Halpern, B. R. James and A. L. W. Kemp, *J. Am. Chem. Soc.*, 1966, **88**, 5142.
22 J. Halpern, J. F. Harrod and B. R. James, *J. Am. Chem. Soc.*, 1966, **88**, 5150.
23 G. Kovács, L. Nádasdi, F. Joó and G. Laurenczy, *C. R. Acad. Sci. Paris, Sér. IIc: Chim.*, 2000, **3**, 601.
24 F. Joó, J. Kovács, Á. Kathó, A. C. Bényei, T. Decuir and D. J. Darensbourg, *Inorg. Synth.*, 1998, **32**, 1.
25 W. A. Herrmann and C. W. Kohlpaintner, *Inorg. Synth.*, 1998, **32**, 8.
26 D. J. Daigle, *Inorg. Synth.*, 1998, **32**, 40.
27 H. Ding, B. B. Bunn and B. E. Hanson, *Inorg. Synth.*, 1998, **32**, 29.
28 D. J. Darensbourg, F. Joó, M. Kannisto, Á. Kathó and J. H. Reibenspies, *Organometallics*, 1992, **11**, 1990.
29 A. Cusanelli, U. Frey, D. T. Richens and A. E. Merbach, *J. Am. Chem. Soc.*, 1996, **118**, 5625.
30 F. Joó and Z. Tóth, *J. Mol. Catal.*, 1980, **8**, 369.
31 G. Laurenczy, F. Joó and L. Nádasdi, *Inorg. Chem.*, 2000, **39**, 5083.
32 P. A. Chaloner, M. A. Esteruelas, F. Joó and L. A. Oro, *Homogeneous Hydrogenation*, Kluwer, Dordrecht, 1994, **29**.
33 F. Joó, J. Kovács, A. Cs. Bényei, L. Nádasdi and G. Laurenczy, *Chem. Eur. J.*, 2001, **7**, 241.
34 L. Nádasdi, A. Ormos, G. Laurenczy and F. Joó, *Abstr. 13th Int. Symp. Homogeneous Catal.*, Tarragona, 2002, 78.

Control of homogeneously catalyzed reactions by phase equilibria†

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Received 6th December 2002
First published as an Advance Article on the web 24th March 2003

Carbon dioxide was used not only as a reaction medium but also as a renewable C_1 feedstock for the palladium catalyzed coupling reaction of butadiene and carbon dioxide. By utilization of nitrile modified phosphine ligands, in the liquid phase complete butadiene conversion and selectivity for the formation of (3E)-3-ethylidene-6-vinyltetrahydro-2H-pyran-2-one (**1**) up to 47% were achieved. Phase equilibrium considerations were used for process development in order to realize single-phase conditions for the reaction. In contrast to a CO_2 enriched phase composition, variation of the density only enables moderate conversion rates also with single-phase conditions and without further catalyst modification.

Introduction

In the last two decades, increasing interest has been devoted to the design and utilization of alternative (green) solvents for catalyzed processes, such as water and ionic liquids.[1] There has also been a large emphasis, both in industrial and academic research, on the development of processes based on supercritical fluids.[2] To develop a new process as a promising alternative to conventional routes, one potential advantage of supercritical fluids – the combination of different process steps into one single process, *e.g.* by integration of reaction and separation – has to surpass the general technical and ecological arguments usually quoted.[3] Generally, to minimize efforts of transportation, heating and separation, the absolute amount of any solvent is also an essential factor. This can not only cause significant activity changes in homogeneously catalyzed reactions but also causes major changes in the phase equilibrium of the reaction mixture.

Our goal is to identify reactions in which such a favourable combination of beneficially tuneable properties using a dense fluid system is achieved in order to allow (i) product recovery or product enrichment, (ii) recovery of a homogeneous catalyst and (iii) recycling of starting materials. In this context, process

Green Context

The use of dense phase CO_2 as a reaction medium gives many options for processing, and has several advantages over conventional systems. However, before it can be optimally utilized, it must be appreciated that the phase diagram which is used to predict solvent properties at given temperature and pressure can change upon the addition of reactants, and indeed may change as the reaction proceeds, and reactants are converted to products. The determination of phase behaviour in real reaction systems is the theme of this paper, focussing on the reaction of butadiene with CO_2 taking place with Pd catalysis. ***DJM***

† This work was presented at the Green Solvents for Catalysis Meeting held in Bruchsal, Germany, 13–16th October 2000.

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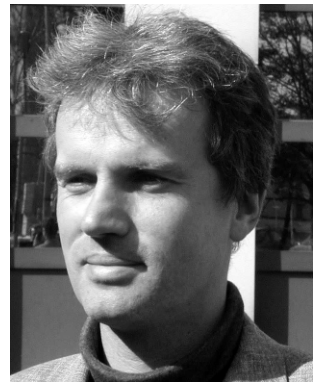
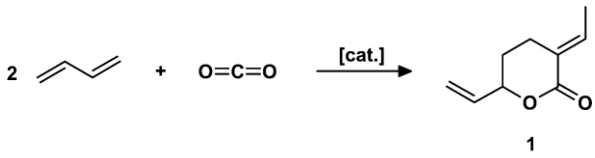


 DOI: 10.1039/b212143n

development becomes a complex task, involving multidisciplinary contributions from different fields of chemistry and engineering, such as catalyst design, off- and on-line analysis, kinetic and thermo physical data, modelling and simulation as well as reaction and process technology aspects.

In dense fluids as the reaction medium, phase equilibria play a central role because the number of phases in equilibrium and their composition can be easily changed by pressure, temperature, and also as a consequence of the conversion of materials by chemical reactions. Thus, reliable experimental data and, based on that, correlation and prediction methods are important tools to find appropriate operation conditions in which reaction and separation steps can be realized.

In this study, we describe the palladium catalyzed coupling reaction of butadiene and carbon dioxide in a reaction medium free of additional solvent and, in particular, the influence of the phase equilibrium on product formation in order to gain advantages for further process development.[4] The results are discussed with focus on the formation of (3E)-3-ethylidene-6-vinyltetrahydro-2H-pyran-2-one (**1**) as the main product (Scheme 1). Depending on the reaction conditions applied,



1

Scheme 1 Synthesis of **1**.

different C_9 and C_{17} carboxylic acid derivatives are formed as by-products, reasonably explained by the catalytic mechanism.[5] In addition, oligomers of butadiene (*e.g.* octatrienes), and the Diels–Alder product 4-vinyl-cyclohexene are also observed. The reaction type is also of general interest: It deals with easily available and cheap substrates and uses CO_2 as a non-fossil carbon source. Besides, several functions are built in one single step that offers several consecutive transformations to high value products.[6]

An essential factor for the potential technical and commercial conversion is the efficiency of the catalyst system. Attempts in the optimization of the homogeneous catalyst have been made by numerous variations of the applied pre-catalyst in combination with different donor ligands.[7] In connection with relatively low reaction rates and catalytic cycles up to 2000 per equivalent palladium no successful technical stage has been reached so far. With diverse strategies during the last years it was tried to raise the usable performance of the palladium catalysts: liquid–liquid-extraction technology allows recycling of the homogeneous catalyst.[8] Another possibility is the immobilization of the homogeneous catalyst on an insoluble support in order to gain the essential advantage of heterogeneous catalysis, namely the recovery of the catalyst by easy separation from the reaction product.[9] It is remarkable that in most cases reported in the literature acetonitrile is the solvent or the co-solvent. From a technical point of view, this is a drawback, because acetonitrile on account of its toxicity requires a very complete feedback in a technical process. The nitrile effect has been found to be caused by the coordination ability of the solvent molecules: nitrile ligands usually coordinate as weak σ-donor ligands and can be simply substituted by other ligands. This has led to the development of novel catalysts where the stabilization of palladium intermediates is not taken over by a nitrile solvent molecule but by an equivalent function in the ligand sphere of the catalyst.[10] This modification is reached by the introduction of hemilabile phosphino nitrile ligands that coordinate on the one hand strongly over a nucleophile phosphino function to the active centre. On the other hand, a weakly coordinating nitrile function in the backbone facilitates the entry of substrate molecules (Fig. 1).

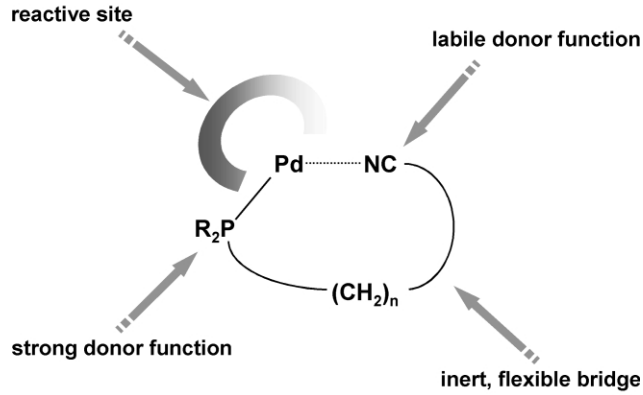


Fig. 1 Hemilabile coordination of phosphino nitrile ligand at the active centre.

Results and discussion

Optimization of the two-phase reaction

We have synthesized a variety of hemilabile P,N ligands, which are distinguished in the distance between both donor functions as well as in the groups bound to the phosphorus (Table 1). It has been shown that hemilability plays a central role: as a η^1-end-on coordinating function, the nitrile group presumably requires a long bridge between the donor functions to realize a chelating coordination.[11] Best results are usually achieved with a $(CH_2)_6$-spacer as in compound **2c**.

Table 1 P,N ligands used for the palladium catalyzed synthesis of **1**[10,11]

	n = 3	*n* = 4	*n* = 5	*n* = 6	*n* = 7	*n* = 8	*n* = 10
$^iPr_2P(CH_2)_nCN$	**2a**		**2b**	**2c**	**2d**	**2e**[a]	**2f**
$Cy_2P(CH_2)_nCN$	**3a**		**3b**	**3c**	**3d**		**3e**
$Ph_2P(CH_2)_nCN$	**4a**		**4b**	**4c**	**4d**		**4e**
$^iPr_2P(CH_2)_nCMe_2CN$		**5**[a]					
$Ph_2P(CH_2)_nCMe_2CN$		**6**[a]					

[a] Not reported previously.

It is demonstrated that with identical reaction conditions *in-situ* catalysts with the modified P,N ligands are affected far less in their activity by the surrounding solvent than was found for *in situ* catalysts with P^iPr_3 (Fig. 2). Particularly remarkable is

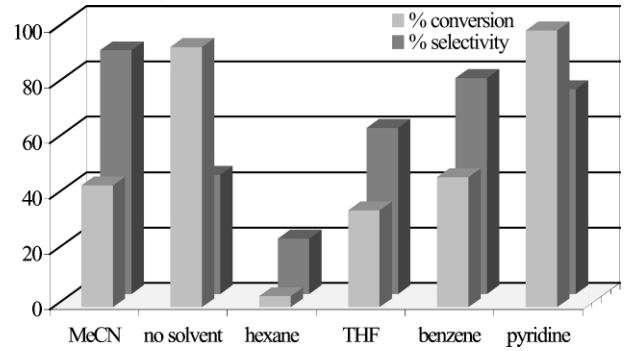


Fig. 2 Catalytic synthesis of **1** in different reaction media.

the fact that in the absence of additional solvent a high activity is also observed, with a total yield similar to the [Pd]/P^iPr_3 catalyst system. The conditions on the lab scale were optimized to a catalyst concentration of less than 0.1 mol% Pd and a temperature range from 60–85 °C (Table 2, refer also to the Experimental section). The ratio of CO_2 : 1,3-butadiene was found to be optimal in the range of 1.6 : 1. The maximum

Table 2 Selected solvent-free synthesis of **1** with catalyst from **2c** and (η^5-C_5H_5)Pd(η^3-C_3H_5) **7**

		Conversion of butadiene (%)		Selectivity for **1** (%)	
Entry	Conditions	lab-scale[a]	TESSA[b]	lab-scale[a]	TESSA[b]
1	60 °C, 20 h, 6.3 MPa, BTD/CO_2 = 1.6	> 78 (> 65)[c]		47 (20)[c]	
2	70 °C, 20 h, 7.0 MPa, BTD/CO_2 = 1.6	> 92	> 99	37	39
3	70 °C, 8 h, 6.3 MPa, BTD/CO_2 = 1.6		> 47		29
4	70 °C, 8 h, 14.3 MPa, BTD/CO_2 = 1.6		> 33		12
5	70 °C, 20 h, 4.6 MPa, BTD/CO_2 = 1	> 84		35	
6	85 °C, 20 h, 4.9 MPa, BTD/CO_2 = 1	> 75		24	

[a] Experiments are performed by addition of 0.17 mmol 4-^{t}Bu-1,2-dihydroxybenzene (butadiene stabilizer). Results are the same as in the absence of the stabilizer. [b] For details refer to Experimental section. [c] The values in brackets indicate the use of **4c** instead of **2c**.

selectivity for **1** for the reaction without additional solvent up to now is 47% (Table 2, entry 1).

Phase equilibrium measurements and single-phase reactions

It can be observed in window autoclaves that under the optimized conditions two phases are present and the liquid phase is yellow colored. Therefore, we suppose that the reaction preferably runs in the liquid phase. Starting with an overall composition of 1.6 : 1 (mol CO_2 : mol 1,3-butadiene) at a selected temperature of 60 °C, a pressure of 6 MPa is attained. According to Fig. 3a and 3b (area A) and neglecting the influence of the catalyst components on the phase equilibrium, the two coexisting phases consist of a liquid phase of 58 mol% CO_2 and a vapour phase of 16 mol% CO_2.[12] Furthermore, applying the lever principle it becomes obvious, that a large amount of liquid, and only a small gas phase coexist under these conditions.

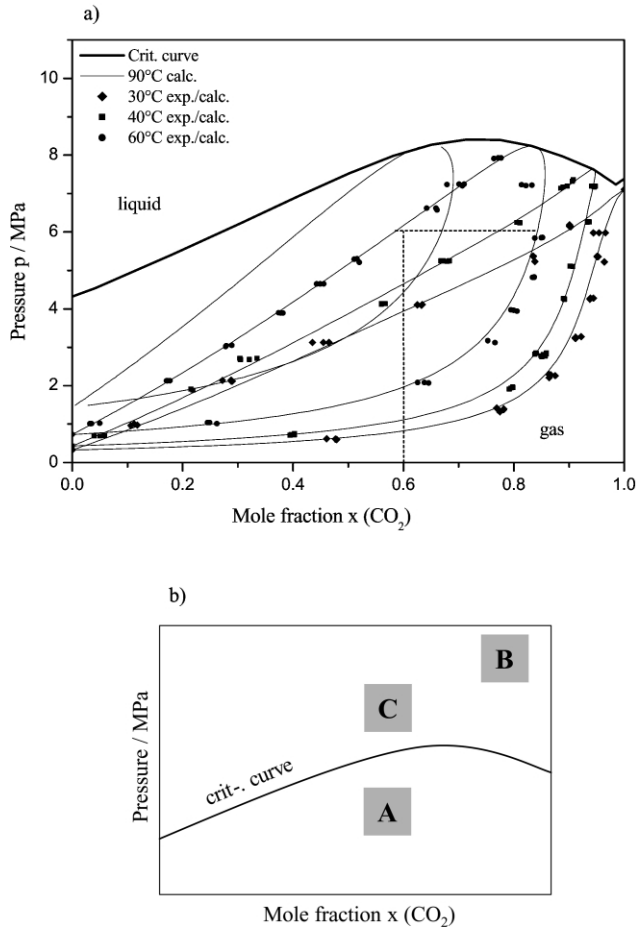


Fig. 3 Phase equilibria for {x(CO_2) + (1−x)1,3-butadiene}. (a) Measured and calculated data. (b) Schematic view of conditions for lactone synthesis applied in this work ($T_A = T_C$, $T_{A,C} < T_B$).

The isotherms have been correlated using a modified Peng–Robinson equation-of-state.[12,13] Based on the temperature dependence of the interaction parameters fitted to the experimental phase equilibrium data, an interpolation and also to a certain extent an extrapolation of data is possible (see *e.g.* the 90 °C isotherm in Fig. 3a). The critical curve is connecting the maxima of the isotherms. It starts for pure CO_2 with the critical pressure of 7.2 MPa and runs through a maximum of 8.5 MPa to meet the critical pressure of pure 1,3-butadiene. Above this curve the substrate mixture is single-phase, independent from the composition.

To explore the usefulness of a single-phase reaction in view to process control or integrated separation steps, experiments at higher pressure have been conducted. In a simple approach, CO_2 was added to increase pressure until the single-phase region was established (Fig. 3b; area B). This strategy turned out to be unsuccessful because the catalyst is not soluble with this phase composition and almost no conversion has taken place.

Two other strategies are promising to realize the single-phase reaction successfully. On the one hand, one can try to increase the solubility of the catalyst by a modification. Today it is a commonly accepted finding that fluorinated substituents in the ligand periphery of the catalyst increase its solubility in CO_2 rich phases. Because quantitative data are rare in the literature we have developed a method to quantify the solubility of catalyst components under single-phase conditions.[14] Syntheses and solubility measurements of catalysts with fluorine modified P,N-ligands are currently underway. This expenditure could be avoided by the second strategy to achieve a homogeneous single-phase reaction. This strategy consists of an increase of the pressure with the same composition as in the two-phase reaction optimized before. In Fig. 3b this corresponds to area C. More than in the CO_2 rich phase, the higher butadiene amount should result in an improved solubility of the catalyst from **7** and **2c** that is already highly soluble in pure butadiene at low temperatures. With an experimental set-up on a larger scale (TESSA, test plant for synthesis applications, refer to Experimental section) and with the reaction time being insufficient for a complete conversion, in the liquid phase half of the amount of butadiene is reacted and the selectivity to the lactone amounts to 29% (Table 2, entry 3b). Single-phase conditions are achieved under retention of the reaction volume in which appropriately higher masses of butadiene and CO_2 are supplied, but also in the relation 1.6 : 1. Then, the amount of raw product corresponds to a butadiene conversion of 33% with selectivity for **1** of 12% (Table 2, entry 4b). Compared to the reaction in the CO_2 rich reaction medium with very low catalyst activity as shown above, this experiment indicates an increased solubility of the catalyst with this phase composition. Possible reasons for the decreased product selectivity compared to the two-phase reaction, *e.g.* the influence of the density on the reaction course

and the formation of by-products, need to be checked in further investigations.

Phase equilibrium considerations

To obtain a complete understanding of phase equilibrium phenomena during the reaction all components involved have to be considered, namely the main product as well as intermediate and side products. The phase equilibrium of the binary mixture butadiene–CO_2 only applies to the starting point of the reaction. At least at the beginning of the reaction it can be assumed that the liquid phase reaction is predominant. During the reaction, the mixture is depleted in butadiene and CO_2. At the end of the reaction a liquid product phase, which is nearly free of 1,3-butadiene due to its high conversion, and a CO_2-rich vapour phase exist. It is expected that the gas phase volume increases during the reaction, which needs to be verified experimentally.

The main product **1** is found to be soluble in CO_2 in mol fractions of below 0.02 at any temperature investigated, as shown in Fig. 4. The two-phase regime at 6 MPa is quite large

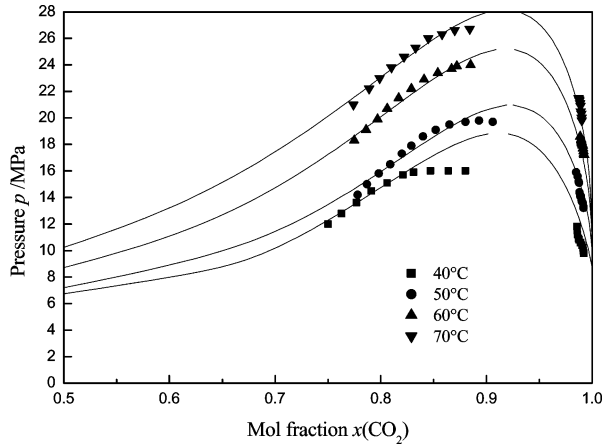


Fig. 4 Solubility of **1** in CO_2 at different temperatures.

in the binary system with the CO_2-rich phase poor in lactone, and a lactone-rich phase with a CO_2 content which does not change very much with temperature, as indicated by the predictive calculations in Fig. 4.[15] It is interesting to note that miscibility in the temperature range of interest is decreasing with increasing temperature. The correlation of the data has been conducted again by the Peng–Robinson equation-of-state.[16,17] Although both branches, the liquid and the vapour equilibrium, have been fitted by separate interaction parameters, the results are not completely satisfying: While the vapour phase is described reasonably, the liquid phase and the critical region are not in good agreement with the experimental findings. A better correlation is desired to allow a modelling of the phase equilibria of the complete reaction mixture on the basis of existing and the more easily accessible binary data. The other by-products are expected to be soluble in a similar extent as **1**, with the exception of the more soluble 4-vinylcyclohexene and octatriene isomers. The residual butadiene is expected to act as an entrainer which leads to an increase in solubility of the products in the vapour phase. Modelling the phase equilibria of the whole reaction mixture at the initial state, during the reaction and finally at the end of the reaction is part of our current work. In a first attempt, the ternary mixture of CO_2, butadiene, and the δ-lactone **1** has been calculated by property determination routines using the process simulation software ChemCAD. Here, the Predictive Soave–Redlich–Kwong routine has been applied.[16]

In Fig. 5, a ternary diagram is depicted at 6 MPa for 70 °C. Assuming a reaction would result in a complete conversion to **1**,

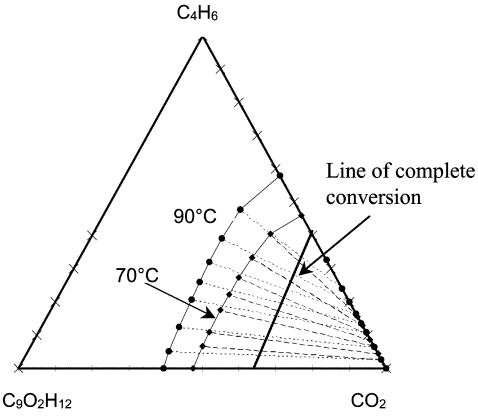


Fig. 5 Prediction of ternary phase behavior of butadiene, δ-lactone, and CO_2 at 6 MPa and 70 or 90 °C

the overall composition would follow the straight line, at both temperatures completely crossing the two-phase region. At higher pressures the two phase surface will withdraw towards the CO_2 rich region. At sufficiently high pressures, the reaction will start and end under single phase conditions. Adjustment of the reactions conditions is imaginable, starting the reaction under (favourable) single-phase conditions and ending up in a two-phase region, where the product is separated. At present, the assumption of 100% selectivity is not reasonable; in Fig. 6

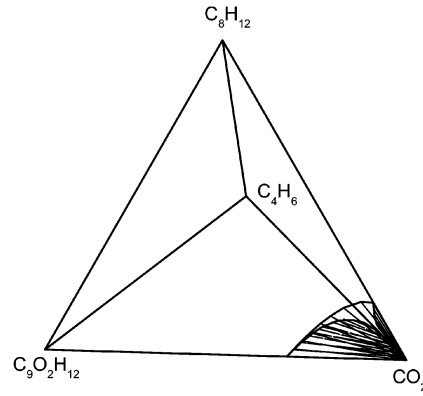


Fig. 6 Prediction of quaternary phase equilibrium at 10 MPa, 70 °C for CO_2, butadiene, **1** and 1,3,7-octatriene (assumed to form 10% as by-product).

a quaternary phase diagram is predicted by the same method, including 1,3,7-octatriene (C_8H_{12}) as a by-product at 70 °C and 10 MPa. Under these conditions CO_2 and 1,3-butadiene are already completely miscible and a two-phase region is only located towards the CO_2 rich region. This also has to be proved for other side-products and intermediates in order to allow phase control in the course of the reaction.

Experimental

All phosphine and catalyst preparations were carried out using Schlenk/vacuum line techniques in an efficient fume hood. All phosphines should generally be treated as potentially highly toxic and were handled accordingly; $^{i}Pr_2P(CH_2)_6CN$ used in this work is an air-sensitive, noxious, foul smelling liquid.

NMR spectra were acquired on a Bruker Avance 250 spectrometer. Chemical shifts are referenced to internal or external TMS (^1H, ^{13}C), respectively. Coupling constants are given in Hz. In experiments using non-deuterated solvents, a coaxial tube with D_2O was inserted as a lock. For GC-MS analysis, a Hewlett Packard gas chromatograph 5890 with 30 m HP5-MS capillary column and equipped with a quadrupole mass analyzer 5970 was used.

Starting materials

All reagents were obtained commercially and used as received unless otherwise stated. Solvents were dried and deoxygenated by standard methods.[17] Carbon dioxide (Messer Griesheim, purity 6.0) was used without further purification. Butadiene (Fluka) was condensed immediately before use in lab-scale experiments. Butadiene (Messer Griesheim, purity 3.5) was used without purification for experiments in the TESSA plant. (η^5-C_5H_5)Pd(η^3-C_3H_5), **7**, was prepared by a literature method [18] and freshly crystallized from pentane at −70 °C. The synthesis of $^{i}Pr_2P(CH_2)_6CN$ was described previously.[10]

Procedure for the catalytic experiments in lab-scale autoclaves

(η^5-C_5H_5)Pd(η^3-C_3H_5), **7** (107.9 mg, 0.508 mmol), is dissolved in butadiene below −10 °C in a 200 ml autoclave and the phosphine ligand (1.016 mmol) is added. Butadiene is condensed immediately before use. The autoclave is equipped with a magnetic stirrer, a thermocouple, and Swagelock connections to external CO_2 and a vacuum/argon line. The reactor is locked and the content is stirred. At ambient temperature the autoclave is pressurized with CO_2, then heated to the desired temperature. After the reaction period, the unreacted gaseous components were removed carefully by stirring below 30 °C under a slow argon stream. The selectivity of **1** in the raw product was determined by ^{1}H-NMR with comparison of the integral values referenced to the O–CH proton (4.8 ppm) in **1**. In cases when the selectivity was found to be less than 15%, the value was determined by quantitative GC analyses. Purification of **1** may be performed as follows: the raw product is concentrated in a vacuum of less than 10^{-3} kPa. Simple distillation following described procedures[19] yields **1** in purity higher than 90%. Further purification is performed by double fractionated distillation *via* a rotary column.

^{1}H-NMR ($CDCl_3$) of **1**: 1.80 dt(3H, CH–C*H*$_3$, ^5J = 1.6, ^3J = 7.2), 1.95–2.21 m(2H, C–C*H*$_2$), 2.32–2.71 m(2H, CH$_2$–C*H*$_2$), 4.79 m(1H), 5.25 ddd(1H, *cis*-*H*$_2$C = CH, ^4J = 0.9, $^3J_{cis}$ = 10.6, ^2J = 1.1), 5.32 ddd(1H, *trans*-*H*$_2$C = CH, ^4J = 0.9, $^3J_{trans}$ = 17.2, ^2J = 1.1), 5.90 ddd(1H, H$_2$C = C*H*, $^3J_{trans}$ = 17.2, $^3J_{cis}$ = 10.6, ^3J = 5.4), 7.13 tq(1H, CH$_3$–C*H*, ^4J = 2.5, ^3J = 7.2)

^{13}C-NMR ($CDCl_3$) of **1**: 13.8 (CH–*C*H$_3$), 21.7 (CH$_2$–*C*H$_2$), 27.4 (C–*C*H$_2$), 78.7 (CH$_2$–*C*H), 116.6 (CH–*C*H$_2$), 125.8 (CH = *C*), 135.6 (CH$_3$–*C*H),140.9 (CH$_2$ = *C*H), 166.0 (*C* = O)

Procedure for the catalytic experiments in the TESSA plant

Based on the extensive data obtained from lab-scale experiments[11] (also this work), a laboratory plant TESSA has been designed and built up. In a first construction stage it is aimed to (i) develop an appropriate process technology for two and single phase reactions, (ii) to verify the experimental data determined before and to study scale-up effects, (iii) to produce pilot samples up to several kilogram, (iv) to switch over from a batch mode to a continuous operation, and finally (v) to develop an integrated separation process. In the second construction stage educt and catalyst recycling as well as product separation will be integrated. In view of handling of flammable and toxic starting materials like butadiene and substances sensitive to oxidation and hydrolysis like many organometallic catalysts, the plant was constructed considering the regulations for explosion prevention and personal protection. Furthermore, inertization of the plant was realized to prevent decomposition of the catalyst and formation of undesired by-products. Repeated evacuating and flushing the device with gaseous CO_2 achieved this. The equipment has been designed for temperatures up to 100 °C and pressures up to 15 MPa. Currently, it is extended to 30 MPa. The liquefied gases, CO_2 and 1,3-butadiene, are delivered by membrane pumps; the desired amount is accurately adjusted by a metering control unit and measured by mass flow meters. Prior to pumping, the liquefied gases are super cooled to prevent gas formation in the pump heads. For this purpose micro structured heat exchangers[20] are utilized, performing an effective cooling at only 10 °C.

Preparing an experiment with two-phase conditions, the piping and reactor (1 dm^3 volume) are repeatedly evacuated and flushed with CO_2. Amounts of components charged into the reactor are: 1,3-butadiene: 2.54 mol (137.2 g); CO_2: 4.09 mol (180.2 g); [Pd]: 2.54 mmol (540 mg); phosphine: 5.08 mmol (1155 mg).

1,3-Butadiene (stabilized by 4-^{t}Bu-catechol) is fed to the reactor, passing two cartridges containing the two components forming the active catalyst subsequently in the reactor. Afterwards, CO_2 is metered to the desired amount and pneumatically operated stirrers agitate the mixture. The reaction temperature is adjusted and controlled over the reaction time of 16–20 hours until complete conversion of 1,3-butadiene has occurred. While the reaction proceeds, the pressure is measured as well by a pressure transducer. In the case of a two-phase reaction the pressure remains nearly constant, as can be expected for a mixture of liquefied gases in a two-phase system. However, at single-phase conditions a pronounced decrease of pressure is observed during the reaction. After reaction, the liquid product, consisting of the desired main product **1** and by-products, mainly 4-vinyl-cyclohexene, is removed from the autoclave by a dip tube *via* a needle valve using the residual CO_2 pressure. The product analysis was performed by GC and NMR spectroscopy (see above). The results obtained in lab-scale experiments were confirmed within an error range of ±10% (rel.) for conversion and selectivity.

Acknowledgement

The authors are thankful for financial support from the German Federal Ministry of Education and Research (*Competence Network Catalysis, "Regulierbare Systeme für die Mehrphasenkatalyse", AZ 03C0338E*) and the Max Planck Society for the Advancement of Science (*"Kohlendioxid als Solvens und Substrat neuer metallaktivierter Reaktionen", AZ 44162*).

References

1 (*a*) *Aqueous-Phase Organometallic Catalysis*, ed. B. Cornils and W. A. Herrmann, Wiley-VCH, Weinheim, 1998; (*b*) *Ionic Liquids in Synthesis*, ed. P. Wasserscheid and T. Welton, Wiley-VCH, Weinheim, 2002.
2 *Chemical Synthesis using Supercritical Fluids*, ed. P. G. Jessop and W. Leitner, Wiley-VCH, Weinheim, 1999, ch. 4.
3 P. G. Jessop and W. Leitner, in *Chemical Synthesis using Supercritical Fluids*, ed. P. G. Jessop and W. Leitner, Wiley-VCH, Weinheim, 1999, ch. 1.
4 (*a*) Y. Sasaki and Y. Inoue, *J. Chem. Soc., Chem. Commun.*, 1976, 605; (*b*) A. Musco, R. Santi and G. Chiusoli, *Ger. Offen.*, 1979, DE 28 38 610 A1.
5 A. Behr, R. He, K.-D. Juszak, C. Krüger and Y. H. Tsay, *Chem. Ber.*, 1986, **119**, 991.
6 (*a*) V. Haack, E. Dinjus and S. Pitter, *Angew. Makromol. Chem.*, 1998, **257**, 19; (*b*) A. Behr and V. Brehme, *Adv. Synth. Catal.*, 2002, **344**, 525.
7 (*a*) P. Braunstein, D. Matt and D. Nobel, *Chem. Rev.*, 1988, **88**, 747; (*b*) A. Behr, *Angew. Chem., Int. Ed. Engl.*, 1988, **27**, 661.
8 A. Behr, *Chem. Eng. Technol.*, 2000, **23**, 952.
9 (*a*) S. Pitter, N. Holzhey and E. Dinjus, DE 197 25 735, 1998 (*b*) S. Pitter and N. Holzhey, *J. Mol. Catal. A: Chem.*, 1999, **146**, 25.
10 S. Pitter, E. Dinjus, B. Jung and H. Görls, *Z. Naturforsch. B: Chem. Sci.*, 1996, **51**, 934.

11 S. Pitter and E. Dinjus, *J. Mol. Catal. A: Chem.*, 1997, **125**, 39.
12 K.-D. Wagner, J. Zappe, A. Reeps, N. Dahmen and E. Dinjus, *Fluid Phase Equilib.*, 1998, **153**, 135.
13 D.-Y. Peng and D. B. Robinson, *Ind. Eng. Chem. Fundam.*, 1976, **15**, 59.
14 K.-D. Wagner, N. Dahmen and E. Dinjus, *J. Chem. Eng. Data*, 2000, **45**, 672.
15 Q. Xu and N. Dahmen, *J. Supercrit. Fluids*, 2002, in press, available on-line (ASAP).
16 S. Horstmann, K. Fischer and J. Gmehling, *Fluid Phase Equilib.*, 2000, **167**, 173.
17 *Purification of Laboratory Chemicals*, ed. W. L. F. Armarego and D. D. Perrin, Butterworth Heinemann, Bath, 4th edn., 1996.
18 Y. Tatsuno, T. Yoshida and S. Otsuka, *Inorg. Synth.*, 1979, **19**, 220.
19 A. Behr and K.-D. Juszak, *J. Organomet. Chem.*, 1983, **255**, 574.
20 K. Schubert, J. Brandner, M. Fichtner, G. Linder, U. Schygulla and A. Wenka, *Thermophys. Eng.*, 2001, **5**, 17.

Highly selective and green aqueous–ionic liquid biphasic hydroxylation of benzene to phenol with hydrogen peroxide†

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Received 13th November 2002
First published as an Advance Article on the web 20th March 2003

With equal molar ratio of benzene and hydrogen peroxide and without any additional volatile organic solvent, a green aqueous–ionic liquid biphasic hydroxylation of benzene to phenol with hydrogen peroxide as oxidant and metal dodecanesulfonate salts such as ferric tri(dodecanesulfonate) as catalyst was conducted with excellent selectivity and enhanced conversion.

Introduction

Direct hydroxylation of benzene with hydrogen peroxide to form phenol has attracted much attention and been extensively investigated.[1–6] The oxidation of benzene and its derivatives by Fenton's reagent (Fe^{2+}–H_2O_2) has been known for a long time.[7] However, its selectivity is rather poor since phenol is more reactive toward oxidation than benzene itself, and classical Fenton chemistry requires large quantities of iron(II) salts, which are consumed stoichiometrically during the reaction.[8] Although much effort has been devoted to new processes that produce phenol directly with high yield and selectivity, nevertheless, relatively few catalytic processes have successfully been developed. Very recently, Bianchi *et al*[9] reported that water–acetonitrile (1 : 1) biphasic reaction medium, in which the resulting phenol was extracted into the organic phase and the catalyst was soluble in the aqueous phase, dramatically enhanced the selectivity of the benzene hydroxylation by reducing the contact between phenol and the catalyst.

Recently, considerable interest has manifested in the use of room temperature ionic liquids, which have negligible vapor pressure, excellent thermal stability and special physicochemical characteristics in comparison with conventional organic and inorganic solvents, as environmentally benign media for catalytic reaction processes or chemical extractions.[10,11] In particular, the ionic liquid based biphasic hydroformylation or hydrogenation reactions resulted in the separation and recovery advantages of catalyst or product. Apart from hydroformylation,[12] hydrogenation,[13] Friedel–Craft reactions,[14] *etc.*, ionic liquids as reaction media were also successfully used in the selective catalytic oxidation reaction.[15]

Herein, an attempt was made to establish an aqueous–ionic liquid biphasic catalytic reaction system for direct oxidation of benzene to phenol with hydrogen peroxide as oxidant and metal dodecanesulfonate salts as catalysts in order to compare or replace traditional aqueous–organic solvent biphasic catalytic reaction systems. In this aqueous–ionic liquid biphasic process, both the catalyst and benzene were dissolved in the ionic liquid, while the oxidant, *i.e.* H_2O_2 was mainly dissolved in the aqueous phase but much less dissolved in the ionic liquid since the water solubility, for example, in the 1-octyl-3-methylimidazolium hexafluorophosphates could be as low as 0.2 g/100 ml[16] and H_2O_2 could be well dissolved in the water. The phenol produced could be extracted into the aqueous phase, thus possible over-oxidation of the resulting phenol could be minimized. The aqueous–ionic liquid biphasic reaction system is schematically shown in Fig. 1. In comparison with the previously reported methods of benzene hydroxylation to phenol, the following advantages were achieved: (1) without any additional volatile organic solvent, (2) low molar ratios of benzene/hydrogen peroxide and catalyst/benzene, (3) highly selective for desired product, and (4) reusable catalyst system. These make such a process not only more environmentally acceptable but also more economically attractive.

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† This work was presented at the Green Solvents for Catalysis Meeting held in Bruchsal, Germany 13–16th October 2002.

Green Context

One of the major difficulties in oxidation chemistry is achieving high selectivity including avoiding over oxidation. In the direct hydroxylation of benzene to phenol, for example – a very important green chemistry target – the product is more reactive under typical hydrogen peroxide conditions, so that over oxidation is commonly observed. One method for overcoming such problems is *via* a biphasic system whereby the desired product is partitioned away from the catalyst or oxidant. Here we see this achieved through novel aqueous–ionic liquid biphasic systems whereby the catalyst and benzene substrate are in the ionic liquid while the oxidant and the desired phenol are concentrated in the water. ***JHC***

 DOI: 10.1039/b211239f

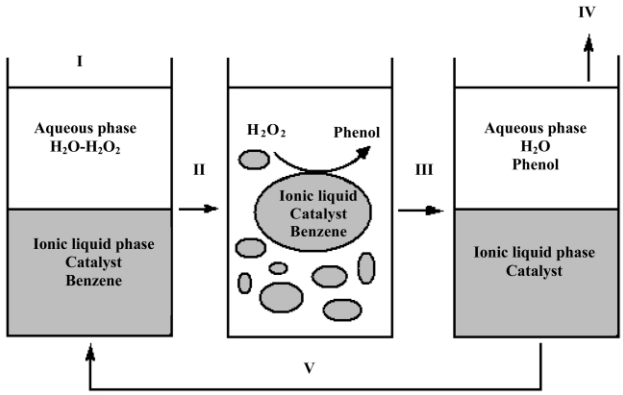

Fig. 1 A schematic representation of the aqueous–ionic liquid biphasic catalytic reaction system for benzene hydroxylation to phenol with H_2O_2. Step **I** charging; Step **II** reaction; Step **III** still; Step **IV** recovery of phenol *via* extraction; Step **V** the ionic liquid and catalyst are reused for another reaction cycle.

Experimental

1-*n*-Butyl-3-methylimidazolium hexafluorophosphate ($BMImPF_6$), 1-*n*-octyl-3-methylimidazolium hexafluorophosphate ($OMImPF_6$), 1-*n*-octyl-3-methylimidazolium tetrafluoroborate ($OMImBF_4$), 1-*n*-decyl-3-methylimidazolium hexafluorophosphate ($DMImPF_6$) and 1-*n*-decyl-3-methylimidazolium tetrafluoroborate ($DMImBF_4$), which were insoluble with water, were respectively synthesized according to the procedures reported in previous literature.[11,17]

Dodecanesulfonate salts with various metal cations, *i.e.* ferric tri(dodecanesulfonate) $Fe(DS)_3$, ferrous bis(dodecanesulfonate) $Fe(DS)_2$, cobalt bis(dodecanesulfonate) $Co(DS)_2$, copper bis(dodecanesulfonate) $Cu(DS)_2$, and nickel bis(dodecanesulfonate) $Ni(DS)_2$, were respectively prepared according to the procedures reported in previous literature.[18]

Aqueous–ionic liquid biphasic hydroxylation of benzene was carried out in a 100 ml round-bottomed flask equipped with a magnetic stirrer and thermometer. Catalyst (0.05 mmol) was dissolved in the ionic liquid (1.0 ml), then benzene (1.0 ml, 11.25 mmol) and H_2O (25.0 ml) containing 50 mM H_2SO_4 was further added. The mixture was vigorously stirred for 0.5 h at 50 °C, then an aqueous solution of hydrogen peroxide (30%, 1.2 ml, 11.25 mmol) was added. The resulting biphasic system was stirred for 6.0 h at 50 °C. At the end of the reaction, the resulting products and unreacted substrate were extracted from the aqueous and ionic liquid phases with ether (5 ml × 3). The extracted liquid mixture was analyzed on a Hewlett-Packard 6890/5793 GC-MS equipped with a HP 5MS column (30 m long, 0.25 mm i.d., 0.25 μm film thickness). The concentration of organic reactant and products was directly given by the GC/MS chemstation system according to the area of each chromatograph peak. The amount of residual hydrogen peroxide in the aqueous phase was determined by titration with potassium permanganate.

Results and discussion

Firstly, the catalytic activities of the dodecanesulfonate salts with Fe^{3+}, Fe^{2+}, Cu^{2+}, Co^{2+} and Ni^{2+} cations were tested in an aqueous–$OMImPF_6$ biphasic system, and the results are summarized in Table 1. For all the catalysts used in this work, the only product detected by GC-MS after reaction was phenol, so the selectivities for phenol, based on benzene, were almost 100%. Beside moderately high conversion of benzene, high selectivity of H_2O_2 for benzene conversion was achieved, indicating that such an aqueous–ionic liquid biphasic reaction system for benzene hydroxylation was successfully established.

Table 1 Results of aqueous–ionic liquid biphasic catalytic oxidation of benzene to phenol

Entry	Ionic liquid (ml)	Catalyst (mmol)	Conversion of benzene (%)	Conversion of H_2O_2 (%)	Selectivity of H_2O_2 (%)[a]
1	$OMImPF_6$ (1.0)	$Fe(DS)_3$ (0.05)	54	60	90
2	$OMImPF_6$ (1.0)	$Fe(DS)_2$ (0.05)	49	56	88
3	$OMImPF_6$ (1.0)	$Co(DS)_2$ (0.05)	35	41	85
4	$OMImPF_6$ (1.0)	$Cu(DS)_2$ (0.05)	38	43	88
5	$OMImPF_6$ (1.0)	$Ni(DS)_2$ (0.05)	38	44	86
6	$OMImPF_6$ (2.0)	$Fe(DS)_3$ (0.05)	51	56	91
7	$OMImPF_6$ (1.0)	$Fe(DS)_3$ (0.04)	52	58	90
8	$OMImPF_6$ (1.0)	$Fe(DS)_3$ (0.02)	43	48	90
9	$BMImPF_6$ (1.0)	$Fe(DS)_3$ (0.05)	39	46	85
10	$DMImPF_6$ (1.0)	$Fe(DS)_3$ (0.05)	51	57	89
11	$DMImBF_4$ (1.0)	$Fe(DS)_3$ (0.05)	40	46	87
12	$OMImBF_4$ (1.0)	$Fe(DS)_3$ (0.05)	44	49	90
13	No ionic liquid	$Fe(DS)_3$ (0.05)	16[b]	21	76
14[c]	$OMImPF_6$ (1.0)	$Fe(DS)_3$ (0.05)	45	52	87

[a] (moles of converted benzene/moles of converted H_2O_2) × 100. [b] Selectivity of phenol based on benzene was 71%. [c] Reused at the 4th times.

Higher activity was observed with the catalyst $Fe(DS)_3$, and the results of entries 1 and 2 (Table 1) suggested that the chemical state of the iron cation had some impact on the catalytic performance.

The influence of the amounts of ionic liquid and catalyst used on the reaction was then tested, entries 6–8. When the volume of the ionic liquid used was increased from 1.0 to 2.0 ml, the conversions of benzene and H_2O_2 decreased from 54 and 60% to 51 and 56%, respectively, and the selectivity of H_2O_2 was almost unchanged. This may be attributed to different concentrations of benzene or catalysts between the water and ionic liquid, which is dependent upon the volume ratio of water and ionic liquid. If the amount of ionic liquid used was excessive, the benzene or catalyst concentration at the interface of the water and ionic liquid may be lower, thus resulting in a decreased reaction rate between benzene and H_2O_2 over the catalyst. As expected, the reaction rate was decreased with decreasing the amount of catalyst added.

It is well-known that the physicochemical properties of ionic liquids can be varied over a wide range through the selection of a suitable cation and anion.[10] The performance of different ionic liquids in the hydroxylation of benzene was also investigated (entries 1, 9–12). Although a detailed mechanism is not clear at this stage, the experimental results showed that both the length of alkyl chains on the 1-alkyl-3-methylimidazolium cations and the anions had some effect on the conversion and selectivity, and the best results were obtained by using $OMImPF_6$ as an ionic liquid phase. $OMImPF_6$, $OMImBF_4$, $DMImPF_6$ and $DMImBF_4$ ionic liquids showed good solubility for the metal dodecanesulfonate salts and formed one phase with benzene, however, these metal dodecanesulfonate salts were only slightly soluble in $BMImPF_6$ and existed as suspended particles in $BMImPF_6$ and $BMImPF_6$ formed two phases with benzene, thus resulting in a poor catalytic performance.

If ionic liquid was not used, lower conversion and selectivity were obtained, entry 13, and some by-products such as hydroquinone and biphenyl were produced. This suggested that the aqueous–ionic liquid biphasic reaction system could not only enhance the selectivity for phenol, but also enhance the benzene conversion.

The possibility of recycling of the aqueous–ionic liquid catalyst system was also examined. After the oxidation products and unreacted substrate were extracted from the aqueous and ionic liquid phase with ether at the end of each reaction, the used aqueous–ionic liquid catalyst system was recharged with benzene and a certain amount of H_2O_2 according to the consumption of H_2O_2 during the previous reaction and the reaction was conducted once again. 45% of benzene conversion

Table 2 Results of aqueous–ionic liquid biphasic catalytic oxidation of toluene

Substrate (ml)	Ionic liquid (ml)	Catalyst (mmol)	Con. of toluene (%)	Product distribution
Toluene (1.0)	$OMImPF_6$ (1.0)	$Fe(DS)_3$ (0.05)	1	benzaldehyde 100%
Toluene (1.0) + benzene (0.02)	$OMImPF_6$ (1.0)	$Fe(DS)_3$ (0.05)	3	2-hydroxybenzaldehyde 15.7% *o*-hydroxytoluene 53.5%, *p*-hydroxytoluene 30.8%

was maintained after the aqueous–ionic liquid catalyst system was repeatedly used for 4 times. The partial decrease in catalytic activity may mainly be caused by slight leaching of the catalyst to the ether phase during each extraction of the product.

When the substrate was replaced with toluene, Table 2, only 1% toluene conversion was obtained and the resulting product was benzaldehyde with almost 100% selectivity, indicating that toluene as a substrate is much less active than benzene in this aqueous–ionic liquid biphasic reaction system and the active oxygen species have a radical character. Surprisingly, when the substrate was toluene, together with the presence of a small amount of benzene, the toluene conversion was enhanced greatly, and 2-hydroxybenzaldehyde (15.7%), *o*-hydroxytoluene (53.5%) and *p*-hydroxytoluene (30.8%) were produced, suggesting that benzene could promote the oxidation of toluene.

Conclusion

A highly selective and green aqueous–ionic liquid is a promising biphasic catalytic reaction system for direct oxidation of benzene to phenol with hydrogen peroxide as oxidant and a ferric dodecanesulfonate salt as catalysts, and was developed with excellent selectivity and enhanced conversion. In such an aqueous–ionic liquid biphasic catalytic reaction process, the use of volatile organic solvents was avoided. The molar ratio of benzene/hydrogen peroxide and catalyst/benzene could be as low as 1 and 0.002, respectively. The aqueous phase containing the desired product could be separated from the ionic liquid containing the catalyst by simple decantation. Recycling and further optimization of the aqueous–ionic liquid biphasic reaction system were possible.

Acknowledgement

This work was financially supported by National Natural Science Foundation of China (No.20225309).

References

1 S. Niwa, M. Eswaramoorthy, J. Nair, A. Raj, N. Itoh, H. Shoji, T. Namba and F. Mizukami, *Science*, 2002, **295**, 105.
2 M. G. Clerici and P. Ingallina, *Catal. Today*, 1998, **41**, 351.
3 Y. Moro-oka and M. Akita, *Catal. Today*, 1998, **41**, 327.
4 T. Miyake, M. Hamada, Y. Sasaki and M. Oguri, *Appl. Catal., A: Gen.*, 1995, **131**, 33.
5 I. Yamanaka, K. Nakagaki, T. Akimoto and K. Otsuka, *J. Chem. Soc., Perkin Trans. 1*, 1996, **2**, 2511.
6 A. Kunai, S. Hata, S. Ito and K. Sasaki, *J. Am. Chem. Soc.*, 1986, **108**, 6012.
7 C. Walling, *J. Am. Chem. Soc.*, 1975, **97**, 363.
8 S. Ito, A. Mitarai, K. Hikino, M. Hirama and K. Sasaki, *J. Org. Chem.*, 1992, **57**, 6937.
9 D. Bianchi, R. Bortolo, R. Tassinari, M. Ricci and R. Vignola, *Angew. Chem., Int. Ed.*, 2000, **39**, 4321.
10 P. Wasserscheid and W. Keim, *Angew. Chem., Int. Ed.*, 2000, **39**, 3773; T. Welton, *Chem. Rev.*, 1999, **99**, 2071–2083; J. G. Huddleston, H. D. Willauer, R. P. Swatloski, A. E. Visser and R. D. Rogers, *Chem. Commun.*, 1998, 1765.
11 A. G. Fadeev and M. M. Meagher, *Chem. Commun.*, 2001, 295.
12 N. Karodia, S. Guise, C. Newlands and J.-A. Andersen, *Chem. Commun.*, 1998, 2341; M. F. Sellin, P. B. Webb and D. J. Cole-Hamilton, *Chem. Commun.*, 2001, 781.
13 Y. Chauvin, L. Mussmann and H. Olivier, *Angew. Chem., Int. Ed.*, 1995, **34**, 2698; A. L. Monteiro, F. K. Zinn, R. F. de Souza and J. Dupont, *Tetrahedron: Asymmetry*, 1997, **8**, 177; R. A. Brown, P. Pollet, E. McKoon, C. A. Eckert, C. L. Liotta and P. G. Jessop, *J. Am. Chem. Soc.*, 2001, **123**, 1254.
14 C. E. Song, W. H. Shim, E. J. Roh and J. H. Choi, *Chem. Commun.*, 2000, 1695.
15 C. E. Song and E. J. Roh, *Chem. Commun.*, 2000, 837; G. S. Owens and M. M. Abu-Omar, *Chem. Commun.*, 2000, 1165; J. Howarth, *Tetrahedron Lett.*, 2000, **41**, 6627.
16 S. Chun, S. Dzyuba and R. A. Bartsch, *Anal. Chem.*, 2001, **73**, 3737.
17 P. A. Z. Suarez, J. E. L. Dullius, S. Einloft, R. F. de Souza and J. Dupont, *Polyhedron*, 1996, **15**, 1217; J. D. Holbrey and K. R. Seddon, *J. Chem. Soc., Dalton Trans.*, 1999, 2133.
18 S. Kobayashi and T. Wakabayashi, *Tetrahedron Lett.*, 1998, **39**, 5389; K. Manabe, Y. Mori and S. Kobayashi, *Tetrahedron*, 1999, **55**, 11203.

Novel hydroamination reactions in a liquid–liquid two-phase catalytic system†

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Received 9th December 2002
First published as an Advance Article on the web 27th March 2003

The direct addition of amines to alkynes and dienes (hydroamination) was efficiently catalyzed in a liquid–liquid two phase system. The latter comprised a polar catalyst phase of $Zn(CF_3SO_3)_2$ in the ionic liquid 1-ethyl-3-methylimidazolium trifluoromethanesulfonate and a substrate mixture in heptane. The possibility to catalyze a variety of intermolecular hydroamination reactions was demonstrated.

Jenõ Bódis (right) is an Associate Professor at Babes-Bolyai University in Cluj, Romania. Presently, he is appointed as a visiting scientist at the Technical University of München. His research topics include heterogeneous and homogeneous catalytic carbonylation of alcohols, hydratocarbonylation and hydroformylation of olefins, reductive amination, hydroamination, polymerisation, and FT-IR spectroscopic investigation of supported catalysts.

The research of Thomas E. Müller (left) is focused on homogeneous and heterogeneous catalysis. Detailed understanding of the elemental reaction steps leads to the development of new synthetic routes and optimised processes to nitrogen containing molecules. Further, new porous materials are developed for applications in catalysis and as low-k-materials.

Johannes A. Lercher (middle), born 1954 in Vienna, Austria studied Chemistry at the TU Wien and obtained his doctorate (Dr. techn.) in 1981. After a visiting lectureship at Yale University, he joined TU Wien as lecturer and Ass. Professor. In 1993 he accepted a professorship in the Department of Chemical Technology at the University Twente, the Netherlands. In 1998 he became Prof. of Chemical Technology at the TU München, Germany. His research is focussed on fundamental and applied aspects of molecular sieve based sorption and catalysis, in situ characterization of catalytic processes and developing new routes to C–N and C–C coupling reactions.

Introduction

The direct reaction of molecules bearing C=C or C≡C bonds with ammonia or primary/secondary amines (hydroamination) is an attractive, atom-economical route for the synthesis of nitrogen containing organic compounds.[1] The resulting amines or imines are of great importance for the chemical industry, especially for pharmaceutical companies. While the new amines are potential drug candidates, industry has a serious deficit concerning their amine libraries.[2] Intensive explorative research has been made worldwide in the last few years in order to develop efficient hydroamination processes.[3] Unfortunately, a real breakthrough did not occur in this area and only one process, the synthesis of *t*-butylamine from ammonia and isobutene in the presence of a zeolite catalyst has been commercialized.[4] Other catalysts (homogeneous or heterogeneous) developed until now do not have sufficient activity for commercial applications.[5]

Since the rate of the hydroamination reactions is directly dependent on the amount of catalyst employed, one of the most efficient strategies to achieve higher reaction rates is the use of a high amount of the catalyst, coupled with an efficient separation. This can be realized in solid–gas, solid–liquid or liquid–liquid heterogeneous systems. The possibility of catalyzing hydroamination reactions with Zn^{2+} ion exchanged zeolites has been demonstrated for the addition of methylamine to propyne (solid–gas system)[6] and for the cyclization of 6-amino-hex-1-yne (solid–liquid system).[7,8] Palladium(II)-species immobilized on silica were also successfully applied as catalysts

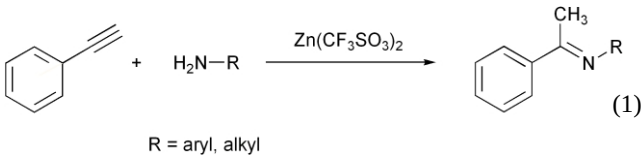
Green Context

The direct addition of ammonia and amines to unsaturated organic compounds is an atom-economical and simple route to useful organonitrogen compounds. One zeolite catalysed process is already commercialised but limitations in the catalysis have prevented others. Here a novel catalytic two-phase system is outlined for the addition of amines to phenylacetylene or cyclohexadiene. By using a polar catalyst and a polar ionic liquid, it is possible to retain the catalyst at high concentration in a separate phase from the organic substrates and products. Thus an atom-economical route is realised with eco-friendly solvents and an efficient, highly recoverable catalyst. ***JHC***

† This work was presented at the Green Solvents for Catalysis Meeting held in Bruchsal, Germany, 13–16th October 2002.

for the cyclization of aminoalkynes, with silica–DMPM complexes being the most active catalysts.[9,10] The first hydroamination reaction in a liquid–liquid two-phase system has been realized for the cyclization of *o*-ethynylanilines to indoles with palladium(II)-salts in CH_2Cl_2 and aqueous HCl.[11]

The challenge of the present study was to develop a new liquid–liquid two-phase system using green solvents, which would allow to perform hydroamination reactions in a more general manner. The selection of the solvent pair faces several boundary conditions: (i) most transition metal catalysts for hydroamination reactions are cationic (*e.g.*, Rh^+, Pd^{2+}, Cu^+, Zn^{2+}),[12–14] and therefore, to dissolve the corresponding salts, a polar solvent is required, (ii) to achieve high reaction rates, the metal ion should be only weakly coordinated by the solvent, and (iii) the catalyst bearing liquid phase has to be immiscible with an appropriate apolar organic solvent in which the reactants and product should have high solubility. For the intramolecular hydroamination of 6-aminohex-1-yne, an ionic liquid (IL), 1-ethyl-3-methylimidazolium trifluoromethanesulfonate, was chosen as polar phase (solvent for the catalyst precursor, $Zn(CF_3SO_3)_2$) and *n*-heptane as apolar phase (solvent for the starting materials and products).[5] Based on the promising results (good conversions and yields, fast reaction, no leaching of the catalyst, possibility of continuous operation), the liquid–liquid two-phase catalytic procedure was extended to similar intermolecular hydroamination reactions.[15] The present contribution is focused on liquid–liquid (ionic liquid–heptane) two-phase catalytic intermolecular hydroamination reactions of two different types of substrates: (i) an alkyne-type substrate (hydroamination of phenylacetylene, (see eqn. 1), and (ii) an alkene-type substrate (hydroamination of 1,3-cyclohexadiene, (see eqn. 2).



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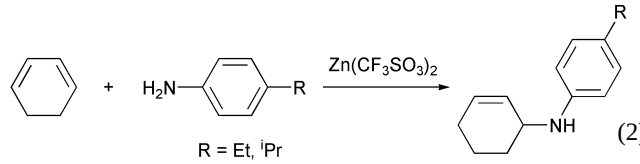

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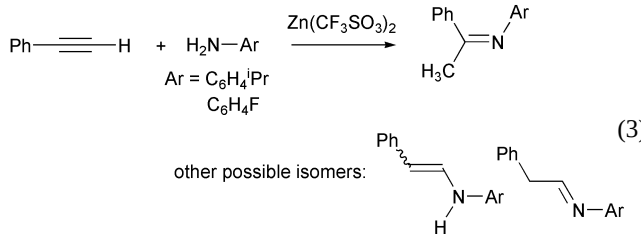
Results and discussion

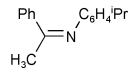
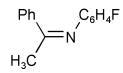
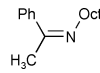
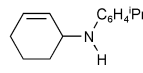
To test the scope and suitability of two-phase catalysis, the hydroamination reactions given in Table 1 were explored. The reactions were performed in the batch mode stirring the reaction mixture sufficiently fast to obtain a fine emulsion of the IL in heptane. In this case, a large surface area was achieved, enabling a relatively fast mass transfer across the phase boundary. The reaction of phenylacetylene with 4-isopropylphenylamine provided (4-isopropyl-phenyl)-(1-phenyl-ethylidene)-amine (eqn. 3). Latter is the result of tautomerization of the initially formed



(3)

enamine (4-isopropyl-phenyl)-(1-phenyl-vinyl)-amine to the corresponding Schiff base. The analogous reaction between phenylacetylene and 4-fluoro-phenylamine gave (4-fluoro-phenyl)-(1-phenyl-ethylidene)-amine as the only product. The product was isolated in close to quantitative yield after two and one days, respectively. The different time required is reflected in the initial rates of product formation (fitted as pseudo first order reaction) which were 29.8 and 46.8 mol $(mol_{cat.}h)^{-1}$, respectively. The difference in reaction time indicates that electron rich anilines, such as 4-isopropyl-phenylamine react

Table 1 Hydroamination reactions investigated in this study

Entry	Alkyne or alkene	Amine	Product	Rate[a] [mol $(mol_{cat.}·h)^{-1}$]	Time (h)	Yield[b] (%)
1	Ph—H	$H_2N—C_6H_4{}^iPr$		29.8	48	98
2	Ph—H	$H_2N—C_6H_4F$		46.8	24	98
3	Ph—H	H2N—Oct		24.6	2	50
4		$H_2N—C_6H_4{}^iPr$		2.4	40	75

[a] Initial rate of product formation. [b] Isolated yield.

Table 2 Summary of the catalytic data for the reaction between phenylacetylene and 4-isopropyl-phenylamine

Entry	Ratio[a]	Catalyst	Rate[b] [mol·$(mol_{cat.}·h)^{-1}$]	Time (h)	Yield[c] (%)
1	1:2	$Zn(CF_3SO_3)_2$	216.0	3	98
2	1:1	$Zn(CF_3SO_3)_2$	29.8	48	98
3	2:1	$Zn(CF_3SO_3)_2$	378.0	0.8	43[d]
4	1:1	CF_3SO_3H	9.8	24	72
5	1:1	$Zn(CF_3SO_3)_2/CF_3SO_3H$	10.4	24	98

[a] Ratio phenylacetylene to 4-isopropyl-phenylamine. [b] Initial rate of product formation. [c] Isolated yield. [d] Conversion in the steady state.

slower with phenylacetylene than electron poor anilines, such as 4-fluoro-phenylamine.

Aliphatic amines, such as *n*-octylamine, were also used. The reaction with phenylacetylene proceeded smoothly at low to medium conversions (< 50%) giving octyl-(1-phenyl-ethylidene)-amine. However, at longer reaction times an increasing amount of by-products, mainly oligomerization products of phenylacetylene, was formed. In comparison to aromatic amines, the rate of product formation was slower for octylamine (24.6 mol $(mol_{cat.}h)^{-1}$).

Furthermore, the potential use of alkenes, in particular dienes, was explored. The reaction between 1,3-cyclohexadiene and 4-isopropyl-phenylamine provided cyclohex-2-enyl-(4-isopropyl-phenyl)-amine as the major product. After 40 h this product was formed in 75% yield. The dimer of 1,3-cyclohexadiene was observed as the major secondary product. 4-Ethyl-phenylamine provided cyclohex-2-enyl-(4-ethyl-phenyl)-amine in 75% yield, but phenylamine and 4-fluoro-phenylamine did not react with 1,3-cyclohexadiene.

For all four reactions, the concentration of the starting materials in the apolar phase decreased rapidly within the first minutes of the reaction. At longer reaction times, the reactants were consumed at a lower rate. The formation of the product was very close to first order kinetics. As a consequence, the mass balance based on the concentrations of each reactant in the heptane phase was open. Thus, we speculate that some of the starting material had dissolved into the IL. To understand this observation, the reaction of phenylacetylene with 4-isopropyl-phenylamine to (4-isopropyl-phenyl)-(1-phenyl-vinyl)-amine was explored in further detail. In this reaction, the mass balance showed a minimum at *ca.* 88% after 30 min (Fig. 1). This indicates that 12% of the initially employed phenylacetylene and 4-isopropyl-phenylamine had dissolved into the IL.

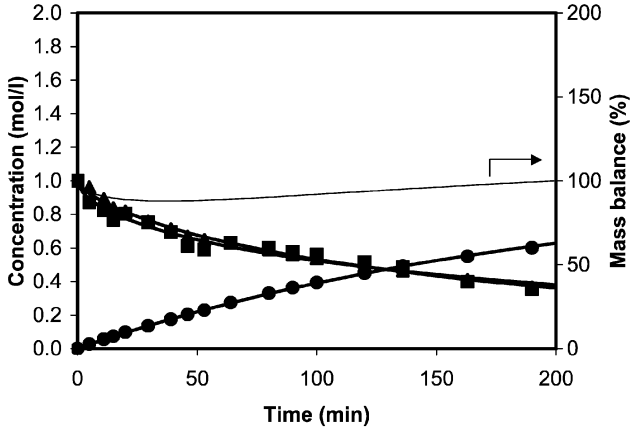


Fig. 1 Time-concentration diagram for the reaction between phenyl-acetylene and 4-isopropyl-phenylamine (stoichiometic ratio) catalysed by $Zn(CF_3SO_3)_2$ (▲ phenylacetylene, ■ 4-isopropyl-phenylamine, ● (4-isopropyl-phenyl)-(1-phenyl-ethylidene)-amine, — mass balance).

Therefore, we estimated the partitioning of each component *i* between the heptane phase and a solution of $Zn(CF_3SO_3)_2$ in the ionic liquid 1-ethyl-3-ethylimidazolium trifluoromethanesulfonate (eqn. 4).[16] Both starting materials, phenylacetylene and

$$K_{eq}^{i} = \frac{c^{i}(Heptane)}{c^{i}(IL)} \quad (4)$$

4-isopropyl-phenylamine, were considerably more soluble in the IL than in heptane. The solubility in the IL increased about 1.5 times relative to the heptane phase when the temperature was increased from 25 °C to reaction temperature (98 °C). Thus, the partitioning coefficient decreased from 0.19 to 0.11 and from 0.27 to 0.18 for phenylacetylene and 4-isopropyl-phenylamine, respectively. In contrast, the product was much less soluble in the IL and was mainly present in the heptane phase. At equilibrium, 18% of phenylacetylene and 12% of 4-isopropyl-phenylamine and < 1% of the product will, thus, be dissolved in the IL, when each component is studied under similar conditions as during the reaction. This correlates well with the mass balance observed in the catalytic experiment. In consequence, the considerable solubility in the IL leads to a high concentration of the starting material in the polar catalyst phase. On the other hand, the low solubility in the IL favors desorption of the product from the catalytically active Zn^{2+} centers and its diffusion into the heptane phase.

To investigate, if the formation of a 1:2 or 2:1 product between phenylacetylene and 4-isopropyl-phenylamine is possible, the reaction was repeated with the corresponding excess of phenylacetylene and 4-isopropyl-phenylamine.

When phenylacetylene and 4-isopropyl-phenylamine were employed in a 1:2 ratio, the reaction was approximately 7 times faster compared to the stoichiometric ratio of the reactants. After 3 h the product was isolated in 98% yield. From the time–concentration diagram (Fig. 2) it is apparent that the concentration of 4-isopropyl-aniline initially decreased very rapidly. This indicates that under the conditions of the catalytic reaction, 4-isopropyl-phenylamine dissolved rapidly and in a high concentration in the IL. At the end of the reaction, 25% of the isopropyl-aniline remained dissolved in the IL. The higher concentration of isopropyl-aniline in the IL compared to the single component is probably related to small amounts of phenylacetylene or product, which lead to a change of the solubility of isopropyl-aniline in the IL. The concentration of phenyl-acetylene initially decreased somewhat faster than expected for first order kinetics. The decrease was roughly correlated with the formation of (4-isopropyl-phenyl)-(1-phenyl-ethylidene)-amine.

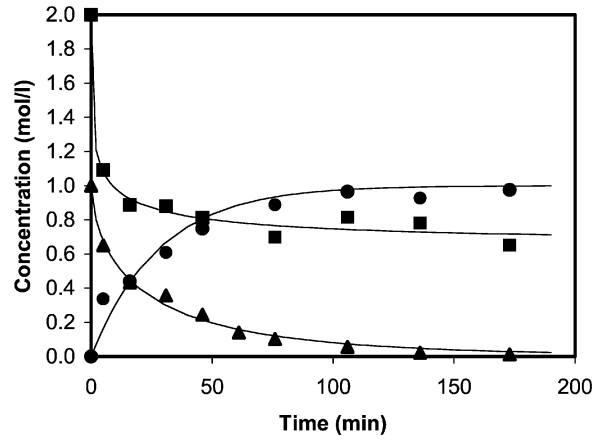


Fig. 2 Time–concentration diagram for the reaction between phenyl-acetylene and 4-isopropyl-phenylamine (ratio 1:2) catalysed by $Zn(CF_3SO_3)_2$ (▲ phenylacetylene, ■ 4-isopropyl-phenylamine, ● (4-isopropyl-phenyl)-(1-phenyl-ethylidene)-amine).

The reaction was very different, when the ratio of phenyl-acetylene to 4-isopropyl-phenylamine was 2:1 (Fig. 3). In this case, the product was initially formed very rapidly (12 times faster than in the experiment employing a stoichiometric ratio of the starting material). However, the reaction stopped at 43% yield. At longer reaction times, the product (4-isopropyl-phenyl)-(1-phenyl-vinyl)-amine reacted to two different isomers (having the same molecular weight in the GC-MS spectra). So far, the isomers could not be isolated and their precise nature remains subject to speculation. Most likely, the isomers are (4-isopropyl-phenyl)-(2-phenyl-vinyl)-amine and (4-isopropyl-phenyl)-(1-phenyl-ethylidene)-amine (see eqn. 3). Closer investigation of the time–concentration diagram shows that the formation of (4-isopropyl-phenyl)-(1-phenyl-vinyl)-amine stopped after 20 min, when no 4-isopropyl-phenylamine was

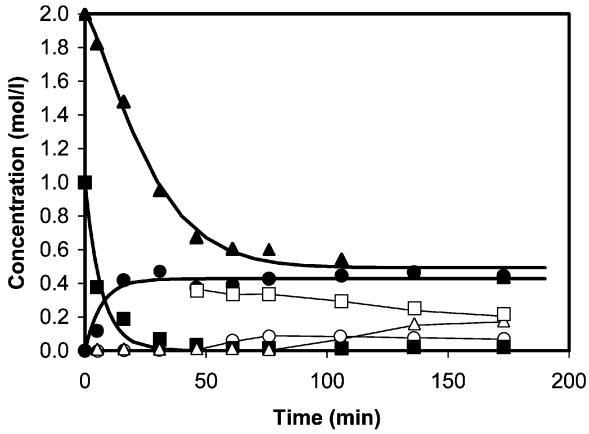


Fig. 3 Time–concentration diagram for the reaction between phenylacetylene and 4-isopropyl-phenylamine (ratio 2:1) catalysed by $Zn(CF_3SO_3)_2$ (▲ phenylacetylene, ■ 4-isopropyl-phenylamine, ● sum of the products, □ (4-isopropyl-phenyl)-(1-phenyl-ethylidene)-amine), ○ and △ isomers of (4-isopropyl-phenyl)-(1-phenyl-ethylidene)-amine).

left in the heptane phase. The complete consumption of 4-isopropyl-phenylamine correlates with the start of the isomerization of (4-isopropyl-phenyl)-(1-phenyl-vinyl)-amine to the other isomers. The concentration of phenylacetylene in the heptane decreased for a longer time (*ca.* 70 min), which was accompanied by formation of oligomers.

In summary, the expected products of a 1:2 or 2:1 addition of phenylacetylene to 4-isopropyl-phenylamine were not observed, when one of the reactants was employed in excess. However, the reaction could be accelerated by employing an excess of 4-isopropyl-phenylamine.

Based on the observation that homogeneous hydroamination reactions could be accelerated by addition of a Brønsted acid, trifluoromethanesulfonic acid was added to the reaction mixture. The same product, (4-isopropyl-phenyl)-(1-phenyl-ethylidene)-amine, was isolated in 98% yield after 2 days. However, the rate of reaction had decreased considerably (10.4 mol $(mol_{cat.}h)^{-1}$). Similarly, the rate of reaction was low, when trifluoromethanesulfonic acid was employed as the only catalyst (9.8 mol $(mol_{cat.}h)^{-1}$). This indicates that the two-phase reaction proceeds best when the catalyst $Zn(CF_3SO_3)_2$ is employed under neutral conditions. Thus, the reaction seems to be Lewis acid catalyzed. A mechanism based on a nucleophilic attack of the amine on a metal coordinated alkyne appears to be most likely.[13,17]

Conclusion

It has been demonstrated that the addition of aliphatic and aromatic amines to phenylacetylene can be efficiently catalyzed in a liquid–liquid two-phase system. Similarly, the reaction between aromatic amines and 1,3-cyclohexadiene can be catalyzed. The major advantage is that after the reaction the catalyst remains quantitatively in the IL, which can be easily separated from the organic phase. The product is obtained in high quality after removal of solvent. Thus, the reaction system is very close to the ideal synthesis.[18]

It was observed that the partitioning coefficients of products and reactants have a strong influence on the two-phase catalysis. In the reaction system described in this study, the starting materials dissolve well in the ionic liquid, whereas the product is only weakly soluble. This leads to a high concentration of the reactants in the catalyst phase and, on the other hand, allows ready desorption of the products. For further optimization of the liquid–liquid two-phase catalysis, the relative solubilities of each component in the binary system needs to be understood, although the relative solubilities under catalytic conditions can deviate considerably from the solubility of each single component.

Experimental

Materials and methods

The ionic-liquid 1-ethyl-3-methylimidazolium trifluoromethanesulfonate ($EtMeIm^+TfO^-$) was synthesized from *N*-methylimidazole (99%, Aldrich) and ethyl-trifluoromethanesulfonate (99%, Aldrich).[19] The ^1H- and $^{13}C\{^1H\}$-NMR spectra of the sample synthesized were identical to a sample obtained from Tokyo Kasei Kogyo Co., Ltd., Japan (water contents ≤0.3%; no other impurities). The solvent *n*-heptane (99%) was obtained dry from Aldrich. Phenylacetylene (98%, Aldrich), 1,3-cyclohexadiene (97%, Aldrich) and the amines (4-isopropyl-phenylamine, 4-fluoro-phenylamine and *n*-octylamine) were obtained in high purity (98–99%) from Aldrich and used as received. Zinc trifluoromethanesulfonate ($Zn(CF_3SO_3)_2$, 98%, Aldrich) and trifluoromethanesulfonic acid (CF_3SO_3H, 99%, Aldrich) were employed as catalysts without further purification.

Physical and analytical methods

^1H- and $^{13}C\{^1H\}$-NMR spectra were recorded on a Bruker GX 360 NMR instrument and referenced in ppm relative to tetramethylsilane using the solvent shift as internal reference.[20] GC-analyses were performed on a HP 5890 A gas chromatograph with FID detector and a HP 5890 series II gas chromatograph with HP 5971 mass selective detector HP 5730A. Both gas chromatographs were equipped a crosslinked 5% diphenyl- 95 % dimethyl-polysiloxane column (30 m, Restek GmbH, Rtx-5 Amine). Infrared spectra were obtained on a Perkin Elmer 2000 FT-IR spectrometer as thin film of the neat compound or KBr discs. Elemental analyses were performed by the Microanalytical Laboratory of the TU München.

Preparation and kinetic measurements. The kinetic experiments were performed in the batch mode in standard Schlenk vessels at the reflux temperature of *n*-heptane (98 °C, reactions of phenylacetylene with aryl amines) and in magnetically stirred custom built 60 cm^3 autoclaves at 180–200 °C and 6–10 bar (reactions of phenylacetylene with alkyl amines and of 1,3-cyclohexadiene with aryl amines). In a typical experiment, the reactor was charged with $Zn(CF_3SO_3)_2$ (0.07 g, 0.2 mmol) and ionic-liquid (0.5 cm^3) under nitrogen. After the catalyst had dissolved in the ionic-liquid (several minutes) *n*-heptane (15 cm^3) and amine (20 mmol) were introduced. The mixture was stirred at 1000 rpm and the reactor heated to the reaction temperature. The alkene or alkyne was then injected either through a septum in the case of Schlenk vessels, or introduced with a HPLC pump in case of autoclaves. Samples were taken for GC analysis. The final reaction mixture was separated, the ionic-liquid phase was washed with *n*-heptane and the unified organic phase concentrated in a partial vacuum. The product either crystallized from the concentrated solution and was purified by recrystallization or was distilled in a partial vacuum.

(4-Fluoro-phenyl)-(1-phenyl-ethylidene)-amine. Yield: 4.18 g, 98%.

Found: C, 79.0; H, 5.7; F, 8.8; N, 6.7%. Calc. for $C_{14}H_{12}FN$: C, 78.9; H, 5.7; F, 8.9; N, 6.6%. $^{13}C\{^1H\}$-NMR (CD_3COCD_3): 166.9 (s, *C*N), 162.2 (s, *C*F), 149.3 (s, Ph), 140.6 (s, Ph), 131.6 (s, Ph), 129.3 (s, Ph), 128.3 (s, Ph), 122.0 (s, Ph), 116.5 (d, Ph), 17.5 (s, CH_3). ^1H-NMR (CD_3COCD_3): 8.07 (dd, 2H, Ph),

7.54–7.47 (mm, 3H, Ph), 7.18 (tt, 2H, Ph), 6.87 (tq, 2H, Ph), 2.30 (s, 3H, CH_3). IR (KBr): 3061 (w), 1632 (s), 1576 (m), 1497 (s), 1448 (m), 1367 (m), 1315 (w), 1290 (m), 1203 (s), 1091 (m), 1025 (w) cm^{-1}. *m*/*z* (FAB) 213 (M^+), 198 ($M^+ - CH_3$).

(4-Isopropyl-phenyl)-(1-phenyl-ethylidene)-amine. Yield: 4.65 g, 98%.

Found: C, 85.7; H, 8.0; N, 5.9%. Calc. for $C_{17}H_{19}N$: C, 86.0; H, 8.1; N, 5.9%. $^{13}C\{^1H\}$-NMR (CD_3COCD_3): 166.2 (s, *C*N), 151.3 (s, *C*^{i}Pr), 145.0 (s, Ph), 141.2 (s, Ph), 131.9 (s, Ph), 129.8 (s, Ph), 128.7 (s, Ph), 128.3 (s, Ph), 120.9 (d, Ph), 35.0 (s, CH), 25.2 (s, 2 CH_3), 18.0 (s, *C*H_3CN). ^{1}H-NMR (CD_3COCD_3): 8.03 (d, 2H, Ph), 7.49 (d, 3H, Ph), 7.25 (d, 2H, Ph), 6.73 (d, 2H, Ph), 2.92 (m, 1H, CH), 2.26 (s, 3H, CH_3), 1.27 (d, 6H, 2 CH_3). IR (KBr): 2960 (s), 1627 (vs), 1576 (m), 1496 (s), 1446 (m), 1384 (w), 1366 (s), 1314 (w), 1286 (s), 1217 (s), 1205 (m) cm^{-1}. *m*/*z* (FAB) 237 (M^+), 222 ($M^+ - CH_3$).

Octyl-(1-phenyl-ethylidene)-amine. Yield: 2.3 g, 50%. Bp 95–100 °C (0.5 mbar). Found: C, 83.7; 10.3; 6.4%. Calc. for $C_{16}H_{25}N$: C, 83.1; H, 10.9; N, 6.1%. $^{13}C\{^1H\}$-NMR ($CDCl_3$): 165.0 (s, *C*N), 142.0 (s, Ph), 129.6 (s, Ph), 128.6 (s, Ph), 127.0 (s, Ph), 52.7 (s, N*C*H_2), 32.3 (s, *C*H_2), 31.4 (s, *C*H_2), 30.0 (s, *C*H_2), 29.7 (s, *C*H_2), 28.1 (s, *C*H_2), 23.1 (s, *C*H_2CH$_3$), 15.7 (s, *C*H_3CN), 14.5 (s, CH_2*C*H_3). ^{1}H-NMR (CD_3COCD_3): 7.98 (dd, 2H, Ph), 7.80 (t, 3H, Ph), 3.50 (t, 2H, NCH_2), 2.25 (s, 3H, N=C*C*H_3), 1.78 (quint, 2H, NCH_2C*H*$_2$), 1.36 (m, 10H, 5 CH_2), 0.93 (t, 3H, CH_3). IR (KBr): 3057 (w), 2955 (s), 2926 (vs), 2854 (s), 1634 (s), 1578 (w), 1492 (w), 1446 (m), 1369 (m), 1282 (s), 1179 (w), 1082 (w), 1027 (w), 916 (w) cm^{-1}. *m*/*z* (FAB) 231 (M^+), 216 ($M^+ - CH_3$).

Cyclohex-2-enyl-(4-isopropyl-phenyl)-amine. Yield: 3.22 g, 75%. Bp 105–107 °C (0.3 mbar). Found: C, 84.2; H, 9.9; N, 6.4%. Calc. for $C_{15}H_{21}N$: C, 83.7; H, 9.8; N, 6.5%. $^{13}C\{^1H\}$-NMR (CD_3COCD_3): 166.2 (s, *C*N), 151.3 (s, *C*^{i}Pr), 145.0 (s, Ph), 141.2 (s, Ph), 131.9 (s, Ph), 129.8 (s, Ph), 128.7 (s, Ph), 128.3 (s, Ph), 120.9 (d, Ph), 35.0 (s, CH), 25.2 (s, 2 CH_3), 18.0 (s, *C*H_3CN). ^{1}H-NMR (CD_3COCD_3): 6.93 (dtd, 2H, Ph), 6.54 (dd, 2H, Ph), 5.89 (mt, 1H, C=C*H*), 5.64 (mq, 1H, *H*C=C), 4.26 (b, 1H, N*H*), 3.47 (m, 1H, NC*H*), 2.75 (sept, 1H, CH), 2.0–1.3 (m, not resolved, 6H, 3 CH_2), 1.19 (d, 6H, 2 CH_3). IR (neat): 3448 (m), 3365 (m), 3017 (s), 2956 (vs), 2929 (vs), 2864 (s), 1622 (vs), 1502 (vs), 1458 (m), 1429 (w), 1381 (w), 1361 (w), 1279 (s), 1156 (w), 1046 (w), 994 (w), 886 (m) cm^{-1}. *m*/*z* (FAB) 215 (M^+), 200 ($M^+ - CH_3$).

Determination of the partitioning coefficient. A mixture of one of the solutions A to J given in Table 3, $Zn(CF_3SO_3)_2$ (0.036 g, 0.1 mmol) and 1-ethyl-3-methylimidazolium trifluoromethanesulfonate (0.25 cm^3) was stirred for 0.5 h at room temperature. A sample of the heptane phase was taken for GC analysis. The mixture was then heated to reflux for 0.5 h, the phases separated and a sample taken for GC analysis.

Table 3 Composition of mixtures A to J used in the determination of the partitioning coefficient

Mixture	4-Isopropyl-phenylamine	Heptane
A	2.7 ml	7.3 ml
B	2.1 ml	8.0 ml
C	1.4 ml	8.6 ml
D	0.7 ml	9.3 ml
E	0.3 ml	9.7 ml
Mixture	**Phenylacetylene**	**Heptane**
F	2.2 ml	7.8 ml
G	1.6 ml	8.4 ml
H	1.1 ml	8.9 ml
I	0.6 ml	9.4 ml
J	0.3 ml	9.7 ml

Acknowledgement

The Deutsche Forschungsgemeinschaft (DFG) is acknowledged for financial support.

References

1 (*a*) T. E. Müller and M. Beller, *Chem. Rev.*, 1998, **98**, 675; (*b*) M. Nobis and B. Drießen-Hölscher, *Angew. Chem., Int. Ed.*, 2001, **40**, 3983; (*c*) T. E. Müller and J. T. Horváth, *Encyclopedia of Catalysis*, John Wiley & Sons, New York, 2002.

2 ICS-UNIDO Workshop on Trends and Applications of Combinatorial Chemistry and Combinatorial Technologies, Budapest, Hungary, October 15–18, 2001.

3 (*a*) M. Tokunaga, M. Eckert and Y. Wakatsuki, *Angew. Chem.*, 1999, **111**, 3416; (*b*) M. Kawatsura and J. F. Hartwig, *J. Am. Chem. Soc.*, 2000, **122**, 9546; (*c*) J. S. Johnson and R. G. Bergman, *J. Am. Chem. Soc.*, 2001, **123**, 2923; (*d*) O. Löber, M. Kawatsura and J. F. Hartwig, *J. Am. Chem. Soc.*, 2001, **123**, 4366; (*e*) C. Cao, J. T. Ciszewski and A. L. Odom, *Organometallics*, 2001, **20**, 5011; (*f*) C. G. Hartung, A. Tillack, H. Trauthwein and M. Beller, *J. Org. Chem.*, 2001, **66**, 6339.

4 W. F. Hoelderich and G. Heitman, *Catal. Today*, 1997, **38**, 227.

5 V. Neff, T. E. Müller and J. A. Lercher, *Chem. Commun.*, 2002, **8**, 906.

6 R. S. Neale, L. Elek and R. E. Malz, *J. Catal.*, 1972, **27**, 432.

7 J. Penzien, T. E. Müller and J. A. Lercher, *Chem. Commun.*, 2000, **18**, 1753.

8 J. Penzien, T. E. Müller and J. A. Lercher, *Micropor. Mesopor. Mater.*, 2001, **48**, 285.

9 M. K. Richmond, S. L. Scott and H. Alper, *J. Am. Chem. Soc.*, 2001, **123**, 10521.

10 M. K. Richmond, S. L. Scott, G. P. A. Yap and H. Alper, *Organometallics*, 2002, **21**, 3395.

11 S. Cacchi, V. Carnicelli and F. Marinelli, *J. Organomet. Chem.*, 1994, **475**, 289.

12 T. E. Müller, M. Grosche, E. Herdtweck, A.-K. Pleier, E. Walter and Y.-K. Yan, *Organometallics*, 2000, **19**, 170.

13 T. E. Müller, M. Berger, M. Grosche, E. Herdtweck and F. P. Schmidtchen, *Organometallics*, 2001, **20**, 4384.

14 R. Q. Su and T. E. Müller, *Tetrahedron*, 2001, **57**, 6027.

15 J. Bodis, Ch. Hauser, T. E. Müller and J. A. Lercher, DECHEMA Conference on *Green Solvents for Catalysis*, Bruchsal, Germany, October 13–16, 2002, B.A., pp. 110.

16 A. E. Visser, W. M. Reichert, R. P. Swatloski, H. D. Willauer, J. G. Huddleston and R. D. Rogers, in *Ionic Liquids – Industrial Applications to Green Chemistry*, eds. R. D. Rogers and K. R. Seddon, *ACS Symposium Series 818*, American Chemical Society, Washington, 2002, pp. 289–308.

17 H. M. Senn, P. E. Blöchl and A. Togni, *J. Am. Chem. Soc.*, 2000, **122**, 4098.

18 P. A. Wender, S. T. Handy and D. L. Wright, *Chem. Ind.*, 1997, 765.

19 P. Bonhote, A.-P. Dias, N. Papageorgiou, K. Kalyanasundaram and M. Grätzel, *Inorg. Chem.*, 1996, **35**, 1168.

20 H. E. Gottlieb, V. Kotlyar and A. Nudelman, *J. Org. Chem.*, 1997, **62**, 7512.

Acrylate dimerisation under ionic liquid–supercritical carbon dioxide conditions†

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Received 3rd January 2003
First published as an Advance Article on the web 18th March 2003

Ionic liquid 1-*n*-butyl-3-methylimidazolium tetrafluoroborate and supercritical CO_2 have been used for the biphasic palladium-catalysed dimerisation of methyl acrylate. Substrate and product distribution between the two phases and extraction capability of *sc*CO_2 are evaluated. The effect of the biphasic medium on the catalyst performance is also addressed. The selectivity for the tail-to-tail dimers is >98%, as high as under monophasic conditions. The same trend stands for turnover number and frequency although there is a lower substrate to palladium ratio in the IL phase. The CO_2-rich phase acts as a substrate and product reservoir, a suitable case for studying the reaction under continuous feed and extraction regime.

Introduction

The catalysed dimerisation of methyl acrylate (MA) to dimethyl Δ^2- and Δ^3-dihydromuconate (DHMs) offers an interesting alternative to the conventional routes of adipic acid manufacture.[1] It has been recently reported that cationic Pd-based catalysts when immobilised in an ionic liquid (IL) such as 1-*n*-butyl-3-methylimidazolium tetrafluoroborate, [BMIM][BF_4], exhibit higher activities than those previously observed in conventional media.[2] A further achievement consists in performing the reaction under biphasic conditions with toluene as the extracting solvent for the organics and IL for immobilising the catalyst. Interestingly enough, this system was demonstrated to be effective in a continuous mode with TON >4000 and selectivity to DHMs >90 %, for a 50 h run. The better performances of the catalytic system under biphasic continuous conditions suggest an inhibition effect by the products which build-up in monophasic batch mode, thus limiting conversion to *ca.* 80%.[2] In continuation of this work, we focus our attention on the replacement of toluene by a greener solvent such as supercritical CO_2 (*sc*CO_2).

It has been demonstrated that CO_2 can be soluble in IL while the same IL has no detectable solubility in *sc*CO_2.[3] These properties have been exploited for immobilising organometallic catalysts in ILs while the organics are extracted by the CO_2-rich phase.[4–7] As part of a program on catalysed C–C coupling in biphasic IL–*sc*CO_2 medium, we here report the first experiments on MA dimerisation catalysed by cationic palladium species. Three aspects of the reaction were examined aimed at (i) measuring MA and DHMs miscibilities in CO_2, (ii) comparing activity and selectivity to those under monophasic

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Green Context

The successful application of the principles of green chemistry will in many cases require a combination of clean technologies. It is insufficient to employ an eco-friendly solvent for example, if the reaction work-up requires a volatile organic solvent. Here we see how the use of a biphasic reaction system employing two "greener" solvents enables not only the catalytic reaction to proceed at a good rate in a non-volatile ionic liquid but also how the presence of supercritical carbon dioxide can be used to continuously feed the substrate and remove the product. The selectivity achieved in this useful acrylate dimerisation is also an attractive feature of this process. ***JHC***

† This work was presented at the Green Solvents for Catalysis Meeting held in Bruchsal, Germany, 13–16th October 2002

 DOI: 10.1039/b300073g

conditions, and (iii) evaluating the extraction efficiency of *sc*CO_2 for the design of a continuous reaction–extraction procedure.

Results and discussion

MA and DHM distributions between IL and CO_2-rich phases

The experiments were conducted in [BMIM][BF_4]–CO_2 without the catalyst components. Preliminary observations with a reactor of 35 cm^3 equipped with sapphire windows allowed us to set properly the sampling device in order to analyse either the IL- or the CO_2-dense phase. Admission of liquid CO_2 at room temperature to a monophasic mixture of MA (15.5 mmol), DHMs (15.3 mmol), and [BMIM][BF_4] (2.0 g) led to the formation of a two-phase system. The concomitant volume contraction (*ca.* 50%) of the lower IL phase suggests that some of the organics have been transferred to the upper CO_2 phase. Under 145 bar of CO_2 at 76 °C, the volume of the IL phase did not change drastically.

The experiments for quantitative analysis were performed according to the following procedure. MA and DHMs were mixed in proportions mimicking 51, 66, and 80% conversion for an initial MA feed of 70 mmol. Then, the homogeneous mixture was added to 3 g of [BMIM][BF_4] to give a clear solution, transferred into a batch reactor (53 cm^3), pressurised with known amounts of CO_2, and finally heated to 80 °C for analysis of the composition of the CO_2-dense phase. The IL : CO_2 ratio was varied in the range 0.025–0.055 mol/mol (0.13–0.28 wt/wt) by changing the CO_2 pressure within the range 90–295 bar. A total of 14 pairs of MA and DHM values were obtained for the three mixtures. At the end of each experiment, the reactor was cooled to room temperature for additional analysis of the composition of the liquid CO_2 phase. It is noteworthy that the experimental set-up was not designed for accurate titration, but provided reproducible data within ±15%. Moreover, complementary analysis of the IL phase gave satisfactory mass balance.

The results obtained point out the quasi-quantitative miscibility of MA in CO_2 in the pressure range studied, whereas DHMs amounts increased with pressure. This pressure effect on solubility is correlated to the increase in density of *sc*CO_2 that has been described as a solvent tuning effect.[8] As a matter of fact, DHMs were found to be highly soluble in liquid CO_2 at room temperature as well as MA. Fig. 1 reports the results in

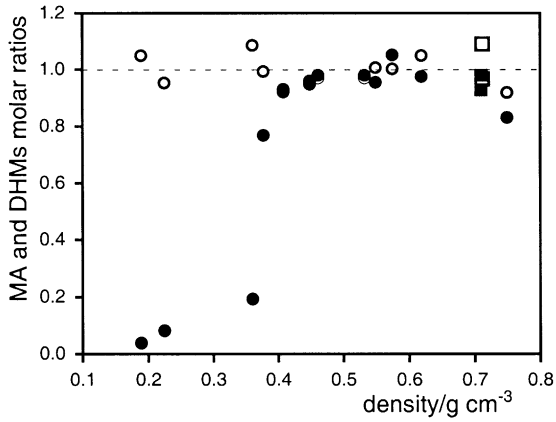


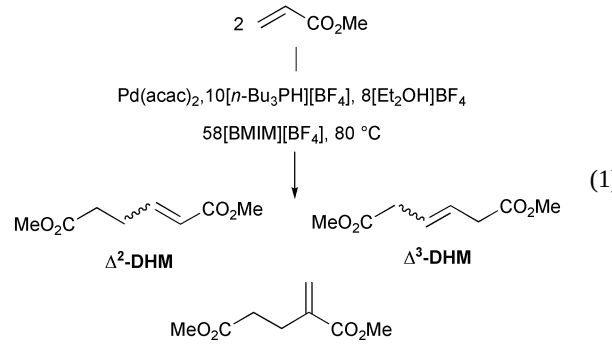
Fig. 1 MA (○) and DHM (●) molar ratios in the CO_2 phase *vs.* CO_2 density, at 80 °C; □, ■ at 25 °C.

comparing the variation of the molar ratio for each compound in the CO_2 phase as a function of CO_2 density. This molar ratio is expressed as MA (or DHMs) found in the CO_2-rich phase divided by the initial amount of the corresponding compound. The density dependence is only evidenced for the dimers that demonstrate a selective solvent tuning effect of CO_2. Under our experimental conditions, a density higher than *ca.* 0.4 g cm^{-3} (*i.e.* > 150 bar at 80 °C) promotes most MA and DHMs solubilisation.

Hence, for catalytic experiments conducted with the same experimental set-up the CO_2 pressure should be kept over 150 bar in order to get relevant kinetic data from the CO_2-rich phase analysis.

Catalytic behaviour under biphasic conditions

In a first approach, we performed for comparison catalytic experiments under monophasic conditions in a Schlenk tube according to eqn. (1) with a molar ratio MA : Pd = 297 (MA = 71.3 mmol). The reaction temperature was fixed at 80 °C for the purpose of this study as the onset was observed at 70 °C. The catalyst converted 55% of MA within 2 h, with TOF = 100 h^{-1} in the first hour. After 15 h, 60% conversion was obtained providing a TON of 180. The DHMs selectivity was > 98% independent of conversion.



(1)

For the biphasic conditions, the reaction was performed under 200 bar of CO_2 with the equipment used for collecting the distribution data. The amounts of catalyst components corresponded to those of the monophasic conditions (see Experimental section). The activity and selectivity for DHMs were determined at 83 °C according to the following characteristics. In our hands, it took 20 min to reach the internal temperature of 70 °C, the onset of reaction, that defined $t = 0$ for plots *vs.* time. Conversion higher than 50% was generally obtained within 3 h. The turnover frequencies (TOF) were calculated from the experimental data of the CO_2-rich phase at $t \leq 2$ h (linear part of conversion *vs.* time). Turnover numbers (TON) were obtained from the isolated dimers for reaction time ≥15 h unless otherwise stated. In addition, successive samplings of IL and CO_2-rich phases at the end of a run were consistent with the mass balance. In general, MA and DHMs in the IL phase accounted for less than 10%.

Fig. 2a reports the conversion of MA into DHMs as a function of time. The calculated TOF value after 1 h run was equal to 95 h^{-1}. Within the first 3 h, 73% conversion was obtained showing that the reaction rate was comparable to that under monophasic conditions; the selectivity was also higher than 98%. Sampling the IL and CO_2 phases after 3 h provided a TON value of 220 (based on MA).

In order to check catalyst stability, the reaction was quenched after a 6 h run by cooling down to room temperature, then, after 60 h, the temperature was raised to 83 °C, and fresh MA was introduced under pressure into the reactor (MA : Pd = 250). The results reported in Fig. 2b show that the catalyst was still active, with the same selectivity. The maximum conversion reached 81.8% providing therefore a higher TON with a cumulative value of 450. As TON increases with MA : Pd, we studied the reaction with a higher initial MA : Pd molar ratio

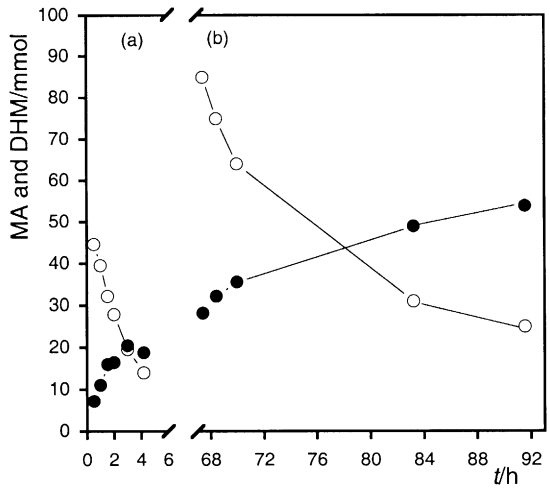


Fig. 2 MA (○) and DHMs (●) in the CO_2-rich phase as a function of time: (a) $[MA]_0$ = 72.5 mmol, (b) + 72.5 mmol of MA. $Pd(acac)_2$: $[HPBu_3][BF_4]$: $[Et_2OH][BF_4]$: $[BMIM][BF_4]$ = 0.23 : 2.3 : 1.8 : 13.9 mmol, T = 83 °C, PCO_2 = 200 bar.

(1000). In order to have a comparable concentration of the organics in the CO_2-rich phase, the volume of the reactor was increased to 127 cm^3. Better performance could even be obtained with TON = 560 and TOF = 195 h^{-1}. Changing $[BMIM][BF_4]$ for $[HBIM][BF_4]$ (HBIM = 1-hydrogeno-3-*n*-butylimidazolium), had no influence on selectivity for tail-to-tail dimers, TON was slightly higher but TOF lower with values of 710 and 150 h^{-1}, respectively.

In summary, the catalyst did work well under IL–*sc*CO_2 biphasic conditions. The selectivity was identical to that of the monophasic system. The TON and TOF values are comparable, increasing with the molar ratio MA : Pd. However, one could have expected a detrimental effect on kinetics in immobilising palladium in one phase and solubilising most of the substrate in the other that led to an effective MA : Pd molar ratio in the range 5–20 in IL. Further insight into kinetics under batch conditions is out of the scope of this study. We were more interested in considering the feasibility of a continuous process, that should in principle also facilitate the kinetic approach. The next paragraph describes extraction experiments at the end of a catalytic run.

Extraction of dimers with dense CO_2

We have reported in the first part of this paper that MA is much more miscible with CO_2 than DHMs dimers. The solvent power increases with density; the dimers became soluble in liquid CO_2 at room temperature. However, it seemed more appropriate to study the extraction efficiency at the reaction temperature (83 °C) in view of a continuous reaction–extraction process. Step by step depressurisation of the reactor was performed from 200 to 110 bar, collecting the extracts for quantification. The temperature of the collecting vessel was maintained at room temperature while its pressure was fixed either at 1 bar or *ca.* 55 bar (liquid–vapor equilibrium). The two procedures showed a maximum efficiency for $P \geq 150$ bar (CO_2 density > 0.4 g cm^{-3}). This observation corroborates the solubility data described in the first part. For example, depressurisation from 190 to 150 bar allowed us to extract 0.08 g of DHMs per g of CO_2 in a non-optimised manner. Further work is in progress for the design and setup of a continuous reactor.

Conclusion

These preliminary results outline that the palladium-catalysed dimerisation of methyl acrylate into dimethyl dihydromuconates is also operative under IL–*sc*CO_2 biphasic conditions. Much lower substrate to palladium ratios in the IL phase provided TON and TOF values equivalent to those under monophasic conditions, with the same selectivity for tail-to-tail dimers (> 98%). The CO_2-rich phase acts as a substrate and product reservoir. The high solubility of the dimers in *sc*CO_2 for P > 150 bar opens up the possibility for the reaction to be conducted under continuous feed and separation conditions with greener solvents.

Experimental

General

All reactions and synthetic mixtures were prepared in Schlenk glassware under argon, then transferred into a stainless steel reactor, pressurised with CO_2, and heated. The solvents were distilled and kept under argon. Tetrafluoroboric acid (54 wt% in ether) was purchased from Fluka, xylene (mixture of isomers) from Riedel-de-Haën, toluene from Carlo-Erba, methyl acrylate, and tri-*n*-butylphosphine from Acros Organics. Methyl acrylate, toluene, and xylene were dried with appropriate dessicants and distilled under argon. $Pd(acac)_2$, $[BMIM][BF_4]$, and $[n\text{-}Bu_3PH][BF_4]$ were prepared according to ref. [9–11], respectively. Dimethyl Δ^2- and Δ^3-dihydromuconate used for synthetic mixtures were obtained according to ref. [10]. The GC analyses were performed with a Shimadzu GC14-A equipped with a 15 m Megabore Carbowax/BTR column and FID detector. The ^1H NMR spectra were recorded in acetone-d_6 on a Bruker Avance 300 spectrometer (300.131 MHz) at 295 K. Chemical shifts (δ, ppm) were determined relative to the solvent (CH_3COCH_3 δ 2.09) and converted to the scale downfield from $(CH_3)_4Si$.

Procedure for solubility determination

In a Schlenk tube were successively added under argon $[BMIM][BF_4]$ (3.00 g), known amounts of dimethyl dihydromuconates (18.1, 22.4, or 28.7 mmol), toluene as the internal standard for GC analysis (*ca.* 5 mol% of the esters), and methyl acrylate (34.7, 22.2, or 14.4 mmol) in order to mimic 51, 66, and 80% conversion. After stirring, the mixture was transferred into a stainless steel reactor (53 cm^3) which was pressurised with CO_2 at room temperature, heated to 80 °C (internal temperature) under stirring, then the pressure was adjusted to the desired value between 90 and 295 bar with a high pressure pneumatic pump. After 0.5–1 h under stirring and a further 0.5–1 h equilibration without stirring, sampling of the IL or CO_2-rich phase was realised under pressure through a two valve system, then depressurised by bubbling either in acetone-d_6 for ^1H NMR analysis (IL phase) or in xylene for GC analysis (CO_2 phase).

Catalytic run

Monophasic conditions. In a Schlenk tube were successively added under argon $[n\text{-}Bu_3PH][BF_4]$ (0.691 g, 2.38 mmol), $[BMIM][BF_4]$ (3.19 g), $[HOEt_2][BF_4]$ (54 wt%, 0.261 cm^3, 1.88 mmol), methyl acrylate (6.142 g, 71.3 mmol), $Pd(acac)_2$ (0.073 g, 0.239 mmol). The mixture was stirred for 0.25 h at room temperature, then the solution was heated at 80 °C, and quenched to room temperature after a given time for the determination of conversion *vs.* time by GC analysis with methyl benzoate as the external standard.

Biphasic conditions. In a Schlenk tube were successively added under argon $[n\text{-}Bu_3PH][BF_4]$ (0.681 g, 2.35 mmol), $[BMIM][BF_4]$ (3.14 g), $[HOEt_2][BF_4]$ (54 wt%, 0.254 cm^3, 1.82

mmol), methyl acrylate (6.245 g, 72.5 mmol), $Pd(acac)_2$ (0.071 g, 0.235 mmol), and toluene (GC internal standard, 0.192 g, 2.08 mmol). The mixture was stirred for 0.25 h at room temperature, then the solution was transferred into the reactor used for solubility determination. A known amount of CO_2 was admitted to reach 200 bar at 83 °C. Finally, the reactor was placed on a pre-heated magnetic stirrer to obtain 83 °C as the internal temperature. Sampling procedure was identical to that for solubility determination. At the end of a run, the reactor was cooled down to room temperature, depressurised, and the remaining dimers extracted with toluene (3×30 cm^3) for TON determination.

Acknowledgement

Financial supports from the CNRS (D. B-T. and M. P.) and BMBF through the ConNeCat lighthouse project ″Smart Solvents, Smart Ligands″ (W. L. and P. W.) are greatly acknowledged. We also wish to thank Dr Igor Tkatchenko for his expertise in Pd-catalyzed coupling reactions.

References

1 K. Weissermel and H.-J. Arpe, Industrial Organic Chemistry, VCH, Weinheim, 1997, p. 239.
2 J. Zimmermann, P. Wasserscheid, I. Tkatchenko and S. Stutzmann, *Chem. Commun.*, 2002, 760.
3 L. A. Blanchard, D. Hancu, E. J. Beckman and J. F. Brennecke, *Nature*, 1999, **399**, 28.
4 R. A. Brown, P. Pollett, E. McKoon, C. A. Eckert, C. L. Liotta and P. G. Jessop, *J. Am. Chem. Soc.*, 2001, **123**, 1254.
5 F. Liu, M. B. Abrams, R. T. Baker and W. Tumas, *Chem. Commun.*, 2001, 433.
6 M. F. Sellin, P. B. Webb and D. J. Cole-Hamilton, *Chem. Commun.*, 2001, 781.
7 A. Bösmann, G. Franciò, E. Janssen, M. Solinas, W. Leitner and P. Wasserscheid, *Angew. Chem., Int. Ed. Engl.*, 2001, **40**, 2697.
8 *Chemical Synthesis using Supercritical Fluids*, ed. P. G. Jessop and W. Leitner, Wiley-VCH, Weinheim, 1999.
9 D. A. White, *J. Chem. Soc. A*, 1971, 143.
10 P. A. Z. Suarez, J. E. L. Dullius, S. Einloft, R. F. de Souza and J. Dupont, *Polyhedron*, 1996, **15**, 1217.
11 M. Picquet, S. Stutzmann, I. Tkatchenko, I. Tommasi, J. Zimmermann and P. Wasserscheid, *Green Chem.*, this issue.

Enzymatic esterification in ionic liquids integrated with pervaporation for water removal†

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Received 15th November 2002
First published as an Advance Article on the web 13th March 2003

The application of ionic liquids as solvents for the enantioselective esterification of (*R*,*S*)-2-chloropropanoic acid with butan-1-ol using *Candida rugosa* lipase is reported. The role of water produced during the reaction and controlling of the water activity with pervaporation was studied. The enantioselective esterification of (*R*,*S*)-2-chloropropanoic acid with butan-1-ol in different organic solvents and ionic liquids was studied. The reaction was effectively catalysed by *Candida rugosa* lipase. From the ionic solvents investigated, the best results were achieved in [bmim]PF_6. The presence of water had a strong effect on the activity of the lipase. Since in esterification reactions with acid and alcohol equimolar amounts of water are formed, the excess of water was removed and the water activity was kept constant using a pervaporation system without any additives. At the optimum water activity *Candida rugosa* lipase showed high thermal stability in [bmim]PF_6 and it could be reused for at least five recycles with only a small lost of activity.

Introduction

An active area of current research in biotechnology is biocatalysis in non-conventional media, containing high properties of organic solvents, supercritical or near supercritical fluids, gaseous phases or solid reactants and products. These non-conventional media with a reduced water content offer a number of advantages for the application of enzymes and whole cells as catalysts in industrial processes.[1,2]

There are numerous advantages of using enzymes in organic solvents compared with in water, such as increased solubility of nonpolar substrates, shifting of thermodynamic equilibria in favour of synthesis over hydrolysis, and elimination of microbial contamination in the reaction mixture.[3]

However, the most suitable hydrophobic organic solvents are usually volatile liquids that evaporate into the atmosphere with detrimental effect to the environment and human health. They are flammable and their low boiling point is more and more hindering their utilisation, especially in cases of thermophilic enzymes produced by genetically modified organisms. Room temperature ionic liquids could be a good alternative to organic solvents for enzyme-catalysed reactions: they have negligible vapour pressure, excellent solvent properties and they are chemically and thermally stable. Using them it may be possible to keep the benefits of non-conventional media, especially those of organic solvents, and to avoid their drawbacks.

Recently some papers on biocatalytic reactions carried out in ionic liquids have been published. For a review see ref. 4 and the references cited therein. Application of lipases in ionic liquids was most extensively studied, as happened in organic solvents, too. As is well known, for the active conformation of lipases a certain amount of water is necessary. To avoid the effect of water produced in the reaction, transesterification processes without water production were mostly investigated.[5–10] During esterification reactions water content was either not considered

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† This work was presented at the Green Solvents for Catalysis Meeting held in Bruchsal, Germany, 13–16th October 2002.

Green Context

The use of enzymes in ionic liquids is well known. For esterification reactions, the removal of water is an important factor, which must be done at relatively low temperatures in order to preserve enzyme activity. This article describes the use of a pervaporation unit to remove the water formed in enzyme-catalysed esterifications under reaction conditions. This avoids the addition of drying agents such as molecular sieves to the reaction mixture, and leads to active stable enzymes. ***DJM***

 DOI: 10.1039/b211342m

at all, or it was adjusted to a constant value. Recently application of salt pairs – a technique introduced and applied in enzymatic esterifications in organic solvents – was adapted for ionic liquids to keep water activity at a constant value.[9,10] This method is based on reliable scientific results; its applicability is well proven in laboratory experiments. Its drawback, however, is – beyond the fact that only given water activity values determined by the known salt pairs can be adjusted – that extra chemicals have to be used, which are difficult to remove from the ionic liquids, thus reducing the possibility of solvent reuse.

Firstly Crespo *et al.*[11] investigated the recovery of volatile solutes from ionic liquids by pervaporation. In our short paper preliminary results of experiments on pervaporative removal of water produced during enzymatic esterification were published.[12] Now we report the application of this simple and environmentally-safe method in detail.

In this work our main aim was to study the role of water content in the reaction mixture. As a test reaction, lipase catalysed enantioselective esterification of (*R*,*S*)-2-chloropropanoic acid was selected. This reaction was earlier investigated in organic solvents by *Candida rugosa* lipase in detail in our laboratory.[13–15] The activity of this particular enzyme determined in ionic liquids was found to be very low according to earlier works.[5,16]

Results and discussion

A comprehensive comparative study on *Candida rugosa* lipase-catalysed esterification was carried out in different organic solvents and ionic liquids. Since the viscosity of ionic liquids is much higher than that of the organic solvents used earlier, firstly the role of mixing was studied. It was found that 400 min^{-1} shaking intensity was necessary in ionic liquids to eliminate the diffusion limitations completely, while 250 min^{-1} was enough in organic solvents.

Although in this work the enantioselectivity of the lipase was not particularly studied, it turned out from the GC results that the enzyme definitely preferred the esterification of (*R*)-2-chloropropanoic acid and the initial reaction rate of the conversion of (*R*)-acid was two orders of magnitude higher than that of (*S*)-acid.

The polarity and the hydrophobicity of the medium are known to dramatically influence the activity of the enzymes.[17] Therefore the organic solvents used for comparative purposes were selected to cover a wide range of log *P* values (parameter employed to describe solvent hydrophobicity quantitatively). Log *P* values of n-hexane, toluene and tetrahydrofurane are 3.5, 2.5 and 0.5, respectively. In Table 1 yields of (*R, S*)-butyl 2-propionate at 40 °C are presented. Surprisingly it was found that – unlike the literature data – the activity of the *Candida rugosa* lipase was quite high in the ionic liquids applied. However, the lack of physical data (log *P* values) for ionic liquids makes difficult to compare the results correctly. It can be stated that the experimental results obtained in [bmim]PF_6 are similar to those gained in n-hexane. The ionic liquid [bmim]PF_6 is a hydrophobic solvent, so the phenomenon is compatible with our earlier results.[13] According to those findings, activity of *Candida rugosa* lipase increased with growing log *P* values of the solvents. This could be explained by the fact that highly hydrophilic solvents of low log *P* value strip the water, which would be essential for the activity of the enzyme, from the enzyme. With the decrease of the hydrophilic character of the solvent, this effect decreased as well and *Candida rugosa* lipase showed maximal activity in the solvent of the highest log *P* value. The hydrophilic ionic liquid [bmim]BF_4 may strip off the tightly bound water molecules and consequently results in low enzyme activity. For the further investigations [bmim]PF_6 was selected as solvent, where the highest enzyme activity was observed.

In Table 2 experimental results obtained using different water contents are compared. Firstly the initial water content of the reaction mixture was varied in the range 0–0.6 w/w%. (In this case the water produced during the reaction continuously increased the water content.) It could be observed that the enzyme showed no activity at all in water-free media. Increasing the initial water content, the ester yield after 2 hours reaction time reached a maximal value at 0.2 w/w% initial water content, then it decreased. This means that the water produced in the reaction had an unfavourable effect on the equilibrium reaction. These results indicate that it is of utmost importance that the water content of the reaction mixture is monitored and controlled.

Results of the measurements at constant water content are presented in Table 2, as well. The water content of the reaction mixture was kept at a constant level by a pervaporation

Table 1 (*R*,*S*)-Butyl 2-chloropropionate yields in different organic solvents and ionic liquids (T = 40 °C, initial water content: 0.3 w/w%, acid : alcohol molar ratio 1 : 6)

	Ester yield (%)					
Time/h	n-Hexane	Toluene	Tetrahydrofurane	[bmim]PF_6	[nmim]PF_6	[bmim]BF_4
1	20.8	8.6	1.4	16.2	6.2	—
2	35.8	16.4	2.5	26.3	14.0	—
3	43.7	24.2	4.2	36.7	20.6	0.8
5	50.8	44.6	8.6	47.8	30.1	1.9
8	52.2	48.8	1.7	50.7	36.8	3.1

Table 2 Effect of water content on the (*R*,*S*)-butyl 2-chloropropionate yield in [bmim]PF_6 (T = 40 °C, t = 2 h)

Initial water content (%)	Ester yield (%)	Constant water content (%)	Ester yield (%)
0	0	0	0
0.1	8.1	0.1	6.3
0.2	28.6	0.2	11.9
0.3	26.3	0.3	19.6
0.4	20.2	0.4	30.7
0.5	17.6	0.5	36.6
0.6	12.9	0.6	25.4

apparatus coupled to the reactor. It was found that the ester yields are remarkably different using a constant water content (water activity). The highest value was achieved at 0.5 w/w% constant water content. (It should be noted that this value is higher than the typical, 0.3–0.4 w/w% value in organic solvents.) The difference between the highest yields obtained in both cases (0.2 and 0.5 w/w%) can be explained by the fact that in the experiments *without water removal* the water produced in the beginning of the reaction contributes to the water content optimal for the enzyme; while in the case of *water removal* using small amount of water content (*e.g.* 0.2 w/w%), the enzyme works faraway from the optimal conditions.

Under optimal conditions, in 0.5 w/w% constant water content the ester yield obtained after 2 hours reaction time was higher than without water removal. These data illustrate clearly the usefulness of water removal by pervaporation.

The optimal temperature for the *Candida rugosa* lipase is 30–40 °C. In organic solvents it was possible to enhance the thermal stability of the lipase by medium engineering,[15] by selecting the optimal reaction parameters and using water-mimicking additives. The enhancement, however, was limited by the low boiling points of the (otherwise) most suitable solvents: aliphatic hydrocarbons. Applying ionic liquids this difficulty can be eliminated. As can be seen from Fig. 1, lipase was able to catalyse the reaction at much higher temperatures, 60 °C in [bmim]PF_6. Data measured showed some deactivation phenomenon only at a temperature of 70 °C. It should be noted that hexafluorophosphate ionic liquids are not perfectly stable *versus* hydrolysis, especially at higher temperatures and in presence of a strong acid. In our case the acid applied was relatively weak so these effects seemed to only show up at the highest temperature of 70 °C.

The stability enhancing effect of ionic liquids is proven by the results gained from the experiments reusing the enzyme. In Fig. 2 experimental results obtained both in organic solvent and ionic liquid at 40 °C were compared. It can be seen that in organic solvent (n-hexane) the enzyme loses approximately 10% of its activity in every cycle and after the 5th usage it has only half of its initial activity. The stability of the lipase was found to be extremely high in ionic liquid. After the 5th reuse the activity was decreased by only 7% of its initial value, which is evidence of the strong stabilization effect of ionic liquids.

The correct explanation for the stability enhancement cannot be given yet; we assume that the reason may be a sort of special interaction of the enzyme–water–ionic liquid system. Experiments with water-mimicking additives might provide a more accurate explanation for this interesting phenomenon.

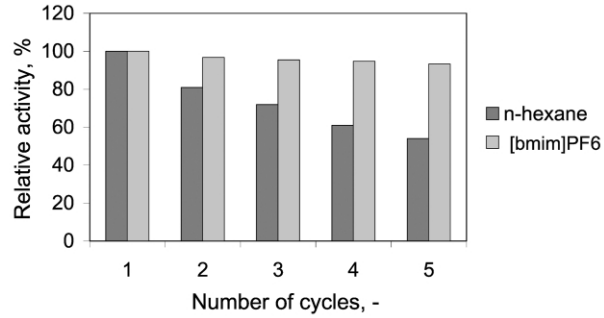

Fig. 2 Recycling of *Candida rugosa* lipase in organic solvent and ionic liquid (t = 5 h)

Concluding remarks & future prospects

Our experiments have proven that *Candida rugosa* lipase is an effective catalyst in ionic liquid and the numbers of enzymes suitable for acting in ionic liquids are widened in this way. It became possible for the enzymatic processes to eliminate several drawbacks of the non-conventional media, while keeping the favourable features. During esterification water is produced and thus the water activity of the reaction mixture is continuously changing. To keep water activity at a constant level different methods (hetero-azeotropic distillation, molecular sieves, salt pairs) have been used so far. Our experiments proved that pervaporation coupled to the reaction is an effective method to remove water produced in the reaction and keep its activity at a constant level. Under the optimal conditions determined, *Candida rugosa* lipase showed high activity and enhanced thermal stability. A further advantage of the method is that there is no need of additives at all, which makes the reuse of the ionic liquid easier.

To prove the applicability of *Candida rugosa* lipase in ionic liquids, other reactions should be studied. However, these can be realised only if solvents having the same (high) quality are used. It is known that a small amount of contamination can dramatically decrease the activity of the enzyme. "Home-made" ionic liquids have been used for the experiments, as can be learned from several publications. Contaminants remaining in the solvent might explain the contradicting phenomena in the literature. Hopefully the quality of the ionic liquids will be unified and their price reduced as the number of suppliers is growing.

In the next step of this research work the effect of ionic liquids on the enantioselectivity of lipases will be studied. Moreover we are looking for an explanation of the enhanced enzyme stability obtained in ionic liquids, using water-mimicking additives in the experiments planned.

Experimental

Candida rugosa lipase (E.C. 3.1.1.3.) (nominal activity: 943 U mg_{enzyme}^{-1}) was from Sigma (St. Louis, MI, USA). Racemic 2-chloropropanoic acid was obtained from Merck (Darmstadt, Germany). The ionic liquids used [bmim]PF_6 (1-butyl-3-methylimidazolium hexafluorophosphate), [nmim]PF_6 (1-methyl-3-nonylimidazolium hexafluorophosphate) and [bmim]BF_4

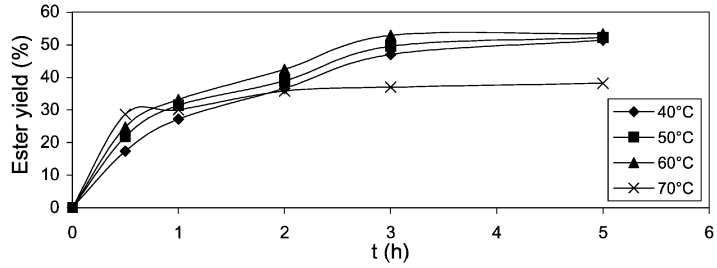

Fig. 1 Effect of reaction temperature on the (*R*,*S*)-butyl 2-chloropropionate yield (constant water content: 0.5 w/w%)

(1-butyl-3-metylimidazolium tetrafluoroborate) were from Solvent Innovation GmbH (Cologne, Germany). Butan-1-ol and all the other solvents used were products of Reanal Ltd (Budapest, Hungary).

In a typical experimental procedure, to 10 ml solvent (organic solvent or ionic liquid) 5 mmol racemic 2-chloropropanoic acid and 30 mmol butan-1-ol were added and the water content of the reaction mixture was controlled and adjusted using a Mettler DL35 automatic Karl–Fischer titrator. The reaction was started by adding 0.1 g of enzyme and the closed flasks were shaken in a New Brunswick G 24 horizontal incubator shaker at the given temperature.

The esterification reaction was followed by an HP 5890A type GC using a 25 m FS-LIPODEX E chiral capillary column from Macherey-Nagel (Aachen, Germany) as described earlier.[15] Aliquots were withdrawn after fixed intervals of time. The samples from organic solvents were directly analysed, that from ionic liquids were extracted three times with n-hexane. The activity of the lipase was characterised by the amounts of (*R*)- and (*S*)-esters produced. All experiments were conducted at least twice and the maximum deviations were less than 6%.

Pervaporation experiments were performed in a standard laboratory pervaporation set-up[18] with an effective membrane area of 0.016 m^2 using hydrophilic membrane.

Acknowledgement

Financial support by the Hungarian Scientific Research Fund, OTKA No T 031760 and T 37628, is gratefully acknowledged.

References

1 A. Pandey, S. Benjamin, C. R. Soccol, P. Nigam, N. Krieger and V. T. Soccol, *Biotechnol. Appl. Biochem.*, 1999, **29**, 119–131.
2 O. Kirk, T. V. Borchert and C. C. Fuglsang, *Curr. Opin. Biotechnol*, 2002, **13**, 345–351.
3 H. Ogino and H. Ishikawa, *J. Biosci. Bioeng.*, 2001, **91**, 109–116.
4 R. A. Sheldon, R. T. Lau, M. J. Sorgedrager, F. Van Rantwijk and K. R. Seddon, *Green Chem.*, 2002, **4**, 147–151.
5 S. H. Schöfer, N. Kaftzik, P. Wasserscheid and U. Kragl, *Chem. Commun.*, 2001, 425–426.
6 S. J. Nara, J. R. Harjani and M. M. Salunkhe, *Tetrahedron Lett.*, 2002, **43**, 2979–2982.
7 P. Kielbasinski, M. Albrycht, J. Luczak and M. Mikolajczyk, *Tetrahedron: Asymmetry*, 2002, **13**, 735–738.
8 P. Lozano, T. De Diego, D. Carrié, M. Vaultier and J. L. Iborra, *J. Mol. Catal. B: Enzym.*, 2002, **754**, 1–5.
9 M. Eckstein, P. Wasserscheid and U. Kragl, *Biotechnol. Lett.*, 2002, **24**, 763–767.
10 M. Eckstein, M. Sesing, U. Kragl and P. Adlercreutz, *Biotechnol. Lett.*, 2002, **24**, 867–872.
11 T. Schäfer, C. M. Rodrigues, C. A. M. Afonso and J. G. Crespo, *Chem. Commun.*, 2001, 1622–1623.
12 K. Bélafi-Bakó, N. Dörmo, O. Ulbert and L. Gubicza, *Desalination*, 2002, **149**, 267–268.
13 L. Gubicza and A. Szakács-Schmidt, *Biocatalysis*, 1994, **9**, 131–143.
14 O. Ulbert, A. Szarka, B. Somogyi, K. Bélafi-Bakó and L. Gubicza, *Biotechnol. Technol.*, 1999, **13**, 299–302.
15 L. Gubicza, K. Székely, O. Ulbert and K. Bélafi-Bakó, *Chem. Pap.*, 2000, **54**, 351–354.
16 T. Itoh, E. Akasaki, K. Kudo and S. Shirakami, *Chem. Lett.*, 2001, **10**, 1507–1509.
17 K. Watanabe and S. Ueji, *Biotechnol. Lett.*, 2000, **22**, 599–603.
18 K. Bélafi-Bakó, N. Dörmo, C. Rodrigues, T. Schäfer, J. G. Crespo and L. Gubicza, *Proc. Eng. Membr.*, Granada, Spain, **vol. I**. 2001, , 287–291.

Green chemistry: synthesis in micro reactors

Tutorial Review

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Received 25th October 2002
First published as an Advance Article on the web 10th February 2003

The importance of minimizing the impact that chemical processing has on the environment is growing, with an increased appreciation of the need to reduce pollution and the depletion of our finite environmental resources. Optimal use of material, energy and consequent waste management can be recognised as important factors for environmental protection. In the case of minimising waste there are two approaches, the traditional approach aims at reducing waste at the end of the pipeline, for example, decreasing emission by catalytic incineration of exhaust fumes. The second approach is based on minimising waste at the source. In this case, innovative procedures have to be employed to change both the method and the technology used throughout the production cycle. The miniaturisation of chemical reactors offers many fundamental and practical advantages of relevance to the pharmaceutical and fine chemicals industry, who are constantly searching for controllable, information rich, high throughput, environmentally friendly methods of producing products with a high degree of chemical selectivity. Indeed, for pharmaceutical companies an informatics-based approach, that micro reactor chemistry can uniquely deliver, may be the trigger for a step change in processes. This review explores how miniaturisation may revolutionise chemical synthesis, highlighting in particular the environmental benefits of this new technology, which include solvent free mixing, *in situ* reagent generation and integrated separation techniques. Furthermore, the possibility of preparing the chemicals in the required volume at point of use, negates the need to store and transport hazardous materials.

1 Introduction

In their simplest form, micro reactor devices consist of a network of micron-sized channels (typical dimensions are in the range 10–300 μm) etched into a solid substrate (see, for example refs. 1–9 for introductory overviews). For solution-based chemistry, the channel networks are connected to a series of reservoirs containing chemical reagents and products to form the complete device or 'chip' with overall dimensions of a few cm.

Reagents can be brought together in a specific sequence, mixed and allowed to react for a specified time in a controlled region of the channel network using electrokinetic (electro-osmotic and electrophoretic) or hydrodynamic pumping. For electrokinetically-driven systems, electrodes are placed in the appropriate reservoirs to which specific voltage sequences can be delivered under automated computer control. This control offers a simple but effective method of moving and separating reactants and products within a micro reactor, without the need for moving parts. Hydrodynamic pumping uses conventional, or micro-scale pumps (notably syringe pumps) to manoeuvre solutions around the channel network, however this technique has the disadvantage of requiring either large external pumps or complex fabrication of small moving parts.

The largest research effort in the field of micro scale devices to date has been in analytical science, where the aim has been to develop a Miniaturised Total Analytical System (μ-TAS).[10–17] Alongside the continuing development of μ-TAS and related analytical applications, a concerted effort has now begun to establish the benefits that micro reactors can bring to the field of reaction chemistry. For example, the ability to manipulate reagent concentrations in both space and time within the channel network of a micro reactor, provides an additional level of reaction control which is not attainable in bulk stirred reactors where concentrations are generally uniform. Furthermore, the spatial and temporal control of chemical reactions in micro reactors, coupled with the features of very small reaction volumes and high surface interactions, is somewhat akin to the situation of reactions within biological cells. Nature exploits the organised distribution of reagents within the micron-sized sub-domains of cells to control and alter chemical reactivity relative to the situation of homogeneous solutions, in a rapid and efficient manner. Consistent with this notion, many reactions have been demonstrated to show altered reactivity, product yield and selectivity when performed in micro reactors as compared with conventional bench top glassware.

To date, the outcome of the reported research has confirmed that micro reactor methodology is applicable to performing both gas and liquid phase reaction chemistry. From the work cited in this review article, the evidence is that the unique *modus operendi* of micro reactors, namely the low-volume spatial and

Green Context

Traditional chemical manufacturing is heavily based on economy of scale with large reactors and associated plants requiring large process batches and associated large scale transport and storage of raw materials and products. All these large scale features present health and safety problems which can lead to major disasters as well as unacceptable levels of risk to operators and the neighbouring community. Microreactor chemistry shows great promise as a novel method on which to build new chemical technology and processes. The desired product is often produced in higher yield and purity, and more quickly. Reactions are much easier to control thus minimising risk and side reactions. Furthermore, solvent free mixing, *in-situ* reagent generation and integrated separation techniques can all help green the chemistry. ***JHC***

 DOI: 10.1039/b210539j

temporal control of reactants and products in a laminar flow diffusive mixing environment in which distinctive thermal and concentration gradients exist, offers a novel method for the chemical manipulation and generation of products. In short, micro reactors are new, safe and more atom efficient tools with which to generate molecules and increase our knowledge of complex chemical processes.

The technology is still in its early development stage and it would be presumptuous at this point to expand too far on the potential applications that micro reactors will find, but some early trends are clear. In the authors' experience, reactions performed in a micro reactor invariably generate relatively pure products in high yield, in comparison to the equivalent bulk reactions, in much shorter times and in sufficient quantities to perform full instrumental characterisation. One of the immediate and obvious applications is therefore in drug and process discovery, where the generation of compounds either with different reagents or under variable conditions is an essential factor. In addition, the opportunity to establish optimal chemical processes including reaction and formulation is an exciting capability of the technology, which could be integrated to appropriate analytical instrumentation. An interesting twist to the chemistry carried out to date in the authors' laboratories is not just the opportunity to separate reactants and products in real time but also the capability to manufacture and use reagents *in situ*. In this review, a brief description of the fabrication and operation of micro reactors is outlined, followed by a detailed description of the type of reactions that can be performed in micro reactors. The environmental significance of performing the reaction in micro reactors, compared with traditional techniques, is subsequently highlighted.

2 Fabrication of micro reactors

A number of materials such as silicon, quartz, glass, metals and polymers have been used to construct micro reactors.[11] Important considerations in material choice include chemical compatibility, ease and reproducibility of fabrication, whether or not the material supports electroosmotic flow (EOF) with the solvents of interest and compatibility with detection methods. Glass is a popular choice since it allows EOF with many common solvents, is chemically inert, enables the use of visible light detection and fabrication methods are well established.

Depending on the material used, a range of channel microfabrication methods such as photolithography, hot embossing, powder blasting, injection moulding and laser micro forming are available.[18] For glass micro reactors, photolithographic fabrication of channel networks is performed as shown schematically in Fig. 1 and described in refs. 19 and 20. First, the channel network is designed and printed using suitable computer drawing software and a film negative of the desired final size is then prepared by photoreduction to form the optical mask. Commercially supplied borosilicate glass photolithographic plates (thickness 3 mm) coated with a thin metal etch mask layer (normally chromium) plus an upper layer of positive photoresist (0.5–2.0 μm depth) are used for channel network fabrication. The pattern of the required network of interconnecting channels is transferred from the optical mask to the photoresist layer. After light exposure, the photoresist is developed and removed, together with the chromium layer, to reveal the areas of glass to be etched. The channels are then etched using a mixture of 1% HF and 5% NH_4F in water at 65 °C, resulting in an etch rate of 0.3–0.5 μm min^{-1}. During the etching process it is important that the system is well agitated to ensure consistent supply of etchant to the surface plus removal of etch debris.

The base plate containing the etched channel network must next be sealed by bonding to an upper plate (17 mm thick)

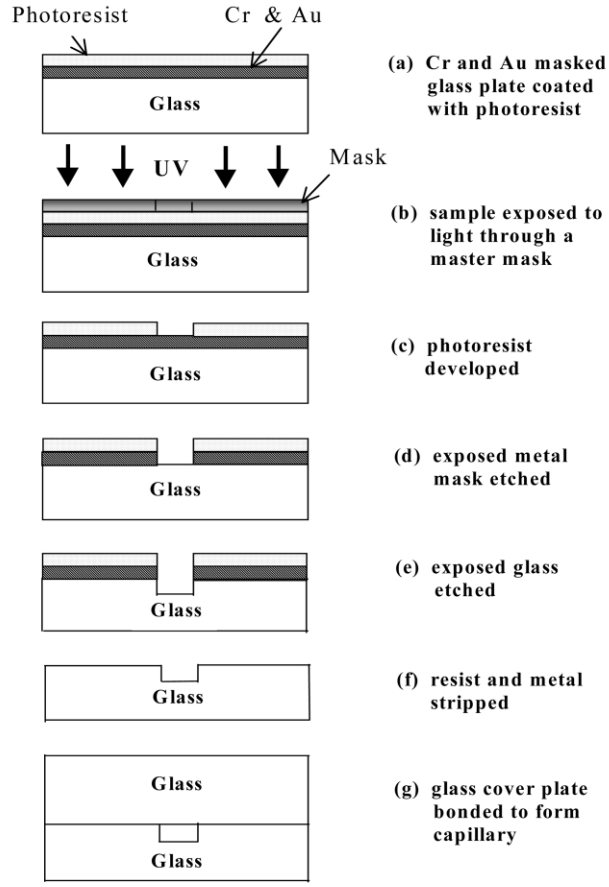


Fig. 1 Photolithographic fabrication of micro reactors.

containing pre-drilled holes which act as reservoirs for reagents and products. In our laboratories, the upper plate is aligned with the channel geometry and thermally bonded to the base plate (typically 575 °C for 3 h).[19,20] Thermal bonding is aided by placing a weighting block of non-adhering quartz of high softening temperature on the upper plate. A photograph of an all-glass device produced by the method described is shown in Fig. 2. For good thermal bonding, it is important to ensure that

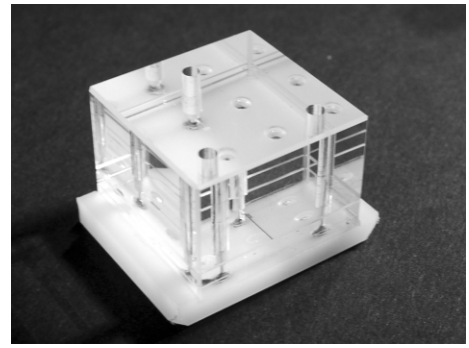


Fig. 2 A borosilicate glass micro reactor.

both the glass types of the upper and lower plates have the correct thermal softening and expansion properties. In addition, the surfaces to be bonded must be clean and flat.

More recently the thermal bonding of ceramic adaptors has enabled hydrodynamic pumping to be more effectively realised.[19] Fig. 3 shows a glass micro reactor with ceramic adaptors enabling HPLC type fittings to be connected directly to the chip.

Fabrication in polymeric materials, whilst attractive from an engineering and cost perspective, does pose a number of reagent compatibility issues. However, recently, the UK Lab on a Chip

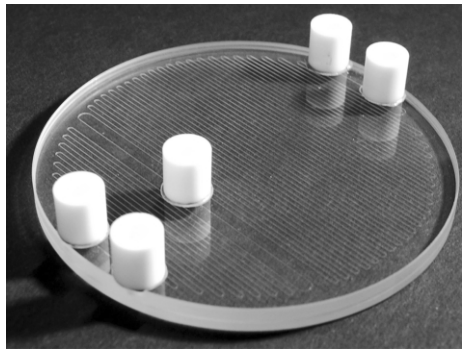


Fig. 3 Micro reactor with ceramic fittings.

Consortium project demonstrated that polymer devices with channels fabricated in SU-8 (an epoxy resin) coated on a polymer support (such as methacrylate) is relatively robust to chemical attack. The first generation of such devices (Fig. 4) are

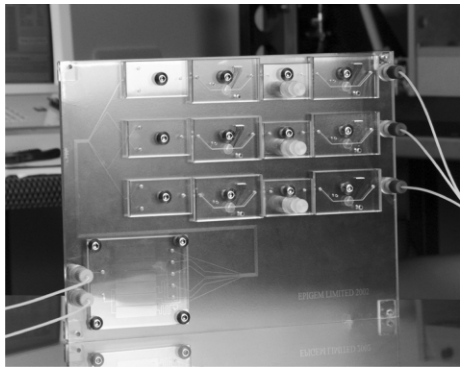


Fig. 4 Micro reactors fabricated from polymers (Photograph courtesy of Epigem Ltd.).

now being evaluated. This methodology has the advantage that the non-wetted bulk of the chip can, if desired, be fabricated from low cost commodity polymers.

Of all the fabrication media, perhaps metals are the most robust in terms of engineering requirements and more specifically, micro mixers have been constructed and applied in chemical processing. This subject is extensively reviewed in ref. 9.

3 Operation of micro reactors using electrokinetic control

Pumping of solutions around a channel network by EOF, using voltages applied *via* electrodes placed in the reservoirs, has several significant advantages over hydrodynamic based pumping methods.[21–24] It can be easily miniaturised since no mechanical moving parts are involved and the required voltage sequences can be readily applied under automated computer control. For a glass micro reactor, the channel wall–solution interface normally has a negative charge, arising from ionisation of surface groups, which are immobile. This immobile surface charge attracts a diffuse layer (of thickness of the order of nm) of mobile, oppositely charged counter-ions in the solution adjacent to the channel wall (cations for a negatively-charged glass channel wall). As shown schematically in Fig. 5, application of an electric field along the channel length causes the nm thick 'skin' of mobile cations to move towards the more negative electrode, which drags all the intervening solution in the bulk of the channel with it. An important feature of EOF is that the liquid EOF velocity is constant across the channel except in the nm thick regions of the diffuse layer of counter-

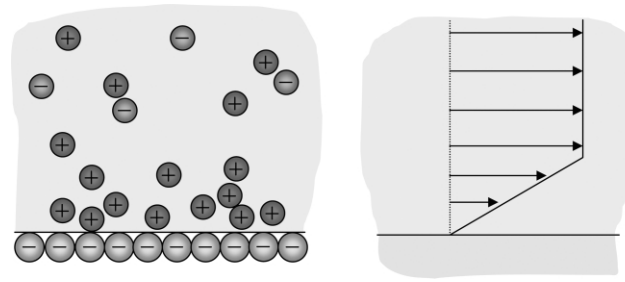


Fig. 5 Profile of electroosmotic flow.

ions very close to the wall. Unlike EOF, pressure-driven flow produces a parabolic velocity profile with high velocities in the channel centre and slow velocities near to the wall, giving rise to increased 'blurring' of reagent zones along a channel length. Imaging of the different velocity profiles induced by EOF and pressure-driven flow has been described by Paul *et al.*[25] It should however be emphasised, that under EOF control, charged solutes move with an electrophoretic velocity in addition to the EOF of the solvent.

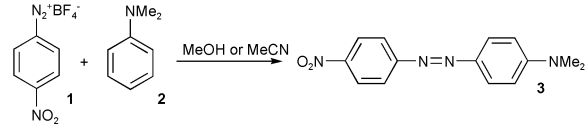
It should be stressed, that for EOF to be achieved polar solvent types need to be used (*e.g.* methanol, DMF, DMSO *etc.*). Clearly this limitation could reduce the scope of micro reactor applications, however the authors are currently developing a combined electrokinetic/hydrodynamic pumping method for manipulating reactants, intermediates and products within a micro reactor device. Such a system offers wider solvent and reagent capability, whilst still enabling the electrophoretic mobility of chemical species to be exploited.

4 Reactions performed in micro reactors

The following section reviews the chemical reactions that have been performed within micro reactor systems to date. The review is divided into three sections, concentrating on solution phase synthesis, catalysed reactions and finally gas phase synthesis.

4(a) Liquid phase reactions

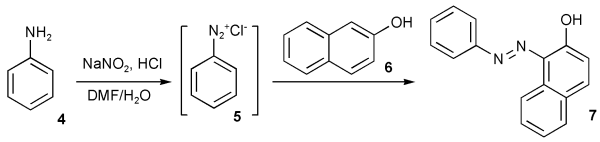
The diazotization of aromatic amines is an industrial process of great importance, however the dangers of diazotization are well known. The explosive nature of diazonium salts necessitates extreme care hence the low volume associated with micro reactors affords a safe route to perform such reactions. Salimi-Moosavi *et al.*[26] have demonstrated the synthesis of diazo dyes within a micro reactor. The authors have reacted 4-nitrobenzenediazonium tetrafluoroborate **1** with *N*,*N*-dimethylaniline **2** in a micro reactor fabricated from glass, to give the red diazo compound **3** (Scheme 1). The reagents were mobilised in



Scheme 1

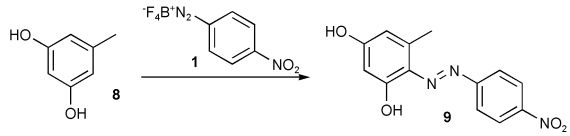
the reactor, using EOF in either a protic (methanol) or an aprotic (acetonitrile) solvent, to give conversions of 37 and 22%, respectively.

In comparison Wootton *et al.*[27] have demonstrated the synthesis of azo dyes using hydrodynamic pumping within a micro reactor. The authors demonstrated that aniline **4** could be converted into the diazonium salt **5** before being reacted *in situ* with β-naphthol **6** to form the azo dye **7** in up to 52% overall conversion (Scheme 2).



Scheme 2

Hisamoto *et al.*[28] have described the first example of a phase-transfer reaction in a micro reactor. The authors have successfully conducted a phase-transfer diazo coupling reaction in which a solution of 5-methylresorcinol **8** in ethyl acetate was reacted with an aqueous solution of 4-nitrobenzenediazonium tetrafluoroborate **1** to form the azo dye **9** (Scheme 3). Syringe

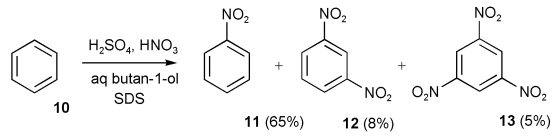


Scheme 3

pumps were used to move the reagents around the reactor manifold and the authors report that the product was isolated in 100% yield.

Nitration reactions also represent an important but hazardous process, in which the use of excess quantities of concentrated nitric and sulfuric acids are used. The reactions are extremely exothermic and it is hence difficult to control the temperature of such reactions when performed on a large scale. As a result, micro reactors have a considerable attraction for these reactions because the reactor enables not only excellent temperature control of the reaction but also product selectivity.

Doku *et al.*[29] have reported the nitration of benzene **10** in a borosilicate glass micro reactor. The benzene was mobilised by electroosmotic flow as a microemulsion using the surfactant, sodium dodecyl sulfate (SDS). The nitronium ions, which were produced *in situ* by mixing sulfuric and nitric acids, underwent electrophoretic-induced mobility (*i.e.* the ions not the reagents moved). A co-solvent, butan-1-ol, was used to enhance the solubility of the benzene in the aqueous system. The authors report that mononitration occurs in 65% conversion to give nitrobenzene **11** (Scheme 4) and that approximately 8% of

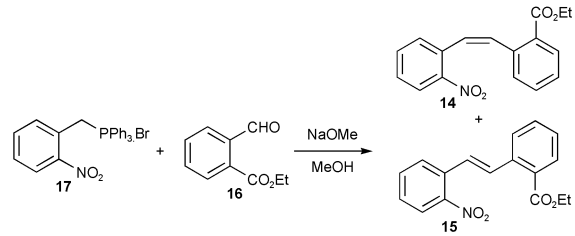


Scheme 4

1,3-dinitrobenzene **12** and 5% of 1,3,5-trinitrobenzene **13** were obtained. Importantly, Doku *et al.* demonstrated that it is possible to mobilise a non-polar liquid, such as benzene, using EOF by dissolving it in a two-phase microemulsion system.

Burns and Ramshaw[30] have also investigated the nitration of benzene and toluene in a micro reactor. They have reported that the conversion has a linear relationship with temperature. More interestingly, they have demonstrated that the conversion may be increased, by reducing the dimensions of the micro reactor channels. They found that reducing the capillary diameter from 250 to 130 nm more than doubled the rate of nitration. The flow rates were additionally determined to be critical, with faster flow rates giving higher conversions. The authors postulate that the increased flows promoted increased mixing within the channels.

Skelton *et al.* have reported the application of micro reactors, prepared from borosilicate glass, for the Wittig reaction.[31,32] The authors used the micro reactor to prepare the *cis*- and *trans*-nitrostilbene esters **14** and **15** using the Wittig reaction (Scheme 5). A number of features such as stoichiometry and stereochemistry were investigated. When two equivalents of the aldehyde **16** to the phosphonium salt **17** were used in the reaction, a conversion of 70% was achieved. The micro reactor

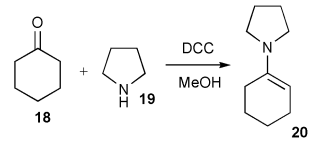


Scheme 5

demonstrated an increase in reaction efficiency of 10% over the traditional batch synthesis. The reaction stoichiometry was subsequently reduced to 1:1, but using a continuous flow of reagents, as above, the conversion was poor (39%). The conversion was increased to 59% using an 'injection' technique, where 'slugs' of the phosphonium salt **17** were injected into a continuous flow of the aldehyde **16**.

The research was further extended to investigate the stereochemistry of the reaction. The ratio of isomers **14** and **15** was controlled by altering the voltages applied to the reagent reservoirs within the device, which in turn affected the EOF and electrophoretic mobility of the reagents. The variation in the external voltage subsequently altered the relative reagent concentration within the device, producing *cis*/*trans* ratios in the region 0.57–5.21. In comparison, the authors report that, when a traditional batch synthesis was performed based on the same reaction time, concentration, solvent and stoichiometry, a *cis*/*trans* ratio of approximately 3:1 was observed. This demonstrated that significant control was possible in a micro reactor compared with batch reactions.

Sands *et al.*[33] have recently reported the preparation of enamines in a micro reactor. Enamines are traditionally prepared under Dean and Stark conditions, where the ketone and secondary amine are heated to reflux in toluene. These conditions remove the water from the reaction to produce the equilibrium-dependent enamine. Using the micro reactor, cyclohexanone **18** was reacted with pyrrolidine **19** using methanol as the solvent, in the presence of dicyclohexylcarbodiimide (DCC), to form the enamine **20** in 42% conversion at room temperature (Scheme 6). Clearly the use of



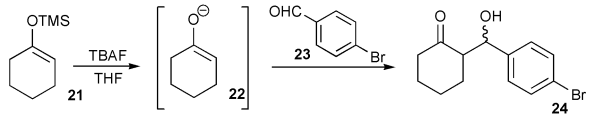
Scheme 6

methanol as solvent at room temperature, compared with the traditional conditions, represents a more environmentally friendly procedure. In this case also, the electrophoretic mobility of the product is thought to be greater than that of water, so enabling product separation and purification *in situ*.

Carbanion chemistry is one of the most common methods of C–C bond formation used in the pharmaceutical industry. In such reactions large volumes of highly pyrophoric bases are frequently employed. In addition, large quanties of heat are frequently generated which means that careful control of the temperature, to prevent by-product formation, is required. Hence, micro reactors have a considerable attraction for these reactions because the reactor enables excellent temperature control of the reaction.

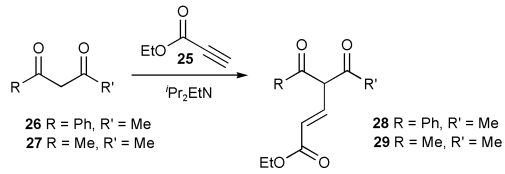
Wiles *et al.*[34] have recently demonstrated the use of silyl enol ethers in the aldol reaction within a micro reactor. Quantitative conversion of the silyl enol ethers to β-hydroxyketones was observed in 20 min compared to traditional batch systems, where quantitative yields were only obtained when extended reaction times of up to 24 h were employed. One example involved the treatment of the TMS enol ether **21** with tetra-*n*-butylammonium fluoride (TBAF), to generate the tetra-*n*-

butylammonium enolate **22** *in situ*, followed by condensation with *p*-bromobenzaldehyde **23** to give the β-hydroxyketone **24** in 100% conversion (Scheme 7).



Scheme 7

Wiles *et al.*[35] have also reported the preparation of the enolates from a series of 1,3-diketones using an organic base and their subsequent reaction with a variety of Michael acceptors such as **25** to afford 1,4-addition products within a micro reactor (Scheme 8).

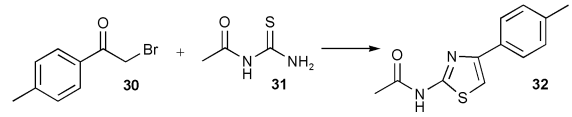


Scheme 8

When using a continuous flow of the reagents **25** and **26**, 15% conversion to the adduct **28** was observed, compared with 56% when the diketone **27** was reacted with **25** forming the Michael adduct **29**. The authors, however, demonstrated enhancements in conversions through the application of the stopped flow technique. This procedure involved the mobilisation of reagents through the device for a designated period of time, using an applied field, and the flow was subsequently paused by the removal of the applied field, prior to re-applying the field. Using the regime of 2.5 s on and 5 s off, the conversion to the product **28** was improved to 34%, while lengthening the stopped flow period to 10 s, resulted in a further increase to 100%. This was compared to the preparation of **29**, in which the regime of 2.5 s on and 5 s off resulted in an increase in conversion to 95%. This demonstrated that the enolate of 2,4-pentanedione **27** was more reactive than the corresponding enolate of benzoyl acetone **26**. The authors propose that the observed increase in conversion, when using the technique of stopped flow, was due to an effective increase in residence time within the device corresponding to the different kinetics associated with these reactions. This approach is clearly relevant to those wishing to study reaction kinetics of such reactions.

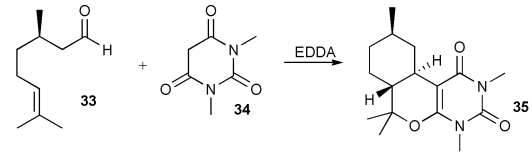
Although the previous result demonstrates the ease with which reaction conditions may be optimised, it is still sometimes necessary to heat reactions in order to achieve high yields of products. Industrially, special equipment is required when performing large-scale reactions at elevated temperature. However, Garcia-Egido *et al.*[36] at GlaxoSmithKline have demonstrated the synthesis of 2-aminothiazoles using a Hantzsch synthesis within a micro reactor. The paper represents the first example of a heated reaction using an organic solvent, within a glass micro reactor under EOF conditions. During the experiments the T-shaped micro reactor was heated to 70 °C using a Peltier heater, which was aligned with the channels and the heat generated by the device was applied to the base of the micro reactor. Reaction of α-bromoketone **30** with thiourea **31**, using *N*-methylpyrrolidine (NMP) as solvent, resulted in the preparation of aminothiazole **32** in up to 85% conversion (Scheme 9).

Fernandez-Suarez *et al.*[37] have reported the synthesis of cycloadducts in a micro reactor using hydrodynamic driven flow. The reactions consisted of Knoevenagel condensation of an aldehyde **33** with a 1,3-diketone **34** in the presence of



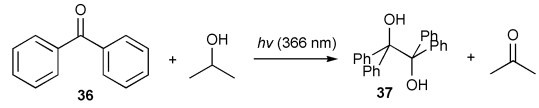
Scheme 9

ethylenediamine acetate (EDDA) as catalyst, in aqueous methanol as solvent. The reaction intermediate underwent an intramolecular hetero-Diels–Alder reaction to form cycloadduct **35** in 60–68% conversion (Scheme 10).



Scheme 10

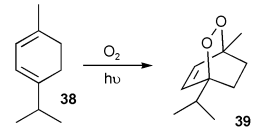
Environmentally attractive photochemically induced reactions are problematic on a large scale because many chemical species strongly absorb the light, effectively reducing the path length, even when powerful irradiation is used. Hence better results are obtained when the desired reaction is scaled down in size and Jenson and coworkers[38] have reported a photochemical reaction within a micro reactor. The reactor was fabricated by bonding a patterned silicon wafer to a quartz wafer, the advantage of this fabrication technique being that the quartz substrate allows reaction and detection using UV light of lower wavelengths than permitted by Pyrex substrates. The authors investigated the pinacol formation reaction of benzophenone **36** using propan-2-ol as solvent (Scheme 11). The reaction is



Scheme 11

known to follow a radical reaction pathway[39] and it is reported that the longer the residence time of the reaction, the greater the conversion to benzopinacol **37**. The authors report that there was no detectable product formation for flow rates greater than 10 μl min^{-1}. With reduced flow rates, having larger residence times, the conversion improves because the amount of light absorbed increases and there is therefore sufficient time for the excited species to diffuse and react with the benzophenone. The authors report conversions of up to 60% when using flow rates of 4 μl min^{-1}.

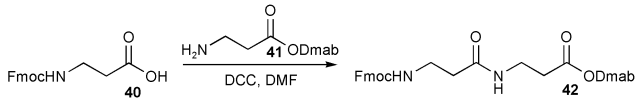
Using a similar approach Wootton *et al.*[40] investigated the photochemical generation of singlet oxygen within micro reactors. The technique allows the generation of singlet oxygen without the inherent dangers of forming large quantities of potentially explosive oxygenated solvents. The singlet oxygen was formed within the reactor channel by irradiation with a 20 W, 6 V tungsten lamp. The authors have used the aforementioned conditions to convert α-terpinene **38** into ascaridole **39** (Scheme 12) in greater than 80% conversion. For safety,



Scheme 12

nitrogen degassing of the product mixture was undertaken as soon as the solution was collected, hence avoiding accumulation of oxygenated solvents.

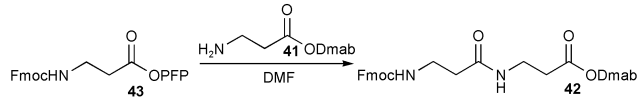
Watts *et al.* have recently demonstrated the first example of a multi-step synthesis in a micro reactor where they have used their devices in peptide synthesis.[41,42] The authors evaluated the reactor using a carbodiimide coupling reaction of Fmoc-β-alanine **40** (Fmoc = fluorenylmethoxycarbonyl) with the amine **41** to give the dipeptide **42** (Scheme 13). When stoichiometric



Scheme 13

quantities of the reagents were used, only *ca.* 10% conversion to the dipeptide **42** was achieved. By using two equivalents of dicyclohexylcarbodiimide (DCC), however, an increase in conversion to *ca.* 20% was observed and by applying a stopped flow technique (2.5 s injection length with stopped flow for 10 s), the conversion of the reaction was further increased to approximately 50%. Using five equivalents of DCC, a conversion of up to 93% of the dipeptide **42** was obtained using the stopped flow technique.

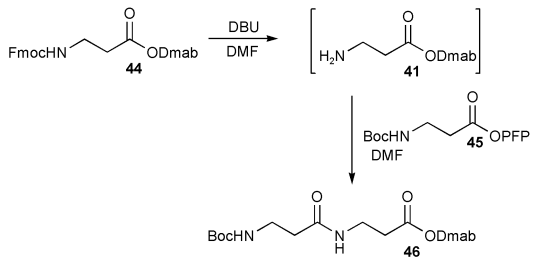
The authors also demonstrated that the dipeptide could be prepared from pre-activated carboxylic acids.[41,42] They report that the reaction of the pentafluorophenyl (PFP) ester of Fmoc-β-alanine **43** with the amine **41** gave the dipeptide **42** quantitatively in 20 min (Scheme 14). This represented a



Scheme 14

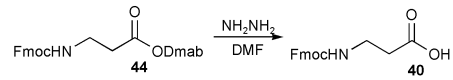
significant increase in yield compared with the traditional batch synthesis, where only a 50% yield was obtained in 24 h.

Having demonstrated that peptide bonds could be successfully formed when using a micro reactor, the authors then found that they could extend the methodology to the preparation of longer-chain peptides. Using the micro reactor, the Dmab ester (Dmab = 4-[*N*-(1-(4,4-dimethyl-2,6-dioxocyclohexylidene)-3-methylbutyl)-3-amino]benzyl) of Fmoc-β-alanine **44** was reacted with one equivalent of piperidine or 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU)[43,44] to give the free amine **41** in quantitative conversion. This is in comparison to solid phase peptide synthesis where 20% piperidine in DMF is frequently employed, which demonstrates the atom efficiency of reactions performed within the devices. The authors then reacted the amine *in situ* with the pentafluorophenyl ester **45** to give the dipeptide **46** (Scheme 15) in 96% overall conversion.



Scheme 15

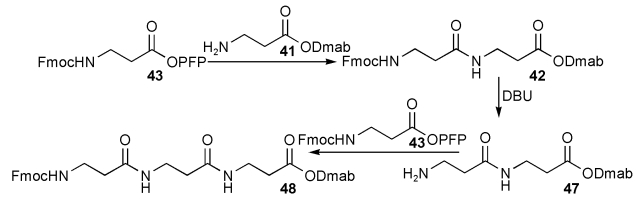
Having shown that more complex peptides could be produced by removal of the *N*-protecting group, the authors then demonstrated that they could remove the Dmab ester using hydrazine. The reaction of the Dmab ester **44** with one equivalent of hydrazine resulted in quantitative deprotection, to afford the carboxylic acid **40** (Scheme 16). This is in



Scheme 16

comparison to the solid phase peptide synthesis where 2% hydrazine in DMF is generally required to effect complete deprotection.[45]

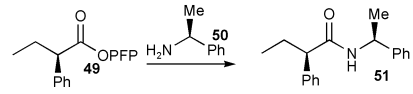
The authors have further extended the approach to the synthesis of tripeptide **48**.[42] Reaction of pentafluorophenyl ester **43** with amine **41** formed dipeptide **42**, which was reacted with DBU to effect Fmoc deprotection. The amine **47** was then reacted *in situ* with another equivalent of pentafluorophenyl ester **43** to prepare tripeptide **48** in 30% overall conversion (Scheme 17). The approach clearly demonstrates that inter-



Scheme 17

mediates may be generated *in situ* and used in subsequent reactions. Although in the above examples the intermediates are relatively non-toxic, it is postulated that the approach may be used to generate highly toxic reagents *in situ*, that one would rather not use in a large-scale synthesis.

Having demonstrated that peptide bonds could be successfully formed when using a micro reactor, the authors then investigated racemisation in peptides derived from α-amino acids.[46] Reaction of the pentafluorophenyl ester of (*R*)-2-phenylbutyric acid **49**, at 0.1 M concentration, with α-methylbenzylamine **50**, gave the product **51** in quantitative conversion with 4.2% racemisation (Scheme 18). Importantly

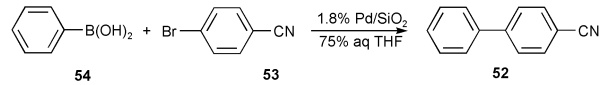


Scheme 18

there was less racemisation than observed in the batch reaction at the same concentration and temperature. The reduced level of racemisation was attributed to the reduced reaction times observed within the micro reactors.

4(b) Catalytic reactions

Greenway *et al.* have demonstrated the Suzuki reaction within a micro reactor.[47] This represented an example of heterogeneous catalysis where 1.8% palladium on silica was placed in the central channel of the micro reactor. The catalyst was immobilised between microporous silica frits prepared from potassium silicate and formamide. The micro reaction was optimised using flow injection analysis principles, producing a conversion of 67% of cyanobiphenyl **52** at room temperature. The flow injection method adopted allowed the periodic injection of the aryl halide **53** into a continuous flow of the phenylboronic acid **54** (Scheme 19). Traditionally, tetra-



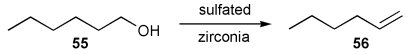
Scheme 19

hydrofuran (THF) is used as the solvent in this reaction, however as has been found with many organic solvents THF has

very low natural EOF properties and for this reason, it was mixed with water (75:25) for use in the reaction. The yields obtained were comparable with Suzuki reactions on a batch scale using homogeneous catalysis. Importantly, there were negligible levels of the palladium catalyst in the product, which was demonstrated using inductively coupled-mass spectrometry (ICP-MS), this illustrating that the catalyst was not leaching from the reactor.

One of the interesting observations of the reaction was that, unlike conventional Suzuki reactions, an additional base was not required. Although the exact reason for this is not clear, it is postulated that the electric field may be sufficient to cause ionisation of the water at the catalyst surface. It is feasible that the hydroxide formed in this way may be sufficient to perform the function of the conventional organic or inorganic base. Alternatively, it has been subsequently proposed that a more basic environment may be formed at the surface of the micro reactor. Once again this effect could have wider implications in the field of clean chemistry.

Wilson and McCreedy[48] have reported the use of a micro reactor to perform the dehydration of hexan-1-ol to hex-1-ene, using a sulfated zirconia catalyst. The micro reactor was fabricated from a glass plate, which was etched using photolithography. A PDMS top block, with pre-drilled holes to act as reservoirs for the reagents, was then aligned with the channel geometry. In order to introduce the catalyst into the micro reactor, it was dusted over the surface of the PDMS face before the base plate was joined to the top plate. This process immobilised the catalyst, while simultaneously increasing its surface area. The overall effect was to produce a catalytically-active wall of the microchannel. A heater, fabricated from Nichrome wire, was also immobilised in the top plate. Pumping was produced with a syringe pump and the products were analysed by gas chromatography (GC). The conversion of hexan-1-ol **55** to hex-1-ene **56** was between 85 and 95% with no additional products being detected (Scheme 20). This yield is



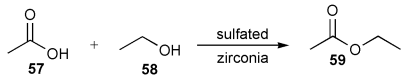
55 56

Scheme 20

extremely good when compared to the 30% yield expected for the industrially used process.

The reaction was also applied to ethanol. At a reaction temperature of 155 °C and using a syringe pump at a flow rate of 3 μl min^{-1}, the product collected was found to contain 68% ethene, 16% ethane and 15% methane, together with trace amounts of ethanol. When electroosmotic pumping was used, the flow rate was between 0.9 and 1.1 μl min^{-1} at a field strength of 200 V cm^{-1}. The only detectable product was methane, indicating that the reaction had progressed beyond dehydration to complete cracking of the ethanol. Additionally, trace amounts of methanol were present in the product. It is proposed that the slow flow rate of the electroosmotic pumping, resulted in longer residence times in the reactor. EOF however cannot be applied to all reactions because organic reactants, such as hexanol, exhibit no natural EOF under an applied potential.

The authors used the same device to investigate esterification reactions, where a 1:1 mixture of acetic acid **57** and ethanol **58** was pumped through the micro reactor using a syringe pump at a flow rate of 2 μl min^{-1} to produce ethyl acetate **59** (Scheme 21).[49] By increasing the temperature of the reaction from room temperature to 180 °C, the conversion of the reaction was



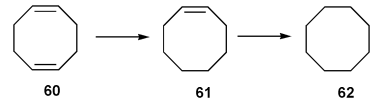
57 58 59

Scheme 21

increased to about 30%. Although the preliminary yield was not great, the procedure has environmental advantages compared to the traditional conditions used in esterification reactions.

4(c) Gas phase reactions

Hönicke and coworkers[50] have reported the gas phase partial oxidation of cyclic dienes, to their corresponding monoalkenes, over palladium and ruthenium/zinc catalysts. The micro reactors consisted of aluminium wafers, with mechanically-etched channels, which were activated by anodic oxidation to obtain a porous oxide layer, which was used as the catalyst support. Impregnation of an organic solution of palladium(II) acetylacetonate resulted in microchannels consisting of an 18 μm thick layer of 0.18% Pd catalyst. The wafers were then stacked in a stainless steel housing to form a micro reactor consisting of 672 microchannels for a stream of reagents to pass through. The authors used the device to investigate the hydrogenation of 1,5-cyclooctadiene **60** to cyclooctene **61** (Scheme 22). The diene **60** was vapourised and mixed with

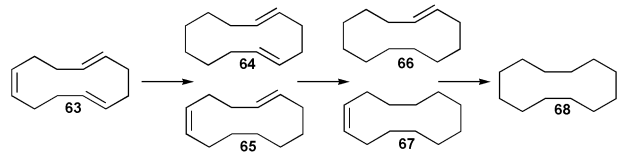


60 61 62

Scheme 22

hydrogen, before being passed through the micro reactor at a temperature of 150 °C. By increasing the residence time of the reaction from 35 to 115 ms the authors report that the conversion increased from 75 to 99.5%. Although the increased residence time resulted in increased quantities of cyclooctane **62** being formed, the selectivity of cyclooctene **61** decreased from 99.5 to 98% under these conditions. The procedure represented a novel method for the immobilisation of potentially toxic catalysts, hence the process has possible environmental advantages.

The authors used the same device to investigate the hydrogenation of *cis*,*trans*,*trans*-1,5,9-cyclododecatriene **63** to the cyclododecenes **64** and **65** (Scheme 23). At a temperature of

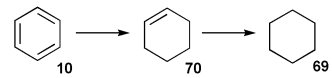


63 64 65 66 67 68

Scheme 23

150 °C, a selectivity of 85 to 90% was reported, where the conversion was approximately 90%. The selectivity of this reaction was lower than the previous example because of the formation of the by-products **66**, **67** and **68**. It was demonstrated, however, that there was a selectivity advantage of the micro reactor compared to a fixed-bed reactor.

The catalytic hydrogenation of benzene **10** was also investigated (Scheme 24), but complete reduction to cyclohexane **69**



10 70 69

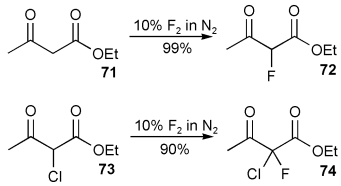
Scheme 24

was observed to take place when using the Pd catalyst. The authors report that hydrogenation of benzene to cyclohexene **70** was accomplished using a micro reactor system consisting of a ruthenium/zinc catalyst, which was incorporated into the micro reactor using the same methodology, but the conversions were

reported to be low (*ca* 10%), with a maximum selectivity of 36%.

The use of elemental fluorine in organic synthesis is problematic as a result of the difficulties associated with the safe handling of gaseous fluorine.[51,52] In addition, fluorination reactions are generally extremely exothermic and it is difficult to control the temperature of such reactions when performed on a large scale. Micro reactors have considerable attraction for direct fluorination processes because there is only a small amount of fluorine in the reactor at any given time. The micro reactor enables excellent temperature control of the reaction as well as an opportunity for scale up, by the simultaneous use of many such reactors.

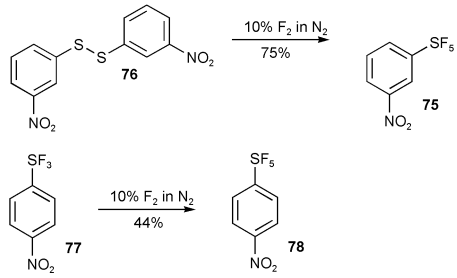
Chambers and Spink[53,54] have reported the use of micro reactors for the fluorination and perfluorination of organic compounds using elemental fluorine. A nickel or copper micro reactor was used for the investigation and the liquid reactants and solvents were introduced into the reaction chamber *via* a syringe using a syringe-pump. Fluorine, in a nitrogen carrier gas, was introduced from a cylinder using a mass-flow controller. The liquid-gas mixing proceeded *via* 'cylindrical flow', where the liquid forms an outer cylinder coating the reactor surface with the gas flowing through the centre. This flow regime has enormous benefits in that it provides very large surface-to-volume ratios for the liquid phase, producing a very efficient reaction over a short distance. The products were trapped in a tube, which was cooled with either a salt/ice bath (0 °C) or an acetone/carbon dioxide bath (−78 °C). The fluorination of β-dicarbonyl compounds proceeded with a high efficiency using 10% fluorine in nitrogen at 5 °C and with formic acid as the solvent. Ethyl acetoacetate **71** was fluorinated in 99% conversion to give ethyl 2-fluoroacetoacetate **72** while ethyl 2-chloroacetoacetate **73** was fluorinated in 90% conversion, yielding ethyl 2-chloro-2-fluoroacetoacetate **74** (Scheme 25). Importantly, under these conditions, no perfluorination of



Scheme 25

the substrates was observed, with only the monofluorinated derivatives being isolated. The authors report that the bulk fluorination of ethyl 2-chloroacetoacetate **73** gives only a low conversion to **74**,[55] illustrating that the flow system is more efficient. This illustrates the catalytic effect of the fluorinated metal surface.

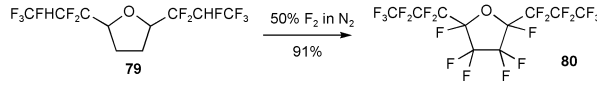
Sulfur pentafluoride derivative **75** was prepared in 75% yield by the reaction of the disulfide **76** with 10% fluorine in nitrogen, using acetonitrile as the solvent (Scheme 26). Similarly,



Scheme 26

treatment of the trifluoride **77** with fluorine gave sulfur pentafluoride derivative **78** in 44% yield.

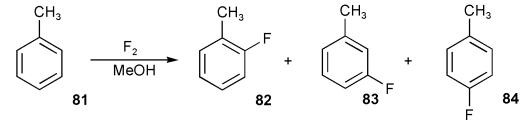
Perfluorination reactions were found to require an additional heating stage for the reaction to go to completion. The reaction of the tetrahydrofuran derivative **79** with 50% fluorine in nitrogen at 280 °C gave the perfluorinated compound **80** in 91% yield (Scheme 27). In conventional reactions, cobalt trifluoride



Scheme 27

would be used to perfluorinate hydrocarbons.[56] Some of the reactions carried out by the authors, however, required much lower temperatures than would be expected if this compound was used.

Jenson and coworkers have also demonstrated the direct fluorination of aromatic compounds in a micro reactor, a process difficult to perform on a conventional scale.[57] The reactor was fabricated from silicon and capped with Pyrex using anodic bonding. The surfaces of the reactor, which were in contact with the reagents, were coated with a nickel film using a metal deposition technique. The authors have used the micro reactor in the fluorination of toluene **81** at room temperature (Scheme 28). Using ten equivalents of fluorine, in methanol as



Scheme 28

the solvent, the authors report an 80% conversion to give the monofluorinated toluenes. The substitution pattern of the *ortho*- **82**, *meta*- **83** and *para*- **84** isomers was determined to be 4 : 1 : 2 by GC.

Srinivasan *et al.*[58] performed the partial oxidation of ammonia using a silicon-based micro reactor. Integrated heaters as well as flow and temperature sensors were fabricated into the sub-mm flow channels. The platinum catalyst was deposited in the reaction channel by electron-beam evaporation *via* a shadow mask. The gaseous reactants were fed from cylinders into the micro reactor by external mass-flow controllers, which maintained the desired flow rates. The product composition was continuously monitored using a mass spectrometer. The authors reported a change in the micro reactor exhaust composition over a range of temperatures and flow rates and they also demonstrated that the conversion and selectivity behaviour of conventional reactors could be reproduced in a micro reactor.

The effective heat transfer of micro reactors provides very accurate temperature control for both exothermic and endothermic reactions, thus eliminating undesired side reactions. An example has been reported by Hessel *et al.*,[59] who demonstrated that a micro reactor could be used to prepare hydrogen cyanide *via* the Andrussow route. In traditional laboratory reactions, the hydrogen cyanide is reported to hydrolyse to ammonia. The use of a microheat exchanger in this experiment, however, prevented this further reaction.

5 Concluding remarks

Micro reactor chemistry is currently showing great promise as a novel method on which to build new chemical technology and processes in which the reactions generally produce the desired product in higher yield and purity, in shorter periods of time, compared with traditional batch reactions. The technology is still in its early development and it would be presumptuous to expand too far on the potential applications that micro reactors will find, but some early trends are clear. One of the immediate and obvious applications is in combinatorial chemistry and drug

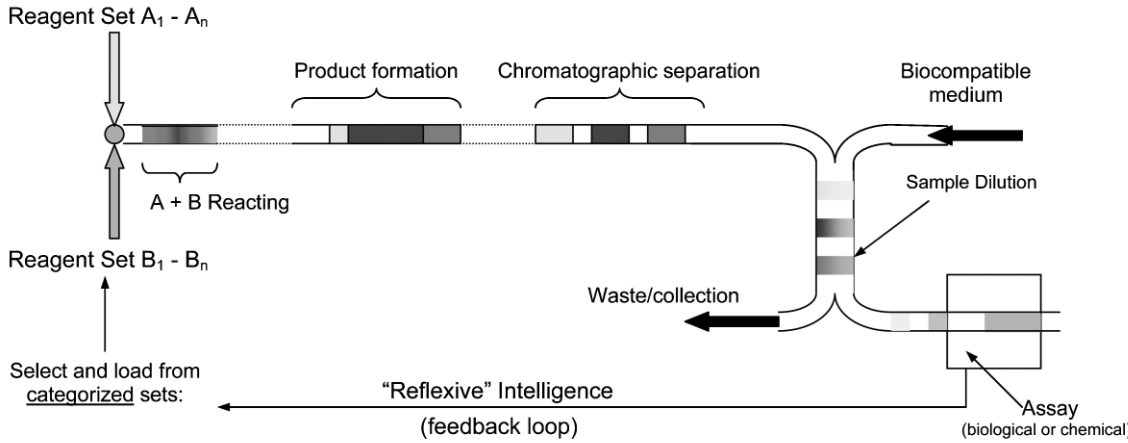


Fig. 6 Integration of a micro reactor with a biological assay system.

discovery, where the generation of compounds with different reagents or under variable conditions is an essential factor. Perhaps more intriguing, is what new angles micro reactors bring to reaction chemistry and these are only now just emerging. For example, extending the heterogeneous catalyst work already described one can see how immobilised or supported reagents could be placed within a device to impart functionality to a reaction whilst maintaining spatial and temporal control. In addition, a microchannel system also provides a potential separation column and integration of a micro reactor device to one of the many highly sensitive microchannel-based biological assay systems may therefore not only be possible, but may also address some of the pharmaceutical industries' potential requirements. Apart from the greatly reduced reaction times demonstrated for the micro reactors, handling times to assay and chemical reagent costs may be virtually eliminated. This paradigm is shown diagramatically in Fig. 6.

Reactions within the micro reactors are found to be more atom efficient, which is of significant environmental importance as this reduces the quantities of raw materials required and minimises waste. Furthermore, the technology allows the temperature of reactions to be controlled, enabling reactions to be conducted safely, where explosion may be observed if the reaction was conducted on a batch scale.

The use of solvent for purification of products is often the largest contributor to waste in a chemical process. Research is currently underway to investigate the purification of chemicals within the micro reactors by exploiting the electrophoretic mobility of the chemical species, which would not require any solvent to be moved within the reactor. This process may be further enhanced through the use of supercritical fluid and ionic liquids, which would be compatible with current micro reactor devices.

In terms of Green Chemistry, micro reactors clearly offer considerable potential in performing safer and more efficient chemical reactions by the use of novel methodologies such as solvent free mixing, *in situ* reagent generation and integrated separation techniques. The capability of producing a parallel network of micro reactors, the so called 'scaling out' of the process, offers a clear route to generating product volume on demand, at the point of use, so reducing the need to store and transport hazardous or reactive chemicals. This is where micro reactors make the greatest contribution to the publics' perception of environmentally clean chemistry.

References

1 D. Bradley, *Eur. Chem.*, 1999, **1**, 17.
2 P. D. I. Fletcher and S. J. Haswell, *Chem. Br.*, 1999, **35**, 38.
3 S. Cowen, *Chem. Ind. (London)*, 1999, 2nd Aug., 584.
4 T. McCreedy, *Chem. Ind. (London)*, 1999, 2nd Aug., 588.
5 D. Barrow, J. Cefai and S. Taylor, *Chem. Ind. (London)*, 1999, 2nd Aug., 591.
6 J. Cooper, D. Disley and T. Cass, *Chem. Ind. (London)*, 2001, 15th Oct., 653.
7 P. D. I. Fletcher, S. J. Haswell, E. Pombo-Villar, B. H. Warrington, P. Watts, S. Y. F. Wong and X. Zhang, *Tetrahedron*, 2002, **58**, 4735.
8 *IMRET 5: Proceedings of the Fifth International Conference on Microreaction Technology*, ed. M. Matlosz, W. Ehrfeld and J. P. Baselt, Springer, Berlin, 2002.
9 W. Ehrfeld, V. Hessel and H. Löwe, *Microreactors: New Technology for Modern Chemistry*, Wiley-VCH, Weinheim, 2000.
10 S. J. Haswell, *Analyst*, 1997, **112**, 1R.
11 A. Manz, D. J. Harrison, E. Verpoorte, J. C. Fettinger, H. Ludi and H. M. Widmer, *Chimia*, 1991, **45**, 103.
12 A. Manz, D. J. Harrison, E. Verpoorte and H. M. Widmer, *Adv. Chromatogr.*, 1993, **33**, 1.
13 A. Manz, C. S. Effenhauser, N. Burggraf, E. Verpoorte, D. E. Raymond and H. M. Widmer, *Anal. Mag.*, 1994, **22**, 25M.
14 *Proceedings of the Micro Total Analytical Systems '98 Workshop*, ed. D. J. Harrison and A. van den Berg, Kluwer Academic Press, Dordrecht, 1998.
15 A. van den Berg and T. S. J. Lammerink, *Top. Curr. Chem.*, 1998, **194**, 21.
16 D. J. Harrison, K. Fluri, K. Seiler, Z. H. Fan, C. S. Effenhauser and A. Manz, *Science*, 1993, **261**, 895.
17 S. C. Jacobson, R. Hergenroder, L. B. Koutny and J. M. Ramsey, *Anal. Chem.*, 1994, **66**, 1114.
18 M. Madou, *Fundamentals of Microfabrication*, CRC Press, Boca Raton, FL, 1997.
19 T. McCreedy, *TrAC, Trends Anal. Chem.*, 2000, **19**, 396.
20 T. McCreedy, *Anal. Chim. Acta.*, 2001, **427**, 39.
21 J. Th. G. Overbeek in *Colloid Science*, ed. H. R. Kruyt, Elsevier, Amsterdam, 1952, vol. 1, ch. V, p. 195.
22 C. L. Rice and R. Whitehead, *J. Phys. Chem.*, 1965, **69**, 4017.
23 R. J. Hunter, *Zeta Potential in Colloid Science*, Academic Press, London, 1981.
24 J. Jednacak, V. Pravdic and W. Haller, *J. Colloid Interface Sci.*, 1974, **49**, 16.
25 P. H. Paul, M. G. Garguilo and D. J. Rakestraw, *Anal. Chem.*, 1998, **70**, 2459.
26 H. Salimi-Moosavi, T. Tang and D. J. Harrison, *J. Am. Chem. Soc.*, 1997, **119**, 8716.
27 R. C. R. Wootton, R. Fortt and A. J. de Mello, *Lab Chip*, 2001, **2**, 5.
28 H. Hisamoto, T. Saito, M. Tokeshi, A. Hibara and T. Kitamori, *Chem. Commun.*, 2001, 2662.
29 G. N. Doku, S. J. Haswell, T. McCreedy and G. M. Greenway, *Analyst*, 2001, **126**, 14.
30 J. R. Burns and C. G. Ramshaw, *IMRET 4: 4th International Conference of Micro Reaction Technology Topical Conference Proceedings, AIChE Spring National Meeting*, March 5–9, 2000, Atlanta, GA, USA, p. 133.
31 V. Skelton, G. M. Greenway, S. J. Haswell, P. Styring, D. O. Morgan, B. Warrington and S. Y. F. Wong, *Analyst*, 2001, **126**, 7.
32 V. Skelton, G. M. Greenway, S. J. Haswell, P. Styring, D. O. Morgan, B. Warrington and S. Y. F. Wong, *Analyst*, 2001, **126**, 11.
33 M. Sands, S. J. Haswell, S. M. Kelly, V. Skelton, D. O. Morgan, P. Styring and B. H. Warrington, *Lab Chip*, 2001, **1**, 64.

34 C. Wiles, P. Watts, S. J. Haswell and E. Pombo-Villar, *Lab Chip*, 2001, **1**, 100.
35 C. Wiles, P. Watts, S. J. Haswell and E. Pombo-Villar, *Lab Chip*, 2002, **2**, 62.
36 E. Garcia-Egido, S. Y. F. Wong and B. H. Warrington, *Lab Chip*, 2002, **2**, 170.
37 M. Fernandez-Suarez, S. Y. F. Wong and B. H. Warrington, *Lab Chip*, 2002, **2**, 31.
38 H. Lu, M. A. Schmidt and K. F. Jenson, *Lab Chip*, 2001, **1**, 22.
39 J. N. Pitts, R. L. Letsinger, R. P. Taylor, J. M. Patterson, G. Recktenwald and R. B. Martin, *J. Am. Chem. Soc.*, 1959, **81**, 1068.
40 R. C. R. Wootton, R. Fortt and A. J. de Mello, *Org. Proc. Res. Dev.*, 2002, **6**, 187.
41 P. Watts, C. Wiles, S. J. Haswell, E. Pombo-Villar and P. Styring, *Chem. Commun.*, 2001, 990.
42 P. Watts, C. Wiles, S. J. Haswell and E. Pombo-Villar, *Tetrahedron*, 2002, **58**, 5427.
43 L. A. Carpino and G. Y. Han, *J. Org. Chem.*, 1972, **37**, 3404.
44 L. A. Carpino, B. J. Cohen, K. E. Stephens, S. Y. Sadat-Aalaee, J-H. Tien and D. E. Langridge, *J. Org. Chem.*, 1986, **51**, 3732.
45 W. C. Chan, B. W. Bycroft, D. J. Evans and P. D. White, *J. Chem. Soc., Chem. Commun.*, 1995, 2209.
46 P. Watts, C. Wiles, S. J. Haswell and E. Pombo-Villar, *Lab Chip*, 2002, **2**, 141.
47 G. M. Greenway, S. J. Haswell, D. O. Morgan, V. Skelton and P. Styring, *Sens. Actuators B*, 2000, **63**, 153.
48 N. G. Wilson and T. McCreedy, *Chem. Commun.*, 2000, 733.
49 T. McCreedy and N. G. Wilson, *Analyst*, 2001, **126**, 21.
50 E. Dietzsch, D. Hönicke, M. Fichtner, K. Schubert and G. Weißmeier, *IMRET 4: 4th International Conference of Micro Reaction Technology Topical Conference Proceedings, AIChE Spring National Meeting*, March 5–9, 2000, Atlanta, GA, USA, p. 89.
51 S. Rozen, *Acc. Chem. Res.*, 1996, **21**, 307.
52 S. T. Purrington, B. S. Kagen and T. B. Patrick, *Chem. Rev.*, 1986, **86**, 997.
53 R. D. Chambers and R. C. H. Spink, *Chem. Commun.*, 1999, 883.
54 R. D. Chambers, D. Holling, R. C. H. Spink and G. Sandford, *Lab Chip*, 2001, **1**, 132.
55 R. D. Chambers, M. P. Greenhall and J. Hutchinson, *Tetrahedron*, 1996, **52**, 1.
56 R. D. Chambers, B. Grievson, F. G. Drakesmith and R. L. Powell, *J. Fluorine Chem.*, 1985, **29**, 323.
57 N. de Mas, R. J. Jackman, M. A. Schmidt and K. F. Jenson, *IMRET 5: Proceedings of the Fifth International Conference on Microreaction Technology*, Springer, Berlin, 2002, p. 60.
58 R. Srinivasan, I-M. Hsing, P. E. Berger, K. F. Jensen, S. L. Firebaugh, M. A. Schmidt, M. P. Harold, J. J. Lerou and J. F. Ryley, *AIChE J.*, 1997, **43**(11), 3059.
59 V. Hessel, , W. Ehrfeld, K. Golbig, C. Hofman, S. Jungwirth, H. Lowe, T. Richter, M. Storz and A. Wolf, *IMRET3: Proceedings of the third conference on microtechnology*, 2000, , 151.

Critical Review

Environmentally friendly sample treatment for speciation analysis by hyphenated techniques

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Received 21st August 2002
First published as an Advance Article on the web 11th March 2003

Trace element speciation has become an important issue in different fields of science. Research interests have moved from total element composition of the sample toward characterization of species that are responsible for biochemical and geochemical behavior of the elements. In this report, two important environmental aspects of trace element speciation by hyphenated techniques are discussed. First, the analytical results that are useful in assessing pollution and evaluating possible toxicological risks followed by designing the remediation strategies are considered. On the other hand, performing the analytical procedures involves a certain environmental impact. Within this context, current hyphenated techniques are reliable analytical tools and also present relatively low environmental hazards. However, the successful application of these techniques for the analysis of complex samples relies on the use of suitable pretreatment procedures that should be considered as the main source of wastes in the analysis. Several modern sample preparation techniques offer improved efficiency and selectivity over classical extractions: short extraction times, reduced solvent utilization and possible miniaturization and automation. In this article, the advantages and limitations of solid phase extraction, solid phase microextraction and supercritical fluid extraction are discussed and their applications in trace element speciation briefly reviewed.

1 Introduction

In different environmental-related fields of science, researchers have long been aware of the possible pollution with metals or more generally, elements. A special concern has arisen with trace elements present at very low levels in all kinds of biological and environmental materials. Initially, these elements were classified into three groups: (i) essential elements referring to those with the known, specific biological function, (ii) toxic elements, potentially harmful even at low concentrations and (iii) neutral elements without any specific effect on health. This classification however, disregarded the fact that in a given eco-system, the elements are distributed among various chemical forms, which include inorganic salts, organic and bio-metallic or bio-metalloid compounds. In the last 30 years it has been recognized that the mobility, bioavailability, retention and specific biological role of an individual element depends on the physicochemical form in which it is present in different biological and environmental compartments. The variety of elemental forms or species includes those naturally occurring, those emitted from different anthropogenic activities as well as products of species transformations through living organisms. The research interest has been focused on relatively few elements (mercury, tin, lead, cadmium, arsenic, chromium *etc.*) that may have a potential impact on the Earth's eco-system.

In the case of mercury, its inorganic forms present low toxicity; however, enzymatic methylation leads to formation of highly toxic methylmercury. The accident in Minamata (1960s, Japan) showed the high risk related with uncontrolled emission of mercury. In Germany, the problem of high soil contamination was caused by mercury emission for over 200 years from the plant producing inorganic salts and different organomercurials for pesticide, fungicide and pharmaceutical uses.[1] Of high environmental concern are also the production and the extensive use of organotin compounds. In agriculture, highly toxic triorganotin compounds are used as fungicides and triphenyl- or tricyclohexyl-tin as insecticides. Tributyltin is an active component in certain marine antifouling paints. Furthermore, the industrial discharges of different intermediates formed in the synthesis of organotin compounds can not be neglected.[2] Arsenic is another element that has long been involved in the production of biocides.[3] Lower oxidation state As(III) is more toxic and unlike mercury, inorganic forms are considered more toxic than organic compounds.[4] Naturally occurring bio-methylation processes lead to the formation of different methylated arsenicals: monoethylarsonic acid, dimethylarsinic acid, arsenocholine and arsenobetaine that, among others, are important in the environment and in living organisms. The main source of lead in the environment has been through the use of tetraethyllead and tetramethyllead as antiknock agents.[5] Until the early 1970s there was little awareness of the possible eco-toxic consequences by the use of leaded gasoline. Even though the utilization of the alkyllead compounds has been regulated and in spite of different degradation and transformation processes occurring after their emission, the persistence of various lead forms in the environment is still an issue. Finally the environmental impact related with the emission of inorganic

Green Context

The generation of waste is associated mainly with the production of industrial scale quantities of products. This paper highlights the fact that a substantial amount of waste is produced in lab based activityies, even small scale processes such as those used in the preparation and running of analytical samples. In particular the extraction of analytes can be cumbersome and wasteful, and when the analyte potentially exists in several different forms, may be even more difficult to achieve accurately and cleanly. This paper reviews the problems and potential solutions in this area. ***DJM***

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 DOI: 10.1039/b208213f

chromium has to be discussed. Different chromium salts are widely used in the leather and textile industries. Trivalent chromium is an essential nutrient needed for glucose metabolism. However, hexavalent Cr has been classified as potent carcinogen.[6]

The examples given above substantiate the fact that environmental, clinical and analytical interests are moving from total element composition of the sample toward characterization of the compounds or forms (species) that govern the biochemical and geochemical behavior of the element.

In this manuscript, some basic aspects of hyphenated techniques used for analytical speciation are introduced. Modern sample pretreatment techniques with enhanced analytical performance over classical extractions are highlighted and three of them are discussed in some detail. Solid phase extraction, solid phase microextraction and supercritical fluid extraction are arguably the most environmentally friendly and reliable tools, which are very suitable for analytical speciation studies. Their possibilities and limitations are presented and some representative applications for elemental speciation are reviewed.

2 Analytical speciation of elements

The term 'speciation' was introduced in 1980s by Florence and Batley[7] for identification and quantification of different physicochemical forms of elements present in the sample. Further development has lead to the following definitions, approved by the respective IUPAC commissions:[8]

Chemical species; species < chemical elements > : specific form of a chemical element defined as to molecular, complex, electronic or nuclear structure.

Speciation analysis: < elemental analysis > : measurement of the quantities of one or more individual chemical species in a sample.

Speciation of an element; speciation: distribution of defined chemical species of an element in a system.

Elemental speciation is now an indispensable tool for studying the biogeochemistry, essentiality and/or toxicity of trace elements. It is also necessary in assessing environmental pollution with elements and in designing remediation strategies. An ideal analytical technique for speciation studies should enable specific and sensitive quantification of all elemental forms directly in the sample. Although ion-selective electrodes, stripping voltammetry, fluorimetry, spectrophotometry or nuclear magnetic resonance seem to meet species-specificity requirements, in general terms these techniques present important selectivity and sensitivity limitations.[9] Because of the lack of direct techniques, the great majority of speciation schemes involve a fractionation step followed by the element determination. In the development of any analytical procedure it is necessary to consider (a) the physicochemical properties of the species to be detected, (b) the need to preserve the natural composition and distribution of species in the sample during the procedure and, finally (c) the selectivity and detection capability of the analytical technique for quantification. Consequently, a careful design of all experimental steps is very important, including sampling, sample preparation, species separation and final quantification. The pretreatment procedures suitable for speciation analysis are usually based on "soft" techniques that minimize risk of species alteration and include: filtration, ultra-filtration, dialysis and different leaching or extraction techniques. Species separation is most often achieved by means of the chromatographic or electrophoretic techniques. Once separation is accomplished, the concentration of the species in the sample can be derived from the total elemental concentration determined in each of the fractions obtained (or in the column effluent). The primary detection devices are element-specific detectors, based on atomic absorption, emission, fluorescence or plasma-source mass spectrometric techniques. In Table 1 species of different elements are listed that are important for environmental evaluations and that have been addressed in analytical speciation studies.[1,2,10–35]

The results of elemental speciation have a direct relationship to green chemistry. These results provide reliable information on environmental pollution, they help to assess possible toxicological risks and also they are useful in designing protective and/or remediative actions. On the other hand, it has been recognized that analytical and research laboratories themselves are potential sources of environmental pollution.[36] A large number of assays produce a considerable volume of highly diversified, often toxic chemical waste. As an example, it was shown that by applying U.S. Environmental Protection Agency Method 625 a release of 5–10 million liters of methylene chloride to the atmosphere per year was possible.[37,38] An important characteristic of laboratory wastes is their complex composition. These wastes contain relatively small individual volumes, but a large variety of chemicals, which makes their safe disposal troublesome and expensive. The analytical community has already recognized this problem and a clear trend can be observed toward elimination of potentially harmful reagents and toward designing 'chemically clean' procedures.

As the methods used for analytical speciation usually involve reagent-based procedures, their applications also represent an increased ecological risk. During the separation step, different chromatographic techniques, especially gas chromatography or liquid chromatography with micro bore columns, produce small amounts of waste. Using element specific detectors, the low solvent and sample volume is completely destroyed during analysis and the combustion products from different plasma

Table 1 Important elemental species of environmental and ecological importance

Main groups of species	Examples for individual elements	Representative references
Redox states	As(III)/As(V) Cr(III)/Cr(VI) Sb(III)/Sb(V) Se(IV)/Se(VI)	10–17
Alkylmetallic species	$R_nSn^{(3-n)+}$ (R = methyl, buthyl or phenyl) R_2Hg, RHg^+ (R = methyl, ethyl) R_2Cd, RCd^+ (R = methyl) $R'_nR''_mPb^{(4-m-n)+}$ (R′ = methyl, R″ = ethyl)	1,2,18–23
Organometalloid species	MMA, DMA, AsB, AsC[a] Seleno amino acids	11,24–28
Biomolecules	Metalloproteins (Cd, Pb, Zn) Phytochelants (Cd, Co, Cu, Zn) Polysaccharides (As, Pb, Sr) Humic substances (Cd, Ni, Pb, Zn)	29,30 31,32 28 33–35

[a] MMA = monomethylarsonic acid, DMA = dimethylarsinic acid, AsB = arsenobetaine, AsC = arsenocholine.

sources are generally not harmful (nitrogen or noble gases used as plasma gas). Though these techniques generate minimal waste, their environmental impact is associated with high-energy requirements and the generation of high electromagnetic fields. The main source of waste in speciation analysis is from the sample treatment procedure. This step is obviously necessary for processing various samples with the aim to solubilize and extract the species of interest to a less complex liquid or gas phase readily accepted by a chromatographic column. Real-world liquid samples often contain complex chemical matrices and very low concentrations of the target species, so a pretreatment procedure is also needed for simplification of chemical composition and pre-concentration of analytes. Traditional solvent-based extractions present a series of disadvantages, such as poor selectivity, incomplete recoveries of species, high solvent consumption, disposal problems and long-term exposure to organic solvents. They are also cumbersome and time-consuming. Recent concerns about environmental and ecological dangers related to chemical waste disposal and emission to the atmosphere have led to the development of alternative extraction methods. These relatively modern approaches include solid phase extraction (SPE), solid phase microextraction (SPME), supercritical fluid extraction (SFE), microwave assisted extraction (MAE) or pressurized liquid extraction (PLE).

3 Hyphenated techniques in analytical speciation

The two most important features of an analytical tool suitable for speciation analysis are good selectivity and high sensitivity. The design of a suitable analytical procedure is difficult, owing to the complex composition of the real-world sample, the diversity of physicochemical forms of the element, their lability and low concentrations. The current analytical approach involves using coupled techniques, based on combining the separation and detection steps into one while operating an on-line system. The number and variety of combinations of chromatography with atomic detectors have been continuously increasing and almost every possibility for coupling (often referred to as hyphenation) has been examined.[39] However, the primary separation techniques have been gas chromatography (GC) and high performance liquid chromatography (HPLC) because of their versatility and high resolving powers. The selection of a suitable technique is always dictated by the properties of the analyte(s) (volatility, stability, polarity, electrical charge, *etc.*) as well as the sample composition. The primary chromatographic techniques used in speciation studies are listed in Table 2 together with the separation principle and the estimated environmental hazard. Because only inert gases are typically used as mobile phases in GC, these separations generate little waste. The direct applications of GC are limited to the separation of a few volatile species (tetraalkyllead, methylselenium or methylmercury species). However, the majority of elemental forms in the environment are polar or ionic forms and can be separated by GC only after suitable derivatization. The most common derivatization procedures include; (i) conversion of inorganic and small organometallic ions into volatile covalent compounds (hydrides, fully ethylated species) in aqueous media, (ii) conversion of larger alkylated cations with Grignard reagents to saturated non-polar species and (iii) conversion of ionic species to volatile chelates (dithiocarbamate, trifluoroacetone, *etc.*).[40] Including the derivatization step into analytical procedure causes an increased environmental impact for this analysis. This effect is most pronounced when Grignard reagents are used (methyl-, ethyl-, propyl-, butyl- and pentyl-magnesium chlorides or bromides), because the reaction requires non-aqueous media. The excess of derivatization reagent has to be destroyed by addition of diluted sulfuric acid. As reviewed by Szpunar *et al.*,[40] Grignard derivatization still remains the primary method for lead speciation analysis. However, in the case of other elements (tin, mercury) it has been gradually replaced by less cumbersome, less time-consuming and more environmentally friendly ethylation. Liquid chromatography allows separation of species that could not be separated by GC and it is the second technique of choice to address elemental speciation analysis. It can be assumed that the waste generated in LC separations is limited only to the mobile phase. In the case of SEC or ion exchange chromatography, the mobile phases consist of diluted, aqueous solutions of inorganic salts and buffers. Slightly higher environmental impact is associated with the use of organic solvents in reversed phase LC (Table 2). It should be mentioned that the application of low-flow and low-volume chromatographic methods (micro bore LC columns or capillary electrophoresis) with inherent analytical advantages, also enable minimization of waste.

Detection systems have used atomic absorption spectrometry or plasma source atomic emission and mass spectrometries. The advantages of using systems with multielemental capabilities involve: (i) monitoring effluents for their elemental composition with high sensitivity, (ii) determination of the target element with high selectivity over co-eluting elements, (iii) compensation of incomplete chromatographic resolution from complex matrices and (iv) detection of a number of elements virtually simultaneously.[41] In particular, the use of inductively coupled plasma–mass spectrometry (ICP–MS) is showing the most rapid growth (Fig. 1).[9,41,42] This technique allows very low detection limits for the majority of elements, has the advantages of linearity over a wide dynamic range, multi-element detection capability, and the ability to perform isotopic analysis with minimum matrix effects as compared to other detection systems.[43,44] It should be stressed that plasma-source detection systems are especially suitable for already mentioned low-flow and low-volume chromatographic methods. The advantages of such interfaces include: outstanding resolution power, low sample loading, decreased consumption of reagents in the separation step as well as better transport efficiency and better analytical performance of the plasma.

A number of excellent reviews on hyphenated techniques in trace element speciation have been recently published, that give detailed reports on the coupling and on various applications accomplished.[45–50]

Table 2 Column chromatographic methods commonly used in elemental speciation analysis together with their potential environmental hazard

Chromatographic technique	Principle of separation	Common mobile phase	Environmental hazard
GC (gas chromatography)	Volatility	Inert gas (N_2, H_2, He)	Low
LC (liquid chromatography)			
Size exclusion chromatography	Molecular size	Diluted aqueous solutions	Low
Reversed phase LC	Hydrophobicity	Aqueous/organic solutions[a]	Considerable
Reversed phase ion-pairing LC	Hydrophobicity of ion pairs	Aqueous solutions with ion-pairing reagent and organic modifier[a]	Considerable
Ion-exchange LC	Electrical charge	Diluted, aqueous solutions	Low

[a] Methanol and acetonitrile up to 30% are the most common organic modifiers used in speciation studies.

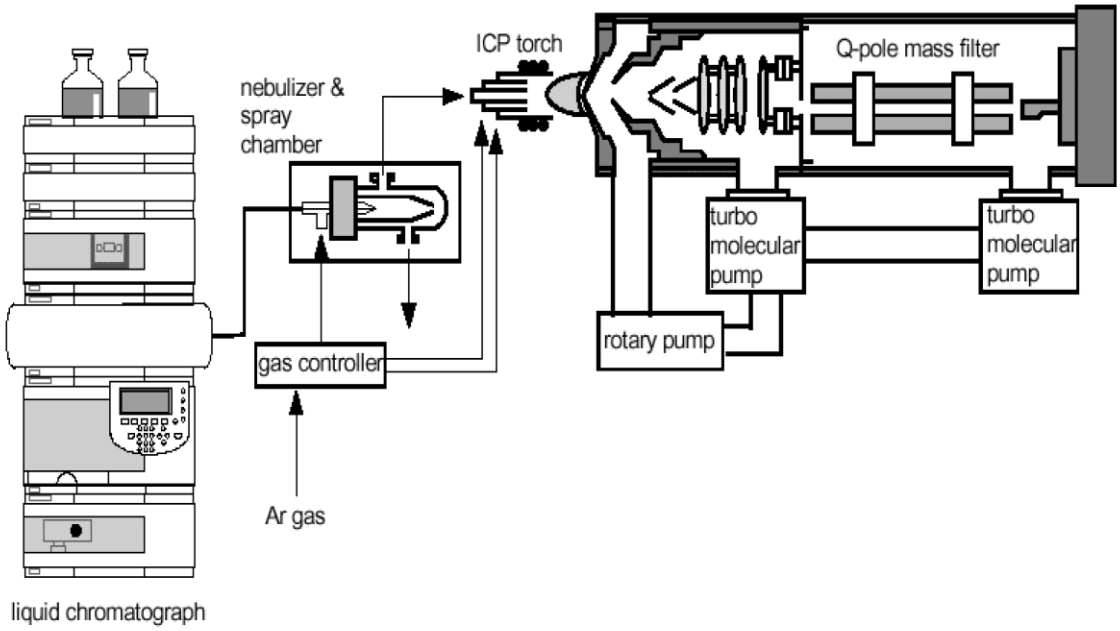

Fig. 1 Schematic diagram of HPLC–ICP–MS coupling.

4 Environmentally friendly techniques of sample treatment in speciation analysis

As already mentioned, the analytical reliability of classical liquid–liquid or liquid–solid extraction techniques may be questionable. They are cumbersome, time-consuming and their applications cause a potential ecological risk due to organic solvent disposal. Furthermore, to accomplish species' preconcentrations, the obtained extracts are often evaporated with the direct emission of harmful vapors to the atmosphere. It should be stressed that miniaturized, automated flow-based methodologies have became very popular over recent decades and they are well established, attractive analytical tools with significantly lower environmental impact.[51,52] On the other hand, alternative approaches to classical extraction techniques have been developed that offer new possibilities in terms of both analytical performance and reduced environmental hazard. These relatively modern techniques, including solid phase extraction (SPE), solid phase micro extraction (SPME), supercritical fluid extraction (SFE), microwave assisted extraction (MAE) and pressurized liquid extraction (PLE), have gained in their popularity and their environmental applications have been increased. Recently, special issues of the *J. Chromatogr. A* (volume 902, 2000) and of *Analytical and Biomedical Chemistry* (volume 373, 2002) were devoted to sample preparation and sample enrichment technology. In approaching trace element speciation the goal is quantitative and possibly selective extraction of target species without affecting the natural distribution of species in the sample. In spite of its popularity for analysis of organic pollutants, microwave assisted extraction has not been used extensively for leaching trace element species (organotin and methylmercury) from biological and soil/sediment samples.[53,54] The main advantages of MAE are the short extraction times, high efficiency, applicability to solid samples and suitability for micro samples. However, it offers only moderate reduction of solvent (10–40 ml per extraction) and does not increase the selectivity of extraction as relative to classical methods. Another technique to be mentioned is pressurized liquid extraction (or accelerated solvent extraction), which uses conventional liquid solvents at elevated temperatures and pressures. Increased temperature accelerates the extraction kinetics, while elevated pressure keeps the solvent below its boiling point, thus enabling safe and rapid extractions. Consequently, high extraction efficiencies are achieved from solid samples in a short time and with the use of lower solvent volumes. Only few applications in speciation studies have been reported so far, namely the extraction of different arsenic species from plant materials and fish tissues.[55–58] A survey of recent literature revealed that SPE, SPME and SFE have been more extensively used for element speciation in environmental materials.[59] In the following sections, these three techniques are briefly described and some representative applications for speciation analysis by hyphenated techniques are reviewed.

4.1 Solid phase extraction

When a liquid or gaseous sample is put in contact with a solid sorbent of suitable properties, the analyte(s) is (are) removed from the sample by sorption on the solid phase. If the solid phase is then separated from the initial solution, other solvents of different physicochemical properties can be used to elute the compounds of interest. As a result, the eluate is a less complex solution relative to the initial sample and usually contains higher analyte(s) concentration (elution with low volume). This is the principle of solid phase extraction (SPE), which was first introduced during the late 1970s. The solid phase sorbent (50 mg–10 g) is usually packed into small tubes or cartridges and resembles a small liquid chromatography column. More recent addition to SPE materials are disks with a solid sorbent loaded

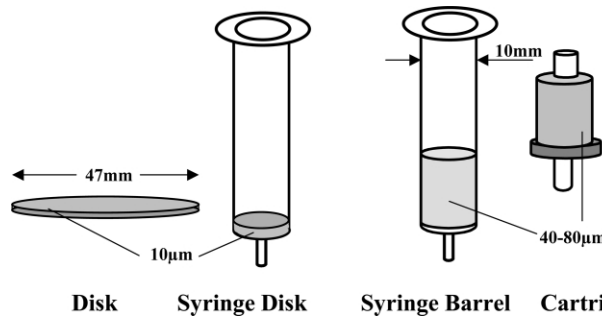

Fig. 2 Cartridge, syringe barrel and disk solid phase extraction setups.

on a membrane (Fig. 2).[60] A disk is approximately 0.5 mm thick and has a diameter in the range 47–70 mm. The method consists of five steps, each of them requires use of a different solvent,

depending upon the characteristics of the analyte(s), sample and sorbent.[61] These steps can be described as follows: (i) wetting and (ii) conditioning the sorbent, (iii) loading the sample, (iv) rinsing or washing the sorbent and (v) eluting the analyte(s) of interest. The wetting step allows the bonded alkyl chains to be solvated assuring better contact between the sorbent and the sample. A solvent or buffer used for conditioning has similar physicochemical properties as the sample. Then, the sample is forced through the 'activated' sorbent material by suction, a vacuum manifold or a plunger. The sorbent material has to be carefully selected to obtain selective sorption of the target species. Washing is performed to eliminate the sample components adsorbed on the surface without removing the analyte(s). Finally the analyte(s) is (are) eluted using a minimum volume of suitable solvent for quantitative release. The successful application of SPE to clean up and preconcentration of the analyte(s) from complex samples relies primarily on the choice of appropriate sorbent and the solvent system. Generally, SPE sorbents can be divided into three classes, normal phase, reversed phase and ion exchange. The most common sorbents are based on silica particles with particle diameters of 40–80 μm in cartridges and 8–12 μm in disks. The polar, reactive silanol groups on the surface can be modified by bonding different functional groups (C1 (methyl), C8 (octyl) or C18 (octadecyl)), thus altering the retention properties of the sorbent. The modification process leaves some free silanol groups and short-chain alkyl groups are introduced to further neutralize these residual groups ('end-capping'). In addition to silica, some other common sorbents are based on florisil, alumina and macroreticular polymers. These reversed phase sorbents more likely retain non-polar compounds and the effective elution is obtained with non-polar solvents (hexane, isooctane, toluene, *etc.*). Unlike reversed phases, the normal phase sorbents have polar functional groups (*e.g.* cyano, amino or diol) and exhibit higher affinity towards polar compounds. In this case, the strong eluting solvents in decreasing order are: water, methanol, acetonitrile, acetone, *etc.* Finally, ion-exchange sorbents have either cationic or anionic functional groups (SCX—benzenesulfonic acid, DEA—diethylammoniopropyl tertiary amine, SAX—trimethylammoniopropyl quaternary amine) and attract ions of the opposite charge. In this case, the important properties of the eluting solvent to be adjusted are pH and ionic strength. In addition to the selection of solid sorbent and solvents, some other parameters also influence the effectiveness of the SPE methodology. The term capacity of the SPE cartridge/disk refers to the number of active sites available on the sorbent and the number of analyte molecules cannot exceed this number, otherwise breakthrough will occur. The flow rate of the sample through the sorbent is also important. Too fast a flow will cause incomplete sorption, while a slow flow rate will involve longer time and a risk of undesirable sorption of other sample components. Usually 3–10 mL min^{-1} is used for cartridges and 10–100 mL min^{-1} is typical for disks.[62] Finally, the sorbent format is important. The most recent disk format has two distinct advantages over conventional SPE cartridges. The physical dimensions of the disk enable the use of smaller particles and facilitate better density and uniformity of packing. The decrease in void volume and increase of the sorbent surface promote partitioning. Hence, a smaller mass of sorbent is required to process a similar volume of sample, also permitting the use of smaller volumes of solvent for elution. Furthermore, a thin sorbent bed and large surface area allow rapid flow rates through a disk. Typically, one liter of water can be passed through a disk in approximately 10 min, whereas with a cartridge system the same volume may take approximately 100 min. However, large flow rates can result in poor recovery due to short time of interaction between sorbent and analyte(s).[62]

SPE presents important advantages over liquid–liquid extraction. It requires less volume of solvent than traditional extraction; it involves simple manipulations that are not time-consuming and makes possible sample treatment in the field. Furthermore, the cartridges or disks can be used for storage of the species and SPE provides high enhancement factors if a large volume of water (1–2 L) is passed through the sorbent without breakthrough.[59]

In studies on elemental speciation, SPE has been used for the analysis of organometallic or metalloid species of tin, arsenic, mercury and selenium as well as for the speciation of trivalent and hexavalent chromium in environmental samples. As recently reviewed by Gomez-Ariza *et al.*,[59] different reversed phase sorbents have been used for cationic organotin species. Both cartridges and disks have been examined, the solid phases included C2, C8 and C18, and the common solvents used for elution were ethyl acetate, methanol and methanol with the addition (up to 1%) of acetic acid, HBr or tropolone. The preconcentration factor as high as 1000 (1 L of water sample, elution with 1 mL tetrahydrofuran–acetic acid with 0.5% tropolone) was reported for methyl-, butyl- and phenyl-tin on a C18 cartridge,[63] the reported recoveries of individual species ranged from 70 to 110%.[64,65] Sequential elution of tin species from C18 cartridge was carried out using solvents of increasing strength: methanol for tributyl- and triphenyl-tin, 0.4% HBr in methanol for dibutyl- and diphenyl-tin, 0.4% HBr + 0.1% tropolone in methanol for monobutyl- and monophenyl-tin.[66] The obtained extracts were introduced to a reversed phase HPLC–MS tandem system,[64] separation was achieved by capillary electrophoresis[67] or organotin species were derivatized with Grignard reagents for their alkylation and then separated by gas chromatography.[65,68]

Due to the amphoteric character of arsenic, the electrical charge of the primary species is pH dependent. Generally, in acidic media the contribution of uncharged molecules of As(v), dimethylarsonic acid (DMA) and monomethylarsinic acid (MMA) becomes higher, arsenobetaine (AsB) can be present as neutral zwitterions or cationic species and As(iii) as uncharged or cationic.[69] Both reversed phase and ionic SPE cartridges have been used for arsenic speciation.[58,59,70,71] In addition to clean up and concentration of arsenic species, a careful choice of solid sorbent in SPE, has also enabled a precolumn-separation of species. For example, to avoid the problem of As(iii) and AsB overlapping during chromatographic separation, As(iii) was retained on an anionic cartridge before introducing the sample to the HPLC column.[71] Yalcin and Le[70] used a resin-based strong cation exchange cartridge for DMA retention (elution with 1 mol L^{-1} hydrochloric acid), a strong anion exchange cartridge for MMA and As(v) (sequential elution, respectively with 60 mol L^{-1} acetic acid and 1 mol L^{-1} hydrochloric acid), while As(iii) remained in the solution. In the case of selenium, primary environmental interest is focused on the analysis of inorganic forms (Se(iv)/Se(vi)), volatile species (dimethyl selenide, dimethyl diselenide, diethyl selenide and diethyl diselenide) and selenoamino acids (Se-methionine, Se-cysteine). Gomez-Ariza *et al.*[72] reported a two-cartridge system stacked together (reversed phase C18 and strong anion exchange SAX) for the retention of volatile species and inorganic forms, respectively. After loading the sample (1 L of natural water), the cartridges were separated. The elution from SAX was performed with formic acid (Se(iv)) and hydrochloric acid (Se(vi)). The elution of volatile species from C18 was achieved with CS_2. For environmental analysis of mercury species, inorganic mercury, methyl- and phenyl-mercury were retained on the reversed phase solid sorbent modified with chelating agents,[73] crown ethers[74] or on a sulfhydryl cotton microcolumn.[75] The discrimination between trivalent and hexavalent chromium as well as the determination of the two redox forms are important in controlling industrial waste water pollution. The two forms were retained on the reversed phase cartridges as their complexes with ammonium pyrrolidine dithiocarbamate (APDC). After elution, the species were

separated by reversed phase HPLC with UV, atomic absorption or inductively coupled mass spectrometric detection.[76,77] Another approach was the use of a strong anion-exchange sorbent for the field sorption of hexavalent chromium. After elution with acid solution, chromium was derivatized with diphenylcarbazide and quantified by UV/Vis spectrophotometry.[78]

Finally, speciation analysis has been only a minor application of SPE in the past. For a broader description of historical and recent developments for SPE in water analysis the reader is referred to the excellent review by Liska.[79]

4.2 Solid phase micro extraction

Although introduced as a modification of SPE,[80] solid phase micro extraction (SPME) presents some substantial differences and is generally considered as a separate sample handling technique. From an environmental point of view, the important advantage of SPME is complete elimination (or further reduction) of solvents required for sample treatment. Unlike SPE, the sorbent material is attached to the surface of a fiber and the species of interest are pre-concentrated by simply dipping the fiber into the aqueous sample (direct mode) or by putting in

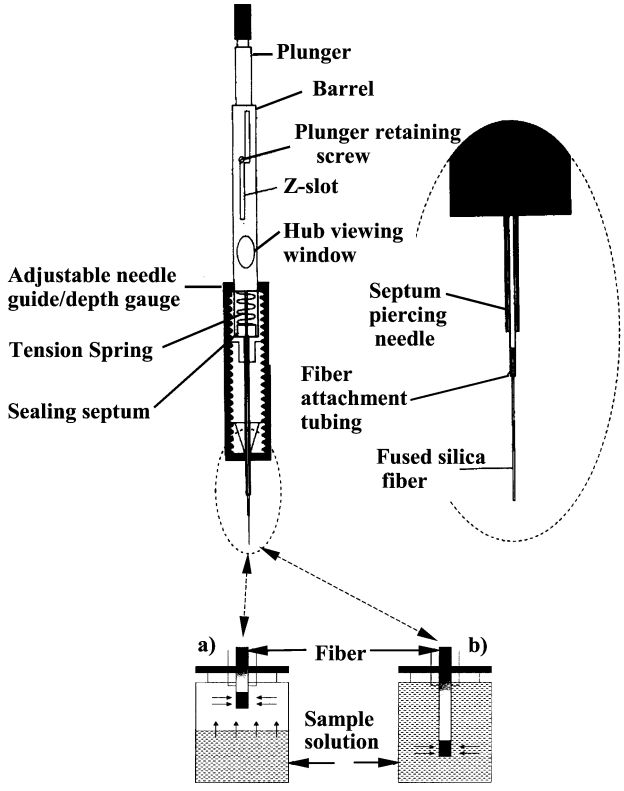

Fig. 3 Solid phase microextraction device and two modes of operation: (a) headspace and (b) direct liquid phase (immersion).

contact with a gaseous phase (headspace mode) (Fig. 3). Generally, the headspace mode enables selective sorption of volatile compounds. However, in the case of liquid samples it also allows modification of the matrix without damaging the fiber. Consequently, parameters such as pH, ionic strength, or others can be adjusted to enhance species volatilization. Furthermore, non-volatile species of interest can be volatilized by suitable chemical derivatization (ethylation, hydride generation, *etc.*). The major methodological difference from SPE is that this technique is based on multiphase equilibration processes (the sample is not forced through the sorbent as in SPE). During sampling, the species of interest is distributed between the liquid sample and/or the headspace and the fiber coating material until reaching the equilibrium, so the recovery obtained is not the same as the classical concept[81] of such. The factor limiting sensitivity in SPME-based hyphenated techniques is the amount of analyte(s) that can be sorbed on the fiber. Increasing the sample volume above a certain value necessary to reach the equilibrium would not enhance the amount of analyte sorbed. Consequently, SPME does not require measurement of sample volume, which facilitates sampling for air analysis and field sampling of aqueous samples.[82–84] The technique is suitable for the analysis of micro samples and, owing to its non-invasive nature, it can be used for equilibrium—distribution—types of analysis. Finally, use of the calibrated pumping system required in SPE is eliminated.[85] In commercial SPME designs, a small diameter fused-silica fiber coated with the extraction phase is mounted in a syringe-like device.[86] The unique feature of SPME is the small physical dimensions of the fiber (1 cm long) coated with small amounts of the extracting phase (typically less than 1 μL). As already discussed for SPE, the choice of this phase is essential to achieve selective and efficient extraction of the compounds to be analyzed. The extracting phases used in SPME include high molecular weight polymeric liquids or solid sorbents. Poly(dimethylsiloxane) (PDMS) is probably the most common liquid-type coating and it has been recommended for volatile, non-polar semivolatile and moderately polar to non-polar semivolatile compounds.[86] When SPME is to be coupled to liquid chromatography, a solid adsorptive coating could be considered.

For desorption of the species, the fiber is transferred into the heated injector of a gas chromatograph. Another approach suitable for non-volatile species (direct mode) involves elution of the species with a minimum volume of a properly selected solvent followed by on-line or off-line analysis by liquid chromatography.[79]

The applications of SPME for trace element speciation have recently been reviewed by Bayona[87] and Mester *et al.*[81] The vast majority of speciation schemes have involved the headspace SPME mode. Direct sorption of volatile species and their analysis by GC with atom specific detectors was reported only for tetraethyllead[88] in aqueous samples, for methyl- and dimethyl-mercury determination and for the analysis of volatile selenium and sulfur species in Se-accumulating plants.[89–91] On the other hand, different derivatization procedures have been used before, during or after the SPME step to convert the species of interest into non-polar, volatile and stable compounds or to enhance the detection capabilities. Ethylation with sodium tetraethylborate in slightly acidic media (pH 4.0–5.3) was used for the analysis of different organotin compounds,[92–95] inorganic and alkyl-mercury[96] as well as inorganic and organic lead species.[97–99] In another study, isobutylchloroformate was applied for acylation of the amine groups and esterification of carboxylic groups of seleno amino acids prior to SPME on the laboratory fabricated fibers.[100] Applications for multielement speciation were also reported.[20,21,101,102] Less popular has been derivatization by hydride generation. Jiang and co-workers[103,104] reported a method for organomercury species, based on the reaction with potassium tetrahydroborate and the use of a laboratory modified fused-silica fiber. The feasibility of hydride generation for SPME–ICP–MS simultaneous determination of arsenic, selenium, tin and antimony was explored by Mester *et al.*[105] Finally, the use of more selective derivatization procedures for SPME applications in speciation analysis should be mentioned. The reaction of Se(IV) with diaminonaphtalene to form a volatile piazselenol compound was used for SPME–GC–ICP–MS speciation of inorganic selenium.[106] Different dithiol compounds were examined for derivatization of organoarsenic species in the environmental samples prior to SPME.[107] Mester *et al.* reported a method for DMA and MMA speciation in urine, after derivatization with thioglycol methylate and sorption on a polydimethylsiloxane coated fiber.[108]

For applications of SPME for sampling of non-volatile ionic compounds from aqueous solutions and their separation by

liquid chromatography, both off-line and on-line coupling can be used. In off-line mode, the analytes are desorbed with a small volume of the suitable solvent to a vial and introduced to the column. For on-line coupling, a laboratory-made or commercial liquid desorption chamber (Supelco Co., PA) are used. Another approach involves the use of an open tubular capillary substitute for the sample introduction loop in the HPLC system.[81] The limiting factor in speciation of non-volatile, ionic compounds is a lack of commercially available fiber coatings that would allow selective sorption of species. Thus, for the two oxidation states of chromium, Cr(III) was complexed with EDTA and Cr(VI) was sorbed on the Carbowax coating.[109] After elution, the two chromium forms were separated by HPLC with UV detection. Laboratory prepared sol–gel coatings were evaluated for SPME–HPLC–ICP–MS analysis of diphenylmercury, trimethylphenyltin and triphenylarsine.[110] Wu *et al.*[111] developed a polypyrrole polymer coating for SPME extraction of small anionic species including selenate, selenite and arsenate anions. Different polymer coatings were used in open capillary tubes for SPME–HPLC with mass spectrometric detection of alkyl lead compounds,[112] organoarsenic,[113] organotin[114] species and also for seleno amino acids.[81]

4.3 Supercritical fluid extraction

In the context of reducing the environmental impact of chemical analysis, supercritical fluid extraction (SFE) is also an attractive tool for sample treatment. This technique exploits the unique properties of gases at temperatures and pressures above the critical point for leaching the species of interest from solid or aqueous samples. The supercritical phase was discovered by Baron Cagniard de la Tour in 1822, by observing that the boundary between a gas and a liquid disappeared for certain substances when the temperature was increased in a sealed glass container.[62] The important characteristic of a supercritical fluid is that its density, viscosity and diffusion coefficient are intermediate between those of the substance in its gaseous and its liquid state. Consequently, the use of supercritical fluids as an extracting agent facilitates a rapid mass transfer of many solutes and faster extractions as compared to liquid extraction agents. The ability of neat carbon dioxide to dissolve large, nonvolatile molecules has found many applications in industrial processes such as extracting caffeine from coffee beans or nicotine from tobacco. Another important aspect of supercritical extraction is that the analytes can be easily recovered by simply allowing the fluid to equilibrate with the atmosphere at relatively low temperatures (the extracting agent evaporates).[115] Among different compounds exhibiting reasonably low values of critical temperature and pressure, the most commonly used is carbon dioxide (31.1 °C, 74.8 atm). This choice is also dictated by low toxicity, chemical inertness, relatively low cost and availability of pure carbon dioxide. It should be stressed that, unlike toxic solvents (methylene chloride, chloroform, diethyl ether, *etc.*), the use of carbon dioxide does not involve fire risk or emission of environmentally hazardous wastes. In the instrumental design for SFE, pressurized gases from the cylinders (carbon dioxide and sometimes an organic modifier) are pumped through a stainless steel extraction vessel, which is equipped with a pressure outlet or restrictor and placed in a controlled-temperature oven. The extracted analytes are recovered in a collection vessel (Fig. 4). The extraction can be achieved from both solid and liquid samples. The supercritical fluid penetrates into solid matrices more rapidly than do liquid solvents, assuring good recoveries within a significantly shorter time (several minutes to one hour *versus* few to several hours by Soxhlet extraction). Typically solids are subjected to SFE even if the initial sample is not in the solid state. This can be achieved by the deposition of the liquid or gaseous sample on natural or synthetic solid supports. The combination of SPE and SFE

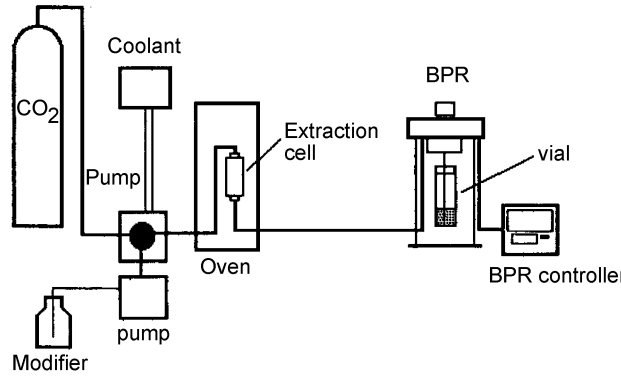

Fig. 4 Schematic diagram of the basic components for a supercritical fluid extraction system.

showed the additional advantage of sample clean-up (if the selective sorption of the analytes can be achieved). Another operational mode involves direct extraction from liquid samples, in which the supercritical fluid is purged through the solution in the extraction vessel. However, with this approach the extraction tends to be less efficient (especially for polar and ionic species) and the matrix effects are more pronounced.

In developing extraction conditions, both the polarity of analyte(s) and the sample composition have to be considered. The parameters to be optimized include the temperature and pressure as well as the composition of the supercritical fluid. The non-polar nature of carbon dioxide makes it suitable for the extraction of non-polar compounds. In order to extend possible applications to polar analytes, an organic modifier (typically methanol) can be added to the supercritical fluid. Another common approach is complexation-chelation or derivatization of the analytes to be extracted to obtain less polar species that are more soluble in neat carbon dioxide.[116,117] The derivatization through alkylation is of special interest, because SFE is typically used as a pretreatment procedure for GC separations. Finally, the selection of suitable solid support may allow a relatively selective retention of analytes.

In spite of being an environmental friendly technique, SFE also presents some important analytical advantages. This technique offers higher selectivity as compared to classical extractions; it allows high preconcentration factors in a short time and with minimum operations. The extraction is usually achieved in several minutes; the analytes are released at relatively low temperatures and collected in a small volume of solvent (10–20 mL), deposited on a suitable solid or directly introduced onto the column. Consequently, the risk of analytical errors due to sample manipulation, possible analyte losses during thermal treatment, or sample contamination is significantly reduced. On the other hand, the key limitations of SFE are due to difficulties in extracting polar analytes and in dealing with complex samples. Different extraction efficiencies have often been reported from spiked and natural samples. Even though SFE is considered a relatively selective technique, clean-up procedures are often needed.[115]

The application of SFE to environmentally related speciation studies often is not as straightforward because of the polar or ionic nature of the primary elemental species. A few comprehensive reviews are available on this topic[38,116,118,119] and here only a brief discussion is given. Research interests have been particularly focused on organotin compounds. Carbon dioxide SF modified with methanol was used for the extraction of tributyltin from sediments[120] and two organotin species (tributyl- and triphenyl-tin) from biological samples.[121] In these early studies, generally low recoveries were reported. The results of interlaboratory trials revealed the suitability of carbon dioxide–methanol SF for the extraction of tri- and tetra-substituted organotin compounds, while the mono- and di-substituted species were extracted with poor efficiency.[122] More recently, the feasibility of other organic modifiers has

been explored for phenyl- and butyl-tins in sediments (carboxylic acids[123]) and for di- and tri-butyltins in mussel reference material (acetic acid[124]). On the other hand, different carbamates[87,123,125] and tropolone[124,126] have been reported as complexing agents for ionic organotin species. Derivatization through alkylation (ethylation or hexylation) enabled the improved extraction of butyl- and phenyl-tin.[116,127] SFE has also been used for the extraction of organomercury compounds from various environmental samples. The derivatization reagents proposed include buthylmagnesium chloride[128] tetraphenylborate and acetylacetone.[129] Other approaches for cationic methylmercury species used a complexation with carbamate compounds[130] or methanol modified carbon dioxide SF.[131] In the case of alkyllead compounds, SFE with methanol modified carbon dioxide enabled quantitative extraction of trimethyl- and triethyl-lead from spiked sediments, while complexation with diethyldithiocarbamate was needed for diethyllead.[132,133] Fluorinated dithiocarbamate and methanol modified carbon dioxide were also used for selective extraction of Cr(VI) from solid samples.[134] SFE was applied for the extraction of arsenic species (As(III), As(V), MMA, DMA) after their derivatization with thioglycolic acid methyl ester.[135] As already mentioned, SFE has been primarily used as the pretreatment technique for the separation of species by GC. In many applications, typical gas chromatographic detectors were used,[116,118,131] however the trend to replace them by more sensitive, atomic specific detectors can be observed.[118,121,122,125,128,129]

5 Conclusions

There are two important aspects of trace element speciation relevant to green chemistry. First, the analytical results of such analyses providing information on possible environmental pollution are useful in assessing toxicological risk and in designing the remediation strategies. The second aspect is related to the possible toxicological and environmental impact of accomplishing the analytical procedures. The need for redesigning the reagent-based assays to minimize the consumption of reagents, of sample material and minimizing generation of waste is now generally accepted.[36] Among the strategies proposed, the use of miniaturized chromatographic techniques, application of flow techniques and automation of the analytical procedures are the most important. Within this context, hyphenated techniques for trace element speciation are reliable analytical tools and also present relatively low environmental hazards. The most important features include on-line operation (easy automation), minimum sample and reagent requirements, low waste production, high selectivity and sensitivity. On the other hand, in the applications to real-world sample pretreatment procedures are usually needed and may be considered as the main source of wastes. Solid phase extraction (SPE), solid phase microextraction (SPME) and supercritical fluid extraction (SFE) discussed in this review are three important environmentally friendly techniques, primarily used in analytical speciation of trace elements. These techniques allow decreased solvent usage, shortening the extraction time, and reducing the number of steps involved in the procedure as compared to classical extraction methods. Actually, SPE is widely accepted for variety of environmental applications, it is easy to operate and amenable to automation. It also enables high preconcentration factors and in-field sampling.

The more recent SPME allows total elimination or further reduction of waste generated during extraction. It is gaining in popularity due to easy operation, low cost, non-invasive nature and exceptional possibilities for the analyses of micro samples. Passive sampling methodology offers the unique possibility of mapping the target compound distributions or to accomplish multiple sampling from this same area. Consequently, SPME has been applied in the fabrication of personal-exposure monitoring devices for airborne pollutants.[136] On the other hand, SPME has some important limitations related to the small amount of extraction phase. In order to improve precision of the analytical results, care during manufacturing of the coating is required to obtain good fiber-to-fiber performance. The gradual degradation of coatings in repetitive usage is another factor limiting the quality of analytical results.

The third technique presented here has proven to be a powerful tool in many environmental analyses. High preconcentration rates, cleanliness and safety, quantitative capability, possibility for in-field sampling, on-line coupling with hyphenated techniques and automation are the chief advantages of SFE. The main limitations are related to difficulty of extracting polar or ionic species and with handling the complex samples. The application of SFE for trace elemental speciation involves derivatization of the analytes to obtain non-polar, preferentially volatile and stable species amenable to GC separations.

References

1 M. Hempel, Y. K. Chau, B. J. Dutka, R. McInnis, K. K. Kwan and D. Liu, *Analyst*, 1995, **120**, 721.
2 J. Kuballa, R. D. Wilken, E. Jantzen, K. K. Kwan and Y. K. Chau, *Analyst*, 1995, **120**, 667.
3 D. Heitkemper, J. Creed and J. Caruso, *J. Anal. At. Spectrom.*, 1989, **4**, 279.
4 C. A. Burtis and E. R. Ashwood, *Tietz Textbook of Clinical Chemistry*, W. B. Saunders Company, Philadelphia, PA, USA 1999.
5 J. O. Nriagu, *Sci. Total Environ.*, 1990, **92**, 13.
6 C. Kornhauser, K. Wrobel, J. M. Malacara, L. E. Nava, L. Gomez and R. Gonzalez, *Ind. Health*, 2002, **40**, 207.
7 T. M. Florence and G. E. Batley, *Crit. Rev. Anal. Chem.*, 1980, **9**, 219.
8 P. Quevauviller, in *Certified reference materials: a tool for quality control of elemental speciation analysis*, ed. K. L. S. J. A. Caruso, K.L. Ackley, Amsterdam, The Netherlands, 2000.
9 E. B. Gonzalez and A. Sanz-Medel, in *Liquid chromatographic techniques for trace element speciation analysis*, ed. J. Caruso, K. L. Sutton and K. L. Ackley, Amsterdam, The Netherlands, 2000.
10 X. P. Yan, R. Kerrich and M. J. Hendry, *Anal. Chem.*, 1998, **70**, 4736.
11 M. Burguera and J. L. Burguera, *Talanta*, 1997, **44**, 1581.
12 F. A. Byrdy, L. K. Olson, N. P. Vela and J. A. Caruso, *J. Chromatogr. A*, 1995, **712**, 311.
13 F. Vanhaecke, S. Saverwyns, G. De Wannemacker, L. Moens and R. Dams, *Anal. Chim. Acta*, 2000, **419**, 55.
14 J. Lintschinger, B. Michalke, S. Schulte-Hostede and P. Schramel, *Int. J. Environ. Anal. Chem.*, 1998, **72**, 11.
15 S. Mazan, N. Gilon, G. Cretier, J. L. Rocca and J. M. Mermet, *J. Anal. At. Spectrom.*, 2002, **17**, 366.
16 D. Wallschlager and R. Roehl, *J. Anal. At. Spectrom.*, 2001, **16**, 922.
17 B. Michalke and P. Schramel, *J. Chromatogr. A*, 1999, **834**, 341.
18 H. Tao, R. B. Rajendran, C. R. Quetel, T. Nakazeto, M. Tominaga and A. Miyazaki, *Anal. Chem.*, 1999, **71**, 4208.
19 J. R. Encinar, P. R. Gonzalez, J. I. G. Alonso and A. Sanz-Medel, *Anal. Chem.*, 2002, **74**, 270.
20 T. De Smaele, L. Moens, P. Sandra and R. Dams, *Mikrochim. Acta*, 1999, **130**, 241.
21 L. Moens, T. DeSmaele, R. Dams, P. VandenBroeck and P. Sandra, *Anal. Chem.*, 1997, **69**, 1604.
22 O. F. X. Donard, E. Krupp, C. Pecheyran, D. Amouroux and R. Ritsema, in *Trends in speciation analysis for routine and new environmental issues*, ed. J. Caruso, K. L. Sutton and K. L. Ackley, Amsterdam, The Netherlands, 2000.
23 R. Lobinski, *Analyst*, 1995, **120**, 615.
24 U. Kohlmeyer, J. Kuballa and E. Jantzen, *Rapid Commun. Mass Spectrom.*, 2002, **16**, 965.
25 R. Tukai, W. A. Maher, I. J. McNaught and M. J. Ellwood, *Anal. Chim. Acta*, 2002, **457**, 173.
26 M. Montes-Bayon, E. G. Yanes, C. P. de Leon, K. Jayasimhulu, A. Stalcup, J. Shann and J. A. Caruso, *Anal. Chem.*, 2002, **74**, 107.
27 M. Kotrebai, M. Birringer, J. F. Tyson, E. Block and P. C. Uden, *Analyst*, 1999, **125**, 71.

28 X. C. Le, X. F. Li, V. Lai, M. Ma, S. Yalcin and J. Feldmann, *Spectrochim. Acta Part B: At. Spectrosc.*, 1998, **53**, 899.
29 C. N. Ferrarello, M. M. Bayon, R. F. de la Campa and A. Sanz-Medel, *J. Anal. At. Spectrom.*, 2000, **15**, 1558.
30 C. N. Ferrarello, M. D. F. de la Campa, J. F. Carrasco and A. Sanz-Medel, *Anal. Chem.*, 2000, **72**, 5874.
31 U. Kramer and A. N. Chardonnens, *Appl. Microbiol. Biotechnol.*, 2001, **55**, 661.
32 M. H. Zenk, *Gene*, 1996, **179**, 21.
33 L. A. Oste, E. J. M. Temminghoff, T. M. Lexmond and W. H. Van Riemsdijk, *Anal. Chem.*, 2002, **74**, 856.
34 C. Liu, A. I. Frenkel, A. Vairavamurthy and P. M. Huang, *Can. J. Soil Sci.*, 2001, **81**, 337.
35 L. K. Koopal, W. H. van Riemsdijk and D. G. Kinniburgh, *Pure Appl. Chem.*, 2001, **73**, 2005.
36 M. Delaguardia and J. Ruzicka, *Analyst*, 1995, **120**, N17.
37 *Methods for the Determination of Organic Compounds in Drinking Water*, Environmental Monitoring System Laboratory, Office of Research and Development, Cincinnati, OH, US EPA, 1988.
38 J. S. Ho, P. H. Tang, J. W. Eichelberger and W. L. Budde, *J. Chromatogr. Sci.*, 1995, **33**, 1.
39 R. Lobinski, *Appl. Spectrosc.*, 1997, **51**, A260.
40 J. Szpunar, B. Bouyssiere and R. Lobinski, in *Sample preparation techniques for elemental speciation studies*, ed. J. Caruso, K. L. Sutton and K. L. Ackley, Amsterdam, The Netherlands, 2000.
41 P. C. Uden, in *Gas chromatographic and supercritical fluid chromatographic techniques for elemental speciation*, ed. J. Caruso, K. L. Sutton and K. L. Ackley, Amsterdam, The Netherlands, 2000.
42 R. M. Harrison and S. Rapsomankis, *Environmental Analysis Using Chromatography Interfaced with Atomic Spectroscopy*, Ellis Horwood, Chichester, UK, 1989.
43 A. A. Specht and D. Beauchemin, *Anal. Chem.*, 1998, **70**, 1036.
44 D. Beauchemin, *Anal. Chem.*, 1995, **67**, 1553.
45 B. Michalke, *TrAC, Trends Anal. Chem.*, 2002, **21**, 142.
46 B. Michalke, *TrAC, Trends Anal. Chem.*, 2002, **21**, 154.
47 R. C. de Campos and P. Grinberg, *Quim. Nova*, 2001, **24**, 220.
48 J. Szpunar, S. McSheehy, K. Polec, V. Vacchina, S. Mounicou, I. Rodriguez and R. Lobinski, *Spectrochim. Acta Part B: At. Spectrosc.*, 2000, **55**, 779.
49 F. Vanhaecke and L. Moens, *Fresenius J. Anal. Chem.*, 1999, **364**, 440.
50 R. Lobinski and F. C. Adams, *Spectrochim. Acta Part B: At. Spectrosc.*, 1997, **52**, 1865.
51 F. R. P. Rocha, J. A. Nobrega and O. Fatibello, *Green Chem.*, 2001, **3**, 216.
52 K. Jinno, *Anal. BioAnal. Chem.*, 2002, **373**, 1.
53 V. Camel, *TrAC, Trends Anal. Chem.*, 2000, **19**, 229.
54 V. Camel, *Anal. BioAnal. Chem.*, 2002, **372**, 39.
55 J. W. McKiernan, J. T. Creed, C. A. Brockhoff, J. A. Caruso and R. M. Lorenzana, *J. Anal. At. Spectrom.*, 1999, **14**, 607.
56 P. A. Gallagher, J. A. Shoemaker, X. Y. Wei, C. A. Brockhoff-Schwegel and J. T. Creed, *Fresenius J. Anal. Chem.*, 2001, **369**, 71.
57 P. A. Gallagher, X. Y. Wei, J. A. Shoemaker, C. A. Brockhoff and J. T. Creed, *J. Anal. At. Spectrom.*, 1999, **14**, 1829.
58 N. P. Vela, D. T. Heitkemper and K. R. Stewart, *Analyst*, 2001, **126**, 1011.
59 J. L. Gomez-Ariza, E. Morales, I. Giraldez, D. Sanchez-Rodas and A. Velasco, *J. Chromatogr. A*, 2001, **938**, 211.
60 E. M. Thurman and K. Snavely, *TrAC, Trends Anal. Chem.*, 2000, **19**, 18.
61 M. Moors, D. L. Massart and R. D. McDowall, *Pure Appl. Chem.*, 1994, **66**, 277.
62 J. R. Dean, *Extraction Methods for Environmental Analysis*, John Wiley & Sons, New York, USA, 1998.
63 K. Kadokami, T. Uehiro, M. Morita and K. Fuwa, *J. Anal. At. Spectrom.*, 1988, **3**, 187.
64 E. Gonzalez-Toledo, R. Compano, M. D. Prat and M. Granados, *J. Chromatogr., A*, 2002, **946**, 1.
65 S. Diez, L. Ortiz and J. M. Bayona, *Chromatographia*, 2000, **52**, 657.
66 J. L. Gomezariza, R. Beltran, E. Morales, I. Giraldez and M. Ruizbenitez, *Appl. Organomet. Chem.*, 1994, **8**, 553.
67 B. G. Sun, M. Macka and P. R. Haddad, *Int. J. Environ. Anal. Chem.*, 2001, **81**, 161.
68 J. M. F. Nogueira, P. Teixeira and M. H. Florencio, *J. Microcolumn Sep.*, 2001, **13**, 48.
69 E. Vassileva, A. Becker and J. A. C. Broekaert, *Anal. Chim. Acta*, 2001, **441**, 135.
70 S. Yalcin and X. C. Le, *J. Environ, Monit.*, 2001, **3**, 81.
71 M. Gomez, C. Camara, M. A. Palacios and A. Lopez-Gonzalvez, *Fresenius J. Anal. Chem.*, 1997, **357**, 844.
72 J. L. Gomez-Ariza, J. A. Pozas, I. Giraldez and E. Morales, *Analyst*, 1999, **124**, 75.
73 D. M. Sanchez, R. Martin, R. Morante, J. Marin and M. L. Munuera, *Talanta*, 2000, **52**, 671.
74 Y. Yamini, N. Alizadeh and M. Shamsipur, *Anal. Chim. Acta*, 1997, **355**, 69.
75 M. L. Mena, C. W. McLeod, P. Jones, A. Withers, V. Minganti, R. Capelli and P. Quevauviller, *Fresenius J. Anal. Chem.*, 1995, **351**, 456.
76 M. Bittner and J. A. C. Broekaert, *Anal. Chim. Acta*, 1998, **364**, 31.
77 C. M. Andrle, N. Jakubowski and J. A. C. Broekaert, *Spectrochim. Acta Part B: At. Spectrosc.*, 1997, **52**, 189.
78 J. Wang, K. Ashley, D. Marlow, E. C. England and O. Carlton, *Anal. Chem.*, 1999, **71**, 1027.
79 I. Liska, *J. Chromatogr. A*, 2000, **885**, 3.
80 J. Pawliszyn and R. P. Belardi, *Water Pollut. Res. J. Can.*, 1989, **24**, 179.
81 Z. Mester, R. Sturgeon and J. Pawliszyn, *Spectrochim. Acta Part B: At. Spectrosc.*, 2001, **56**, 233.
82 T. Gorecki and J. Pawliszyn, *Field Anal. Chem. Technol.*, 1997, **1**, 277.
83 M. Y. Jia, J. Koziel and J. Pawliszyn, *Field Anal. Chem. Technol.*, 2000, **4**, 73.
84 J. Koziel, M. Y. Jia, A. Khaled, J. Noah and J. Pawliszyn, *Anal. Chim. Acta*, 1999, **400**, 153.
85 J. Pawliszyn, *J. Chromatogr. Sci.*, 2000, **38**, 270.
86 L. Muller, T. Górecki and J. Pawliszyn, in *Encyclopedia of Analytical Chemistry*, ed. R. A. Meyers, John Wiley & Sons Ltd., Chichester, UK,2000, **vol. V**, pp. 3815.
87 J. M. Bayona, in *Applications of solid phase extraction*, ed. J. Pawliszyn, Royal Society of Chemistry, Cambridge, 1999, pp. 284–296.
88 T. Gorecki and J. Pawliszyn, *Anal. Chem.*, 1996, **68**, 3008.
89 Z. N. Mester, J. Lam, R. Sturgeon and J. Pawliszyn, *J. Anal. At. Spectrom.*, 2000, **15**, 837.
90 J. P. Snell, W. Frech and Y. Thomassen, *Analyst*, 1996, **121**, 1055.
91 J. Mejia, M. Montes-Bayon, D. L. LeDuc, N. Terry and J. A. Caruso, *Anal. Chem.*, 2002, 5837.
92 S. Aguerre, C. Pecheyran, G. Lespes, E. Krupp, O. F. X. Donard and M. Potin-Gautier, *J. Anal. At. Spectrom.*, 2001, **16**, 1429.
93 E. Millan and J. Pawliszyn, *J. Chromatogr. A*, 2000, **873**, 63.
94 G. Lespes, V. Desauziers, C. Montigny and M. Potin-Gautier, *J. Chromatogr. A*, 1998, **826**, 67.
95 Y. Morcillo, Y. Cai and J. M. Bayona, *HRC,J. High Resolut. Chromatogr.*, 1995, **18**, 767.
96 Y. Cai, S. Monsalud, K. G. Furton, R. Jaffe and R. D. Jones, *Appl. Organomet. Chem.*, 1998, **12**, 565.
97 Z. Mester, H. Lord and J. Pawliszyn, *J. Anal. At. Spectrom.*, 2000, **15**, 595.
98 X. M. Yu and J. Pawliszyn, *Anal. Chem.*, 2000, **72**, 1788.
99 X. M. Yu, H. D. Yuan, T. Gorecki and J. Pawliszyn, *Anal. Chem.*, 1999, **71**, 2998.
100 A. P. Vonderheide, M. Montes-Bayon and J. A. Caruso, *Analyst*, 2002, **127**, 49.
101 L. Dunemann, H. Hajimiragha and J. Begerow, *Fresenius J. Anal. Chem.*, 1999, **363**, 466.
102 S. Tutschku, S. Mothes and R. Wennrich, *Fresenius J. Anal. Chem.*, 1996, **354**, 587.
103 B. He and G. B. Jiang, *Fresenius J. Anal. Chem.*, 1999, **365**, 615.
104 B. He, G. B. Jiang and Z. M. Ni, *J. Anal. At. Spectrom.*, 1998, **13**, 1141.
105 Z. Mester, R. E. Sturgeon and J. W. Lam, *J. Anal. At. Spectrom.*, 2000, **15**, 1461.
106 M. Guidotti, G. Ravaioli and M. Vitali, *HRC, J. High Resolut. Chromatogr.*, 1999, **22**, 414.
107 B. Szostek and J. H. Aldstadt, *J. Chromatogr. A*, 1998, **807**, 253.
108 Z. Mester and J. Pawliszyn, *J. Chromatogr. A*, 2000, **873**, 129.
109 A. A. Boyd-Boland, in *Applications of solid phase extraction*, ed. J. Pawliszyn, Royal Society of Chemistry, Cambridge, 1999, 327–333.
110 T. P. Gbatu, K. L. Sutton and J. A. Caruso, *Anal. Chim. Acta*, 1999, **402**, 67.
111 J. C. Wu, X. M. Yu, H. Lord and J. Pawliszyn, *Analyst*, 2000, **125**, 391.
112 Z. Mester and J. Pawliszyn, *Rapid Commun. Mass Spectrom.*, 1999, **13**, 1999.
113 J. C. Wu, Z. Mester and J. Pawliszyn, *Anal. Chim. Acta*, 2000, **424**, 211.

114 J. C. Wu, Z. Mester and J. Pawliszyn, *J. Anal. At. Spectrom.*, 2001, **16**, 159.
115 M. D. L. de Castro and M. M. Jimenez-Carmona, *TrAC, Trends Anal. Chem.*, 2000, **19**, 223.
116 J. M. Bayona, *TrAC, Trends Anal. Chem.*, 2000, **19**, 107.
117 L. Lojkova and J. Vejrosta, *Chem. Listy*, 1998, **92**, 988.
118 J. M. Bayona and Y. Cai, *TrAC, Trends Anal. Chem.*, 1994, **13**, 327.
119 C. M. Wai and S. F. Wang, *J. Chromatogr. A*, 1997, **785**, 369.
120 J. Dachs, R. Alzaga, J. M. Bayona and P. Quevauviller, *Anal. Chim. Acta*, 1994, **286**, 319.
121 U. T. Kumar, N. P. Vela, J. G. Dorsey and J. A. Caruso, *J. Chromatogr. A*, 1993, **655**, 340.
122 V. LopezAvila, Y. Liu and W. F. Beckert, *J. Chromatogr. A*, 1997, **785**, 279.
123 Y. Cai, M. Abalos and J. M. Bayona, *Appl. Organomet. Chem.*, 1998, **12**, 577.
124 R. Morabito, H. Muntau, W. Cofino and P. Quevauviller, *J. Environ. Monit.*, 1999, **1**, 75.
125 Y. Liu, V. Lopezavila, M. Alcaraz and W. F. Beckert, *Anal. Chem.*, 1994, **66**, 3788.
126 I. Fernandez-Escobar and J. M. Bayona, *Anal. Chim. Acta*, 1997, **355**, 269.
127 Y. Cai and J. M. Bayona, *J. Chromatogr. Sci.*, 1995, **33**, 89.
128 H. Emteborg, E. Bjorklund, F. Odman, L. Karlsson, L. Mathiasson, W. Frech and D. C. Baxter, *Analyst*, 1996, **121**, 19.
129 Y. C. Sun, Y. T. Chung and J. Mierzwa, *Analyst*, 2001, **126**, 1694.
130 M. Ashraf-Khorassani and L. T. Taylor, *Anal. Chim. Acta*, 1999, **379**, 1.
131 R. A. Lorenzo, M. J. Vazquez, A. M. Carro and R. Cela, *TrAC, Trends Anal. Chem.*, 1999, **18**, 410.
132 M. Johansson, T. Berglof, D. C. Baxter and W. Frech, *Analyst*, 1995, **120**, 755.
133 P. Quevauviller, L. Ebdon, R. M. Harrison and Y. Wang, *Appl. Organomet. Chem.*, 1999, **13**, 1.
134 G. P. Foy and G. E. Pacey, *Talanta*, 2000, **51**, 339.
135 B. W. Wenclawiak and M. Krah, *Fresenius J. Anal. Chem.*, 1995, **351**, 134.
136 P. A. Martos and J. Pawliszyn, *Anal. Chem.*, 1999, **71**, 1513.

Debromination of flame retardant high impact polystyrene (HIPS-Br) by hydrothermal treatment and recovery of bromine free plastics

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Received 10th July 2002
First published as an Advance Article on the web 21st February 2003

The bromine content from high impact polystyrene containing decabromo diphenyl oxide flame retardant (HIPS-Br) was removed by hydrothermal treatment using an autoclave. The debromination process was promoted by the addition of PP to HIPS-Br. A temperature of 280 °C was found to be optimum for a high yield of recovered plastic with maximum debromination of HIPS-Br. The recovered plastic can be used as a substitute for liquid fuel, which is the product during feedstock recycling. The process is very simple, but more attractive than feedstock recycling as this process eliminates the costly and complicated catalytic process for the removal of halogen from the waste plastic derived oil.

Introduction

Plastics are among the best 'fruits' of the chemical industry and are used extensively in our daily life. Between 1975 and 1998 in Japan, the amount of post consumer plastic waste increased 3.8 times, plastic production 2.7 times, and the consumption of plastics 3.2 times.[1] Waste plastic disposal in Japan (during 2000) was about 9.97 million tons, consisting of both domestic general waste (5.08 million tons) and industrial waste (4.89 million tons). Municipal and industrial plastic wastes are predominantly treated in three ways: landfill, incineration (energy recovery by incineration) and material recycling. Each of these methods has disadvantages. Landfill treatment is undesirable due to poor biodegradability of plastics; and incineration is unacceptable due to the possibility of toxic emissions.[2] True material recycling (the conversion of scrap polymer into new products) is a preferable method of treatment but the recycled plastic products often cost more than virgin plastic[3] and the secondary plastics have less market value. One alternative strategy is feedstock recycling with the aim of converting waste polymers into basic petrochemicals to be used as fuel or for a variety of downstream processes.

New pathways in plastics recycling and the current status of plastic recycling as a source of raw materials have been discussed by Kaminsky and Hartmann.[4] Chemical recycling of plastics into useful organic compounds, including monomers for the polymerization, by oxidative degradation[5] has been proposed for the widely used addition polymers such as polystyrene, polyethylene, and polypropylene. The recycling of these polymers is currently problematic owing to the high costs of collection and sorting, the small difference in prices for virgin and recycled resins and the reduction in polymer properties caused by the incompatability of different plastic components.[6]

Chemical recycling, which has been increasingly applied in recent years, is defined as the breakdown of polymeric waste into materials that are reusable as fuel or chemicals, including monomers. Of the 27 million tons of plastic material produced in the USA each year, 25% are condensation polymers, while addition polymers constitute 75% of this weight.[6] Other recycling methods include vacuum pyrolysis of commingled plastics containing PVC, which was carried out by Miranda *et al.*,[7] and thermal degradation of polymers such as polyethylene, polypropylene and polystyrene carried out under elevated pressure.[8] More detailed information on the recycling of plastic waste and also different alternatives developed for the feedstock have been discussed.[9] We have earlier reported the feedstock recycling of halogenated mixed plastic (PP/PE/PS/PVC and HIPS–Br) pyrolysis with Ca–C (calcium carbonate carbon composite).[10] Many research groups in universities and industry are investigating not only direct recycling but also the use of plastics as raw materials when the polymer molecules are degraded into small, organic base materials which can be purified by distillation or other methods.[4] However, because of chemical and technical problems as well as economic and legal factors, all processes for recycling mass-produced plastics as raw materials have not been cost effective until now.[4]

Green Context

Plastic waste is one of the major problems facing the consumer societies in Europe, Japan and North America. There is an urgent need to reduce the quantity of non-biodegradable plastics going to landfill in particular. The most attractive option for waste plastic treatment is probably recycling with the aim of converting the waste into basic petrochemicals (for fuel or other processes) being both practical and quite attractive. One of the major difficulties of this approach is the need to remove hazardous components notably organobromine flame-retardants. Here a very simple but effective method is described which uses high temperature water to debrominate the plastic before it is converted into liquid feedstocks. ***JHC***

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 DOI: 10.1039/b206704h

In the present investigation, we propose a novel method using an autoclave and hydrothermal conditions to remove the halogen content from a plastic mixture without converting it into liquid products and use the recovered plastic directly as an alternative to the liquid fuel (see Fig. 1). This process is simpler

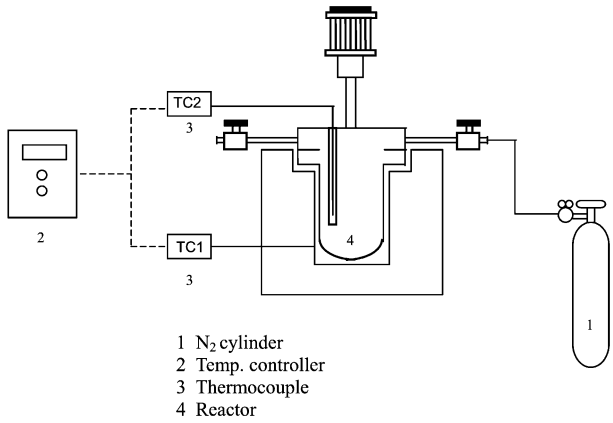

Fig. 1 Schematic experimental setup of the autoclave for the debromination process.

than feedstock recycling as it has a shorter reaction time and does not use a catalyst. After the reaction, the separation of water and recovered plastic is easy. High impact polystyrene containing brominated flame retardant (HIPS–Br); a HIPS–Br and polypropylene (PP) mixture; and a HIPS–Br and polyethylene (PE) mixture were debrominated in the present investigation. The effect of hydrothermal conditions such as temperature and amount of water on the extent of debromination is discussed.

Result and discussion

The debromination of HIPS–Br was carried out with various reaction parameters and optimal conditions for the removal of bromine from the plastic and a high yield of plastic recovery were investigated. The effects of reaction temperature, addition of PE and PP to HIPS–Br, and water on the debromination of HIPS–Br were studied. The effect of temperature on the removal of bromine from HIPS-Br using an autoclave was studied at 250, 260, 280 °C and the results, including recovered plastic yield, the distribution of bromine, and HBr in water, are shown in Fig. 2 The water content (20 ml) was kept constant .during the reaction with various temperatures for debromination. For comparison, the reaction was also carried out at 260 °C

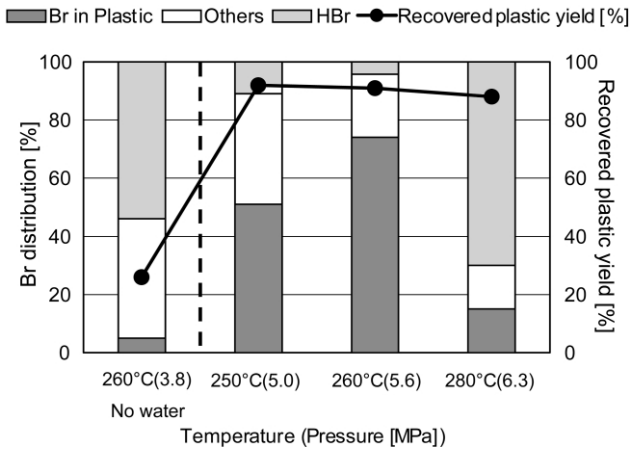

Fig. 2 The effect of temperature on the debromination and plastic recovery rate. Weight of HIPS-Br: 4 g. Amount of water: 20 ml.

without water and with only HIPS–Br (4 g). The self-generated pressure by water in the autoclave at various temperatures was recorded and is presented in Fig. 2. It is clear from Fig. 2 that the pressure in the autoclave increased with temperature. The recovered plastic yield varied slightly across the temperature range studied. However, the level of bromine in the recovered plastic was drastically decreased at a temperature of 280 °C. It is interesting to note that in the absence of water the bromine content in the treated plastic is less, but the recovery of plastic is about 30%. The remaining plastic (70%) was converted into a fine carbon black, which is impossible to recover. The presence of water (20 ml) facilitated the recovery of plastic as approximately 90% was recovered in the presence of 20 ml water and the color of the recovered plastic is almost same as virgin plastic (for temperatures of 250 and 260 °C). However, at 280 °C, the surface of recovered plastics was blackened, indicating that the degradation of plastic had commenced; and 70% of Br was extracted in water as HBr, but 15% of Br remained in the plastic (Fig. 2). The above results suggest the presence of water is essential for the recovery of plastic and the increase of temperature increased the bromine removal from HIPS-Br. The reaction was also carried out at 300 °C but the plastics degraded into oil and could not be recovered from the reactor.

Assessment of the effect of addition of PE and PP to HIPS–Br for debromination using an autoclave was carried out with the addition of 20 ml water. Weight ratios of PE or PP to HIPS–Br were varied, 1 : 1 and 1 : 3, and the reactions were carried out at 260 °C and 280 °C. The results are presented in Fig. 3 and Fig.

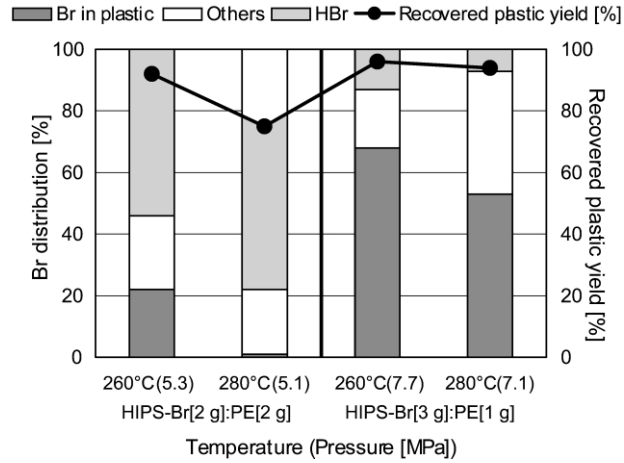

Fig. 3 The effect of PE addition to HIPS-Br on debromination and plastic recovery. Amount of water: 20 ml.

4. Fig. 3 shows the effect of PE addition to HIPS–Br during debromination. In the case of the HIPS–Br : PE (2 g : 2 g) mixture at 280 °C, 78% of Br was removed and converted to HBr in water (Fig. 3) and the reaction at 260 °C showed a plastic recovery of about 94% with 24% bromine remaining in the HIPS–Br. In the case of the 3 g : 1 g mixture of HIPS–Br/PE, a small amount of Br was removed from HIPS–Br. This clearly indicates that the addition of PE to HIPS–Br has no additional effect on the removal of bromine compared to the case of HIPS–Br (4 g) with 20 ml water at 280 °C. Fig. 4 shows the effect of PP addition to HIPS–Br for debromination. In the case of HIPS–Br : PP (3 g : 1 g) debromination at 280 °C, about 96% of Br was removed from the HIPS–Br as HBr and only about 1.2% of the Br remained in the plastic. The results indicate that the addition of PP promoted the debromination of HIPS–Br during heat treatment. In a similar experiment carried out at 260 °C, the bromine content in the recovered plastic was high (about 79%). Fig. 4 also shows the effect of a weight composition of PP to HIPS–Br of 1 : 1 at 260 and 280 °C. The results suggest that PP promotes the debromination process and a temperature of 280

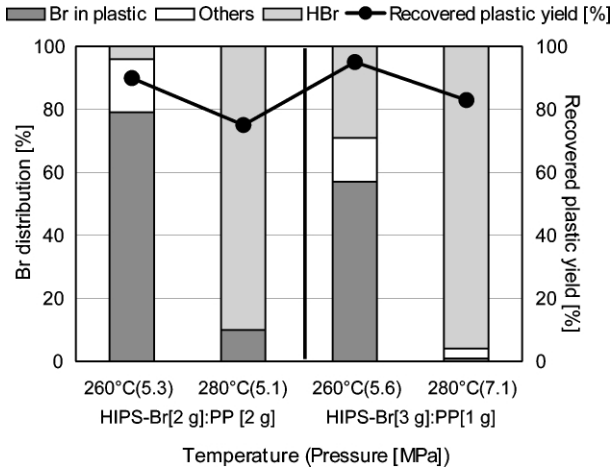

Fig. 4 The effect of PP addition to HIPS-Br on debromination and plastic recovery. Amount of water: 20 ml.

°C is necessary for the maximum recovery of plastic and removal of bromine. It might be the presence of tertiary hydrogen in PP that promoted the formation of HBr.

The effect of water addition to HIPS–Br : PP (3 g : 1 g) was studied at 260 °C from 0 to 30 ml water. Fig. 5 shows the

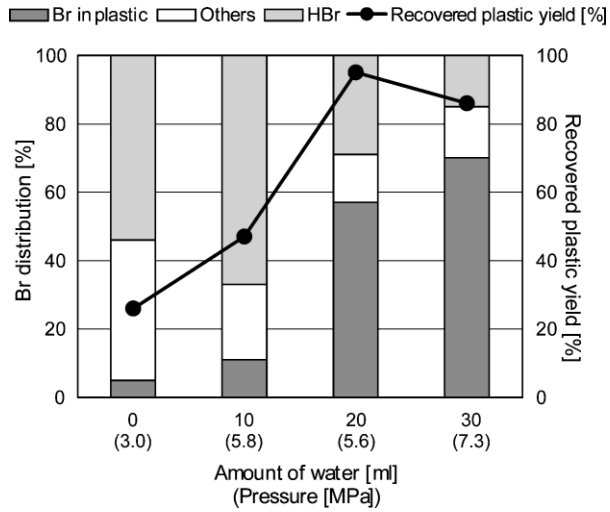

Fig. 5 The effect of water quantity on debromination and plastic recovery. Weight of HIPS-Br: 3 g. Weight of PP: 1 g. Temperature: 260 °C.

amount of water and self generated pressure of water on the *x*-axis and the Br distribution and recovered plastic yield on the *y*-axis. It is evident that 20 ml water is suitable for the maximum (95%) amount of plastic recovery. The gaseous products were analyzed by a gas chromatograph equipped with a thermal conductivity detector and showed the presence of hydrocarbons from C_1 to C_5. Atomic absorption spectroscopy (AAS) analysis confirmed the presence of Sb_2O_3 (2.5%) in the recovered plastic samples and also in water (2.0%). In addition, several experiments were repeated to see the overall product reproducibility. The "others" in Fig. 2–5 might be the bromine products present in gaseous products and we are unable to analyze gaseous bromine compounds.

Experimental

Materials

High impact polystyrene with decabromo diphenyl oxide flame retardant (HIPS–Br) with synergist Sb_2O_3 [HIPS–Br, Br: 15 wt%; Sb_2O_3: 4.5%] was used in the present study. Polypropylene (PP) obtained from Ube Chemical Industries Co. Ltd., Japan and high-density polyethylene (PE) from Mitsui Chemical Co. Ltd., Japan. The grain size of HIPS-Br, PP, PE was about 3 × 2 mm.

Experimental procedure

The schematic experimental setup of the autoclave reactor for the removal of bromine from the HIPS–Br plastics is presented in Fig. 1. Briefly, HIPS–Br was loaded into the autoclave (Taiatsu Glass Industries Co. Ltd., TAS-02; capacity 200 ml) with ion-exchanged water. After properly setting the autoclave reactor, the reactor was purged with nitrogen gas and the nitrogen gas was then cut off; the autoclave reactor temperature was increased to the required treatment temperatures. The amount of water varied from 10 to 30 ml. The self-generated pressure (water to steam) increased gradually as the autoclave reactor temperature increased. It was kept for 1 h after reaching the required reaction temperature. After cooling the autoclave reactor to room temperature, a known quantity of (about 60 ml) ion-exchanged water was added to extract HBr from the walls of the reactor. Finally, water and plastics were recovered separately. The heat treatment of HIPS–Br was carried out in the absence of ion-exchanged water to see the effect of water on the debromination reaction. In a similar way, the effect of addition of PE and PP to HIPS–Br was studied.

Analysis procedure

The Br content of the ion-exchanged water was analyzed using an ion chromatograph (DIONEX, DX-120 Ion Chromatograph). The treated plastics were recovered from the autoclave reactor and the bromine content of the recovered plastics was measured quantitatively using a combustion flask and ion chromatographic analysis. In brief, a small portion (about 8 mg) of recovered plastic sample was combusted with O_2 in a Pyrex flask, containing a pair of electric wires, a Pt sample pan held by the panholder, and a Pt filament for firing the sample. The combustion products were absorbed in about 40 ml water containing H_2O_2 (0.3 ml) and subsequently analyzed by ion chromatography. The gaseous products were collected from the reactor once it reached room temperature and analyzed by a gas chromatograph equipped with a thermal conductivity detector (TCD) (Yanaco: G180).

Conclusions

A laboratory scale investigation of debromination of HIPS-Br (3 g) mixed with PP (1 g) by autoclave using water (20 ml) was performed at 280 °C and recovered plastics containing 1.2% of the initial bromine. The addition of PP to HIPS-Br promoted the debromination process and PP acted as a source of hydrogen. The hydrothermal treatment for the removal of bromine from HIPS-Br was successfully carried out.

Acknowledgements

The authors would like to thank New Energy Development Organization (NEDO), Japan for financial support to carry out this research work under the Chugoku regional consortium

project (2000–2003). We are grateful to Dr. Katsuhide Murata for his valuable discussions.

References

1 Report of Waste Plastic Management Institute, Japan, June 1998.
2 F. Rodriguez, *Principles of Polymer Systems*, 3rd edn., Hemisphere, Washington, DC, 1989, p. 241.
3 M. Lee, *Chem. Br.*, 1995, **7**, 515.
4 W. Kaminsky and F. Hartmann, *Angew. Chem., Int. Ed.*, 2000, **39**, 331.
5 A. Pifer and A. Sen, *Angew. Chem., Int. Ed.*, 1998, **37**, 3306.
6 C. P. Rader, S. D. Baldwin, D. D. Cornell, G. D. Sadler and R. F. Stockel, *Plastics, Rubber and Paper Recycling*, American Chemical Society, Washington, DC, 1995.
7 R. Miranda, H. Pakdel, C. Roy and C. Vasile, *Poly. Degrad. Stab.*, 2001, **73**, 47.
8 K. Murata, M. Mihori and Y. Sakata, *Proceedings of Modest*, The 1st International Conference on Polymer Modification, Degradation, and Stabilisation, Palermo, Italy, September 2000, O2/Th/12.15.
9 J. Aguado and D. Serrano, *Feedstock Recycling of Plastic Wastes*, *RSC Clean Technology monographs*, series ed. J. H. Clark, Royal Society of Chemistry, Cambridge, UK, 1999.
10 T. Bhaskar, T. Matsui, J. Kaneko, Md. Azhar Uddin, A. Muto and Y. Sakata, *Green Chem.*, 2002, **4**, 372.

$InBr_3$–[bmim]PF_6: a novel and recyclable catalytic system for the synthesis of 1,3-dioxane derivatives

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Received 4th December 2002
First published as an Advance Article on the web 6th March 2003

Alkenes smoothly undergo condensation with paraformaldehyde in the presence of 10 mol% indium tribromide in ionic liquids (ILs) such as 1-butyl-3-methylimidazolium hexafluorophosphate [bmim]PF_6 or 1-butyl-3-methylimidazolium tetrafluoroborate [bmim]BF_4 under mild reaction conditions to afford the corresponding 1,3-dioxane derivatives in excellent yields with high selectivity. The recovered ionic liquid containing catalyst has been recycled in three to four subsequent runs.

Introduction

The acid-catalyzed condensation of olefins with aldehydes, known as the Prins reaction, is an important carbon–carbon bond forming reaction in organic synthesis.[1] The major products of the classical Prins reaction are normally 1,3-diols, 1,3-dioxanes, unsaturated alcohols, and the products obtained from acid-catalyzed polymerization of the olefins.[2] Particularly, 1,3-diols are important building blocks in the total synthesis of various bioactive natural products.[3] The simple and the most straightforward method for the synthesis of 1,3-diols is the addition of olefins to paraformaldehyde in the presence of acid catalysts. Generally, Lewis acids as well as Brønsted acids are employed in both catalytic and stoichiometric amounts to promote this transformation.[4,5] However, many of these methods involve the use of corrosive or toxic reagents, prolonged reaction times and also require high temperature reaction conditions resulting in low to moderate yields of products due to the polymerization of starting materials. Furthermore, many of these methods often require tedious aqueous work-up to isolate the products and thus produce a large amount of toxic waste. Therefore, the development of an efficient and versatile catalytic system for the Prins reaction is an active ongoing research area and thus, there is scope for further improvements toward milder reaction conditions and better yields.

Environment protection laws and corporate pressure to minimize the amount of toxic waste arising from chemical processes have motivated the development of innovative and environmentally-friendly chemical technologies. In this context, ionic liquids are emerging as a set of green solvents mainly as replacements for volatile organic solvents.[6] They are referred to as 'designer solvents' as their properties can be fine-tuned by changing the anion or the alkyl group attached to cation. These structural variations offer flexibility to the chemist to devise the most idealized solvent, catering for the needs of any particular process. Thus, they are particularly promising as solvents for catalysis.[7] Their high polarity and their ability to solubilise both organic and inorganic compounds can result in enhanced rates of chemical processes and they can provide higher selectivities compared to conventional solvents. The use of room temperature ionic liquids has made significant advancement in the development of clean chemical processes in organic synthesis targeted to avoid or at least minimize the use of toxic or waste generating reagents or solvents. Because of their distinct advantages, ionic liquids can make a great contribution to green chemistry.

In recent years, indium halides have emerged as mild and water-tolerant Lewis acids imparting high regio- and chemoselectivity in various organic transformations.[8] Compared to conventional Lewis acids, indium halides have advantages of low catalyst loading, moisture stability and catalyst recycling. Particularly, indium tribromide is found to be a more effective catalyst in promoting various transformations such as glycosidation, thioacetalization, cyanation of ketones, and conjugate addition reactions.[9,10] However, there are no examples of the use of indium halides as catalysts for this transformation.

Results and discussion

In view of the emerging importance of ionic liquids as novel reaction media, we herein report the synthesis of 1,3-dioxane derivatives using a catalytic amount of indium tribromide in ionic liquids. Thus treatment of styrene with paraformaldehyde in the presence of 10 mol% indium tribromide in 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim]PF_6) ionic liquid afforded the 4-phenyl-1,3-dioxane derivative in 91% yield (Scheme 1).

A variety of styrene derivatives reacted smoothly with paraformaldehyde under similar reaction conditions to give the corresponding 1,3-dioxane derivatives in excellent yields. In all cases, the reactions proceeded efficiently at 25 °C with high selectivity. Interestingly, α-methyl styrene also reacted with

Green Context

The development of safe, atom efficient acid-catalyzed organic processes is one of the most important challenges for Green Chemistry. While acid catalysis remains the most widely used type of catalysis, the commonly used acid catalysts continue to present serious problems through health and safety hazards and through separation based on destructive aqueous quenches. The Prins reaction is a superficially simple condensation of olefins with aldehydes yet the normal need for hazardous soluble acid catalysts make the process difficult and polluting. Here the combination of the easy to use Lewis acid, $InBr_3$ and an ionic liquid offer a safe, efficient and recyclable greener methodology.

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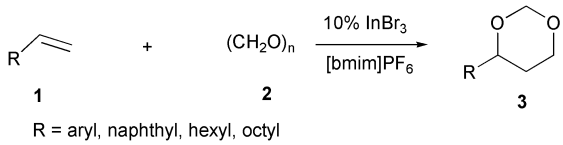
 DOI: 10.1039/b212044p

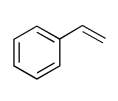
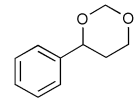
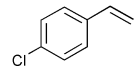
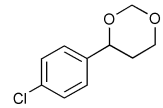
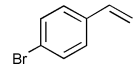
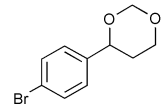
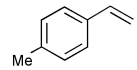
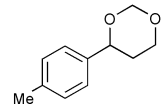
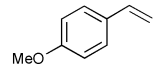
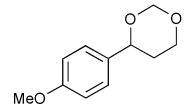
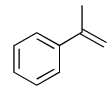
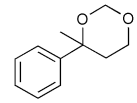
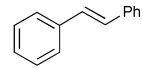
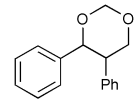
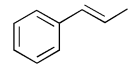
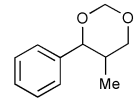
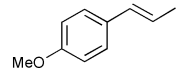
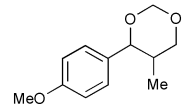
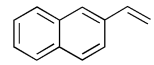
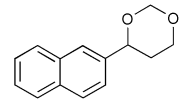
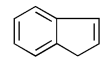
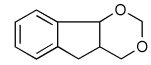
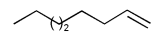
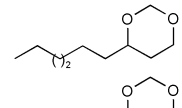
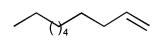
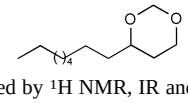


Scheme 1

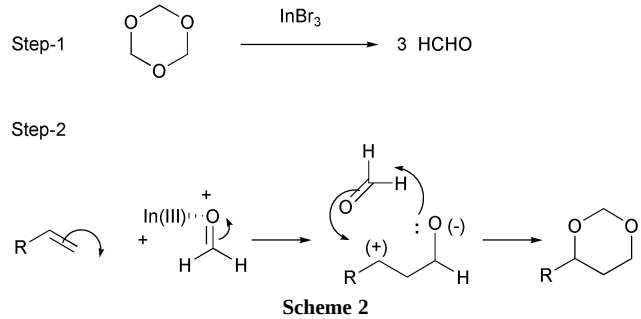
paraformaldehyde to produce the corresponding 1,3-dioxane derivative without the formation of ene-product which was normally formed in most of the reported conditions.[11] We also observed the formation of ene-product from the reaction of α-methyl styrene and paraformaldehyde in the presence 5 mol% $In(OTf)_3$ in dichloromethane at ambient temperature. Furthermore, indene, which normally shows extremely low reactivity in the Prins reaction, afforded tetrahydroindeno[1,2-*d*][1,3]dioxane in 85% yield under these conditions. Similarly, *p*-chloro, *p*-bromo-, *p*-methoxy, *p*-methyl, α-methyl and β-methyl styrenes and *trans*-stilbene afforded the corresponding 1,3-dioxane derivatives in excellent yields. Best results were achieved when the reactions were carried out at room temperature for 3.5–6.5 h in the presence of 10 mol% indium tribromide in ionic liquids. The results are presented in Table 1. Compared to conventional solvents, enhanced reaction rates, improved yields and high selectivity are the features obtained in ionic liquids. For example, the treatment of *trans*-stilbene with paraformaldehyde in the presence of 10 mol% indium tribromide in $[bmim]PF_6$ for 5.5 h afforded the corresponding 4,5-diphenyl-1,3-dioxane **3g** in 90% yield with *trans*-selectivity whereas the same reaction in dichloromethane after 8.0 h gave the product in 70% yield as *cis*- and *trans*-isomers in 2 : 8 ratio. Another advantage of the use of ionic liquids as a novel reaction medium for this transformation is that these ionic solvents can be easily recovered after completion of the reaction and can be reused in subsequent reactions. The products were easily separated by simple extraction with ether and characterized by ^1H, ^{13}C NMR, IR and mass spectroscopy and also by comparison with authentic samples.[12] The remaining oily ionic liquid was thoroughly washed with ether and dried at 80 °C under reduced pressure and recycled in three runs without any loss of activity. The products obtained were of the same purity as in the first run and no decrease in yields was obtained in runs carried out using recycled ionic liquid. For example, the treatment of styrene with paraformaldehyde in the presence of 10 mol% $InBr_3$ in $[bmim]PF_6$ afforded 91, 90 and 89% yields over three cycles. There are no considerable differences in reaction rates and yields either with $[bmim]PF_6$–$InBr_3$ or with the $[bmim]BF_4$–$InBr_3$ catalytic system. However, the reactions took longer reaction times (6–10 h) in the presence of the 10 mol% $InCl_3$–$[bmim]PF_6$ catalytic system to achieve comparable yields to those obtained with indium tribromide in $[bmim]PF_6$ ionic liquid. In the absence of catalyst, the reactions did not yield any product even after a long reaction time in ionic liquids. Furthermore, alkyl-substituted olefins afforded the corresponding 1,3-dioxanes in low yields (40–55%), when compared to styrene derivatives. The reaction probably proceeds through the initially formed monomeric formaldehyde by the interaction of paraformaldehyde with indium tribromide.[13] Subsequent addition of the olefin to activated formaldehyde followed by cyclization with another molecule of formaldehyde would result in the formation of 1,3-dioxane (Scheme 2).

In this reaction, the efficiency of the ionic liquid was strongly influenced by the nature of the anion. This reaction did not proceed even in the presence of 10 mol% indium tribromide in other molten salts such as *n*-tetrabutyl ammonium chloride (*n*-Bu_4NCl) or 1-*n*-butyl-3-methylimidazolium chloride ([bmim]Cl). These results indicate that both cation and anion play an important role as the solvent. Furthermore, the recovery and reuse of indium tribromide is especially simple in ionic liquids compared to organic solvents.

Table 1 $InBr_3$-catalyzed synthesis of 1,3-dioxane derivatives in ionic liquids

Entry	Alkene	Product[a]	Reaction time/h	Yield[b] (%)
a			3.5	91
b			4.5	85
c			5.5	82
d			3.5	91
e			4.5	85
f			5.0	87
g			5.5	90[c]
h			4.0	89[d]
i			4.5	85[e]
j			6.0	88
k			6.5	85
l			8.5	49[f]
m			9.5	55[f]

[a] All products were characterized by ^1H NMR, IR and mass spectroscopy. [b] Isolated and unoptimized yields. [c] *trans*-isomer was identified by ^1H NMR. [d] *cis–trans*-isomers were obtained in 2 : 8 and 1 : 9 ratios respectively. [e] *cis–trans*-isomers were obtained in 2 : 8 and 1 : 9 ratios respectively. [f] Reactions were carried out at 90 °C



Scheme 2

Conclusion

This paper describes a simple and efficient method for the synthesis of 1,3-dioxane derivatives through the condensation of olefins with paraformaldehyde using 10 mol% $InBr_3$ in [bmim]PF_6 ionic liquid as a novel catalytic system. The simple experimental and product isolation procedures combined with ease of recovery and reuse of this novel reaction media is expected to contribute to the development of a green strategy for the preparation of 1,3-diols. Furthermore, the use of the $InBr_3$–[bmim]PF_6 catalytic system for this transformation avoids the use of toxic or corrosive reagents and high temperature reaction conditions and it also provides a convenient procedure to carry out the reactions at ambient temperature.

Experimental

[Bmim]BF_4 and [bmim]PF_6 ionic liquids were prepared according to the procedures reported in the previous literature.[14]

Experimental procedure. A mixture of alkene (1 mmol), paraformaldehyde (1.5 mmol), and 10 mol% $InBr_3$ in [bmim]PF_6 or in [bmim]BF_4 (1 mL) was stirred at 25 °C for the appropriate time (Table 1). After completion of the reaction, as indicated by TLC, the reaction mixture was washed with diethyl ether (3 × 10 mL). The combined ether extracts were concentrated *in vacuo* and the resulting product was directly charged onto a small silica gel column and eluted with a mixture of ethyl acetate : *n*-hexane (1 : 9) to afford pure 1,3-dioxane. The rest of the viscous ionic liquid was further washed with ether and recycled in subsequent reactions. In the case of liquids, the products were easily separated by distillation. However, in the case of aliphatic alkenes the reactions were carried out at 90 °C.

Spectral data for selected products: **3a** (**4-phenyl-1,3-dioxane**): colorless oil, IR (KBr): ν 3060, 2938, 1598, 1450, 1330, 1160, 1092, 758. ^{1}H NMR (300 MHz, $CDCl_3$): 1.55–1.65 (m, 1H), 1.95–2.05 (m, 1H), 3.75 (dt, 1H, J = 2.5, 11.0 Hz), 4.10 (dd, 1H, J = 6.5, 11.0 Hz), 4.55 (dd, 1H, J = 2.5, 11.0 Hz), 4.80 (d, 1H J = 6.5 Hz), 5.10 (d, 1H, J = 6.5 Hz), 7.23–7.30 (m, 5H). EIMS: *m*/*z*: 164 M^+, 134, 118, 105, 77, 51. ^{13}C NMR (proton decoupled, 75 MHz, $CDCl_3$): δ 33.8, 66.7, 78.5, 94.1, 125.6, 127.8, 128.5, 141.3. **3f** (**4-methyl-4-phenyl-1,3-dioxane**): colorless oil, IR (KBr): ν 3057, 2931, 1591, 1457, 1329, 1162, 1097, 759. ^{1}H NMR (300 MHz, $CDCl_3$): 1.45 (s, 3H), 2.10–2.30 (m, 2H), 3.65 (dt, 1H, J = 2.4, 11.0 Hz), 3.90–3.95 (m, 1H), 4.75 (d, 1H, J = 6.5 Hz), 4.90 (d, 1H, J = 6.5 Hz), 7.21–7.30 (m, 5H). EIMS: *m*/*z*: 178 M^+, 163, 132, 117, 105, 91, 77, 51. ^{13}C NMR (proton decoupled, 75 MHz, $CDCl_3$): δ 32.1, 35.0, 63.5, 75.7, 89.1, 125.7, 127.0, 128.6, 144.1. **3i** (**4-(methoxyphenyl)-5-methyl-1,3-dioxane**) (major *trans*-isomer): pale yellow oil, IR (KBr): ν 3061, 2931, 1594, 1451, 1328, 1167, 1095, 747. ^{1}H NMR (300 MHz, $CDCl_3$): 0.55 (d, 3H, J = 6.7 Hz), 1.95–2.10 (m, 1H), 3.35 (t, 1H, J = 11.0 Hz), 3.75 (s, 3H), 4.05 (d, 1H, J = 10.3 Hz), 4.07 (dd, 1H, J = 4.0, 11.0 Hz), 4.70 (d, 1H J = 6.5 Hz), 5.10 (d, J = 6.5 Hz), 6.80 (d, 2H, J = 8.4 Hz), 7.20 (d, 2H, J = 8.4 Hz). EIMS: *m*/*z*: 208 M^+, 137, 122, 77, 51, 42. ^{13}C NMR (proton decoupled, 75 MHz, $CDCl_3$): δ 12.5, 36.3, 55.0, 72.9, 85.6, 94.2, 113.8, 128.5, 131.8, 159.5.

Acknowledgements

B. V. S. Reddy thanks CSIR New Delhi for an award of fellowship.

References

1 H. J. Prins, *Chem. Weekbl.*, 1919, **16**, 1072.
2 (*a*) D. R. Adams and S. P. Bhatnagar, *Synthesis*, 1977, 661; (*b*) E. Arundale and L. A. Mikeska, *Chem. Rev.*, 1952, **51**, 505.
3 (*a*) K. C. Nicolaou, R. A. Daines, Y. Ogawa and T. K. Chakraborty, *J. Am. Chem. Soc.*, 1988, **110**, 4696; (*b*) S. D. Rychnovsky, G. Griesegraber and J. Kim, *J. Am. Chem. Soc.*, 1994, **116**, 2621 and references cited therein.
4 (*a*) M. Koichi and S. Masaki, *Tetrahedron*, 1996, **52**, 7287; (*b*) S. D. Rychnovsky, G. Yang, Y. Hu and U. R. Khiere, *J. Org. Chem.*, 1997, **62**, 3022; (*c*) M. Delmas and A. Gaset, *Synthesis*, 1980, 871; (*d*) R. E. Gharbi, M. Delmas and A. Gaset, *Synthesis*, 1981, 361.
5 (*a*) E. A. Kobzar, D. V. Korchagina, N. F. Salakhutdinov, K. G. Ione and V. A. Barkhash, *J. Org. Chem. USSR (Engl. Transl.)*, 1992, **28**, 1030; (*b*) J. Tateiwa, K. Hashimoto, T. Yamauchi and S. Uemura, *Bull. Chem. Soc. Jpn.*, 1996, **69**, 2361; (*c*) S. Chandrasekhar and B. V. S. Reddy, *Synlett*, 1998, 851; (*d*) T. Bach and J. Lobel, *Synthesis*, 2002, 2521.
6 (*a*) T. Welton, *Chem. Rev.*, 1999, **99**, 2071; (*b*) P. Wasserscheid and W. Keim, *Angew. Chem., Int. Ed.*, 2000, **39**, 3772.
7 R. Sheldon, *J. Chem. Soc., Chem. Commun.*, 2001, 2399.
8 (*a*) C.-J. Li and T.-H. Chan, *Tetrahedron*, 1999, **55**, 11149; (*b*) G. Babu and P. T. Perumal, *Aldrichimica Acta*, 2000, **33**, 16; (*c*) R. Ghosh, *Indian J. Chem., Sect. B*, 2001, **40**, 550.
9 (*a*) M. Bandini, P. G. Cozzi, P. Melchiorre and A. Umani-Ronchi, *Tetrahedron Lett.*, 2001, **42**, 3041; (*b*) M. A. Ceschi, L. A. Felix and C. Peppe, *Tetrahedron Lett.*, 2000, **41**, 9695; (*c*) M. Bandini, P. G. Cozzi, M. Giocomini, P. Melchiorre, S. Selva and A. Umani-Ronchi, *J. Org. Chem.*, 2002, **67**, 3700.
10 (*a*) J. S. Yadav, B. V. S. Reddy, A. K. Raju and C. V. Rao, *Tetrahedron Lett.*, 2002, **43**, 5437; (*b*) J. S. Yadav and B. V. S. Reddy, *Synthesis*, 2002, 511.
11 (*a*) J. Tateiwa, A. Kimura, M. Takasuka and S. Uemura, *J. Chem. Soc., Perkin Trans. 1*, 1997, 2169; (*b*) V. K. Aggarwal, G. P. Vennall, P. N. Davey and C. Newman, *Tetrahedron Lett.*, 1998, **39**, 1997.
12 J.-P. Durand, M. Davidson, M. Hellin and F. Coussemant, *Bull. Soc. Chim. Fr.*, 1970, 4355.
13 B. B. Snider, in *Comprehensive Organic Synthesis*, vol. 2, ed. B. M. Trost and I. Fleming, Pergamon, London, 1991, 527.
14 Preparation of ionic liquids: (*a*) S. Park and R. J. Kazlauskas, *J. Org. Chem.*, 2001, **66**, 8395; (*b*) P. A. Z. Suarez, J. E. L. Dullius, S. Einloft, R. F. De Souza and J. Dupont, *Polyhedron*, 1996, **15**, 1217.

An ionic liquid as a recyclable medium for the green preparation of α,α′-bis (substituted benzylidene)cycloalkanones catalyzed by $FeCl_3·6H_2O$

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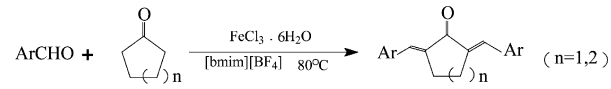
Received 6th December 2002
First published as an Advance Article on the web 11th March 2003

The utilization of the ionic liquid 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim][BF_4]) as reaction medium, and of iron (III) chloride hexahydrate as a catalyst is described for the efficient preparation of α,α′-bis(substituted benzylidene)cycloalkanones. The preparative process presented here is operationally simple, environmentally benign and has the advantage of enhanced atom utilization. Furthermore, the solvent and the catalyst used can be recovered conveniently and reused efficiently.

Introduction

Due to the importance of α,α′-bis(substituted benzylidene)cycloalkanones as useful precursors to potentially bioactive pyrimidine derivatives, condensation of cycloalkanones with aldehydes to give the corresponding α,α′-bis(substituted benzylidene)cycloalkanones is of special interest.[1] Usually, this purpose can be realized with the aid of strong acid or base catalysts. However, the presence of strong acid or base can make this condensation process suffer from reverse and side reactions and thus give the corresponding products in low yields.[2] Several catalytic procedures using different complexes of metal (II) ions, such as Mn (II), Fe (II), Co (II), Ni (II), Cu (II) and Zn (II), as catalysts have also been reported.[3] Among these complexes, Co (II)-bipyridyl has been found to be most reactive, but the yield of the condensation product of cyclopentanone with benzaldehyde is only 38%. In another case, cyclohexanone was reported to undergo condensation reaction with aromatic aldehyde under the promotion of Rh (III) porphyrine and gave the corresponding product in 30% yield.[4] In other cases, Cp_2TiPh_2[5] and anhydrous $RuCl_3$[6] have also been used to catalyze the cross-aldol condensations. However, a good yield of the products can only be obtained at high temperature in sealed ampoules or tubes. It is therefore important to develop more convenient and efficient methods for the preparation of this kind of compound.

Ionic liquids have recently been found to be excellent environmentally benign solvents for a variety of reactions.[7] Since these liquids have the advantages of being non-volatile, non-flammable, non-explosive and recyclable, they offer an attractive alternative to conventional organic solvents. Of particular interests are air and moisture stable imidazolium ionic liquids, which have been used as solvents for a variety of transition metal catalyzed reactions (*e.g.* oxidation,[8a] allylation,[8b] living radical polymerization[8c] and hydrogenation[8d]). In this paper, we report our preliminary results on the efficient preparation of α,α′-bis (substituted benzylidene)cycloalkanones (**3**) from benzaldehydes (**1**) and cycloalkanones (**2**) promoted by $FeCl_3·6H_2O$ using an ionic liquid, 1-butyl-3-methylimidazolium tetrafluoroborate([bmim][BF_4]), as the solvent (Scheme 1). To the best of our knowledge, this is the first example in which $FeCl_3·6H_2O$ can be used in ionic liquid medium to facilitate the aldol condensation of ketones with aldehydes to give enones.

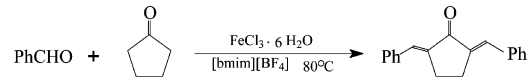


1 **2** **3**

Scheme 1

Results and discussion

Utilization of Lewis acids as catalytic promoter for the carbon–carbon band formation reaction is an important topic in organic synthesis. Up to now, many kinds of Lewis acids have been studied for this purpose. Among them, $FeCl_3·6H_2O$ was considered to be environmentally benign and has been used as efficient catalyst for several kinds of reactions.[9] As a continuation of our research program aimed at greener chemistry, $FeCl_3·6H_2O$ was chosen as a promoter to catalyze the condensation of benzaldehyde with cyclopentanone in ionic liquid [bmim][BF_4] (Scheme 2).



Scheme 2

Firstly, the mixture of benzaldehyde (1 mmol) and cyclopentanone (1 mmol) was treated with $FeCl_3·6H_2O$ (0.1 mmol) in 2 mL [bmim][BF_4] at room temperature. After being stirred for several hours, it gave no product. Then the mixture was heated at 80 °C for 6 h, the desired α,α′-dibenzylidene cyclopentanone was obtained in a rather low yield (9%,Table 1, entry 2), while

Green Context

Benzylidene cycloalkanones are useful precursors of biologically active pyrimidine compounds. They can be prepared by the condensation of cycloalkanones with aldehydes although the normal need for strong acids or bases to achieve this can lead to side reactions. Here it is shown that these reactions can be efficiently performed using a simple iron catalyst in an ionic liquid solvent. ***JHC***

Table 1 Effect of the amount of $FeCl_3·6H_2O$ and TMSCl on the preparation of α,α′-dibenzylidene cyclopentanone[a]

Entry	Amount of $FeCl_3·6H_2O$ (mmol)	Amount of TMSCl (mmol)	Isolated yield (%)
1	0	0	0
2	0.1	0	9
3	0.2	0	32
4	0.5	0	47
5	1	0	49
6	0.5	0.2	60
7	0.5	0.5	79
8	0.5	1	92
9	0.5	2	90
10	0	1	0

[a] Reaction conditions: 2 mL [bmim][BF_4], 1 mmol benzaldehyde, 1 mmol cyclopentanone, 80 °C, 6 h.

under similar reaction conditions but in the absence of $FeCl_3·6H_2O$, no reaction would take place (Table 1, entry 1). Further studies showed that increase of the dosage of $FeCl_3·6H_2O$ can improve the yields significantly (Table 1, entries 2–4). However, the yield could not be improved further when the amount of $FeCl_3·6H_2O$ exceeded 0.5 equiv. (Table 1, entries 4–5). At this point, the yield is only 47%. This is not a very satisfactory result because of the low yield.

Bearing in mind that some trimethylsilylenol ethers of ketones have been successfully used for the cross aldol condensation with aldehydes in the presence of Lewis acid,[10] we then added a little amount of trimethylchlorosilane (TMSCl) to the reaction mixture and tried to obtain a better yield. Fortunately, the expected product was obtained with much improved yield (Table 1, entry 4 and entry 6). Further studies in relation to the effect of the amount of TMSCl used on the yield showed that the yield could increase to as high as 92% when 1 mmol TMSCl was used together with 0.5 mmol $FeCl_3·6H_2O$ (Table 1, entry 8). The great improvement of the yield may attribute to the formation of a trimethylsilylenol ether intermediate from cyclopentanone and TMSCl with the aid of $FeCl_3·6H_2O$. In addition, it should be noted that when only TMSCl was present, no product could be obtained (Table 1, entry 4 and entry 10).

Based on the results obtained above, other substrates have also been studied for the preparation of α,α′-bis(substituted benzylidene)cycloalkanone derivatives (Scheme 1). The results were listed in Table 2. It shows that in the presence of

Table 2 Preparation of α,α′-bis(substituted benzylidene)cycloalkanones in [bmim][BF_4] at 80 °C

Entry	Ar	*n*	Reaction time/h	Products	Isolated yield (%)
1	C_6H_5	1	6	**3a**	92
2	p-ClC_6H_5	1	6	**3b**	89
3	p-$CH_3C_6H_5$	1	6	**3c**	90
4	o-ClC_6H_5	1	6	**3d**	87
5	m-BrC_6H_5	1	6	**3e**	88
6	C_6H_5CH=CH	1	10	**3f**	80
7	C_6H_5	2	6	**3g**	90
8	p-ClC_6H_5	2	6	**3h**	93
9	p-$CH_3C_6H_5$	2	6	**3i**	94
10	p-$NO_2C_6H_5$	2	6	**3j**	91
11	m-$NO_2C_6H_5$	2	6	**3k**	89
12	C_6H_5CH=CH	2	10	**3l**	82

$FeCl_3·6H_2O$ and TMSCl, all the substrates investigated can undergo a condensation process efficiently and give the corresponding products in fair yields in ionic liquid [bmim][BF_4]. In a typical experimental procedure, a solution of cycloalkanone (1 mmol) and aromatic aldehyde (1 mmol) in [bmim][BF_4] was heated at 80 °C in the presence of a catalytic amount of $FeCl_3·6H_2O$ (0.5 mmol) and TMSCl (1 mmol) for a certain period of time as required to complete the reaction (monitored by TLC). At completion, the reaction mixture was allowed to cool to room temperature. The solid thus precipitated was isolated by filtration, rinsed with water and ethanol and then dried to give α,α′-bis(substituted benzylidene)cycloalkanone in good yield with high purity. All the products were fully characterized by their ^{1}H NMR, IR, MS spectra and by comparison with the authentic samples.

In view of 'green chemistry', recovery and reuse of the catalyst and solvent is highly preferable. In our process, the catalyst Fe (III) could be immobilized in [bmim][BF_4] at the end of the condensation reaction. After filtration of the product, the solvent [bmim][BF_4] and the catalyst could be recovered easily by drying at 100 °C for several hours. Investigations by using benzaldehyde and cyclopentanone as model substrates showed that successive reuse of the recovered ionic liquids and the catalyst in the same reaction gave the product with a yield almost as high as that of the first round (Table 3, entry 2). It

Table 3 Studies on the reuse of Fe (III) and [bmim][BF_4]

Round	Yield (%)	Ionic liquid recovered (%)
1	92	99
2	90	98
3	88	98
4	88	99
5	86	98

should be noted that even in the fifth round, reuse of the molten salt and the catalyst recovered from the fourth round can produce the corresponding product with fairly good yield (Table 3, entry 5). After quenching the fifth round, ionic liquid could be recovered in more than 90% yield compared with that used in the first round.

In addition, ionic liquid [bmim][BF_4] and Fe (III) could also be reused for the reaction of other substrates after simple treatment of them by washing with diethyl ether and then drying at 100 °C for several hours.

On the other hand, it has been reported that ionic liquids are not only able to be used as green recyclable alternative to classical organic solvents, but also has the advantages of accelerating the reaction rate and increasing the yields compared with classical molecular solvents.[11] In order to investigate whether [bmim][BF_4] has such advantages in the aldol condensation reaction of aldehydes and cycloalkanones, several classical organic solvents, such as methanol, toluene and THF, were chosen as the medium for a comparison. Investigations by using benzaldehyde and cyclopentanone as the model substrates gave the following results (shown in Table 4).

Table 4 Condensation reaction of benzaldehyde and cyclopentanone in different solvents[a]

Entry	Solvent	Reaction temp./°C	Reaction time/h	Isolated yield (%)
1	THF	Reflux	6	41
2	Toluene	80	6	28
3	Methanol	Reflux	6	70
4	[bmim][BF_4]	80	6	92

[a] Reaction conditions: 2 mL solvent, 1 mmol benzaldehyde, 1 mmol cyclopentanone, 0.5 mmol $FeCl_3·6H_2O$, 1 mmol TMSCl.

It has been shown that of the four solvents used, [bmim][BF_4] gave the highest yield for the desired product **3a** (92%, Table 4, entry 4). When THF or toluene was used as the solvent, the reaction can not be completed after reflux or stirring at 80 °C for 6 h, and unidentified by-products were also obtained. Moreover, using [bmim][BF_4] as the reaction medium also made the separation process much easier than using other solvents. For example, with [bmim][BF_4] as the solvent, the product can be

obtained with high purity through simple filtration and rinsing of the filtrates with a little amount of water and ethanol. However, when toluene and THF were used as the solvents, a homogenous mixture was obtained at the end of the reaction. So subsequent washing with water, extraction with organic solvents, removing of the solvents under reduced pressure and recrystallization of the solid were necessitated.

In conclusion, we have developed an efficient and much improved modification of the cross coupling reaction of cycloalkanones with benzaldehydes and thus provided a simple access to α,α′-bis(substituted benzylidene)cycloalkanones in high yields. The advantages of this methodology include: (i) simple procedure. The fact that the utilization of Fe (III) as catalyst does not require any inert or anhydrous conditions together with the air and moisture stability of [bmim][BF_4] makes the reaction procedure reasonably easy; (ii) being a green process. Not only is [bmim][BF_4] an environmental benign solvent with non-volatility, but also Fe (III) has environmentally friendly nature; (iii) bearing the characteristic of atom economy. Since Fe (III) can facilitate the aldol condensation under mild and neutral conditions, side-reactions resulted from strong basic conditions are avoided. Moreover, the solvent [bmim][BF_4] and the catalyst can be recovered conveniently and reused efficiently. With all the advantages mentioned above, the method presented in this paper may provide an attractive alternative to the preparation of α,α′-bis(substituted benzylidene)cycloalkanones.

Experimental

Melting points were measured by a Kofler micromelting point apparatus and were uncorrected. Infrared spectra were recorded on a Bruker Vector 22 spectrometer in KBr with absorption in cm^{-1}. ^1H NMR spectra were determined on a Bruker AC 400 spectrometer as $CDCl_3$ solutions. Chemical shifts (δ) were expressed in ppm downfield from the internal standard tetramethylsilane and coupling constants J were given in Hz. Mass spectra were recorded on a HP5989B mass spectrometer. Elemental analyses were performed on an EA-1110 instrument.

General procedure for the preparation of α,α′-bis(substituted benzylidene) cycloalkanones

A mixture of cycloalkanone (**2**, 1 mmol) and aromatic aldehyde (**1**, 1 mmol) was added to the ionic liquid ([bmim][BF_4], 2 mL) containing $FeCl_3{\cdot}6H_2O$ (0.5 mmol) and TMSCl (1 mmol). The solution was stirred at 80 °C for a certain period of time to complete the reaction (monitored by TLC). After cooling, the solid precipitated was isolated by filtration, rinsed with water and ethanol and then dried to give **3** with high purity. The ionic solution containing the Fe (III) was then recovered for reuse by drying at 100 °C for several hours.

3a. mp 188–189 °C (lit.[12]189 °C); ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.61–7.64 (m, 6H), 7.38–7.48 (m, 6H), 3.43 (s, 4H); IR (KBr) ν: 3052, 3017, 2910, 1688, 1625, 1600 cm^{-1}.

3b. mp 227–228 °C (lit.[13] 231 °C); ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.55–7.57 (m, 6H), 7.44–7.46(m, 4H), 3.12 (s, 4H); IR (KBr) ν: 2911, 1692, 1620, 1605, 1580 cm^{-1}.

3c. mp 244–245 °C (lit.[13] 245–246 °C); ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.50–7.58 (m, 6H), 7.25–7.27 (m, 4H), 3.10 (s, 4H), 2.40 (s, 6H); IR (KBr) ν: 2911, 1686, 1622, 1602, 1589 cm^{-1}.

3d. mp 151–152 °C (lit.[5] 152.3–152.6 °C); ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.89 (s, 2H), 7.50–7.53 (m, 2 H), 7.42–7.44 (m, 2 H), 7.23–7.30 (m, 4H), 2.97 (s, 4 H); IR (KBr) ν: 3048, 2918, 1687, 1620, 1600, 1588 cm^{-1};

3e. mp 210–212 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.72 (s, 2H), 7.50–7.52 (m, 6 H), 7.31 (t, 2 H, J = 8.0 Hz), 3.12 (s, 4 H); IR (KBr) ν: 3059, 2920, 1687, 1623, 1603, 1554, 1180 cm^{-1}; MS (70eV) m/z(%): 420(M^{+}+ 4, 19.30), 418(M^{+}+ 2, 41.02), 416(M^{+}, 20.91), 339(71.48), 337(72.44), 129(42.56), 115(100); Anal. Calcd for $C_{19}H_{14}Br_2O$: C 54.58, H 3.38; Found C 54.52, H 3.43%.

3f. mp213–214 °C (lit.[14] 215–216 °C); ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.53 (d, 4H, J = 7.2 Hz), 7.25–7.42 (m, 8H), 6.98–7.02 (m, 4H), 2.95 (s, 4H); IR (KBr) ν: 3027, 1671, 1616, 1585 cm^{-1}.

3g. mp 115–116 °C (lit.[15] 116–117 °C); ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.30–7.60 (m, 10H), 7.18 (s, 2H), 2.80 (t, 4H, J = 5.6 Hz), 1.50–1.85 (m, 2H); IR (KBr) ν: 3042, 2892, 1670, 1602 cm^{-1}.

3h. mp 144–145 °C (lit.[16] 146–149 °C); ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.70(s, 2H), 7.35–7.39(m, 8H), 2.85(t, 4H, J = 5.6 Hz), 1.78–2.10(m, 2H); IR (KBr) ν: 2928, 1667, 1606 cm^{-1}.

3i. mp 163–164 °C (lit.[16] 164–166 °C); ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.75(s, 2H), 7.16–7.40(m, 8H), 2.90(t, 4H, J = 5.6 Hz), 2.37(s, 6H), 1.75–1.79(m, 2H); IR (KBr) ν: 2939, 2916, 1661, 1601 cm^{-1}

3j. mp 199–200 °C (lit.[16] 200–203 °C);^1H NMR ($CDCl_3$, 400 MHz) δ: 8.12 (s, 2 H), 7.50–8.02 (m, 8 H), 2.78–2.91(t, 4 H,J = 5.6 Hz), 1.85–1.37 (m, 2 H); IR (KBr) ν: 3025, 2915, 1675, 1605 cm^{-1}.

3k. mp 187–188 °C (lit.[16] 189–191 °C); ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.90 (s, 2 H), 7.50–7.82 (m, 8 H), 2.70–2.83 (t, 4 H,J = 5.6 Hz), 1.33–1.85 (m, 2 H); IR (KBr) ν: 3035, 2035, 1680, 1615 cm^{-1}.

3l. mp 177–178 °C (lit.[14] 179–180 °C); ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.65 (m, 10 H), 7.35–7.02(s, 2 H), 2.91–2.74 (t, 4 H,J = 5.6 Hz), 1.75 (m, 2 H); IR (KBr) ν: 3050, 2900, 1690, 1600 cm^{-1}.

Acknowledgement

This work was financially supported by the National Natural Science Foundation of China under NSFC grant No. 20273109.

References

1 J. Deli, T. Lorand, D. Szabo and A. Foldesi, *Pharmazie*, 1984, **39**, 539.
2 B. A. Hathaway, *J. Chem. Educ.*, 1987, **64**, 367.
3 K. Irie and K. Watanabe, *Bull. Chem. Soc. Jpn.*, 1980, **53**, 1366.
4 Y. Aoyama, Y. Tanaka, T. Yoshida, H. Toi and H. Ogoshi, *J. Oganometal. Chem.*, 1987, **329**, 251.
5 T. Nakano and T. Migita, *Chem. Lett.*, 1993, **12**, 2157.
6 N. Iranpoor and F. Kazemi, *Tetrahedron*, 1998, **54**, 9475.
7 (*a*) D. B. Zhao, M. Wu, Y. Kou and E. Z. Min, *Catal. Today*, 2002, **74**, 157; (*b*) H. Olivier-Bourbigou and L. Magna, *J. Mol. Catal. A: Chemical*, 2002, **182–183**, 419; (*c*) C. M. Gordon, *Appl. Catal. A: General*, 2001, **222**, 101; (*d*) T. Welton, *Chem. Rev.*, 1999, **99**, 2071; (*e*) P. Wasserscheid and W. Keim, *Angew. Chem., Int. Ed.*, 2000, **39**, 3773; (*f*) D. W. Morrison, D. C. Forbes and J. H. Davis, Jr., *Tetrahedron Lett.*, 2001, **42**, 6053.
8 (*a*) C. E. Song and E. J. Roh, *J. Chem. Soc., Chem. Commun.*, 2000, 837; J. Howarth, *Tetrahedron Lett.*, 2000, **41**, 6627; (*b*) W. Chen, L. Xu, C. Chatterton and J. Xiao, *J. Chem. Soc., Chem. Commun.*, 1999, 1247; (*c*) A. J. Carmichael, D. M. Haddleton, S. A. F. Bon and K. R. Seddon, *J. Chem. Soc., Chem. Commun.*, 2000, 1237; (*d*) R. A. Brown, P. Pollet, E. McKoon, C. A. Eckert, C. L. Liotta and P. G. Jessop, *J. Am. Chem. Soc.*, 2001, **123**, 1254.
9 (*a*) J. Christoffers, *J. Chem. Soc., Perkin Trans. 1*, 1997, 3141; (*b*) J. Lu, H. R. Ma and W. H. Li, *Chin. J. Org. Chem.*, 2000, **20**, 815.
10 T. Mukaiyama, K. Banno and K. Narasaka, *J. Am. Chem. Soc.*, 1974, **96**, 7304.
11 Y. Y. Xie, Z. C. Chen and Q. G. Zheng, *Synthesis*, 2002, 1505.
12 *Bellstein's Handbuch der Org. Chem.*, **7**, , 513.
13 H. Frey, G. Behmann and G. Kaupp, *Chem. Ber.*, 1987, **120**, 387.
14 W. L. Bao, Y. M. Zhang and T. K. Ying, *Synth. Commun.*, 1996, **26**, 503.
15 C. Chuit, R. J. P. Corriu and C. Reye, *Synthesis*, 1983, 294.
16 *Chem. Abstr.*, 1968, **69**, , 51812y.

Electrochemical treatment of distillery effluent using catalytic anodes

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Received 29th August 2002
First published as an Advance Article on the web 26th February 2003

Electrochemical treatment processes can provide valuable contributions to the protection of the environment through the minimization of waste and toxic materials in effluents. Complete decolourisation of the distillery effluent is a difficult task. The industry treated effluent still has a brown colour. This paper reports complete colour removal of industry treated distillery effluent through an electrochemical technique. Electrolysis of distillery effluent was carried out in a static electrochemical reactor. Two different types of anodes, planar graphite (Gr) and titanium substrate insoluble anodes (TSIA) were chosen for the treatment of distillery effluent. Lead dioxide coated on titanium (PbO_2–Ti) and ruthenium oxide coated on titanium (RuO_2–Ti) electrodes were used as TSIA. Current density (C.D.) was varied from 1.5 to 5.5 A dm^{-2}. Complete decolourisation was obtained in both cases. A maximum of 92% of chemical oxygen demand (COD) reduction, 98.1% of biological oxygen demand (BOD) reduction and 99.5% of absorbance reduction were obtained in the set up in which RuO_2–Ti as anode and stainless steel as cathode were used. A probable mechanism has been proposed for the oxidation of organics present in the effluent.

Introduction

The growth in industry and changes in manufacturing processes have resulted in an increase in the volume and complexity of wastewater discharged to the environment. The distillery effluent contains a dark brown pigment, melanoidin. The empirical formula of melanoidin is $C_{17–18}H_{26–27}O_{10}N$. It is a product of non-enzymatic reaction between sugars and amino compounds. The molecular weight distribution is between 5000 and 40000. It is acidic, polymeric and composed of highly dispersed colloids, which are negatively charged due to the dissociation of carboxylic acids and phenolic groups. The presence of melanoidin leads to the dark brown colour of the distillery effluent.[1] Biological methods of primary treatment are unable to degrade the colouring compounds. Many traditional processes are being modified and new treatment processes are being developed for effluent treatment. Various secondary treatments were tried for the removal of colour from the effluent. Strong oxidants like ozone and hydrogen peroxide were used. Though they result in decolourisation, they are not accepted at present because of economic reasons. Inorganic flocculants such as iron sulfate, iron chloride and aluminium sulfate will aid the separation of colouring matter. Complete decolourisation is usually not possible by this method. Oxidation by ozone combined with hydrogen peroxide is found to be very effective in the degradation of some aromatics present in wastewater.[2,3] Considering the economics and scale of wastewater purification operations, an electrochemical procedure has been found to be the most suitable. Over the years, different techniques including electrooxidation, electroreduction, electrodialysis and electroflocculation have been employed. The oxidation could be either direct or through intermediates formed during electrolysis. The oxidation of phenolic compounds in wastewater treatment was done using catalytic anodes.[4] A reticulated vitreous carbon cathode cell was found to be very convenient for the removal of organic compounds like phenol, cresol and aniline *etc*.[5] Fluidized bed electrolysis using various electrodes was an effective industrial process in metal recovery.[6] Earlier works proposed that electrooxidation could be used in the treatment of distillery effluent[7,8] and dye effluent[9] in various cell setups. The oxidative performance of three different anode materials graphite (Gr), lead dioxide coated titanium (PbO_2–Ti) and ruthenium oxide coated titanium (RuO_2–Ti) anodes on the electrooxidation of industry treated distillery effluent are discussed in this paper.

Results and discussion

Treatment using graphite electrodes

The effluent was placed in the cell and the graphite anode and cathode were inserted. The electrolysis was carried out without adding sodium chloride. Even after a long duration of electrolysis, complete decolourisation and considerable reduction in COD and BOD values were not obtained. Hence, 3 g dm^{-3} NaCl was added and the electrolysis was carried out.

The cell voltage and electrode potentials were measured and correlated with the duration of electrolysis. Fig. 1 shows the variation of cell voltage and electrode potentials with time.

Green Context

Green Chemistry in the context of chemical processes should include not only manufacturing processes ("clean synthesis") but the many other chemical processes we use in today's society. The treatment of industrial and other wastewater is a good example. Here we see the application of a less resource demanding and less environment threatening method for the treatment of distillery effluent. Traditional chemical methods include combined oxidants such as ozone and hydrogen peroxide but even these are not always that successful. Electrochemical treatment is shown to result in complete decolourisation of the wastewater – a quite simple, relatively safe and efficient procedure. ***JHC***

 DOI: 10.1039/b208424b

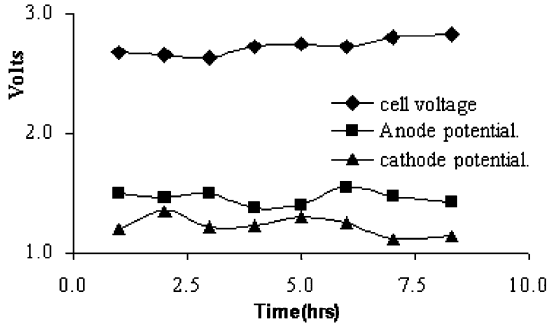

Fig. 1 Plots of cell voltage and electrode potentials with respect to time on graphite in the presence of NaCl at C.D. 1.5 A dm^{-2} and 0.33 A.

These parameters remain more or less constant throughout the electrolysis, indicating no adsorption or passivation of the electrode. The percentage of COD destruction, percentage of BOD reduction, percentage of absorption reduction, current efficiency (C.E.) and power consumption (P.C.) were calculated for various current densities and are presented in Table 1. The effluent prior to treatment was dark brown whereas after treatment it was completely colourless. The pH of the treated effluent was around 6.0 under various experimental conditions. A maximum of 95.6% absorbance reduction and complete decolourisation of the effluent were achieved at current density (C.D.) 1.5 A dm^{-2}. Removal of a higher amount of organics from the effluent was understood from the 80.6% COD reduction and 90% BOD reduction. A small amount of organic matter, either present in the effluent or formed during the treatment, may be the cause for not attaining 100% COD reduction. Higher current efficiency and lower power consumption were obtained at this current density. The off-gases from the cell were collected and tested. When the gas was passed through limewater, it turned milky indicating the formation of carbon dioxide during electrolysis. The removal of organics *via* an electrogenerated oxidising agent already has an established position through systems, which employ chlorine and/or hypochlorite.[10,11] In general, the following reactions take place during electrolysis of the effluent. At the anode:

$$2Cl^- \rightarrow Cl_2 + 2e^- \quad (1)$$

$$4OH^- \rightarrow O_2 + 2H_2O + 4e^- \quad (2)$$

At the cathode:

$$2H_2O + 2e^- \rightarrow H_2 + 2OH^- \quad (3)$$

In the undivided cell, chlorine formed at the anode and hydroxides formed at the cathode react to form chloride and hypochlorites. Both the hypochlorite and free chlorine are chemically reactive and oxidise organics in the effluent to carbon dioxide and water.

Treatment using PbO_2–Ti and RuO_2–Ti as anodes with stainless steel as cathode

Electrocatalytic anodes were used to achieve higher efficiency in effluent treatments.[11] The titanium substrate insoluble anode (TSIA) materials favoured the oxidation of organics containing higher aromatic rings with the formation of carboxylic acids. 0.22 dm^2 TSIA and same dimension stainless steel plate cathode were used. Experiments were carried out with and without 3 g dm^{-3} of sodium chloride.

The current density was varied from 1.5 to 5.5 A dm^{-2} in the presence of supporting electrolyte sodium chloride (3 g dm^{-3}). The COD, BOD and absorbance at wavelength 675 nm were determined in each variation and the percentage of COD reduction, BOD reduction and absorbance reductions were

Table 1 Treatment results from using in the presence of NaCl

C.D. A dm^{-2}	Current/A	Anode	Cell voltage/ volts	% of COD Redn.	% of BOD Redn.	% of Abs. Redn.	P.C.	C.E.
1.5	0.33	Gr	2.8	80.6	90.0	95.6	1.13	178.0
		PbO_2	4.7	90.8	95.6	98.5	1.31	250.8
		RuO_2	4.6	92.1	98.1	99.5	1.19	258.9
2.0	0.45	Gr	3.2	52.4	60.0	91.7	1.29	169.0
		PbO_2	5.2	72.5	80.0	89.5	1.44	233.2
		RuO_2	4.8	80.0	90.8	92.0	1.49	225.1
2.5	0.56	Gr	4.5	53.4	60.0	91.7	1.73	172.0
		PbO_2	5.6	76.6	84.2	91.8	1.60	246.3
		RuO_2	5.4	82.3	92.0	95.0	1.57	230.8
3.5	0.80	Gr	5.0	54.5	63.5	90.5	1.97	175.0
		PbO_2	7.4	53.1	65.0	83.2	2.89	170.8
		RuO_2	6.8	75.0	83.0	90.0	2.16	211.0
4.0	0.90	Gr	5.6	56.0	65.1	95.4	2.12	180.0
		PbO_2	7.6	50.2	62.1	81.8	3.14	161.4
		RuO_2	7.2	75.1	84.2	92.5	2.29	211.1
4.5	1.00	Gr	6.2	50.0	56.2	95.3	2.56	161.1
		PbO_2	8.1	60.3	72.0	85.8	2.75	194.0
		RuO_2	7.7	82.0	91.0	95.0	2.26	225.1
5.5	1.20	Gr	6.9	30.8	50.0	85.6	4.93	91.0
		PbO_2	9.9	39.4	52.3	58.5	3.39	191.2
		RuO_2	9.0	85.8	93.6	98.0	2.52	239.2

Gr – Graphite, Abs – Absorbance at 675 nm, P.C – Power consumption (kWh kg^{-1} of COD).

calculated (Table 1). Maximum percentage removal of pollutants was observed only with lower current density, 1.5 A dm^{-2}. The cell voltage and electrode potentials at the optimised current density, 1.5 A dm^{-2} were measured and correlated with time (Fig. 2 and 3). The cell voltage and electrode potentials

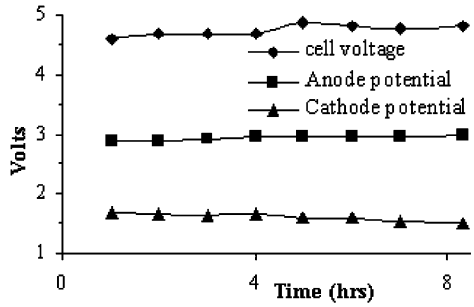

Fig. 2 Plots of cell voltage and electrode potentials with respect to time in the presence of NaCl at C.D. 1.5 A dm^{-2} and 0.33 A. (Anode = PbO_2–Ti & cathode = stainless steel.)

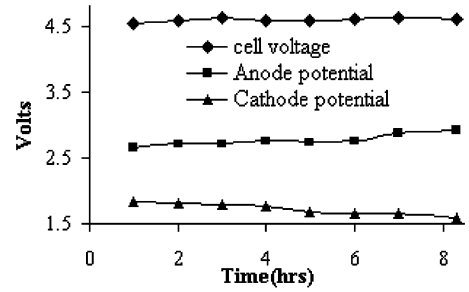

Fig. 3 Plots of cell voltage and electrode potentials with respect to time in the presence of NaCl at C.D. 1.5 A dm^{-2} and 0.33 A. (Anode = RuO_2–Ti & cathode = stainless steel.)

remain almost constant during electrolysis. This demonstrates that the electrochemical cell constituents are unaffected during the entire period of electrolysis. This indicates the absence of adsorption, passivation and anodic dissolution of the anode during electrolysis.

The percentage of COD reduction, BOD reduction and absorbance reductions were compared for both the TSIA (RuO_2–Ti and PbO_2–Ti). A maximum of 99.5% absorbance reduction was observed with the usage of RuO_2–Ti. The percentage of COD and BOD reductions were higher with RuO_2–Ti than that with PbO_2–Ti which in turn are higher than that with the graphite electrode. The current efficiency and power consumption also showed a similar trend. These results clearly indicate the catalytic effect of the PbO_2–Ti and RuO_2–Ti anodes. Of the two, RuO_2–Ti shows better performances and it can be used as a better anode for the electrochemical treatment of distillery effluent. At higher concentrations of sodium chloride, the destruction of organics may be due to chlorine and hypochlorites as proposed for graphite. The formation of carbon dioxide gas was also confirmed as previously. The pH of the treated effluent was decreased to 6.0 after the electrolysis. This may be due to dissolved carbon dioxide.

Since the usage of sodium chloride led to a decrease in pH, the same experiments were carried out in the absence of sodium chloride. The cell voltage and electrode potentials were unchanged during electrolysis at current density, 1.5 A dm^{-2} (Fig. 4 and 5) suggesting the absence of electrode degradations. The higher values of cell voltage in the absence of sodium chloride may be due to the absence of the supporting electrolyte, sodium chloride. As previously, the COD, BOD and absorbance measurements were done and the results are presented in Table 2. Here, 56.3 and 62.0% COD reductions were observed as maximum with PbO_2–Ti and RuO_2–Ti anodes, respectively. In the absence of chloride, the electrochemical oxidation took

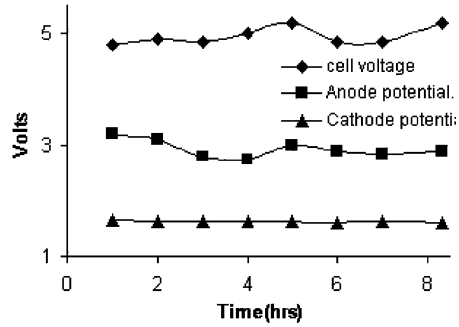

Fig. 4 Plots of cell voltage and electrode potentials with respect to time in the absence of NaCl at C.D. 1.5 A dm^{-2} and 0.33 A. (Anode = PbO_2–Ti & cathode = stainless steel.)

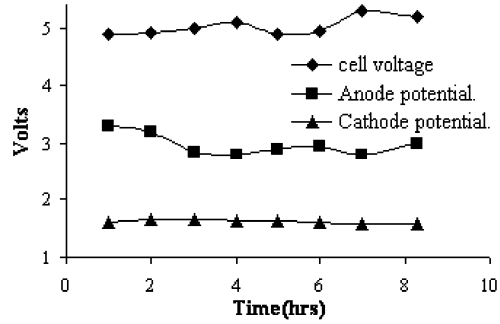

Fig. 5 Plots of cell voltage and electrode potentials with respect to time in the absence of NaCl at C.D. 1.5 A dm^{-2} and 0.33 A. (Anode = RuO_2–Ti & cathode = stainless steel.)

place only through the catalytic effect of the electrodes. The mechanism of oxidation is different from the previous one. The combustion of organics on the oxide anode (MO_x) can generally be considered to take place through physisorbed and chemisorbed active oxygen. In the first step, OH^0 free radical, formed from the oxidation of water through discharge of H_2O or OH^- from acid or alkali solutions, is physisorbed on the oxide electrode (eqn. 4). In the second step, the physisorbed OH^0 radical may interact with the oxygen already present in the oxide anode (eqn. 5).

$$MO_x + H_2O \rightarrow MO_x(OH^0) + H^+ + e- \quad (4)$$

$$MO_x\,(OH^0) \rightarrow MO_{x+1} + H^+ + e^- \quad (5)$$

In the presence of oxidisable organics, the physisorbed active oxygen oxidises the organics completely (eqn. 6) and chemisorbed active oxygen participates in the formation of selective oxidation products (eqn. 7).

$$R + MO_x(OH)_z \rightarrow CO_2 + zH^+ + ze^- + MO_x \quad (6)$$

$$R + MO_{x+1} \rightarrow RO + MO_x \quad (7)$$

Dioxygen also participates in the combustion of organics. In the first step, organic radicals are formed by hydrogen abstraction (eqn. 8) and in the second step dioxygen reacts with the organic radical (eqn. 9).

$$RH + OH^0 \rightarrow R^0 + H_2O \quad (8)$$

$$R^0 + O_2 \rightarrow ROO^0 \quad (9)$$

Further abstraction of a hydrogen atom leads to the formation of organic hydroperoxide (ROOH) and another organic radical.

$$ROO^0 + R'H \rightarrow ROOH + R'^0 \quad (10)$$

Since the organic hydroperoxides formed are relatively unstable, decomposition of such intermediates often leads to molecular breakdown and formation of subsequent intermediates with lower carbon numbers. Because of the complications in the oxidation mechanism, some intermediate organics

Table 2 Treatment results from using the PbO_2–Ti and RuO_2–Ti electrodes in the absence of NaCl

	C.D. A dm^{-2}	Current/A	Cell voltage/ volts	% of COD Redn.	% of BOD Redn.	% of Abs. Redn.	P.C	C.E
PbO_2/Ti	1.5	0.33	5.1	56.3	62.5	85.4	2.23	180.0
	2.0	0.45	5.6	35.0	52.3	62.2	3.37	112.0
	2.5	0.56	5.8	40.0	56.1	73.9	3.02	129.0
	3.5	0.80	7.0	43.3	60.0	82.8	3.49	139.0
	4.0	0.90	7.6	30.0	48.6	61.7	5.35	96.0
	4.5	1.00	8.7	23.3	40.0	54.5	7.60	75.0
	5.5	1.20	10.2	55.9	61.2	85.3	3.70	180.0
RuO_2/Ti	1.5	0.33	5.2	62.0	80.8	88.0	1.91	182.8
	2.0	0.45	5.8	60.0	78.9	86.0	2.19	176.9
	2.5	0.56	6.3	55.5	70.0	60.0	2.68	162.1
	3.5	0.80	8.0	63.3	86.5	90.0	2.89	185.7
	4.0	0.90	8.3	45.5	65.0	80.0	4.14	132.7
	4.5	1.00	8.8	58.0	78.0	82.0	3.49	170.9
	5.5	1.20	10.2	60.2	81.0	90.0	3.98	176.9

are produced during electrolysis. Hence, the percentage of COD and BOD reductions are less compared to the results obtained in the presence of sodium chloride.

Determination of instantaneous current efficiency (ICE)

Instantaneous current efficiency (ICE) is the current efficiency measured at a particular time or at constant time intervals during the electrochemical treatment of wastewater. Measurements of ICE give information about the formation of polymeric products at the anode during treatment. Melanoidin, a polymeric material present in the distillery effluent may be adsorbed on the electrode surface and may decrease the efficiency of the electrode. Hence, a detailed study about ICE was warranted. ICE for electrooxidation of organics at given experimental conditions was calculated by two methods (i) an oxygen flow method (ii) a COD method.[5,11] The choice of method used to measure ICE depends on the solubility of the electrolysis product. The COD method is used only if the electrolytic products are soluble in the electrolyte. The oxygen flow rate method is used where the electrolysis products are soluble or insoluble. Since the products were water and carbon dioxide in this study, ICE values were calculated by the COD method using the following relation

$$\frac{[(\mathrm{COD})_t - (\mathrm{COD})_{t+\Delta t}]FV}{8I\Delta t} = \mathrm{ICE}$$

where $(\mathrm{COD})_t$ and $(\mathrm{COD})_{t+\Delta t}$ are the chemical oxygen demands at times t and $t + \Delta t$ (in mg O_2 dm^{-3}), respectively, I is the current (A), F is the Faraday (96487 C mol^{-1}) and V is the volume of electrolyte (dm^3).

Calculated ICE values were plotted with respect to time (Fig. 6). An initial increase in the ICE values was observed with time

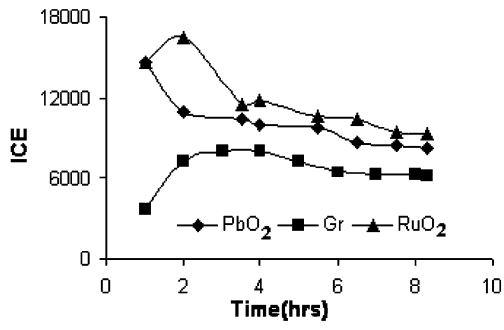

Fig. 6 Plots of ICE values with respect to time using various anodes.

when the graphite electrode was employed. The slow increase in ICE in the initial hours may be due to initial polarization of the electrode and the formation of fresh active electrode surface. After this, the ICE maintains almost constancy because of the steady state obtained between the mass and charge transfers (Fig. 6). This reveals the absence of adsorption of polymeric materials present in the effluent and polymeric film formation on the electrode surface. With titanium substrate insoluble anodes (TSIA), ICE values were plotted with respect to time interval for PbO_2 and RuO_2 coated anodes. An initial increase and maintaining constancy of ICE is also observed with the RuO_2 coated titanium electrode. An initial decrease and maintaining constancy of ICE is observed with the PbO_2 coated titanium electrode. The initial decrease may be due to partial coverage of the active electrode surface by bulky molecules in the medium. Because of continuous oxidations, the increase in the surface coverage is not increased further. At longer durations, not much change in ICE is observed. This indicates that the electrode surface reactions are not affected much during the electrolysis. The electrochemical treatment of distillery effluent was carried out by direct catalytic oxidation and indirect mediated oxidation using chloride–hypochlorite mechanisms. Both mechanisms are simultaneously operated during electrochemical treatment. Since catalysis is involved in the treatment process, the ICE values of the above process exhibit higher values compared to the graphite anode.

From the above results, the catalytic anodes are found to be suitable for the treatment of distillery effluent in the presence and absence of NaCl. Better performances are observed only when the destruction is carried out in the presence of NaCl. The presence of the supporting electrolyte decreases the cell voltage, which leads to a decrease in power consumption. The characteristics of the effluent before and after treatment are presented in Table 3. There is an increase in TDS after

Table 3 The characteristics of untreated (10 times diluted) and treated effluent

Parameters	Untreated effluent	Treated effluent
pH	6.9–7.2	5.0–6.3
Temperature/°C	27	38–42
Colour	Brown	Colourless
Odour	Burnt sugar	Nil
BOD (ppm)	7000–7200	250–300
COD (ppm)	12000–15000	525–600
Total dissolved solids (TDS in ppm)	2200	3500
Chloride (ppm)	500–600	700–800
Nitrogen (ppm)	120–150	50–80
Potassium (ppm)	1000–1300	950–1200
Calcium (ppm)	210–300	180–250
Magnesium (ppm)	200–330	190–300

treatment. However, this problem can be solved by recycling the treated water without adding sodium chloride solution to the

effluent before electrolysis. The comparative results are presented in Fig. 7. Among the catalytic anodes used, ruthenium oxide is found to be very effective for the treatment of distillery effluent.

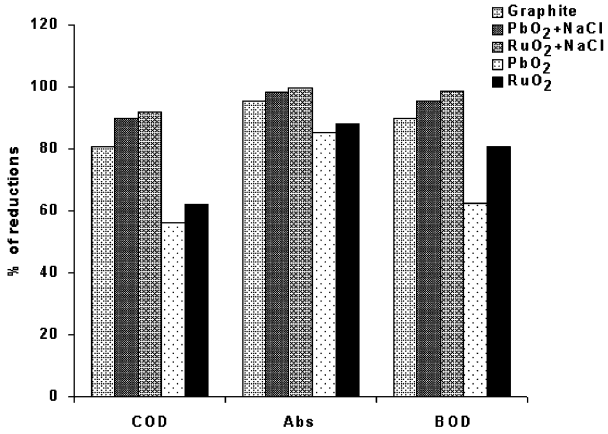

Fig. 7 Comparative plots of percentages of COD, BOD and absorbance reduction.

Experimental

A static undivided electrochemical reactor was employed in this study. The reactor, a cylindrical vessel which can hold 200 ml of ten times diluted effluent, was subjected to treatment electrolyte. A planar graphite electrode of length 4.5 cm, height 8.2 cm and thickness 0.5 cm was used as the working electrode (anode). Another graphite electrode of the same dimensions served as counter electrode (cathode). The area of the electrode exposed for the electrolysis was fixed to be 0.225 dm^2 and the remaining area of the electrode was prevented from exposure with lacquer. The same dimensions of oxide anodes PbO_2 and RuO_2 coated on titanium mesh substrates and stainless steel cathode plates were also used. Sodium chloride solution (3 g dm^{-3}) was used as supporting electrolyte.

Initially a trial run was carried out at 1 A dm^{-2} and the samples were drawn at constant intervals for examination with respect to decolourisation. Based on the results, the total quantity of electricity required for complete decolourisation was found out from the curve of percentage transmittance *vs.* time of electrolysis. This was used as a guide for studying the effect of current density. Experiments were carried out under galvanostatic conditions. The current density varied from 1.5 to 5.5 A dm^{-2} in seven steps keeping the total quantity of electricity constant at 2.5 Ah. As the current densities varied, the duration of electrolysis is also changed, in turn the time intervals changed. For example, the time interval was one hour when the best current density, 1.5 A dm^{-2} was applied. The cell voltage, anode potential and cathode potential *vs.* SCE were measured using a precision multimeter. During electrolysis, samples were collected at constant intervals and the COD was estimated using the standard procedure as per ASTM standards. BOD was measured using a direct reading BOD COUNT Spectralab Instrument. Absorbance values were determined using a Systronics 166 Spectrophotometer at a λ_{max} of 675 nm. The effluent under study was collected from the primary lagoons of an industrial alcohol plant. The chemical characterisation[12] of distillery effluent before and after treatment is given in Table 3. Each electrolytic experiment was repeated three times and all the measurements were made in each experiment. The average of the three measurements was calculated. The percentage RSD value is between 2–4%. This study was carried out for two more effluent samples collected at different periods and the range obtained was reported here.

Acknowledgement

The authors gratefully acknowledge the financial support of AICTE (All India Council of Technical Education) for the work reported here.

References

1 P. Manisankar, S. Viswanathan and C. Rani, *Complete Decolourisation of Distillery Effluent by Electrochemical Method, Proceedings of National Seminar on Industrial Pollution and its Control*, Banaras Hindu Universiry, Varanasi, India, February 2000.
2 F. J. Beltran, M. Gonzalez and F. J. Rivas, *J. Environ. Sci. Health*, 1996, **9**, 2193.
3 I. A. Balcioglu and Y. Inel, *J. Environ. Sci. Health*, 1996, **1**, 123.
4 Ch. Comninellis and C. Pulgarin, *J. Appl. Electrochem.*, 1993, **23**, 108.
5 A. A. Gallegos and D. Pletcher, *Electrochim. Acta*, 1999, **44**, 2483.
6 K. Juttner, U. Galla and H. Schmieder, *Electrochim. Acta*, 2000, **45**, 2575.
7 L. J. Berchmans and R. Vijayavalli, *Electrochemical Oxidation as a Tool for Pollution Control; Part II Treatment of Waste Water from Distillery Industry, Paper 8.4,, Proceedings of the International Symposium on Advances in Electrochemical Science and Technology*, CECRI, Karaikudi, India, December 1984.
8 L. J. Berchmans. and R. Vijayavalli, *Indian J. Environ. Health*, 1989, **31**, 309.
9 P. Manisankar, C. Rani and S. Viswanathan, *J. Indian Association for Environmental Management*, 2000, **27**, 304.
10 D. Pletcher and F. C. Walsh, *Industrial Electrochemistry*, Chapman and Hall, London, 1990.
11 *Environmental Oriented Electrochemistry*, ed. C. A. C. Sequeira, Elsevier, Amsterdam, The Netherlands, 1994.
12 V. Venugopal, D. C. Sharma, G. S. Sastry and K. M. Agrawal, *Application Of Cleaner Technology in a Distillery to achieve Zero-Discharge; A case study on Somaiya Organo chemicals Ltd., Indian Association for Environmental Management Annual Conference*, NEERI, Nagpur, India, December 1999.

Heterogeneous catalysis in the synthesis and reactivity of allantoin

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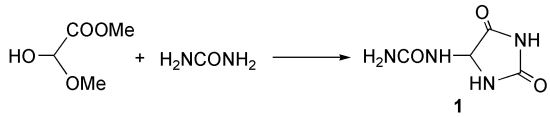
Received 17th December 2002
First published as an Advance Article on the web 20th February 2003

The synthesis of allantoin from glyoxylic acid and urea has been studied using several heterogeneous catalysts. Organic resins and nanocomposites, particularly sulfonic resins, lead to higher yields than zeolites. Polymer morphology has a significant influence on the performance of the catalyst. The possibility of using the same type of solid acid in the reaction of allantoin with phenol has also been explored. However, this route requires a larger amount of acid and leads to lower *para*/*ortho* selectivity than the direct route from glyoxylic acid and urea.

Introduction

Allantoin [*N*-(2,5-dioxoimidazolidin-4-yl)urea] (**1**) is a product of purine and protein metabolism that is found in mammalian urine and in some plants, such as aloe. This compound is associated with many beneficial effects for the skin and, therefore, it is used in the formulation of cosmetics and ointments for the treatment of skin ulcers. Allantoin and some of its derivatives are also used in cancer prophylaxis and treatment. In addition to its applications in pharmacy and cosmetics, allantoin can be used as a reagent in the synthesis of *dl*-5-(4-hydroxyphenyl)hydantoin,[1] a precursor in the enzymatic synthesis of *d*-(4-hydroxyphenyl)glycine.

Allantoin has been prepared by oxidation of urea with different oxidants,[2] by reaction of urea with 5-chloro-[3] or 5-bromohydantoin,[4] as well as with 2,2-disubstituted acetic acid or related esters.[5] In this regard a very interesting synthesis, starting from methyl 2-hydroxy-2-methoxyacetate, has been described[6] (Scheme 1).



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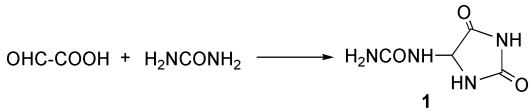
Scheme 1

A method closely related to those outlined above involves the synthesis of allantoin by reaction of glyoxylic acid (or a glyoxylate) with urea in the presence of an acid[7] (Scheme 2). In



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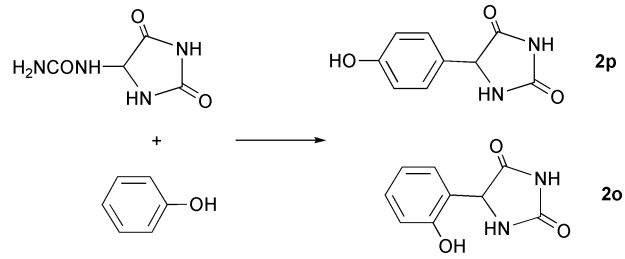
Scheme 2

an attempt to avoid the problems associated with the use of homogeneous catalysts, methods employing heteropolyacids have been investigated. However, it was found that a large excess of urea is needed in these cases.[8]

The work described here concerns a study of the use of heterogeneous acids as catalysts in the reaction between glyoxylic acid and urea. The replacement of strong mineral acids by recoverable solids in Fine Chemicals synthesis is an important objective in the field of Green Chemistry. A second aspect of this work involves the use of the same solids in the reaction between allantoin and phenol, with the aim of obtaining the valuable compound *dl*-5-(4-hydroxyphenyl)hydantoin (**2p**) (Scheme 3). The overall aim of this approach was to implement



Scheme 3

a fully heterogeneous system able to improve the results obtained with solid acids in the direct synthesis of allantoin from glyoxylic acid, urea and phenol.[9]

Results and discussion

Synthesis of allantoin

The first problem to be solved in this study was to find a simple and reliable method to compare the results for the different

Green Context

Allantoin has many applications in cosmetics, ointments and in the treatment of some cancers. One method for the synthesis of allantoin involves the acid-catalysed reaction of glyoxylic acid with urea. As with so many acid-catalysed reactions it would be environmentally advantageous to use a recoverable and reusable solid acid and this paper compares the effectiveness of different materials in this category. Sulfonic resins proved to be most effective giving moderate to good yields at relatively low levels of catalyst. The catalyst is reusable. ***JHC***

reactions. After several tests, we decided to determine the allantoin : urea ratio by ^{1}H-NMR spectroscopy, using the signal from urea at 5.41 ppm (4H) and three different signals from allantoin at 6.88 (1H), 5.78 (2H) and 5.24 ppm (1H). One of the main drawbacks of this method is the possible hydrolysis of urea and allantoin in the presence of strong acids. However, the use of solid acids allows a mass balance to be carried out because the catalyst is separated by filtration prior to work up of the reaction. In these cases the recovered weight was always more than 95% of the expected weight based on the yield determined by ^{1}H-NMR spectroscopy. A second problem inherent in this method is the possible formation of by-products. However, small signals due to by-products were detected in the ^{1}H-NMR spectra only in the cases of the low-yield reactions. Finally, the mass balance could be erroneous due to the presence of water, even after drying the product under vacuum. This possibility was ruled out on the basis of thermogravimetric analysis results. These results show that below 393 K the weight loss is less than 3%. The weight loss between 393 and 473 K corresponds to the decomposition of the remaining urea, a situation in agreement with the ^{1}H-NMR analysis. Finally, the weight loss at temperatures above 473 K corresponds to allantoin decomposition. In conclusion, for high yield reactions the error in this method can be estimated in the order of 5%. Further confirmation of the validity of this method is the recovery of 80% yield of allantoin after crystallization of the product.

Once the reliability of the method for yield determination had been demonstrated, several heterogeneous catalysts were tested in the reaction between glyoxylic acid and urea under conditions previously optimized for concentrated HCl. The results obtained in these reactions are gathered in Table 1.

Table 1 Results obtained from the reaction of glyoxylic acid and urea promoted by solid acids[a]

Catalyst	Run	mg catalyst/ mmol glyox.	% yield allantoin
Y zeolite	1	445	22
β zeolite	1	544	50
Nafion®	1	850	53
SAC-13	1	3400	76
Dowex® 50W × 8	1	136	92
	2[b]	136	67
	3[b]	136	47
Dowex® 50W × 2	1	136	81

[a] Reaction conditions: molar ratio glyoxylic : urea : acid = 1 : 3.85 : 0.68, 343 K, 17 h. [b] Catalyst recovered by filtration, washed with water and dried under vacuum at room temperature.

Although zeolites Y and β are able to promote the reaction, the allantoin yields are lower than those obtained with sulfonic catalysts. The comparison between Nafion and Nafion–silica nanocomposite (SAC-13) clearly shows the importance of the surface area. The diffusion restrictions imposed by the low surface area of Nafion seem to be the origin of the lower yield obtained with this catalyst.

Dowex sulfonic resins are significantly more efficient than Nafion-based solids, indicating that stronger acids are not necessarily better catalysts for this reaction. The morphology of the polymer is also an important factor, as demonstrated by the results obtained with the two different Dowex resins. Both solids are polystyrene–divinylbenzene resins with the same functionalization in terms of sulfonic groups. However, the two solids have different cross-linking degrees (8% divinylbenzene in Dowex 50W × 8 and 2% in Dowex 50W × 2) and different particle sizes (80–150 μm in Dowex 50W × 8 and 150–300 μm in Dowex 50W × 2). It is important to note that the reaction is carried out in water due to the highly polar nature of the reagents, but the water does not cause considerable swelling in this kind of resin due to the non-polar character of the polymeric matrix. Under these conditions it is expected that diffusion of the reagents to the catalytic sites would play an important role. The best results are therefore obtained with the polymer that has a smaller particle size and a higher cross-linking degree. The reuse of the catalyst is important from a practical point of view and, as such, this property was also investigated. The used Dowex 50W × 8 was washed with water and dried under vacuum at room temperature without any further activation treatment. The activity of the solid was lower in each subsequent run, but it is worth noting that after three reactions the amount of allantoin obtained was 3 mmol per mmol acid sites – an excellent turnover for this type of reaction.

During the course of this work we realized that the activation of the polymer was very important. For this reason we examined several pre-treatment methods using the best resin in order to ensure reproducibility of the results. It can be seen from the results in Table 2 that the pre-treatment of the resin had a marked influence on the reaction yield. The best results were obtained when the resin was washed with boiling water or, even better, with dilute sulfuric acid. It is not clear what role this pre-treatment plays, but it can be speculated that some impurities are removed with washing and, in this sense, the solubility of these impurities in the washing medium would be the key factor.

Table 2 Results obtained from the reaction of glyoxylic acid and urea promoted by Dowex® 50W × 8 pretreated in different ways[a]

Pretreatment	*t*/h	% yield allantoin
H_2SO_4 (10%)	5	62
H_2SO_4 (10%)	8	92
HCl (1 M)	8	65
Boiling H_2O	8	83
Cold H_2O	8	59

[a] Reaction conditions: molar ratio glyoxylic : urea : acid = 1 : 3.85 : 0.68, 343 K.

From the results discussed above it can be concluded that Dowex 50W × 8 is a good heterogeneous catalyst for the reaction between glyoxylic acid and urea to give allantoin as the main product. The reason for the success of this material is that it combines the appropriate acid strength and polymer morphology to promote the direct reaction in water. Moreover, this solid has a high degree of functionalization, which is an important advantage from a practical point of view.

Reaction between allantoin and phenol

The main problems concerning the reported heterogeneous method for the direct synthesis of *dl*-5-(4-hydroxyphenyl)hydantoin (**2p**) from glyoxylic acid, urea and phenol[9] are the need for an excess of acid (2.22–3.34 mmol acid/mmol glyoxylic), the moderate yield of 5-hydroxyphenylhydantoins (**2p** and **2o**) and the *para*/*ortho* selectivity. We tested the sulfonic resins in the reaction of allantoin with phenol (Scheme 3) in an attempt to improve some of these aspects. The results are gathered in Table 3. As can be seen, the use of an excess of acid, similar to that used in the direct synthesis, does not lead to significant reaction with any of the sulfonic and fluorosulfonic resins and composites. The poor behaviour of urea as a leaving group and the ability of allantoin to poison a considerable number of acid sites are plausible reasons for the lack of activity. Given the advantage of the higher functionalization, we decided to test Dowex 50W × 8 in an even larger excess (6 mmol acid/mmol allantoin). Under these conditions the reaction gives 55% yield of 5-hydroxyphenylhydantoins with a *para*/*ortho* selectivity of 4.5. The same resin gives much better results in the direct

Table 3 Results obtained from the reaction of allantoin and phenol promoted by solid acids[a]

Catalyst	mmol catalyst/ mmol allantoin	% yield (**2p**+**2o**)[b]	**2p**/**2o**[c]
Nafion®	2.17	0	—
SAC-13	2.17	1	n.d.
Dowex® 50W × 8	2.17	1	n.d.
Dowex® 50W × 8	6.0	55	4.5

[a] Reaction conditions: molar ratio allantoin : phenol = 1 : 1.2, 343 K, 21 h. [b] Determined by HPLC. [c] Determined by HPLC and ^{1}H-NMR spectroscopy.

synthesis of *dl*-5-(4-hydroxyphenyl)hydantoin from glyoxylic acid, phenol and urea,[9] showing that these acid solids are more suitable for the direct synthesis route than for the preparation from allantoin itself. Although the result described above is not of interest from a practical point of view, it shows that the reaction between phenol and allantoin takes place with lower *para*/*ortho* selectivity and requires a larger amount of acid.

Experimental

β and Y zeolites in their ammonium form were purchased from Zeolyst. The acid form was obtained by calcination of the ammonium form under an air flow at 823 K for 10 h (1 K min^{-1} heating) prior to use. Nafion® was purchased from Aldrich. Nafion–silica nanocomposite SAC-13 (13% Nafion w/w) [10] was obtained from DuPont. The two Nafion-type solids were dried at 353 K under vacuum prior to use. Dowex® 50W × 8 and 50W × 2 were purchased from Fluka. The two resins were treated by washing a column of the solid with water, then passing through the column a solution of acid (see Table 2) until acid pH was attained, and finally washing with water until neutral pH. The resins were dried under vacuum until constant weight was achieved.

Synthesis of allantoin

To a solution of glyoxylic acid (50% in water) and urea (3.85 mmol/mmol glyoxylic acid) in water (0.15 ml/mmol urea) was added the corresponding amount of solid acid (Table 1). The mixture was stirred at 343 K for the corresponding time (see Tables 1 and 2). The solid was filtered off while hot and thoroughly washed with boiling water. An aliquot of the resulting solution was evaporated under reduced pressure, the residue was dried under vacuum, weighed and analyzed by ^{1}H-NMR spectroscopy to determine the urea : allantoin ratio.

^{1}H-NMR spectra (Varian Unity 300, δ ppm, J Hz): Urea: 5.41 (s, 4H). Allantoin: 10.53 (s, 1H), 8.05 (s, 1H), 6.88 (d, 1H, J = 8.1), 5.78 (s, 2H), 5.24 (d, 1H, J = 8.1).

Reaction between allantoin and phenol

A mixture of phenol (464 mg, 90%, 4.44 mmol), allantoin (581 mg, 3.7 mmol) and the solid acid in water (0.8 ml/mmol acid) was stirred at 343 K for 21 h. The hot mixture was filtered and the solid acid was washed with hot water until the filtrate was transparent. The solution was diluted to 100 ml, a 2 ml aliquot was evaporated under reduced pressure and the solid was analysed by HPLC and NMR spectroscopy.

HPLC analysis (Waters 2690 Alliance): Licrospher 100RP-18 (5 μm, 125 × 4.6 mm) at 313 K; NaH_2PO_4 buffer (0.02 M, pH = 2.5)–methanol (88 : 12) as eluent (1 ml min^{-1}); UV detection: 220 nm; retention times: **2p** 3.3 min, **2o** 5.7 min.

NMR spectra (Varian Unity 300, δ ppm, J Hz): *dl*-5-(4-Hydroxyphenyl)hydantoin (**2p**): ^{1}H NMR: 10.69 (s, 1H), 9.51 (s, OH), 8.28 (s, 1H), 7.10 (d, 2H, J = 8.5), 6.76 (d, 2H, J = 8.5), 5.00 (s, 1H). ^{13}C NMR: 174.7, 157.4, 128.0, 126.3, 115.4, 60.9. *dl*-5-(2-Hydroxyphenyl)hydantoin (**2o**): ^{1}H NMR: 10.59 (s, 1H), 9.75 (s, OH), 7.98 (s, 1H), 7.12 (m, 2H), 6.78 (m, 2H), 5.11 (s, 1H). ^{13}C NMR: 175.1, 157.8, 155.9, 130.2, 129.6, 122.4, 118.9, 115.6, 58.5.

Acknowledgements

We are indebted to Dr. Mark A. Harmer, from DuPont Research and Development, for the generous gift of SAC-13. The financial support of DSM Deretil and the Spanish M.C.Y.T. (project PPQ2000-0322-P4) are acknowledged.

References

1 (*a*) T. Nagamachi, T. Ohashi and H. Fukumitsu, Jp. Patent 78 112 874 [C.A., 1979, **90**, 72193w]; (*b*) Y. Christidis, Fr. Patent 2 458 546, 1981.
2 *Org. Synth. Coll.*, **vol. II**, 1943, p. 23.
3 J. Abblard and A. Meynaud, *Bull. Soc. Chim. Fr.*, 1971, 942.
4 H. Yasuda, Eur. Patent 0 647 630, 1995.
5 (*a*) C. N. Zellner and J. R. Stevens, US Patent 2 158 098, 1939; (*b*) J. Xue, Z. Lu, F. Li and M. Qin, *Zhongguo Kangshengsu Zazhi*, 1999, **24**, 224 [C.A., 2000, **132**, 166149] (*c*) S. Matias de Alencar, N. G. Rumjanek, F. J. Silas Varella and M. C. P. Neves, Br. Patent 9 704 540, 1999.
6 K. Schermanz and K. Fitzinger, Eur. Patent 0 460 412, 1991.
7 (*a*) W. Mesch, O.-A. Grosskinsky and N. Lösch, German Patent 1 939 924, 1969; (*b*) A. Eguchi, F. Kakizaki and K. Izawa, Jp. Patent 79 106 469 [C.A., 1980, **92**, 58782x]; (*c*) Permachem Asia Ltd, Jp. Patent 8 250 969 [C.A., 1982, **97**, 55808c]; (*d*) Permachem Asia Ltd, Jp. Patent 8 250 970 [C.A., 1982, **97**, 55807b]; (*e*) Y. Han and C. Wang, *Huaxue Shijie*, 1991, **32**, 451 [C.A., 1992, **116**, 128478t].
8 S. M. Zhang, F. L. Zhao and W. Q. Wang, *Chin. Chem. Lett.*, 1995, **6**, 337 [C.A., 1995, **123**, 9249d].
9 C. Cativiela, J. M. Fraile, J. I. García, B. Lázaro, J. A. Mayoral and A. Pallarés, *Appl. Catal., A*, 2002, **224**, 153.
10 M. A. Harmer, W. E. Farneth and Q. Sun, *J. Am. Chem. Soc.*, 1996, **118**, 7708.

A facile synthesis of 1,4-benzothiazines under solvent free conditions

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Received 4th December 2002
First published as an Advance Article on the web 13th March 2003

A rapid, solvent free synthetic strategy for the oxidative cyclocondensation of 2-aminobenzenethiols and 1,3-dicarbonyls using a catalytic amount of hydrazine hydrate has been developed in order to obtain 2,3-disubstituted-1,4-benzothiazines in high yields (83–96%).

Introduction

1,4-Benzothiazines resemble phenothiazines, well established anti-psychotic drugs,[1,2] in having a fold along the nitrogen–sulfur axis and can be anticipated to possess biological activities like phenothiazines. The basic unit present in mammalian red hair and feather is the 1,4-benzothiazine nucleus.[3,4] Luciferin and Rafamycin are 1,4-benzothiazine derivatives, obtained by biosynthesis and are found to possess pharmacological activity. 1,4-Benzothiazines are known for their utility as dyestuffs,[5] photographic developers,[6] ultraviolet light absorbers and anti-oxidants.[7] Semotiadil, a derivative of 1,4-benzothiazine, is used as an anti-hypertensive and anti-anginal drug.[8]

These multifarious applications of 1,4-benzothiazines have directed organic chemists to synthesize new 1,4-benzothiazines bearing heteryl pharmacophores. In view of this, we are working on the synthesis of new 1,4-benzothiazines[9–11] and on the development of an eco-friendly synthetic strategy. Hence we report our findings.

Results and discussion

1,4-Benzothiazines are usually prepared by the reaction of 2-aminobenzenethiols with α-haloketones or α-haloesters and oxidative cyclocondensation of 2-aminobenzenethiols with 1,3-dicarbonyl compounds using dimethylsulfoxide (DMSO). The former method requires the use of lachrymatory α-haloketones or α-haloesters as one of the reactants and the products isolated are in low yields (50–65%) and as isomeric mixtures.[3] In the latter method, the yields and purities of products are better but dimethylsulfoxide, a dipolar aprotic solvent with several unfavourable properties, is necessary to act as both solvent and oxidant. These methods do therefore need to be improved.

In DMSO a two-step mechanism has been suggested for the oxidative cyclocondensation[12] of 2-aminobenzethiols and 1,3-dicarbonyls. In the first step, 2-aminobenzethiols are oxidized to the corresponding disulfides by dimethylsulfoxide, followed by condensation with the 1,3-dicarbonyls to yield 1,4-benzothiazines.

A literature search reveals that thiols are easily oxidized to disulfides by using hydrogen peroxide,[13] DMSO–iodine,[14] bromine under phase transfer conditions,[15] thallium(III) acetate,[16] methoxytributyltin–$FeCl_3$,[17] sodium perborate[18]and a mixture of NO and NO_2.[19] Even the oxygen in the air oxidizes thiols on standing, particularly if a small amount of base is present.[20] The mechanism of the base catalysed air oxidation of thiols has been reported.[20] Recently Iyengar *et al.*,[21] have reported an efficient and mild procedure for the conversion of thiols to disulfides using a catalytic amount of hydrazine hydrate. To confirm the role of hydrazine hydrate, attempts were made to oxidize thiols in the presence of a stoichiometric amount of hydrazine hydrate under an inert medium, nitrogen–argon. It was found that thiols on their own were unreactive but in the presence of hydrazine hydrate and air at room temperature a quantitative yield of disulfides was obtained. The hydrazine hydrate is therefore acting as a base catalyst.

Bearing in mind the mechanism of formation of disulfides from 2-aminobenzenethiols using a catalytic amount of hydrazine hydrate in the presence of air, we progressed to condense equimolar quantities of 2-aminobenzenethiols with 1,3-dicarbonyls using a catalytic amount of hydrazine hydrate at 100 °C and in the absence of solvent. The products of the condensation were found to be 2,3-disubstituted 1,4-benzothiazines and their melting points and spectral data are in good agreement with those reported in the literature.[22,23] The probable mechanism of the condensation is depicted in Scheme 1. Melting points as well as the observed yields of the products are presented in Table 1.

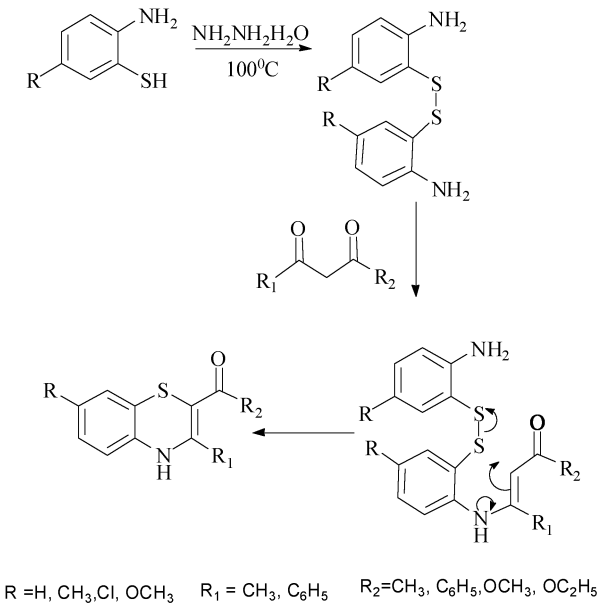
Experimental procedure

A mixture of 2-aminobenzenethiol (10 mmol) and hydrazine hydrate (1 mmol) was heated at 100 °C for 2–3 minutes before introducing the 1,3-dicarbonyl (10 mmol) and warming the reaction mixture to 100 °C for a further 10 minutes. After cooling to room temperature, 4–5 ml of ethyl alcohol was

Green Context

1,4-Benzothiazines have diverse applications in areas including dyestuff, photography, antioxidants and pharmaceuticals. Their normal preparation route involves either lachrymatory haloorganic substrates or toxic and expensive solvents. Here a cleaner, easier and convenient one-pot synthesis is described. The method is based on the condensation of 2-aminobenzenethiols and 1,3-dicarbonyl compounds using catalytic hydrazine hydrate. The product separation is also simple and involves only ethanol as an auxiliary. ***JHC***

 DOI: 10.1039/b212042a



R =H, CH_3,Cl, OCH_3 R_1 = CH_3, C_6H_5 R_2=CH_3, C_6H_5,OCH_3, OC_2H_5

Scheme 1

Table 1 Melting points (°C) and yields (%) of products

Sr. No.	R	R_1	R_2	mp/°C	Yield (%)
1	H	CH_3	CH_3	196[a]	89
2	H	CH_3	OC_2H_5	145[a]	92
3	H	C_6H_5	CH_3	189[a]	95
4	H	CH_3	OCH_3	216[a]	89
5	CH_3	CH_3	CH_3	186[b]	96
6	CH_3	C_6H_5	CH_3	137[b]	91
7	Cl	CH_3	CH_3	192[b]	88
8	Cl	C_6H_5	CH_3	120[b]	83
9	OCH_3	C_6H_5	CH_3	140[b]	90

[a] Reference 22. [b] Reference 23.

added. The solid that separated was filtered and recrystallized from ethyl alcohol.

Conclusion

The condensation of 1,3-dicarbonyls and 2-aminobenzenethiols, performed in the presence of a catalytic amount of hydrazine hydrate and air under solvent free conditions has been found to give high yields of 2,3-disubstituted 1,4-benzothiazines. The developed strategy to synthesize the 1,4-benzothiazines is one pot, rapid, solvent free and environmentally benign.

Acknowledgements

One of the authors (S. B. M.) wishes to thank the University Grants Commission, New Delhi for financial support. The authors are grateful to Prof. D. B. Ingle, Department of Chemistry, Dr. Babasaheb Ambedkar Marathwada University, Aurangabad, for his invaluable suggestions.

References

1 U. Siegelberg and G. Kleu, *Arzneim. Forsch.*, 1967, **17**, 159.
2 J. C. Barker and M. Miller, *Br. J. Psychiatry*, 1969, **115**, 169.
3 *Phenothiazines and 1,4-benzothiazines chemical and biomedical aspects*, ed. R. R. Gupta, Elsevier, Amsterdam, 1988.
4 *Thiazines and structurally related compounds, Proceedings of sixth international conference of phenothiazines and structurally psychotropic compounds*, Pasadena, CA, ed. H. Keyzer, G. M. Eskert, I. S. Forrest, R. R. Gupta, F. Gutmamn and J. Molnar, Kriger Publishing Co., Malbar, FL, USA, 1992.
5 R. Tanaka, K. Teramura and S. Yokoyama, *Jpn. Pat.*, 1966, 5833; *Chem. Abstr.*, 1966, **65**, 9062.
6 W. H. Strain and J. B. Dickey, *US Pat.*, 2381935; *Chem. Abstr*, 1946, **40**, 1889.
7 C. R. Rasmussen, *US Pat.*, 37877400; *Chem. Abstr*, 1974, **80**, 95987.
8 A. Kanda and H. Hashimoto, *Jpn. J. Pharmacol.*, 1993, **63**, 121.
9 R. V. Dengle, R. D. Ingle, S. P. Bondge and R. A. Mane, *Ind. J. Chem., Sect. B*, 1999, **38**, 390–393.
10 V. S. Ingle, A. R. Sawale, R. D. Ingle and R. A. Mane, *Ind. J. Chem., Sect. B*, 2001, **40**, 124–128.
11 R. D. Ingle, S. P. Bondge, V. E. Bhingolikar and R. A. Mane, *Ind. J. Chem., Sect. B*, in press.
12 S. Miyano, N. Abe and K. Sumoto, *J. Chem. Soc., Chem. Commun.*, 1975, 760.
13 B. J. Evans, J. T. Doi and W. K. Musker, *J. Org. Chem.*, 1990, **55**, 2337.
14 W. E. Fristad and J. R. Peterson, *Synth. Commun.*, 1985, **15**, 1.
15 J. Drabowicz and M. Mikolajczyk, *Synthesis*, 1980, 32.
16 S. Uemura, S. Tanaka and M. Okano, *Bull. Chem. Soc. Jpn.*, 1977, **50**, 220.
17 T. Sato, J. Otera and H. Nozaki, *Tetrahedron Lett.*, 1990, **31**, 3591.
18 A. McKillop and D. Koyuncu, *Tetrahedron Lett.*, 1990, **31**, 5007.
19 W. A. Pryor, D. F. Church, C. K. Govindan and G. Crank, *J. Org. Chem.*, 1982, **47**, 156.
20 T. J. Wallace, A. Schriesheim and W. Bartok, *J. Org. Chem.*, 1963, **28**, 1311.
21 S. Rajaram, G. S. Reddy and D. S. Iyengar, *Ind. J. Chem., Sect. B*, 1999, **38**, 639–640.
22 S. Miyano, N. Abe, K. Sumoto and K. Teramoto, *J. Chem. Soc., Perkin Trans. 1*, 1976, 1146–1149.
23 R. R. Gupta, G. S. Kalwania and R. Kumar, *Bull. Chem. Soc. Jpn.*, 1984, **57**, 2343–2344.

Dehydration of fructose to 5-hydroxymethylfurfural in sub- and supercritical acetone

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Received 22nd November 2002
First published as an Advance Article on the web 10th February 2003

The dehydration of D-fructose (**1**) to 5-hydroxymethylfurfural (HMF, **2**) is a well known reaction (acid-induced elimination of three moles of water), performed by many investigators during the last three decades.[1,2] HMF and its oxidation product 2,5-furandicarboxylic acid are so called 'sleeping giants' in the field of intermediate chemicals from regrowing resources. HMF is a key substance between carbohydrate chemistry and mineral oil-based industrial chemistry and it has the potential of a commodity like terephthalic acid.[3] Surprisingly, no technical process has been constructed until now. The reason is that high selectivities (in this context selectivity means yield divided by conversion in mol%) can only be obtained in high boiling polar solvents like dimethyl sulfoxide, dimethylformamide, acetonitrile, poly(glycol ether) *etc.* so that separation procedures are very expensive.[4] Unfortunately, in aqueous systems (supercritical water), only low selectivities can be achieved.[1] Considering the specifications for a modern sustainable and economical process, the use of green solvents like acetone, methanol or acetic acid in their sub- or supercritical states should be accounted for. The results for this reaction performed in sub- and supercritical acetone are presented here.

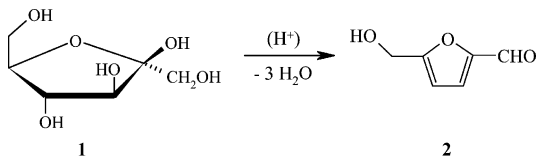
1 Introduction

Since the beginning of the 20th century the use of mineral oil as a source for both energy and resource for the production of goods has increased immensely. The world's oil-consumption in 1995 was 3.3 billion tons per year while the supply of oil was 135 billion tons in easily deducible reserves.[5] This implicates the finite pool of these precious raw materials. Finding new forms of resources for the production of goods for mankind is therefore an essential task.

Carbohydrates possess a remarkable potential to act as a future resource as following numbers show: Nature produces a respectable amount of 200 billion tons biomass per year by photosynthesis, 95% of that can be assigned to the class of carbohydrates. Surprisingly, only 3–4% of these compounds are used by man for the food- and non-food sector.[6]

The main problem for the industrial use of carbohydrates lies in the over-functionality of their molecules due to the large number of OH-groups which obtain almost the same chemical reactivity. Therefore selective chemistry is difficult to perform. One possible solution for this problem is to convert the carbohydrates into compounds that contain C–C-double bonds or carbonyl groups instead of hydroxyl groups in their (still intact) carbon framework. Such a molecule would hold a key position at the interface between carbohydrate- and petrochemistry.[7]

5-Hydroxymethylfurfural (HMF, **2**) represents such a key substance. It is the precursor of a compound that is structurally analogue to terephthalic acid which is used for the production of polymers. HMF can be obtained by acid-induced dehydration of D-fructose (**1**) or other fructose-containing carbohydrates like sucrose or inulin.[7]



1 **2**

Antal and Mok,[2] Kuster[4] and Hirth[8] performed investigations on this reaction in sub- and supercritical water. In this reaction media only unsatisfactory selectivities below 50% were obtained. An innovative approach to achieve much higher selectivities and establish an economic production method/process is the use of sub- and supercritical organic solvents. This paper presents the results for the dehydration of fructose performed in sub- and supercritical acetone.

2 State of the art

Cottier[9] divides several HMF-processes into five methods depending on the kind of solvent and processing temperature:

- aqueous processes below 200 °C
- aqueous processes above 200 °C

Green Context

The exploitation of renewable resources as alternative feedstocks for the manufacture of useful chemicals is often frustrated by process difficulties. The formation of the versatile intermediate 5-hydroxymethylfurfural from carbohydrates is a good example of this since the dehydration reaction required is normally only effective in largely environmentally unacceptable polar solvents such as dimethyl sulfoxide. Here it is shown that sub- and supercritical acetone is an effective solvent for the conversion of fructose to the furfural. Carbon atom efficiency is quite good and no solid impurities are formed. The authors report the potential for a technical process based on this whereby a reasonable price of *ca.* 2€/kg can be aimed for. ***JHC***

 DOI: 10.1039/b211468b

- processes in non-aqueous media
- processes in mixed solvents
- processes without solvent/microwave processes

Aqueous processes are favourable in respect of ecological aspects but are unfortunately not efficient. The Südzucker process only achieves selectivities of about 30%,[10] Cottier[9] reports on yields up to 28% when acidic ion-exchange resins are used. Both of them report no influence of a high dilution effecting the yield. When water is used as the solvent unsolvable huminic acids occur.

Yields can be raised up to 58% when using non-aqueous media at even shorter reaction times.[4] DMF, acetonitrile, poly(glycol ether) and DMSO were investigated. Instead of insoluble huminic acids, soluble polymers were found. Due to the nonpolar character of these solvents high fructose dilution is necessary to effect solution.

Teunissen suggested a mixture of organic solvents with water as reaction media. Experiments with aqueous *n*-butanol, dioxan and poly(ethylene glycol) show a decrease in the laevulinic acid yield.[4]

Processes without a solvent show this behaviour, too. Production of laevulinic and humic acids is decreased and HMF can be achieved with a 70% yield when using equimolar amounts of pyridine salts.[1]

Cottier[9] describes a microwave process that produces HMF with 28% yield.

3 Experimental

3.1 Apparatus for measuring critical constants and densities of SCFs

Critical constants and densities of SCFs can be measured in a cell made of corrosion resistant Inconel 625 with a inner volume of about 32 ml. The cylindrical cell is closed with sapphire windows allowing visual observation of the inside. The cell can be heated by four heating cartridges which are evenly distributed among the cell's coating. The compounds are pumped into the cell by screw presses while pressure is generated. The mixture is stirred by a magnetic bar made of an Al–Ni–Co-alloy and coated by Inconel 625 to prevent corrosion. This bar is set into rotation by a magnetic stirrer located under the cell. It is also possible to mix two non-miscible fluids or a gas and a fluid in this apparatus to determine the critical constants or densities of the mixture. Fig. 1 schematically shows this apparatus.

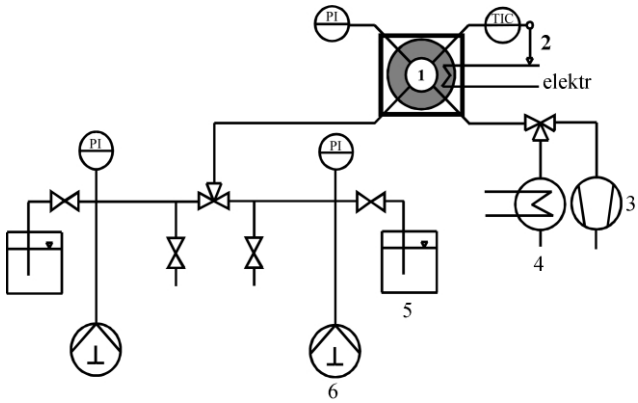


Fig. 1 Apparatus for measuring critical constants and densities of SCFs: 1 cell, 2 electrical heating circuit, 3 vacuum pump, 4 condensate trap, 5 supply of fluid, 6 screw press.

3.2 High pressure tube reactor

The reactor is made of either a 3.175 mm o.d. 2.0 mm i.d. or a 1.5875 mm o.d. 0.5 mm i.d. stainless steel tube, respectively. Tube 1 has a length of 710 mm, an inner volume of 2.23 cm^3 and a relative heat exchange area of 318 $m^2\ m^{-3}$. Tube 2 has a length of 400 mm, 0.078 cm^3 inner volume and a relative heat exchange area of 2540 $m^2\ m^{-3}$. These reactors are constructed as pipe-in-pipe-systems and can be heated by a heat transfer oil (Marlotherm SH®, Sasol Company) up to 350 °C. Fig. 2 describes the high pressure tube reactor schematically.

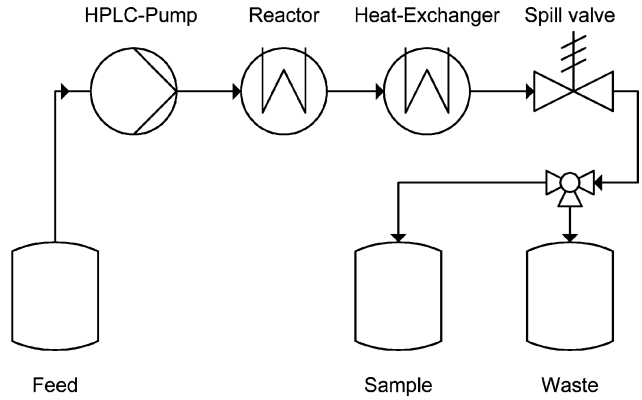


Fig. 2 High pressure tube reactor.

A HPLC pump delivers the feed into the reactor. A heat exchanger (also a pipe-in-pipe system) cools down the fluid after reaction. Pressure is relieved in a overflow valve. After that, a three-way valve permits switching between waste or sample reservoirs.

3.3 Analysis

A quantitative analysis of the reactor samples was done by HPLC. Before injecting 20 μL on a cation exchanger column (ION-300H, Interaction Chromatography, Inc.) a sample preparation method was used to prevent the overloading of the column with organic solvents and contamination with heavy metal ions. Each sample was diluted with distilled water and stirred over an acidic cation exchanger (Amberlite IR-120H, Fluka Company) for 30 min. It was confirmed that this procedure had no effect on the sample's composition. The column was held at 50 °C, the RI-Detector's temperature was set on 40 °C. 2 mM sulfuric acid was the eluent. Qualitative analysis was performed by GC/MS on a GCQ Finninge MAT apparatus using a F&W DB5 FSAP 50 m column, spilt injection at 275 °C and helium as the carrier gas.

4 Results

4.1 Solubility of fructose in acetone–water mixtures

The solubility of fructose in pure acetone is negligible but may be enhanced by adding water to the acetone. Therefore, several acetone–water mixtures were placed in temperable glass vessels. Fructose was added in excess and the mixture was stirred for 30 min at 25 °C. After this, a filtered sample was analysed *via* HPLC. The results are given in Table 1.

Table 1 Solubility of fructose in acetone–water mixtures at 25 °C

Acetone–water (L L^{-1})	Solubility/g L^{-1}
100/0	0.5
98/2	1.1
95/5	3.9
91/9	10.6
83/17	37

A compromise between water content and fructose solubility decided the use of a acetone–water mixture (90 : 10) as reaction media with a fructose content of 10 g L^{-1}.

4.2 Critical constants and densities

The critical constants and densities of the acetone–water mixture (90 : 10) were measured as described in section 2.1. The results are shown in Tables 2 and 3.

Table 2 Critical constants of water, acetone and acetone–water (90 : 10)

SCF	T_C/°C	p_C/MPa
Water	374.0	22.1
Acetone	235.0	4.6
Acetone–water	247.5	6.4

Table 3 Densities ρ in g cm^{-3} of an acetone–water mixture (90 : 90)

p/MPa	150 °C	180 °C	210 °C	240 °C	270 °C	300 °C
4	0.7028	0.6851	0.5920			
6	0.7083	0.6905	0.6055			
8	0.7135	0.6959	0.6162	0.5276		
9				0.5406	0.3362	0.2067
10	0.7185	0.7016	0.6256	0.5501	0.4086	0.2417
12	0.7232	0.7072	0.6336	0.5669	0.4595	0.3375
14	0.7276	0.7119	0.6407	0.5793	0.4936	0.4033
16	0.7319	0.7172	0.6472	0.5906	0.5156	0.4414
18	0.7359	0.7211	0.6527	0.6005	0.5330	0.4688
20	0.7397	0.7245	0.6580	0.6084	0.5486	0.4906
22	0.7432	0.7275	0.6628	0.6161	0.5604	0.5080
24	0.7466	0.7306	0.6671	0.6230	0.5699	0.5225
26	0.7499	0.7335	0.6713	0.6292	0.5780	0.5340
28	0.7530	0.7364	0.6754	0.6347	0.5856	0.5447
30	0.7561	0.7387	0.6791	0.6400	0.5919	0.5539

4.3 Dehydration of D-fructose

The dehydration of D-fructose (10 g L^{-1}) in a acetone–water mixture (90 : 10) with sulfuric acid as catalyst was studied by varying the parameters:

- temperature
- pressure
- catalyst concentration
- solvent composition
- residence time

The residence time τ was calculated by eqn. (1):

$$\tau = \frac{V_R \rho_{sol,reactor}}{\dot{V} \rho_{sol,NTP}}. \quad (1)$$

τ = residence time/s; V_R = reactor volume/cm^3; $\rho_{sol,reactor}$ = fluid density at process pressure and temperature/g cm^{-3}; $\rho_{sol,reactor}$ = fluid density at normal temperature and pressure/g cm^{-3}; and $\dot{V}$ = volume flow/cm^3 s^{-1}.

For kinetic analysis concentrations under reaction conditions are relevant. Therefore a corrected concentration c_{corr} was used which can be obtained by eqn. (2):

$$c_{corr}(i) = c_{NTP}(i) \frac{\rho_{sol,reactor}}{\rho_{sol,NTP}}. \quad (2)$$

$c_{corr}(i)$ = corrected concentration of compound i; $c_{NTP}(i)$ = concentration of compound i at normal temperature and pressure.

4.3.1 Influence of the temperature. Fig. 3 shows the influence of the temperature with respect to the selectivity of HMF. The catalyst concentration was kept constant at 3 mmol L^{-1}. High selectivities of HMF can be obtained at lower temperatures and longer residence times.

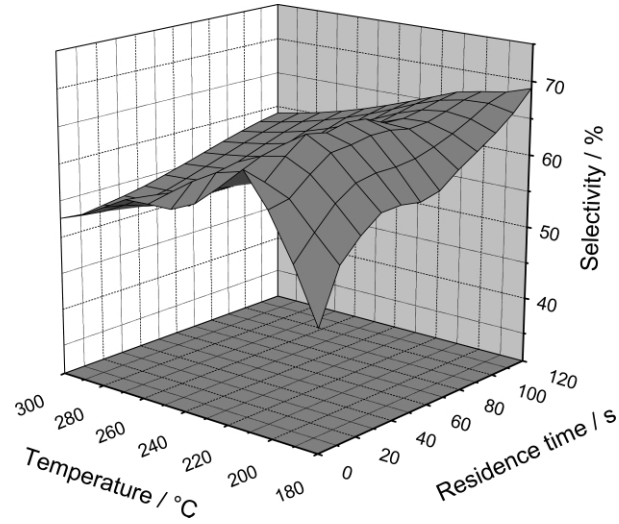


Fig. 3 Influence of the temperature range 180–300 °C and τ = 0.5–120 s at constant sulfuric acid concentration of 3 mmol L^{-1} and 20 MPa in terms of selectivity.

4.3.2 Influence of the pressure. Figs. 4 and 5 show selectivities of HMF and conversions of fructose under various pressures. The fluid density is also given. There is no significant influence of that parameter respective selectivity and conversion.

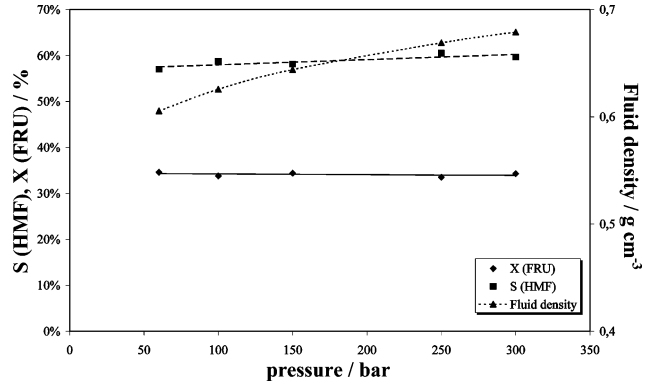


Fig. 4 Selectivity (S), conversion (X) and fluid density subject to pressure: T = 210 °C, τ = 2 s, 5 mmol L^{-1} sulfuric acid. The reaction media is in its subcritical state.

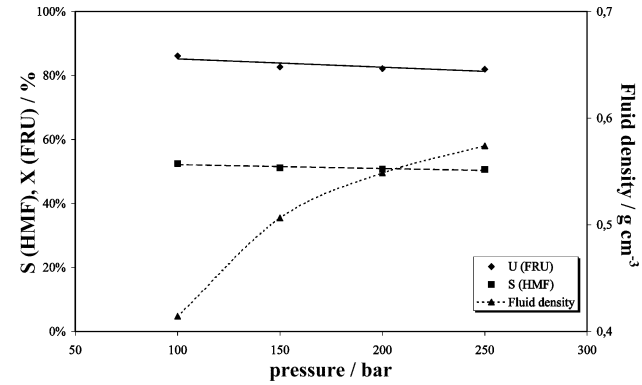


Fig. 5 Selectivity (S), conversion (X) and fluid density subject to pressure: T = 270 °C, τ = 2 s, 5 mmol L^{-1} sulfuric acid. The reaction media is in its supercritical state.

4.3.3 Influence of the catalyst concentration. Fig. 6 shows the influence of the catalyst concentration with respect to the selectivity of HMF. The temperature was kept constant at 180 °C. High selectivities of HMF can be obtained at higher sulfuric

acid concentrations. Above a catalyst concentration of 20 mmol L^{-1} the selectivity reaches a plateau at around 75 %.

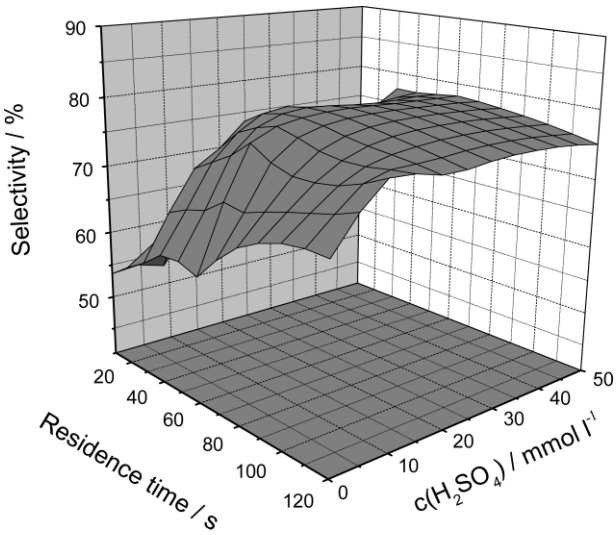


Fig. 6 Influence of the sulfuric acid concentration 3–50 mmol L^{-1} and τ = 0.5–120 s at constant sulfuric acid concentration of 3 mmol L^{-1} and 20 MPa in terms of selectivity.

4.3.4 Influence of the water content. Figs. 7 and 8 show selectivities of HMF and conversions of fructose in various reaction media. The mixture was varied from 10 Vol.-% water in acetone to pure water. The sulfuric acid concentration, the temperature and the pressure were kept constant at 10 mmol L^{-1}, 180 °C and 20 MPa, respectively. Both selectivity and conversion rate increase with decreasing water contents.

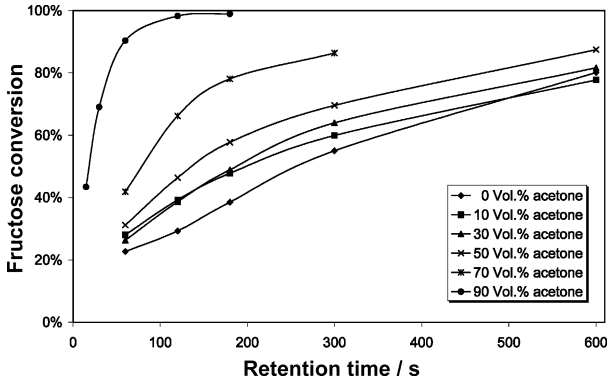


Fig. 7 Influence of the reaction media's composition on the fructose conversion. For further reaction parameters see text above.

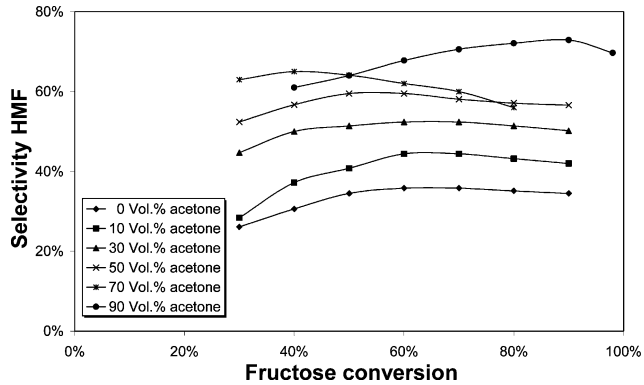


Fig. 8 Influence of the reaction media's composition on the HMF selectivity. For further reaction parameters see text above.

4.3.5 Kinetic analysis. Kuster[4] reports a reaction order of one for this process. According to this, kinetic analysis of the dehydration of fructose in acetone–water (90 : 10) was performed. First order kinetic constants were obtained *via* ln (1 − *X*) *vs.* τ plots. With those constants an Arrhenius plot was generated. Table 4 shows the kinetic constants and activation energies of the reaction.

Table 4 Kinetic constants and activation energies for the dehydration of D-fructose

Temperature/°C	$c(H_2SO_4)$ = 0 mmol l^{-1}	$c(H_2SO_4)$ = 3 mmol l^{-1}	$c(H_2SO_4)$ = 5 mmol l^{-1}
180		0.0285	0.0408
210		0.1306	0.1818
240	0.0082	0.5690	0.8498
270	0.0733	1.9672	2.7671
300	0.3956	6.9978	9.3641
Activation energy/kJ mol^{-1}	158	99	98

Antal and Mok[2] give an activation energy of 100 kJ mol^{-1} for the dehydration of glucose under sulfuric acid concentration of 5 mmol L^{-1}.[2] Hirth obtained an activation energy of 96 kJ mol^{-1} for the dehydration of fructose in subcritical water.[8]

4.3.6 By-products. The main by-product is furfural. The selectivity of this compound is about 4–6%. Other by-products are glucose, methylglyoxal, dihydroxyacetone and levulinic acid. Selectivities of these compounds are between 0.5 and 2%.

Under the influence of acids, acetone di- or trimerizes in an aldol-type reaction. Possible products are diacetone alcohol, mesityl oxide and mesitylene. Fig. 9 gives information of the production of these by-products.

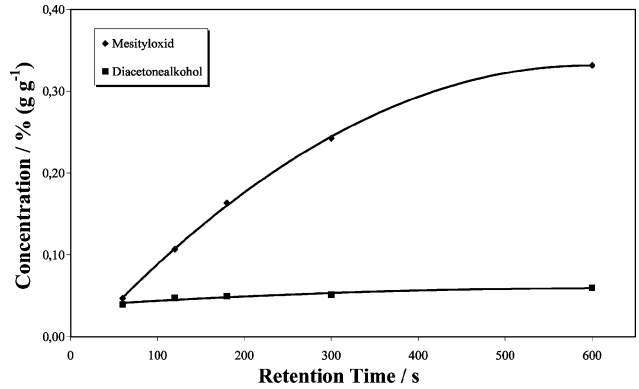


Fig. 9 Production of aldol-by-products at 180 °C, 20 MPa and 10 mmol L^{-1} sulfuric acid as catalyst in acetone–water (90 : 10). Mesitylene was not found.

5 Discussion and conclusion

About 90% of carbon was recovered according to HPLC analysis. There were no solids (humic acids) produced, contrary to the reaction performed in supercritical water. This makes the use of a acetone–water mixture even more preferable to water only as the reaction media. There are several natural products containing carbohydrates that can also be converted to HMF. The dehydration of glucose, sucrose and inulin (from dahlia tubers) was also investigated. Fig. 10 shows these results.

As 5-hydroxymethylfurfural is best produced from fructose in its furanoid form (see reaction equation in the introduction section), a possible explanation for the high selectivity obtained in this special reaction media is that the equilibrium of the several possible fructose isomers (furanoid, pyranoid, open chain) lies on a furanoid one. NMR spectroscopy experiments

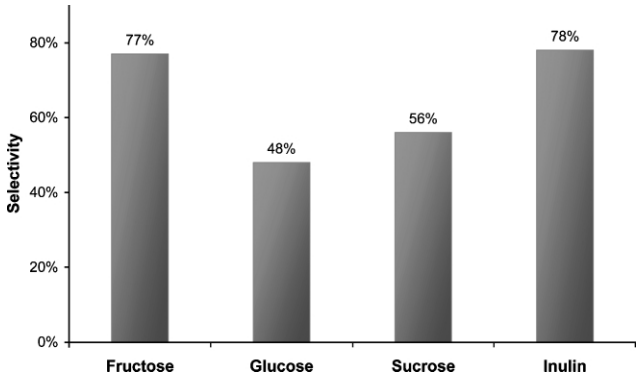


Fig. 10 Dehydration of several natural products at 180 °C, 20 MPa and 10 mmol L^{-1} sulfuric acid as catalyst in acetone–water (90 : 10).

will show whether this explanation is true or not and the results of this investigation will be presented in our next paper. The dehydration of fructose was also performed in sub- and supercritical methanol and acetic acid. These very interesting results will also be presented in our next paper which will be available in the near future.

A technical process, based on these low boiling organic solvents as reaction media for the dehydration of fructose to HMF, has the potential to establish HMF as a universal, polyfunctional intermediate on the world market with an acceptable price of about 2 €/kg if fructose (or fructose-containing biomass) is available at a price of 0.50 €/kg.

6 References

1 J. Lewkonski, *Narutowicza*, 2001, **68**, 90–136.
2 M. J. Antal, Jr. and W. S. L. Mok, *Carbohydr. Res.*, 1990, **199**, 91–109.
3 M. Kunz, *Stud. Plant Sci.*, 1993, **3**, 149–160.
4 B. F. M. Kuster, *Starch/Stärke*, 1990, **42**, 314–321.
5 *Römpp Lexikon Chemie*, Hrsg. J. Falbe and M. Regitz, 5.Aufl., G. Thieme Verlag, Stuttgart/NewYork, 1995.
6 Zuckerindustrie, *Weltzuckerproduktion für den Zeitraum 1995/96–1997/98*, Berlin, vol. 123, p. 473.
7 K. M. Rapp and J. Daub, in *Nachwachsende Rohstoffe: Perspektiven für die Chemie*, ed. M.Eggersdorfer, S. Warwel and G. Wulff, VCH-Verlag, Weinheim/New York, 1993, pp. 183–196.
8 J. Hirth, *Ph.D. Dissertation*, Technische Universität Darmstadt, 2002, D17.
9 L. Cottier and G. Descotes, *Trends Heterocycl. Chem.*, 1991, **2**, 233–248.
10 K. M. Rapp (Südzucker AG.), *Eur Pat.*, EP 0230250B1, 1987.