Green Chemistry: Can we rally together, or will we fragment into pieces?

Chemistry has, of course, never looked greener. But what about the future of the field we call Green Chemistry? We continue to hear encouraging news from the UK, Scandinavia and other parts of Western Europe. There is also great chemistry being developed in some Eastern European laboratories. Innovation and greening of chemistry continue to proceed rapidly in both the United States and many Asian countries. Luckily, these advances are not confined to the academic arena, but are clearly being practiced by an increasing number of commercial organizations. So, is there anything wrong with this picture? I would say, "Yes".

Green chemistry is so diverse that we often have trouble communicating amongst ourselves, and often spend too much time arguing about what is really Green. These misunderstandings and arguments drain away our precious time for doing Green chemistry. When it comes to definitions of the field, there are purists and there are revisionists; there are the dogmatic and the lackadaisical. When it comes to chemistry, there are those who do it and those who talk about it, those who set policy and fund grants, and those who spend money generously provided by government and private funding agencies. All of these groups play vitally important roles in the health of the field. In the United States, we have clearly seen of funding and regulatory agencies leading rather than following scientists into this new arena.

I want to offer my personal take on what is Chemistry and what is Green, and how to navigate the political waters that seem to have a few more sharks in them every year. I see societies benefiting greatly from industrial chemistry, whether it is commodity chemistry, fine chemistry, or pharmaceutical chemistry. I also see a large number of “legacy chemical processes" that date back to be exciting early days when industrial chemistry was created, largely in British, German and Italian laboratories. These processes tend to generate large amounts of waste, side products, and undesirable or even toxic byproducts.

In my view, any chemical advance or engineering advance that significantly reduces the burden placed on the environment by current industrial processes is helping to clean up the environment, by definition. Many of these advances may not be fully Green: there may still be some waste generated, there may still be lifecycle issues that have not fully been considered, and there may still be unforeseen consequences that this new chemistry presents to the environment. We must be as vigilant as possible to avoid doing any greater harm while we attack the obvious problem processes with new vision. However, if we see a new process that clearly eliminates millions of tons of waste a year, I believe we should lend its a welcome ear and view it as a marvelous step in the right direction, even if the chemistry is not yet perfect.

I would like to see similar principles applied in the evaluation of academic work on the subject of Green chemistry. In many cases, we will have to take small steps towards the ultimate greening of a particular chemical reaction. As long as these steps move the chemistry in the right direction, I believe they should be heard by the community and collected in this journal. I can easily imagine, and in fact have often witnessed, catalytic cycles being put together by two different research groups, each one of which has developed a beautiful new half reaction. I can also imagine a third research groups adapting such chemistry to one of the greener solvents now recognized by the community. The stepwise creation of Verdant Reactions will be just as valuable as the much rarer, all-in-one, instantly perfect replacement for a 50-year-old chemical process.

I hope that in the upcoming Italian summer school, Gordon Research Conference, and other meeting places for those of us who practice, preach, and believe in Green chemistry, we will see plenty of vigorous and even contentious debate on where we should focus our attention to bring about the greening of the environment and the Industry. But I also hope that the discussions and debates will leave room for the full spectrum of Green chemistry practitioners, and will ultimately respect the various ways that each of us tries to impact industry, academics and the environment.

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Rate the sustainability grade of your scientific work

Achim Diehlmann† and Guenter Kreisel‡ of the Friedrich Schiller University in Jena, Germany, propose a new nomenclature for sustainablity in chemistry which aids appreciation of the different levels at which sustainability can be considered

Introduction

Sustainability is one of the outstanding objectives in chemistry. Therefore, various research programs have been set up, numerous conferences have been held and a high number of research papers have been published on this topic. The high quality of the published work on sustainability shows that the scientists involved are on the right track. Nevertheless, many papers could be criticised because of their broad and diffuse interpretation of the term ‘sustainable’. To avoid misunderstanding, to specify the proposition of scientific work, and to prevent ambiguity of the term ‘sustainable’, we propose a nomenclature for sustainability in chemistry that could help return to the concept of sustainable development the importance it deserves.

Sustainable development

Sustainable development, with its widely accepted principles, is one of the important goals of the future. The Brundtland Report[1] initially defined sustainable development as a development “to meet the needs of the present without compromising the ability of future generations to meet their own needs”. The development should bring about improvements in economical, ecological and social conditions for present and future generations worldwide. Since the Brundtland Report, and especially since the Rio Declaration of Sustainable Development,[2] a great number of scientists have been working in different research areas of sustainability. In chemistry, where the special area of Green Chemistry has been founded, a lot of work has been done in this field of investigation.[3,4] Almost all of the published work has attempted to minimise environmental burden, *e.g.* by reducing waste production of synthesis, by using less harmful substances or by saving energy. But are all of these improvements *per se* sustainable or green?

The three areas of sustainability

Sustainable development is based on an improvement of the three sustainable areas—economy, ecology and sociology. Natural scientists, and chemists in particular, very often improve just one part of sustainability—the ecological side—because they are experts in this field. The other parts—the economical and social aspects—may also be enhanced by the ecological improvement or they may be negatively affected. Since these aspects were not the focus of research, whether the improvement is economically and socially sustainable or not cannot be determined without further research investigation. This further research must be carried out by experts in economic and social sciences to give a balanced assessment of sustainability. If investigations in all three fields is not carried out, a new chemical process with minor environmental impact is only sustainable in terms of ecology. To evaluate new processes in the three sustainable areas, and to define and standardise the term ‘sustainable’ to avoid misuse and exaggeration, we propose a nomenclature that indicates which part of sustainability of a process has been investigated and which part has not. We suggest using an ‘S’ to indicate sustainability and adding ‘econ’, ‘ecol’ and ‘soc’ to indicate which areas have been researched (Fig. 1).

An example should illustrate the idea. Within a chemical synthesis, a toxic solvent is being substituted by a less toxic or nontoxic solvent. Ostensibly, the new synthesis is more sustainable than the former, and can be represented by $S^{\text{econ, ecol, soc}}$. However, if the new solvent is more expensive than the one it substitutes, the process is less sustainable in terms of the economical sustainability. The sustainability classification would therefore become $S^{\text{econ, ecol}}$. If it is further assumed that the producer of the toxic solvent has to dismiss a worker because

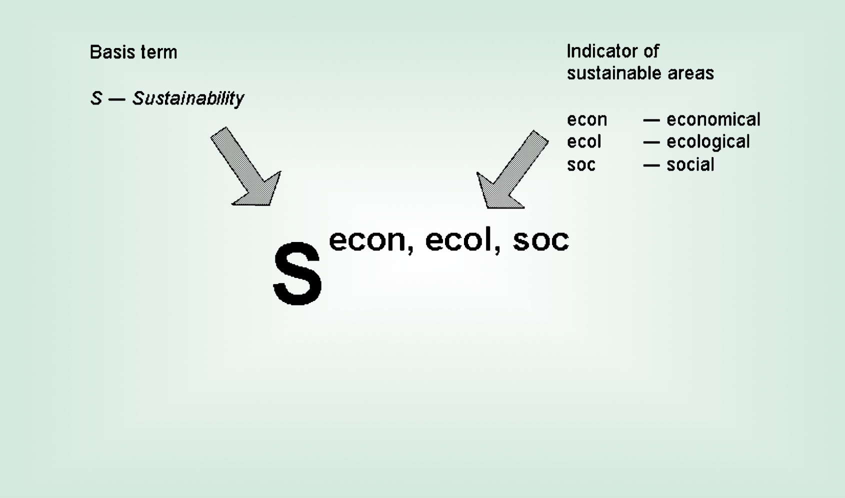

Fig 1 Indicator of sustainable areas.

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he cannot find customers for the solvent, the process now becomes only S^{ecol} because of the lost working place. The term $S^{econ,\ ecol,\ soc}$, therefore, is only valid if all three parts of sustainability have been improved.

The holistic view of sustainability

A further, and often subconsciously neglected, claim of sustainable development is an improvement, not only in small process steps, but over the whole life cycle. The ignoring of upstream and downstream products and processes could be a matter of insufficient data, or a lack of awareness.

It is often essential to focus an investigation within the narrow borders of a process. However, if the view is limited to a process, one must be aware of potential problems that could arise in a holistic context. This awareness is often problematical since scientists are trained to solve a specific problem without taking upstream and downstream processes into account. Here, further education seems to be necessary. It is essential, when publishing results, always to state whether sustainability has been taken into account in a process or a 'cradle-to-grave' view. We therefore suggest indicating the view with a 'H' for the holistic approach '$_{H}S$', and a 'P' for a process-oriented approach '$_{P}S$' (Fig. 2). The above example indicates the importance of this approach.

If use of the new less toxic solvent from the previous example

- were more expensive than the old process because it needed more production steps
- generated a higher amount of waste that could also be toxic
- required more energy to produce

then to state that the new process is more sustainable, would be correct in a process view, but incorrect in a holistic view. Using the proposed nomenclature would prevent misunderstanding and encourage scientists to examine and hopefully improve processes.

The scale of sustainable development

Coming back to the Brundtland Report and the Rio Declaration, there is another reason for setting up a standardised nomenclature. The Report and the Declaration focus on human needs. But these needs are, beside the necessities like access to sufficient fresh water and nutrition, based on geographical differences. These differences derive from climatic variations, from religious constraints and from cultural differences. The needs of a Mediterranean citizen, for instance, are essentially different from the needs of a Scandinavian citizen. Focusing on environmental issues there are questions of scale. An accident with toxic chemicals for example, might harm the environment locally, and perhaps regionally, if the amount of toxic substance is great enough, but it is not a global threat. A contribution to the greenhouse effect, however, can affect the whole world and is therefore a global problem. Sustainability, therefore, has a local, regional and global character. Developments that lead to local improvements do not necessarily have an effect on a regional and global scale, whereas a global scale improvement brings benefits to everyone. We recommend extending the proposed nomenclature to include the scale on which the invention is sustainable, *i.e.* on a local (S_{loc}), regional (S_{reg}), or global scale (S_{glob}) (Fig. 3).

Using this nomenclature will help avoid misunderstanding, since it is clear what has been done and what still has to be done. Furthermore, the nomenclature will help to prevent inappropriate comparisons, *e.g.* local ecological sustainability and social sustainability.

To demonstrate the advantage of the suggested nomenclature, we refer to our example a third time. Assume that the producer of the toxic solvent has to dismiss a worker because he cannot find a new customer for the solvent. The process may now still be $S_{glob}^{ecol.\ soc.}$ since the manufacturer of the new solvent may hire a worker, but on a local scale it may also be only$S_{loc}^{ecol.}$ because of the lost working place. Fig. 4 shows the complete structure of the proposed nomenclature.

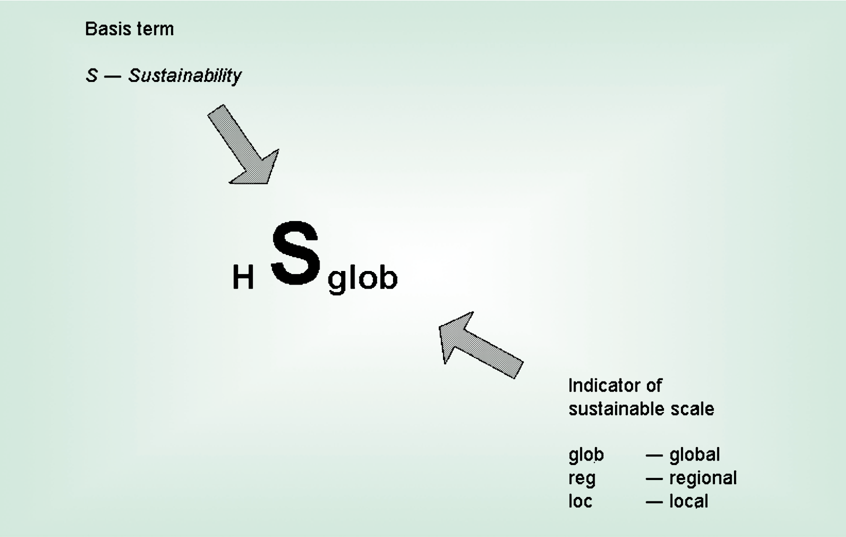

Fig. 3 Indicator of the sustainable scale.

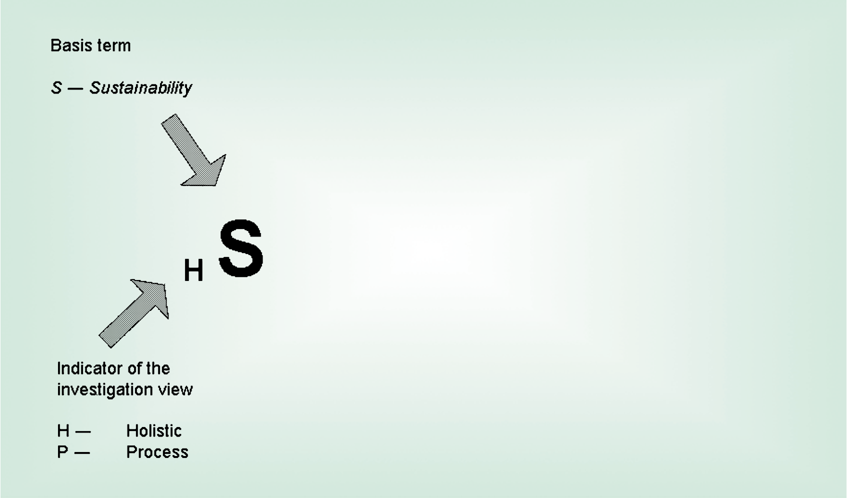

Fig. 2 Indicator of the investigation view.

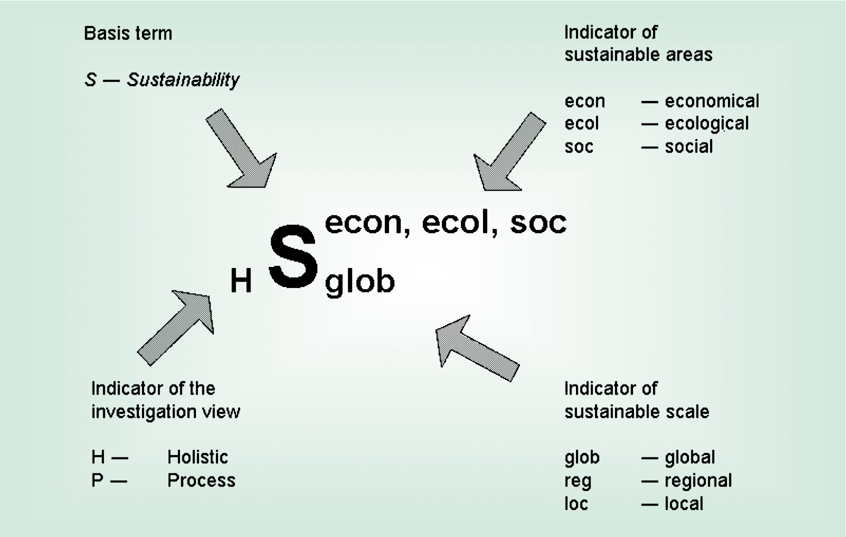

Fig. 4 The complete structure of the nomenclature.

Conclusion

The proposed nomenclature system is a first attempt to handle the problems of communicating sustainable chemistry progress. It is an open system and may be widened if necessary. As shown, the suggested nomenclature of sustainability is useful to specify the proposition of scientific work in three major areas. Standardised nomenclature further helps to prevent ambiguity of the term 'sustainable', and to give it back the importance that it deserves.

We would like to thank Prof. Dr. B. Jastorff for his suggestions for improvement. Further we would like to thank Prof. Dr. B. Koenig, spokesman for the project group of the 'New organic chemistry practical for the new millennium' project, for the helpful commentaries.

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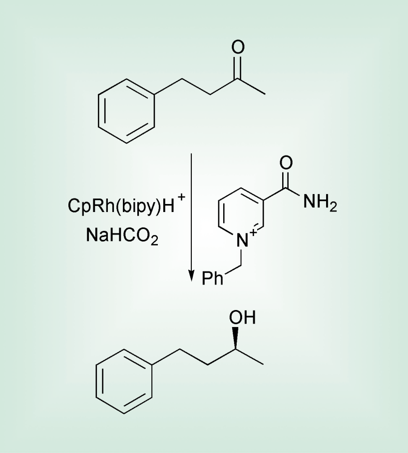
Highlights

Duncan Macquarrie reviews the recent literature on green chemistry

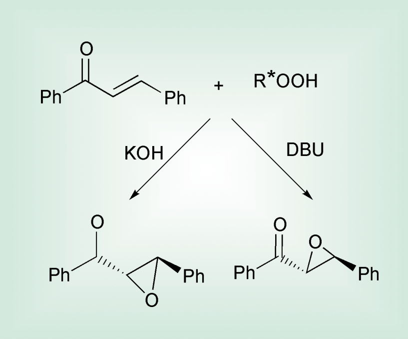
Biocatalysis

The potential of biocatalysis to provide chiral products from achiral raw materials is enormous. However, one drawback which is often encountered is the requirement for a cofactor, and its need to be regenerated rapidly and efficiently. Richard Fish and Christine Lo of the University of California at Berkeley, USA, have demonstrated that NADH mimics can be successfully utilised for this purpose in horse liver alcohol dehydrogenase (HLADH)-catalysed reduction of ketones (*Angew. Chem., Int. Ed.*, 2002, **41,** 478). They used a rhodium hydride catalytic cycle to reduce nicotinamide derivatives, which then functioned with HLADH to reduce a series of ketones to alcohols in high yield and enantioselectivity.



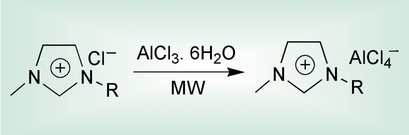
Enantioselective epoxidation

The enantioselective epoxidation of a,ß-unsaturated ketones is a key step in the synthesis of a range of important molecules. Waldemar Adam and co-workers at the University of Würzburg, Germany, have now shown that optically active hydroperoxides can be used to form these products in high yield and good enantioselectivity (*Eur. J. Org. Chem.*, 2002, 630). What is particularly fascinating is that the choice of base catalyst is critical. With KOH as base, the reaction produces one enantiomer, the use of diazabicycloundecane (DBU) leads to the other isomer. These differences are accounted for in terms of different coordination of the species involved in each of the two cases.



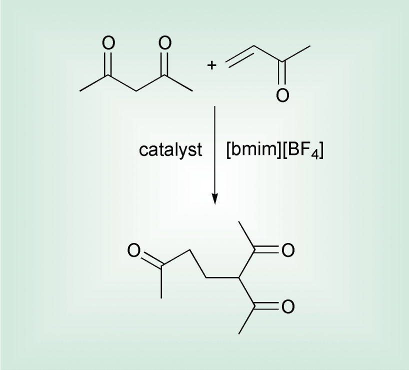
Ionic liquids

Ionic liquids are attracting significant attention as potential replacements for organic solvents. One such type of ionic liquid is the *N*-alkyl,*N′*-methyl-imidazolium tetrachloroaluminate, which also functions as an acid catalyst. Raj Varma and Vasudavan Namboodiri



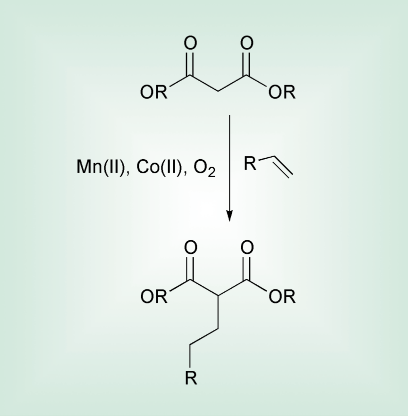
of the US Environmental Protection Agency have now described a novel microwave-assisted route to these liquids, which reduces reaction time and energy use significantly (*Chem. Commun.*, 2002, 342) and also the use of traces of these compounds for the tetrahydropyranylation of alcohols, again under microwave irradiation. Both reactions proceed in excellent yield.

The behaviour of various metal catalysts for the Michael reaction in ionic liquids has thrown up some very interesting results. Cosimo Nobile and colleagues at the University of Bari, Italy, have investigated the addition of pentane-2,4-dione with methyl vinyl ketone in butyl methylimidazolium tetrafluoroborate using three different metal based catalysts (*Chem. Commun.*, 2002, 434). They found that Ni(acac) catalysts dramatically enhanced the rate of reaction when used in ionic liquids, but were much poorer in dioxane, and also were slower in the absence of solvent. Excellent yields were obtained in the ionic liquid, and the catalytic solution could be reused several times upon direct distillation of the reaction product and re-charging of fresh reagents. Conversely, when either Yb(III) or Fe(III) catalysts were used, the reaction was much slower in ionic liquids than neat, but the selectivity was much higher than the 50–60% found neat. (The neat reactions proceeded much further than those in ionic liquids in these two cases, something which may explain the changes in selectivity).



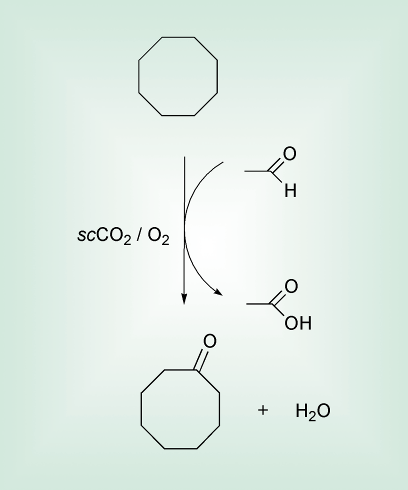
Malonates

The mono-functionalisation of malonates at the CH_2 group is a very useful strategy to build up functional building blocks. Such reactions can be achieved via the Knoevenagel reaction and subsequent hydrogenation, but can have some drawbacks. Yasutaka Ishii and co-workers at Kansai University in Osaka, Japan, have now demonstrated a one-step catalytic method for this reaction, involving the oxidative addition of malonate to alkenes using a Mn(II) / Co(II) / O_2 system in acetic acid solvent (*J. Org. Chem.*, 2002, **67**, 970). Yields are very good and selectivity is also high. Other C-acids can be used and alkynes also show some reactivity.



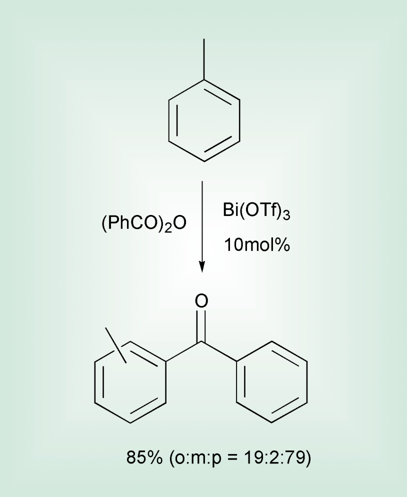
Supercritical CO_2

The use of supercritical CO_2 as reaction medium has been used by Nils Theyssen and Walter Leitner of the Max-Planck Institute in Mülheim an der Ruhr, Germany, for the selective oxidation of cyclooctane to cyclooctanone using oxygen and acetaldehyde as sacrificial reductant (*Chem. Commun.*, 2002, 410). They found that conversions of almost 40% were possible, with the production of cyclohexanone as major product along with smaller amounts of the alcohol and the 1,4-dione being also formed, the latter providing supporting evidence for a radical pathway.



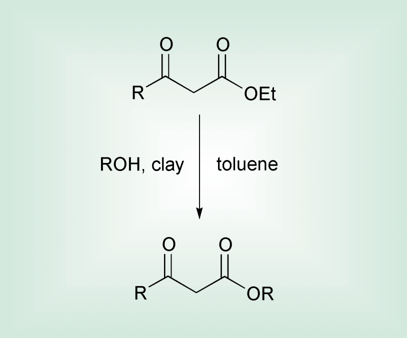
Bismuth catalysts

A short review has appeared in *Synlett*, where Cristophe Le Roux and Jacques Dubac of the Universite Paul Sabatier in Toulouse, France, discuss catalytic aspects of bismuth salts (*Synlett*, 2002, 181). Bismuth is the least toxic of the heavy metals, and its application in a range of acid catalysed reactions is discussed, with mechanistic insights being derived about the actual catalytic species. For example, bismuth triflate serves as an effective catalyst for the difficult acylation of unactivated aromatics such as benzene, toluene and halobenzenes, giving high yields of acylated product in reasonable times with either acid chlorides or anhydrides. Sulfonylations are also readily achieved with a few percent catalyst.



Transesterification

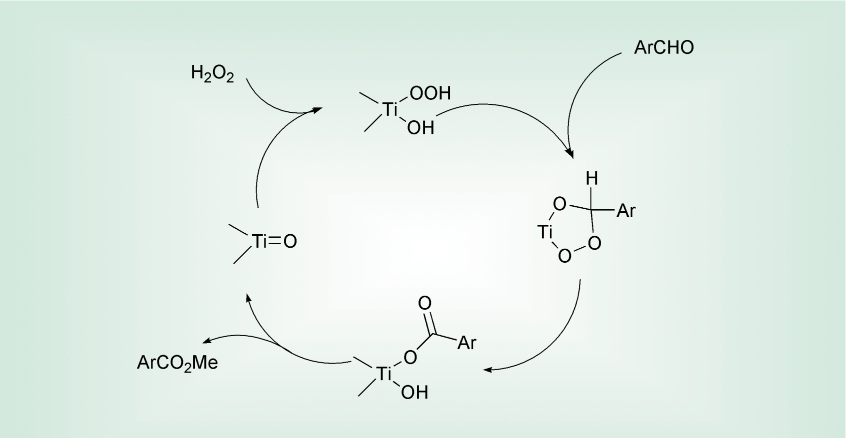
Transesterification of esters is a reaction type of great significance in a variety of areas. Solid acids are well suited as catalysts for this transformation, since they can be easily removed without the addition of water, which can cause hydrolysis. Vitor Ferreira and colleagues from the Universidada Federal Fluminense in Niteroi, Brazil, have found that some clays are excellent catalysts for



the transesterification of ketoesters and carbohydrates (*Tetrahedron Lett.*, 2002, **43**, 1165). They found that smectite, vermiculite and atapulgite all catalysed these reactions in good to excellent yields. More traditional acid clays such as K10 were relatively inactive.

Aromatic aldehydes → esters

The direct conversion of aromatic aldehydes to esters has been described by a group led by Subhash Chavan of the National chemical Laboratory in Pune, India (*Synlett*, 2002, 267). They have utilised an oxidative process involving the aldehyde, methanol, hydrogen peroxide and the titanium-silicate zeolite TS-1 as catalyst. Yields range from 65–99% under reflux in methanol for a few hours. Aliphatic aldehydes are also converted to esters, but in lower yields. The authors suggest the mechanism shown below as a plausible explanation for the process.



Process technology

A fascinating special feature section in *Organic Process Research and Development* (*Org. Proc. Res. Dev.*, 2001, **5**, 612–664) has been published, focussing on Intensive Processing and Continuous Processing in industrial production of fine chemicals. A series of articles from industrialists discuss the advantages available from innovative reactor design, and how this can be used to enhance reaction rates, conversions, and reduce the potential for hazardous incidents. Several examples are shown utilising a range of techniques and reactor types featuring miniaturisation or intensive mixing features. Such considerations of process technology are an integral part of designing a safe, energy and chemical-efficient process.

Sustainable development

A review has been published by Jürgen Metzger and colleagues from the University of Oldenburg, Germany, to coincide with the World Summit on sustainable development in Johannesburg, South Africa *(Angew. Chem., Int. Ed.,* 2002, **41**, 414). This overview describes the societal context of chemistry within sustainable development, and sets out the challenges for chemistry in contributing to this area. Key challenges are seen as the development of cleaner processes, especially for large volume common intermediates, and successes in the production of propylene oxide and adipic acid are described. A further area of importance is the development of novel separation methods, which underpin the majority of processes and are critical to a genuinely clean process (as opposed to a clean reaction).

The importance of improving regulation in encouraging the development and adoption of greener chemical processes and products

Michael Warhurst,† Safer Chemicals Campaigner at Friends of the Earth in London, UK, argues that, in addition to the Principles of Green Chemistry, there is a need for the development of a regulatory system that encourages the application of green chemistry

Introduction

The editorial in the first edition of Green Chemistry[1] included a definition of Green Chemistry, which had been originally proposed by Paul Anastas and John Warner:

"Green Chemistry is the utilisation of a set of principles that reduces or eliminates the use or generation of hazardous substances in the design, manufacture and application of chemical products"

In this paper I will argue that it is vital that this 'set of principles' includes the development of a regulatory system that encourages the application of greener chemistry, as in many cases it is only through regulation that we will be able to 'reduce or eliminate the use or generation of hazardous substances'. I will also argue that it is the responsibility of the green chemistry community to get involved in this regulatory debate, rather than leaving it to the usual suspects—the chemical industry, the regulators, and the non-governmental organisations such as Friends of the Earth. Green Chemistry will not contribute to sustainability unless it is implemented. The current systems for regulating the production and use of chemicals do not encourage the development of greener products and processes, and in many cases actually do the opposite. An important reason for examining the role of regulation on greener chemistry at this time is that the European Union is currently reviewing this legislation. The signs are that this review will result in substantial changes in the legislation, which could improve the drivers for greener chemistry.

The role of regulation in the adoption of green chemistry

There are three main ways in which regulation impacts on the adoption of green chemistry: influencing prices (or costs); restricting options, and influencing demand. I will briefly outline how these impacts occur.

Influencing prices

Regulation has a huge impact on the prices or costs attached to using chemicals. Such cost may, in some cases, be deliberately intended to internalise some of the external impacts caused by the use of a product into the price of the product. Impacts occur throughout the lifecycle of a material, for example:

- *Raw materials*. The cost of raw materials can be very dependent on regulation, for example through legal restrictions on extraction (*e.g.* planning controls), or through environmental taxation (*e.g.* carbon tax).
- *Regulation of production processes.* The price of a more hazardous chemical may be more expensive because of additional production costs, for example due to pollution control regulations.
- *Costs of using a material*. More hazardous materials are likely to cost more to handle due to Health and Safety regulations.
- *Disposal costs*. Regulations define permissible disposal routes, and generally mean that the most hazardous material will cost the most to dispose of. Regulation will define whether the cheapest routes of disposal *(e.g.* discharge into the local river) are available.

Restricting options

Regulations that ban or heavily restrict the use of certain chemicals or processes will clearly impact both on the economics of these chemicals and processes, and on the market for substitutes, for example:

- *Phase out or restriction on specific chemicals*. Once it is known that a chemical is to be phased out or heavily restricted, the development (or improvement) of substitutes becomes essential. In addition, it is quite possible for these substitutes to be more expensive, since it is not the market that is controlling the decline in use of the restricted chemical.
- *Phase out or restrictions on specific processes*. Processes may also be affected by phase out or restriction, for example the use of mercury cells in production of chlorine in the EU. Again, this provides huge practical and economic incentives for the development of greener alternatives.

Influencing demand

'Softer' regulatory approaches can also influence demand for a product or process and its alternatives, by either encouraging or discouraging its use:

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† From 2/4/02, Senior EU Toxics Campaigner, WWF, Brussels, Belgium.

- *Discouraging the use of a product*. Several methods of discouraging the use of a product have already been mentioned, for example through increasing its price through environmental taxation or by announcing that it will shortly be banned. However, there are also other methods available, for example adding it to a list of less desirable chemicals (e.g. the Swedish 'Observation List', below) or by excluding its use in the criteria for products with an ecolabel.
- *Encouraging the use of a product*. The use of a greener product can be encouraged through reductions in taxation (as happened initially with unleaded petrol), or by a range of 'promotional' activities. For example, a Government (or other institution) could assist companies moving to greener products by providing advice to companies on what alternatives are available, and by publicising the existence of these alternatives.

The impact of regulation

The above outline has flagged up a large number of relevant regulations which have a direct impact on the market for greener chemicals. Looking purely at the European situation, important regulations include:

- *chemical substance related legislation*, *e.g.* Marketing and Use, Classification and Labelling, New and Existing Substances (see below)
- *factory emissions legislation*, *e.g.* Integrated Pollution Prevention and Control Directive
- *waste disposal legislation*, *e.g.* Landfill Directive
- *factory safety legislation*, *e.g.* Control of Major Accident Hazards Directive
- *product-related legislation*, *e.g.* Ecolabelling

If there was no regulation at all, there would be minimal financial pressure for the adoption of greener chemistry. With no regulation it would be most cost effective to discharge most of a company's waste into the local river—as happened during the 19th century.

Given therefore that regulation is essential for the adoption of greener chemistry, it is surprising how little research and debate there is within the Green Chemistry community on what is the best regulation.

What about the voluntary approach?

One argument, particularly from industry, is that a combination of market pressures and voluntary action will be sufficient to ensure the adoption of greener chemistry. As discussed above, many of the price signals that affect the profitability of greener chemistry in fact come from regulations in any case, so these 'market' pressures are, in reality, hugely influenced by regulation.

There is little evidence that pure 'voluntary' action is effective. Companies may act before regulation forces them to, but this is primarily a response to the changing market place as the regulatory deadlines approach. Companies may also respond to public pressure regarding a particular chemical, or to concerns that such pressure may come in the future. Even with more elaborate environmental management systems such as ISO 14001 and EMAS, there is currently no clear evidence of a link with good environmental performance.[2] The predominant focuses of the industry are on whether a process or product is legal and whether it is profitable (*i.e.* whether it adds to shareholder value). It is, however, true that a few companies take a longer term view of profitability and shareholder value, which can assist in their approach to sustainability.

It is worth noting that in some countries (*e.g.* The Netherlands), voluntary agreements are actually legally binding contracts. This increases their chances of success, as they are in effect another form of regulation.

The chemical industry makes much of voluntary programmes such as 'Responsible Care' and 'Product Stewardship',[3] and has various impressive sounding statistics to back them up. Yet these claims ignore changes that have occurred in the regulatory environment. For example, there have been many changes in the UK regulations for factory emissions in the past decade, including the introduction of 'Best Available Technology Not Exceeding Excessive Cost' in Integrated Pollution Control, the creation of the Environment Agency, and now the EU-wide Integrated Pollution Prevention and Control system, introducing 'Best Available Technology (BAT)', with BAT reference documents being created to cover the whole of Europe. Yet industry statistics on emission reductions due to 'Responsible Care' ignore regulatory changes.

A particular issue with sustainability and the use of hazardous chemicals is the fact that one 'worst of sector' company can cause huge damage through continuing to market and produce undesirable chemicals. A chemical banned in the EU (*e.g.* tetraethyllead) can still be manufactured in the EU for export to the developing world (this is still the case with tetraethyllead).

Is the current EU regulatory system contributing to greener chemistry?

Most aspects of the regulation of the production and use of chemicals in Europe are regulated at an EU level, with individual Member States having only limited flexibility to impose their own regulation. This is not the place for a detailed description of the regulatory process (a more detailed summary is available in chapter 4 of the 'Crisis in Chemicals' report[4]), but the regulations relating to marketing and use of 'Industrial Chemicals' (not pesticides, biocides or pharmaceuticals, which all have their own systems) can be summarised as consisting of four elements:

- *Classification and labelling*. A process whereby classifications are agreed for substances, based on the safety data which is available. Classifications including, for example, toxic to reproduction, are agreed and then may affect how the substance is labelled when it is sold, and may also impact upon what it can be used for.
- *Marketing and use*. A reactive process, in which concerns over substances can be investigated and decisions on restrictions on the use of that substance can be agreed, if there is sufficient information is available on the harm that the chemical can cause.
- *New chemicals*. The beginnings of a move to a more pro-active regulatory system, the New Chemicals system requires that all chemicals introduced to the market after 1981 must have a set of safety data available. A new chemical is any chemical that is not included on the European Inventory of Existing Commercial Chemical Substances (EINECS) described below.
- *Existing chemicals*. Existing chemicals are those that were claimed by industry to have been on the EU market at any point between 1971 and 1981. Industry submitted the names of these substances to the European Inventory of Existing Commercial Chemical Substances (EINECS), which meant that these substances did not have to go through the new chemicals process. The list contains 100,106 substances, though it is estimated by that there are, in reality, around 30,000 existing substances on the market at more than

1 tonne per annum in the EU.[5] Although the Existing Chemicals process does not oblige companies to generate new safety data on their chemicals, they are supposed to have submitted what data they had to the European Chemical Bureau (ECB, the body that administers EU chemicals regulation). This data is then supposed to be used to decide which chemicals are a priority for further investigation, culminating with a complex risk assessment and risk management process.

Problems with the current regulatory system, and how they impact on the development of greener chemistry

The current EU system is now widely acknowledged to be failing. This failure has, in recent years, led to increasing discussion on how to improve things, culminating in the current debate on the nature of a new regulatory system. I will focus on five deficiencies which are particularly relevant to the adoption of greener chemistry:

- the lack of any obligation to deliver safety data on Existing Chemicals, in contrast to New Chemicals;
- the high burden of evidence that is required to remove a chemical from the market;
- the lack of precautionary action against chemicals that accumulate in our bodies or the environment;
- the lack of an obligation on industry to use the safest available chemicals in their products;
- the considerable secrecy about what chemicals are used in products, and the lack of accessible safety information for downstream users and the public.

The data problem

The lack of any obligation on industry to generate the same quality and quantity of safety data on Existing Chemicals has created a huge data vacuum. A survey by the European Chemicals Bureau of their database found that only 14% of the EU high production volume chemicals—those 2593 chemicals produced and imported at over 1000 tonnes/year—have a full 'base set' of safety data publicly available.

Jan Hammer of the Swedish National Chemicals Inspectorate, summed up the problem at a conference in December 1999: *"If it is not possible to perform a hazard assessment for 95% of the substances on the market then in reality these substances are not covered by the current legislation. This is a major problem in a nutshell: most substances on the market are in reality not covered by the current legislation."* [6]

However, safety data must be generated for 'New Chemicals'. As any Existing Chemical on the EINECS list can be used without safety data, such chemicals are in effect subsidised. This, therefore, discourages the development of greener, newer chemicals.

The evidence problem

The regulatory system puts many barriers in the way of taking action on chemicals for which concerns have been raised. This is partly due to the lack of safety data available, problems in determining the uses of many chemicals, and a slow and complex regulatory process. However, a major contributor is the high burden of evidence that is required before restrictions can be put in place.

This high burden of evidence has led to inaction on many chemicals of concern, notably endocrine disrupting chemicals (EDCs), even where there is substantial evidence of concern. Such delays are in contrast to pressures for precautionary action, coming from scientific bodies such as the Royal Society in the UK, whose report in June 2000[7] stated "*Despite the uncertainty, it is prudent to minimise exposure of humans, especially pregnant women, to EDCs*".

A lack of regulatory action on chemicals of concern reduces the pressure for development and use of greener alternatives.

Little action on persistent or bioaccumulative chemicals

A key element of many approaches to sustainability is the belief that we should not be causing any build up of chemicals in the environment above background levels. Many would also believe that it is unacceptable to be contaminating our bodies—and those of wildlife—with man-made chemicals, whether we currently know them to be toxic or not. But we are—a WWF review in 1999 found that "*several hundred man-made chemicals have been found as contaminants in human body fat, and many of these can be passed on to babies at a particularly sensitive stage in their development, via the placenta and during lactation*".[8] The continued routine use of persistent and/or bioaccumulative chemicals is particularly surprising given previous experience (and continuing problems) with chemicals such as polychlorinated biphenyls and CFCs.[9]

However, the current regulatory system, with its emphasis on proving that harm will be caused before taking action, is not able to deal with the problems caused by chemicals that are persistent or can bioaccumulate. It is almost impossible for such chemicals to be controlled in the current system, so their use continues.

Lack of an obligation to use the safest available chemicals

The current regulatory system does not put pressure on industry to use the safest (or greenest) chemicals available; companies will more commonly use the cheapest. Some sort of obligation to use the safest available chemical will have a huge impact on the economics of research and development of safer alternatives.

Currently there is a considerable commercial incentive for companies to continue manufacturing and marketing less safe but cheaper chemicals even if they themselves are marketing the safer alternative. One example of this is the production of alkylphenol ethoxylate surfactants. Despite the manufacture of alternative surfactants (and the gradual tightening of EU regulations on these chemicals[10]), the industry continues to manufacture these poorly-degradable, hormone disrupting chemicals. At a meeting of the UK Government's Stakeholder Forum on Chemicals in December 2001 it was argued by one company representative that that if their customers didn't get alkylphenols from them they would get them from someone else. This statement also demonstrates the importance of regulatory restrictions on problem chemicals, otherwise less responsible companies will always be able to use this argument.

Secrecy

The current regulations do not oblige producers to inform downstream users or the public of what is in the products they are using. This can make it extremely difficult for a downstream user or retailer to find out whether they are using chemicals that they may be concerned about, and whether other products are available that do not use this chemical. A common problem with the EU risk assessment process is that insufficient information is available on the actual uses of a chemical of concern, making it difficult for risks to be assessed.

A more open system, with information flowing freely up and down the supply chain, would enable the uses of chemicals of concern to be clearly visible, assisting in the development and promotion of greener alternatives.

A new approach

Chemicals regulation in Europe is now under review, with Sweden leading the way with its own proposals.

The Swedish approach

Sweden, one of the first countries to ban PCBs, has been implementing more precautionary regulation of chemicals for many years, and has recently moved to extend this regulation in a new chemicals bill.[11]
Their regulatory system includes both ‘soft’ and ‘hard’ regulation:

- *Soft regulation*. The Government publishes an 'Observation List' of less desirable chemicals, based on clear criteria.[12] This list does not result in legal restriction, but industry is encouraged to substitute listed chemicals by less hazardous alternatives. This reduces the profitability of the less desirable chemicals.
- *Hard regulation*. The new chemicals bill calls for new products for sale to general consumers to be "as free as possible" from substances which are carcinogenic, mutagenic or toxic to reproduction (frequently abbreviated to CMR) by 2007. It also calls for a ban by 2005 on new organic bioaccumulative and persistent substances; by 2010 on other organic substances which are "very persistent and very bioaccumulative,"; and by 2015 on other organic persistent and bioaccumulative substances. In addition, it requires safety data to be provided for all chemicals in use by 2010, and that all products containing hazardous substances are labelled by this date.

Sweden has stated that it wishes to see its approach to chemicals regulation reflected in the new EU system.

The debate on a new EU system

A fundamental review of EU chemicals regulations is underway. A key part of the debate is the contrast between approaches similar to the Swedish Government’s, and more traditional approaches which focus on proving harm from a chemical before regulating it.

After a number of stakeholder meetings, and tough internal debate, the Commission published a White Paper on a new chemicals policy in February 2001.[5] This White Paper has been discussed by the Member States, with Environment Council (made up of EU Environment Ministers) agreeing conclusions on it in June 2001.[13] It was then discussed by the European Parliament, who produced a report on it in November 2001.[14]

Current proposals for a new EU regulatory system

The current proposal for a new regulatory system includes the following key points:

- that all chemicals produced at >1 tonne/year should have safety data provided by 2012. In addition, it increases the thresholds for testing requirement for new chemicals, thus making it cheaper for industry to introduce new products by reducing the testing required for lower tonnages
- the creation of an 'Authorisation' scheme for chemicals of high concern, where use of the chemicals will be phased out except for specific authorised uses. The definition of 'high concern' is currently under dispute. The White Paper proposed that this should include carcinogens, mutagens and reproductive toxins (CMR), and chemicals which meet the criteria for persistent organic pollutants, as defined in the UNEP POPs treaty. It also proposed adding persitent, bioaccumulative and toxic chemicals (PBT) and very persistent, very bioaccumulative chemicals (vPvB) once criteria have been agreed. Environment Council supported extension to PBT and vPvB, and also proposed addition of proven endocrine disrupters and sensitisers. In contrast, the Parliament—in a very close vote—backed limiting authorisation just to CMRs and POPs
- a new centralised 'Chemicals Agency'
- more responsibility to industry, and increased flow of information up and down the supply chain

The view of Environment and Consumer NGOs

Environment and Consumer NGOs have been collaborating on a common position on the chemicals review, including the agreement in December 1999 of the 'Copenhagen Charter', a summary of their demands:
We demand from the EU review of chemicals policy:

- A full right to know, including what chemicals are present in products.
- A deadline by which all chemicals on the market must have had their safety independently assessed. All uses of a chemical should be approved and should be demonstrated to be safe beyond reasonable doubt.
- A phase out of persistent or bioaccumulative chemicals.
- A requirement to substitute less safe chemicals with safer alternatives.
- A commitment to stop all releases to the environment of hazardous substances by 2020.
- A more detailed discussion of how these principles could be applied to the EU regulatory system is given in the Crisis in Chemicals report, which also examines the impacts of the biomedical revolution on chemicals regulation.[4]

The chemical industry’s approach to the policy review

The chemical industry, through their European lobbying organisation CEFIC, is heavily involved in the chemicals policy review. Some of the positions that they are promoting which are particularly relevant to the promotion of green chemistry include:

- opposition to the authorisation process. Initially CEFIC spokespeople were totally opposed to the authorisation approach, later they moved to a policy of only accepting a very limited process, covering only CMRs and UNEP POPs, only if other legislation did not already apply to the chemicals concerned and a risk assessment proved that there was a risk[15]
- opposition to taking action on vPvB or PBT chemicals except if they are shown to be a proven risk in risk assessment. CEFIC do not support any action on chemicals unless their known toxicity is sufficient to be a proven risk;
- opposition to observation lists and general obligations to use the safest chemicals.

In addition, CEFIC and their its sector groups frequently lobby against restrictions on individual chemicals as they are passing through the current EU risk assessment process, for example during the debate on the brominated flame retardant 'penta', which is increasing in concentration in breast milk.[16] US chemical manufacturers also frequently put pressure on the EU process, for example arguing against controls on alkylphenols.[17]

The process from here

The Commission has set up a number of technical working groups to examine various aspects of the new legislation. It is hoped that new draft legislation will be published in Summer 2002, and it will then be debated in both Environment Council and the European Parliament—both of which must agree the final legislation. Therefore the policy approach taken by the Governments of all the EU member states will be crucial to the outcome of the Environment Council debate, whilst the European Parliament's conclusions will be determined by the policy position taken by the MEPs and their party groups.

It will probably take around two years to complete the process, which is likely to include two readings in the parliament, and finally the 'Conciliation' process, in which Council and the Parliament must reach a compromise position.

The role of green chemistry research in the regulatory debate

Regulation has a major impact on the economics and application of Green Chemistry. A large part of this regulation is now under review in Europe, providing an opportunity to improve these regulatory drivers. Therefore there is an opportunity for a debate on what regulatory methods best drive greener chemistry. Key questions include:

- how regulations can be designed to encourage—and force—positive innovation?
- what is the best method of encouraging or forcing substitution? What is the potential for Swedish-style observation lists, and when might it be necessary to use more complex 'Comparative Assessment' methodologies?
- what methods are available for rapid decision making on whether a product or process is, overall, greener, more sustainable and safer than an alternative?

Those 'Green Chemists' who are interested in the subject might also find it beneficial to learn more about the issue from the numerous reports and other documents available (e.g. ref. 18 and ref. 19).

In addition, they could discuss the issue with their political representatives and Governments. For example, it is unfortunate that the UK Government's Department for Trade and Industry has tended to lobby against tighter regulation of chemicals use, [20] rather than promoting the role of regulation in encouraging innovation.

Conclusions

Green Chemistry aims to minimise environmental impacts from the production and use of chemicals. A crucial part of this minimisation of impact is the presence of regulations that discourage or prevent the use of more hazardous chemicals, and which provide incentives for the use of greener alternatives. Without technology-forcing regulation the status quo is frequently easier and cheaper, which is crucial since profitability and legality will remain the main drivers for the chemical industry (and most, if not all, other industries).

Most of the major environmental improvements that have occurred have been created by new regulations, not by voluntary or market mechanisms. Examples include the control of urban smog through clean air acts (banning the use of various fuels), the phase out of lead in petrol in the developed world (through a legal phase out combined with financial incentives) and the role of the Montreal protocol in reducing, and eventually (in the future) stopping the destruction of the ozone layer (through legally binding phase out of ozone depleting chemicals).

The current EU review of chemicals regulation provides an opportunity to promote the use of greener chemicals in Europe. In addition, the results of this European review will have an impact on the development of a global approach to chemicals control, a process which is now underway within the United Nations Environment Programme.

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Ionic liquids

Professor Kenneth Seddon, from Queen's University, Belfast, introduces this special issue on ionic liquids

The more observant of our readers will have noticed that this issue of *Green Chemistry* contains rather more papers concerning ionic liquids than is normal. Indeed, there are more papers on this subject in this one issue than were published anywhere in 1988. Let me make it quite clear, then, that ionic liquids are not dominating the field of green chemistry! As the most cited paper in the first years of *Green Chemistry* was about ionic liquids, an Editorial Board decision was taken to have a Special Issue devoted primarily to ionic liquids. As the appointed Guest Editor, I invited papers from key researchers in the field for inclusion. However, although papers were invited, it should be clear that they underwent the normal full and rigorous refereeing and editorial process to which all RSC papers are subjected (after all, this is a society, not a commercial, journal!). For my part, I was honoured to be asked to do this, and it was an extremely pleasurable experience—like organising a conference of world experts, without the logistics! I believe that the papers included here, ranging from organic synthesis to nuclear chemistry, from catalysis to atomistic simulation, from archival history to physical properties, represent an exciting cross-section of the research being carried out, both in industry and academia, at the moment. They illustrate, elegantly, the breadth and diversity of ionic liquids research, their green nature, the international dimension, and their potential for industrial application. I defy anyone who has an interest in chemistry, whatever their field, to read the papers in this issue, and fail to be excited.

Figure 1 illustrates the rise in publications concerning ionic liquids over the past few decades (and these are just the papers using the term "ionic liquid"). It will not be long before we are approaching 500 papers per year. A similar trend is found in the patent literature. There is little doubt that this phenomenal interest will continue. But is this good news? The simplistic, but nevertheless correct, answer is "yes"; if ionic liquids are to impact the field of green chemistry, then we need to know much more about them, experimentally and theoretically, than we do now. Ionic liquids are the least developed of the viable green solvents; our ability to predict results and engineer processes is limited by the sparsity of extant data (especially physical, thermodynamic, kinetic and engineering data). We are only just starting to climb the 'S' curve of knowledge, whereas heterogeneous catalysts are approaching the plateau. So this burgeoning of interest, with the concomitant rise in published observations and data, is to be welcomed: without it, ionic liquids will become a transient phenomenon, an interesting academic footnote in the chemical archive.

However, everything has a price. With increasing activity comes the inevitable increasing "garbage" factor. In recent years we have seen papers reporting physical data on ionic liquids that were demonstrably impure, liquids reported as solids and solids reported as liquids because of the impurity level, communications "rediscovering" and publishing work (without citation) already published in the patent literature, the synthesis of water-sensitive ionic liquids under conditions that inevitably result in hydrolysis, and academically weak publications appearing in commercial journals with lax refereeing standards. On the positive side, individual reactions, such as the Heck reaction and the Diels–Alder reaction, are being studied by a number of research groups, and so there is an establishing comfort zone when similar results are obtained, and an excellent discussion forum in the case of apparently

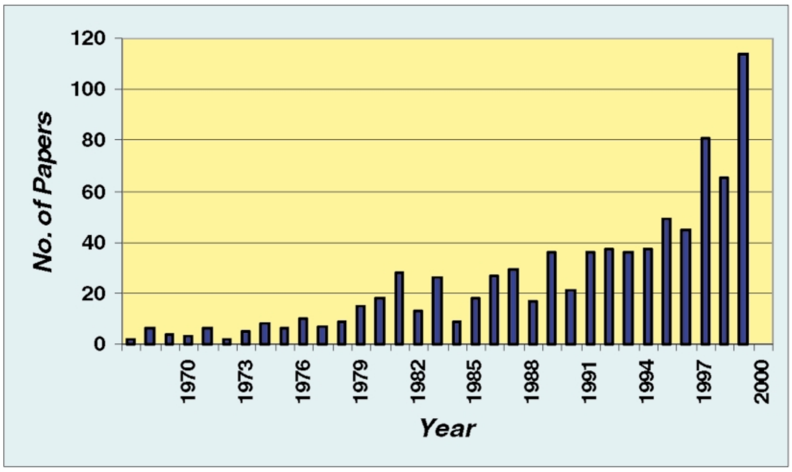

Figure 1. The rise in publications concerning ionic liquids as a function of time, as determined using SciFinder.

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diverse findings.

Following the first international conference focussing entirely on ionic liquids (a NATO ARW on Green Industrial Applications of Ionic Liquids, Heraklion, Crete, 12–16 April 2000), there were ten sessions concerning the green applications of ionic liquids at the Spring 2001 ACS National Meeting in San Diego, ten sessions are planned concerning the green applications of ionic liquids at the Autumn 2002 ACS National Meeting in Boston, and a DeChema meeting on Green Solvents for Catalysis will be held in Bruchsal, Germany in October 2002. Also, 2002 will see the publication of three edited books devoted entirely to ionic liquids, and there is this special issue of *Green Chemistry*.

Figure 2. The attendees at the First International Meeting on Ionic Liquids, a NATO ARW on Green Industrial Applications of Ionic Liquids, Heraklion, Crete, 12-16 April 2000.

The above is part of the healthy development of any significant area of chemistry. But it is essential that the diversity of the audience is maintained. One of the glories and fascinations of ionic liquids is that they impact on every area and aspect of chemistry, and overlap with many areas of physics, biochemistry, chemical engineering and even (recently) space flight! There are, and have been, a number of attempts to launch a journal of ionic liquids. It is my belief, and that of many others, that this would be a disastrous move for the field. Ionic liquid results should be dispersed over a broad base of academic disciplines, not concentrated in one place, which would inevitably create the impression of a niche area. Indeed, green chemistry will have succeeded when it is so well accepted that the adjective green can be dropped; ionic liquids will have succeeded when they are used for synthesis without especial comment, in the way that methanol is used today. Would we ever have seriously considered a *Journal of Methanol*?

If the above developments can be described as healthy, then we must also beware the cancer. A serious threat to the area of ionic liquids is the quite incredible attempt of a small American business, holding a US Patent on ionic liquid synthesis, to stifle the academic freedom of American researchers. Following the Spring 2001 ACS National Meeting in San Diego, all the American university attendees, but none of the European, received a letter. Amongst other statements was included: “we wish to advise you that Patent Law grants no [such] exemption to academic institutions or to the employees thereof. Therefore, an academic investigator (like any other investigator) who wishes to make or use ionic liquids that fall under the scope of [our] patent must first obtain our permission to do so. In respect to making such ionic liquids, the investigator must take a license from [us]. In respect to using such ionic liquids, the investigator must either obtain them from [us], or come to an agreement with [us] that authorizes their procurement from a third party source. To practice our patented technology without our permission will be construed by [us] as infringement. [We] reserve the right to protect [our] Intellectual Property as [we] deem necessary.” I will leave it to the reader to come their own conclusion about the motives of the writer, but this is not only a blatant attempt to stifle academic freedom and control the direction of academic research, but it also suppresses American research at the expense of European research. It would be immensely damaging if anyone took this letter seriously, not least to the company involved, who can only themselves benefit as new applications for their patented materials emerge.

To conclude this commentary upon the current state of ionic liquids, it is worth saying that their impact is already immense. Apart from the excitement of the research, they are entering University undergraduate and postgraduate courses, and even some schools. They are routinely mentioned as part of governmental green chemistry policy, and have moved from academic curiosity to mainstream research in less than a decade. But the acid test is looming; there is now a need to see ionic liquid technology practised in industry, to parallel the recent commercialisation of supercritical fluid technology by Thomas Swan, in a newly commissioned plant in Consett (County Durham). To quote Professor Paul T. Anastas, White House Office of Science and Technology Policy in Washington D.C., and advisor to both President Clinton and President Bush (as reported in *Chemical & Engineering News*): “Green chemistry aims to design the hazards out of chemical products and processes, including solvents. With ionic liquids, you do not have the same concerns as you have with, for example, volatile organic solvents, which can contribute to air pollution. Ionic liquid chemistry is a very new area that is not only extremely interesting from a fundamental chemistry point of view, but could also have a very large impact on industry.” It is up to us to prove this to be right!

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Review

A short history of ionic liquids—from molten salts to neoteric solvents

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Ionic liquids, defined here as salts with melting temperatures below 100 °C, evolved from traditional high temperature molten salts. Some materials we would now recognize as ionic liquids were observed as far back as the mid 19th century. The quest for useful molten salts with lower melting temperatures led to inorganic chloroaluminates, to organic chloroaluminates, then to the water and air stable salts now being developed for green chemistry applications.

Introduction

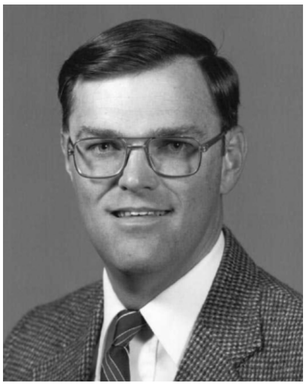
The history of ionic liquids may be viewed as a relatively recent one, or one extending back to the 19th century. Which history you choose depends on your definition of 'ionic liquid' and how deeply you look for progenitors of the present materials receiving so much interest for green chemistry applications. Accordingly, this may be the birth of new and important industrial materials, or we are witnesses to a *renaissance* of molten salt chemistry. I believe both are happening.

A working definition suitable for a historical view of ionic liquids, and perhaps a practical view, is that an ionic liquid is a salt with a melting temperature below the boiling point of water. Most salts identified in the literature as ionic liquids are liquid at room temperature, and often to substantially lower temperatures. One fairly general feature of ionic liquids that is not part of the definition is that most have organic cations and inorganic anions. There are many synonyms used for ionic liquids that complicate a literature search. 'Molten salts' is the most common and most broadly applied term for ionic compounds in the liquid state. Unfortunately the term 'ionic liquids' was also used to mean the same thing long before there was much literature on low melting salts.[1,2] It may seem that the difference between ionic liquids and molten salts is just a matter of degree (literally), however the practical differences are sufficient to justify a separately identified niche for the salts that are liquid around room temperature. That is, in practice the ionic liquids usually may be handled like ordinary solvents. There are also some fundamental features of ionic liquids, such as strong ion–ion interactions that are not often seen in higher temperature molten salts. Synonyms for materials that meet the working definition of ionic liquid are 'room temperature molten salt,' 'low temperature molten salt,' 'ambient temperature molten salt,' 'ionic fluid' and 'liquid organic salt.'

The term 'neoteric solvent' has been used in recent years to mean new types of solvents, or older materials that are finding new applications as solvents. Supercritical fluids and ionic liquids are good examples of neoteric solvents that have been known for a long time, but are being considered as process solvents.

The link between ionic liquids and green chemistry is clearly related to the solvent properties of ionic liquids. Most of the papers in this volume will be somehow related to ionic liquids as solvents, and the one property that stands out above all others is the huge liquidus range. Liquidus range is the span of temperatures between the freezing point and boiling point of a liquid. The consequence for green chemistry is that ionic liquids are the ultimate non-volatile organic solvent, with emphasis on the 'non-'. No molecular solvent (other than molten polymers) comes even close to the low volatility of ionic liquids.

Dr Wilkes is Professor of Chemistry and the Director of the Chemistry Research Center at the United States Air Force Academy in Colorado Springs, Colorado. He was born in 1947 in the Panama Canal Zone (a U.S. territory at the time), and spent his childhood in Europe, Asia, and numerous locations in the U.S. as part of a military family. He has a BA in chemistry from the State University of New York at Buffalo, and an MS and PhD from Northwestern University. Dr Wilkes did active military service in the U.S. Air Force, and has been a civilian at the U.S. Air Force Academy continuously since 1978. His past and present research has concerned ionic liquids, as well as DNA synthesis, explosives, nonlinear optical materials and hydrogen storage materials.



Green Context

Is this about Green Chemistry? Well . . . . actually, no!! Green chemistry wasn't even a twinkle in Paul Anastas' eye for much of the period covered by this fascinating overview. What we have here is a first-hand account from one of the three grandfathers of ionic liquids (the others being, as is clear from the article, Prof. Chuck Hussey and Prof. Bob Osteryoung) of the birth of a field of research which would become a key component of green chemical strategies. Reviews nowadays are typically so anodyne and automated (search a database, summarise all the papers, avoid personal comment or any form of criticism) that this personal view makes a refreshing change. This should be compulsory reading for all workers in the area, and for most students, to show them anew the joy of chemistry. ***KRS***

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A history of ionic liquids will necessarily be biased by the view of the reporter. Another author may put a different emphasis on people, events and materials that contributed to where we are at the end of the year 2001. So, this history is a perspective viewed from the path I took at the U.S. Air Force Academy over the last three decades (plus the present one), which started with what we would now call high temperature molten salts, then the chloroaluminate ionic liquids, then proceeding to the water stable ionic liquids that are responsible for the recent exponential growth of the literature of ionic liquids. Most of this historical perspective is built upon the people and papers of the time. Don't expect a comprehensive review of the literature here. For literature reviews refer to Hussey,[3] Wilkes and Carlin,[4] or Welton.[5]

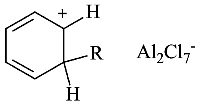
The Prehistory

Almost every 'new' discovery was preceded by earlier work upon which you based your research, but also developments that you wish you had known about before you started. Often the roots go back to more than one hundred years, which is the case for ionic liquids. Clearly, the roots of ionic liquids are firmly planted in traditional high temperature molten salts.

An important question to ask and answer is: Why work in high temperature molten salts when water and other molecular solvents are so much more convenient? The answer to this will serve as the *raison d'être* for both molten salts and ionic liquids. Molten salts have several properties that compel their use as reaction media. First and foremost is the great stability of salts—thermal, chemical, and electrochemical. For example, aluminium(III) can be electrochemically reduced in molten cryolite ($NaAlF_6$) to elemental aluminium, but this is not practical in molecular media. At the same time, inorganic molten salts generally have a very wide liquidus range owing to the combination of thermal stability and non-volatility. That allows the production of liquid Al in the aforementioned Hall process at 980 °C. Inorganic molten salts also tend to be rather cheap and available in large quantities, since they are usually derived from naturally occurring minerals. Finally, the high concentrations of ions and the high temperatures of molten salts make them premier electrolytes for some electrochemical processes. This is due to wide electrochemical window and very high electric conductivity. There are also some good reasons not to use molten salts. First, they are usually hot; very hot. For example sodium chloride has a melting temperature of 800 °C, and the popular 'low-melting' alkali halide eutectic mixture LiCl–KCl has a 355 °C melting point. The high operating temperatures result in serious materials incompatibilities for reactions done at any scale, and industrial scale processes incur considerable energy costs to maintain the high temperature. Finally molten salt chemistry is generally unfamiliar to most chemists not working in the field, thus molten salts are not even considered as a solvent by most chemists.

We will see that ionic liquids have many of the advantages of molten salts, and they avoid the worst disadvantages caused by high temperature. In fact they are better viewed as a new type of non-aqueous solvent, that is a neoteric solvent. The ignorance issue still is a problem, but one being dealt with by this volume.

The first documented observation of ionic liquids by chemists was the so-called 'red oil' formed during Friedel–Crafts reactions. The prototypical Friedel–Crafts reaction is the reaction of the aromatic substrate benzene with the incipient electrophile chloromethane to form toluene. A Lewis acid, such as $AlCl_3$, catalyzes the reaction. Often during the course of this reaction a separate red-colored phase appears, but the composition of the red oil was not known when this was first observed in the mid-19th century. When NMR spectroscopy became widely used by chemists, the structure of the red oil was identified as a salt having a cation that was the long-presumed stable intermediate in Friedel–Crafts reactions called the sigma complex. For $AlCl_3$-catalyzed reactions, the structure proposed for the liquid was the heptachlorodialuminate salt shown as formula **1**. I thank Prof. Jerry Atwood of the University of Missouri for pointing out this early ionic liquid. This red oil ionic liquid and more complicated variations were patented as a useful material, but I know of no major industrial use.[8]



1

Simple alkylammonium nitrates of the type in formula **2** were found to be liquids in the early 20th century. For example ethylammonium nitrate has a melting temperature of 12 °C, which definitely would be called an ionic liquid if discovered today.[7] Ionic liquids of this class have actually found some utility in recent times. A program to develop liquid propellants for naval guns and artillery led to the discovery of more complicated nitrates. These are somewhat difficult to find in the literature, since *Chemical Abstracts* lists them as mixtures of molecular compounds. An example of the *Chemical Abstracts* representation of one of the nitrate ionic liquid gun propellants is in Fig. 1.[8] One can see that the acid–base chemistry of the components results in a binary ionic liquid material, which is a mixture of two nitrate salts. The particular example is a glass forming salt with a glass transition temperature of −100 °C.[9] This ionic liquid is not a one-off curiosity, since there have been 59 papers and patents for this example alone between 1979 and 2001.

$$CH_3CH_2NH_3^+NO_3^-$$

2

Another progenitor of current ionic liquids was the work of Prof. John Yoke at Oregon State University. In the 1960s he found that mixtures of copper(I) chloride and alkylammonium chlorides were liquid near room temperature. For example CuCl and triethylammonium chloride (Et_3NHCl) are both solids, but form a liquid at room temperature when mixed as in eqn. (1).[10]

$$\mathrm{CuCl\ (s) + Et_3NHCl\ (s) \longrightarrow Et_3NHCuCl_2}\ (l) \tag{1}$$

Reactions among various chlorocuprate anions and chloride are analogous to those known to occur in chloroaluminates. This

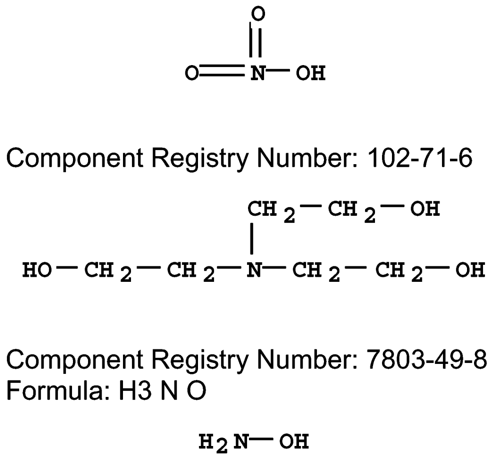


Fig. 1 *Chemical Abstracts* representation of the liquid gun propellant LGP 1846, which is actually an ionic liquid.

ionic liquid proved somewhat useful for spectroscopy, but was not widely used for other purposes.

The compounds known as liquid clathrates are materials that we now recognize as ionic liquids. These unusual materials were discovered and characterized in the 1970s by Prof. Jerry Atwood and his group, then at the University of Alabama (See Fig. 2). Liquid clathrates are composed of a salt combined with an aluminium alkyl, which then forms a compound with one or more aromatic molecules.[11] A formula for the ionic portion is $M[Al_2(CH_3)_6X]$. The anion in the salt MX forms an Al–X–Al bridged anion with the trimethylaluminium, which then forms an inclusion compound with an aromatic guest as the temperature is raised (eqn. (2)). While these liquid clathrates are not strictly ionic liquids due to the aromatic molecules, they have been patented for use in coal liquefaction and petroleum recovery from tar sands.[12] The liquid clathrates discovered by Prof. Atwood have an interesting but indirect connection to modern-day ionic liquids. Four of Atwood's students at the University of Alabama were Robin Rogers, Richard Carlin, Michael Zaworotko and Joan Fuller. These names will appear later in the saga of ionic liquids.

$$M[Al_2(CH_3)_6X] + n\text{Aromatic} \underset{\text{low temp.}}{\overset{\text{high temp.}}{\rightleftarrows}} \underset{\text{liquid clathrate}}{M[Al_2(CH_3)_6X] \cdot n\text{Aromatic}} \quad (2)$$

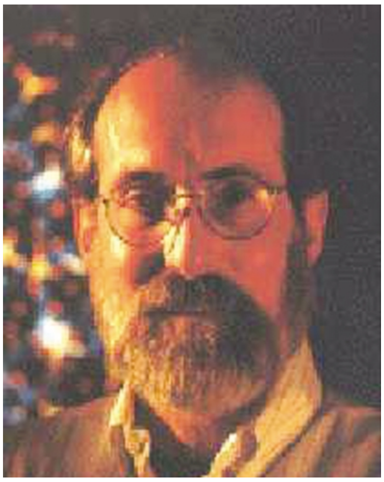


Fig. 2 Professor Jerry Atwood, University of Alabama (now at University of Missouri).

One of those students in the Atwood group during that time appears to have had the ionic liquids seed planted in his mind in the 1970s, but it took another 20 years for it to germinate. Robin D. Rogers, who is now Professor Rogers at the University of Alabama (see Fig. 3), studied numerous alkylaluminate salts while he was a grad student. His principal interest was crystallography, so liquids probably were not what he focused on. However, one paper from his graduate work was the crystal structure of the salt $NMe_4^+AlMe_3I^-$, which has a melting temperature of 253 °C.[13] That salt with ethyl groups instead of methyls has a melting point of 50 °C, and the closely related salt $NEt_4^+Al_2Et_6I^-$ is liquid at room temperature. Prof Rogers very nearly entered the ionic liquids long ago, before he became a leader in green chemistry in general and ionic liquids in particular.

Fig. 3 Professor Robin D. Rogers (center). Photo taken in April 2000 in Heraklion, Greece.

The chloroaluminates—high temperature

The currently popular ionic liquids that have quaternary heterocyclic cations (like alkylpyridinium or dialkylimidazolium) and inorganic anions have an ancestry traceable to traditional high temperature molten salts. The salts that were the transition between the truly high temperature molten salts (like cryolite or LiCl–KCl) and the present ionic liquids were the inorganic chloroaluminates. It is interesting to note that 30 years ago these salts were called ‘low temperature molten salts.’ Everything is relative. The high temperature chloroaluminates are transition materials in history and in temperature. Sodium chloride–aluminium chloride eutectic has a melting temperature of 107 °C—very nearly meeting our present definition of an ionic liquid.

The locus of the development of chloroaluminate molten salts was the U.S. Air Force Academy in Colorado Springs, plus many other collaborators funded by the Air Force and National Science Foundation. The Air Force Academy has had a continuous research effort in molten salts/ionic liquids since the early 1960s, and there have been only three principal investigators of that project over the last 40 years. The originator of this research area was Lowell A. King, then a Major in the Air Force and now retired (see Fig. 4). Since 1981 the program has been led by myself, and by Richard T. Carlin (Fig. 5).

The motivation for studying the inorganic chloroaluminates was a problem with thermal batteries. Thermal batteries have a molten salt electrolyte, usually LiCl–KCl that is heated by a pyrotechnic when the battery is activated. Temperatures in these batteries are commonly 375–550 °C. Such high temperature causes materials problems inside the battery, and incompatibilities with nearby devices. The goal of the Air Force Academy group in the 1960s and 1970s was to develop a molten salt electrolyte with a much lower melting temperature, thus solving most of the temperature-related problems. Dr King chose the (then) little-known alkali chloride–aluminium chloride system.

Fig. 4 Lieutenant Colonel (Dr) Lowell A. King. Photos were taken in 1961 (left) when he initiated the research in molten salts at the Air Force Academy, and in 1997 (right), when he returned as a visiting professor.

If one proposes a new material for use in practical applications, then someone must provide the physical and chemical properties data that will allow engineers to use the material in a device. Ionic liquids face this issue right now. The Air Force Academy group embarked on a many-year effort to study both the fundamentals and the practicalities of the alkali chloroaluminates. Properties such as phase equilibria, density, viscosity, electric conductivity, electrochemistry and vapour pressure were carefully measured and published. This was a difficult task for two reasons. First, the alkali chloroaluminate salts (*e.g.* $NaCl–AlCl_3$) are not simple binary salts as they appear on paper. Aluminium chloride is a molecular compound in the liquid and vapor state (as Al_2Cl_6), and reacts as a very strong Lewis acid in all phases. Second, even though the inorganic chloroaluminates are low-melting relative to most other molten salts, they still require some inconvenient lab techniques to accommodate the 175 °C temperature needed for most experiments.

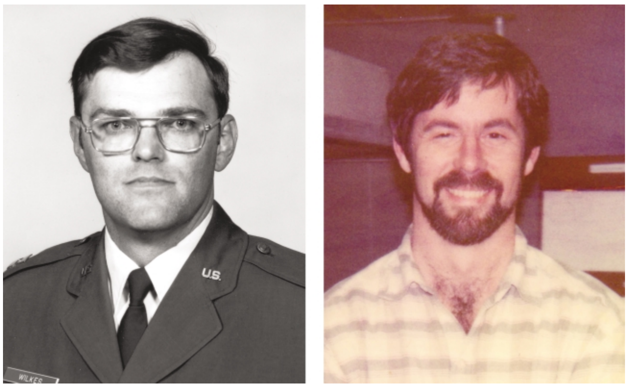


Fig. 5 Dr John S. Wilkes (left) in 1978 and Dr Richard T. Carlin (right) in 1990. A more recent image of Wilkes is in the upper left of Fig. 3.

Dr King established close working collaborations with other groups in the U.S. and Europe in order to get a complete understanding of the high temperature chloroaluminates. The two academic groups in the U.S. headed by Prof. Robert A. Osteryoung (then at Colorado State University) and Prof. Gleb Mamantov (at the University of Tennessee) were essential to this effort (see Fig. 6). Not coincidentally, Dr Bernard Gilbert, now a Professor at the University of Liege, Belgium was a post-doctoral student with both Osteryoung and Mamantov during those years. There were strong and productive collaborations with two academic groups in Europe, one headed by Prof. Niels Bjerrum at the Technical University of Denmark and the other by Harald Øye at the Norwegian University of Science and Technology (Fig. 7). Space does not permit a presentation of the details of the important and high quality research done by these groups.

The electrochemistry of solutes that could be used as energy producing battery couples in the high temperature chloroaluminate molten salts was entirely unknown at the conception of the project. Fortunately Charles Hussey, then an active duty Air Force officer, was assigned to the Air Force Academy (Fig. 8). He proceeded to do difficult but careful studies of many electroactive materials in inorganic chloroaluminate molten salts, culminating in a patent for a thermal battery containing the $NaCl–AlCl_3$ electrolyte that was actually manufactured in small quantities.

The chloroaluminates—low temperature

The alkali chloroaluminate molten salts research was an excellent combination of basic research and practical applica-

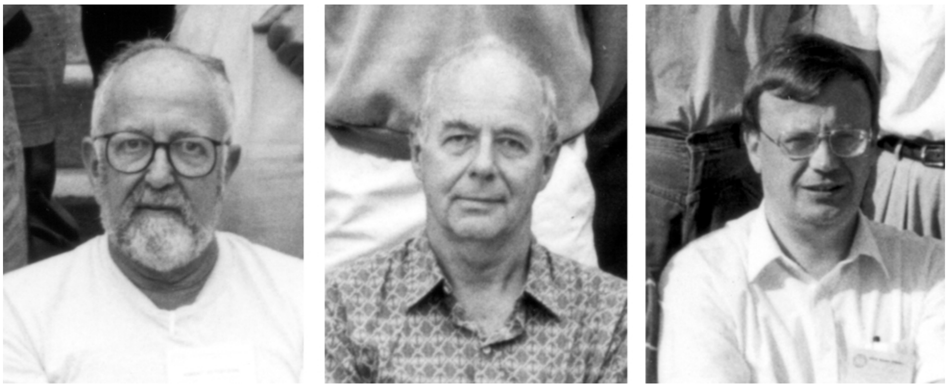
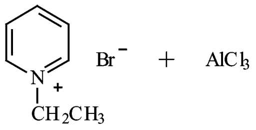


Fig. 6 Professor Robert Osteryoung (left), Professor Gleb Mamantov (center) and Dr Bernard Gilbert (right). The photos were taken at Gordon Research Conferences during the 1980s.

Fig. 7 Professor Niels Bjerrum (left) at a Gordon Research Conference in 1993, Professor Harald Øye (right) being awarded Knight First Class of the Royal Norwegian Order of St. Olav in 1999.

Fig. 8 Major Charles L. Hussey at the Air Force Academy. He is now a Professor at the University of Mississippi.

tions, but the salts were not ionic liquids by our current definition. Early in their work on molten salt electrolytes for thermal batteries, the Air Force Academy researchers surveyed the aluminium electroplating literature for electrolyte baths that might be suitable for a battery with an aluminium metal anode and chlorine cathode. They found references to work done at the Rice Institute by Frank Hurley and Thomas Wier on electrodeposition of aluminium in some $AlCl_3$-based molten salts that were liquid at room temperature.[14] The electrolytes were mixtures of $AlCl_3$ and 1-ethylpyridinium halides, mainly the bromide, **3**. In 1968 the Air Force Academy group assembled cells with the aluminium and chlorine electrodes with various molten salt electrolytes, including a 1 : 2 ethylpyridinium bromide–$AlCl_3$ mixture that we would now term an ionic liquid.[15] Except for ref. 15 and another electroplating paper[16] published in 1952, there was little interest in the pyridinium ionic liquids as electrochemistry electrolyte until much later. Victor Koch (Fig. 9), a post-doc at Colorado State University did use this ionic liquid as a medium for some organic reactions in the mid-1970s.[17]



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I would mark the start of the modern era of ionic liquids as the simultaneous collaborative discovery and development of the 1-butylpyridinium chloride–aluminium chloride mixture (BPC–$AlCl_3$), **4**, by the groups at Colorado State University and the Air Force Academy. This all-chloride system was a substantial improvement on the mixed bromide–chloride ionic liquid of Hurley and Wier. The fact that the Osteryoung group published the first paper[18] on the (BPC–$AlCl_3$ system and the Air Force Academy group was granted the patent[19] shows how close the collaboration was. Since this was a new material, practical use would depend on the availability of its physical and chemical properties. The physical properties, such as density, viscosity and conductivity were done at the Air Force Academy, the early spectroscopy at Colorado State University, and many electrochemical experiments were done at both places.

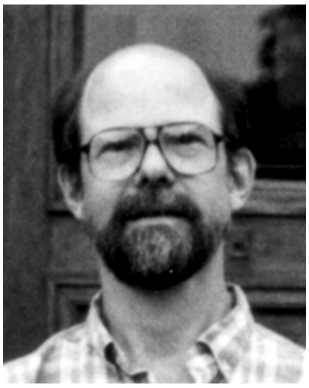
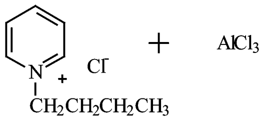


Fig. 9 Dr Victor R. Koch, an early participant in the development of ionic liquids starting in the mid-1970s. He is active in searching for commercial uses of ionic liquids as the CEO of Covalent Associates Inc.



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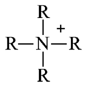
The BPC–$AlCl_3$ ionic liquid has two unfortunate features. First, the melting temperature of the equimolar composition is 40 °C, so it is not a room-temperature liquid at the composition that has the highest conductivity. Second, in the basic compositions ($AlCl_3$ mole fraction < 0.5) the butylpyridinium cation is easily reduced. This fact results in a much narrower electrochemical window than NaCl–$AlCl_3$, and an incompatibility with Al electrodes. This prompted us to search for a salt with even lower melting temperatures, and which would contain a cation that was substantially more difficult to reduce. The approach to lower melting points was based on a rather intuitive explanation for the abnormally low melting temperatures of chloroaluminate salts in general. The formation of a chloroaluminate binary salt involves the formation of $AlCl_4^-$, $Al_2Cl_7^-$ and in very $AlCl_3$-rich melts, $Al_3Cl_{10}^-$ anions. The mixtures of large anions with many degrees of freedom should inhibit crystallization until much lower temperatures. The ionic liquids with large cations in addition to large anions should have even lower melting points, which is exactly what is observed. Asymmetry in the cation should also result in lower melting temperatures by this argument. The relatively high viscosity of these ionic liquids at low temperatures also inhibits crystallization, and promotes glass formation.

Predicting the reduction potentials of the cations had a more quantitative basis. At just about the time we were searching for less easily reduced cations, M. J. S. Dewar at the University of Texas released the software for performing MNDO semi-empirical molecular orbital calculations (MNDO = Modified Neglect of Differential Overlap). The method was extremely fast, since the core electron energies were parameterized with thermodynamic data, and did not have to be calculated as in *ab initio* methods. The practical result was that molecules or ions the size of pyridinium cations could be calculated in just a week or two on the main frame computers of the late 1970s.[20] The output of the calculations contained an optimized geometry, the heat of formation, and the energies of all orbitals. We reasoned that the energy (reported in eV) of the highest occupied molecular orbital (HOMO) would be roughly correlated with the electrochemical oxidation potential in solution, and the lowest unoccupied molecular orbital (LUMO) energy would correlate with the electrochemical reduction potential (E_{red}).

In 1979 Charles Hussey (by then moved to the University of Mississippi) and I started an effort to find an alternative chloride salt that would make a low-melting chloroaluminate ionic liquid, but would be more difficult to reduce. This involved calculations, syntheses and electrochemical measurements. The cations we considered contained quaternary-N, and most were heterocyclic. Cations of the types **5–14** were initially considered, and one class stood out as an excellent candidate for a new ionic liquid with a wider electrochemical window. The dialkylimidazolium cation class **13** was predicted to have a reduction potential about 0.9 V more negative than the alkylpyridinium cations **8** that we had found earlier to be unacceptably prone to reduction in electrochemical experiments.



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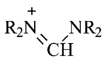

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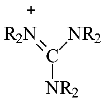

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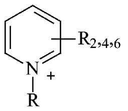

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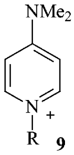

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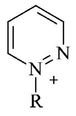

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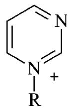

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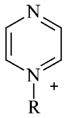

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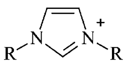

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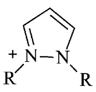

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A quick search of Beilstein showed us that iodide salts of numerous examples of dialkylimidazolium cations were prepared in the 1880s in Germany.[21] The iodides were simple to prepare in one step from commercially available starting materials, then the chloride salts were obtained by ion exchange. We soon found that the chlorides could be made directly in one step.[22] When a dialkylimidazolium chloride salt (1-ethyl-3-methylimidazolium chloride, emimCl, for example) was mixed with aluminium chloride, an ionic liquid was formed that had a freezing point below room temperature for all compositions between 0.33 and 0.67 $AlCl_3$ mole fraction, as seen in the phase diagram in Fig. 10. Furthermore, the imidazolium cation in these melts was more stable toward electrochemical reduction by −0.9 V compared to the alkylpyridinium cations. This was exactly as predicted by the MNDO calculations. Soon after this we measured the phase transitions, densities, viscosities and conductivities of chloroaluminate ionic liquids made from a series of dialkylimidazolium chlorides with varying lengths of alkyl substituents.[23] We finally settled on the ionic liquids containing the 1-ethyl-3-methylimidazolium cation as the best compromise of ease of synthesis plus good physical, chemical and electrochemical properties.

Not too long after publication of our initial work on the emimCl–$AlCl_3$ ionic liquid, the Air Force's scientific liaison office in London arranged a visit to the Air Force Academy by a young academic named Ken Seddon (see Fig. 11). He was attracted to this new medium by its very high but adjustable chloride content in the total absence of water, as well as its suitability as a spectroscopic solvent. By coincidence Chuck Hussey from the University of Mississippi was visiting the Air Force Academy at the same time, an event that resulted in a long-term collaboration between the Mississippi and Sussex (now Belfast) groups. The room temperature chloroaluminate medium did in fact allow for the preparation of metal ion chlorocomplexes that had not been seen before.[24] The story of how this esoteric interest in inorganic complexes became QUILL, a major facilitator for industrialization of ionic liquids, is a story best told by Ken Seddon when he writes a story such as this one.

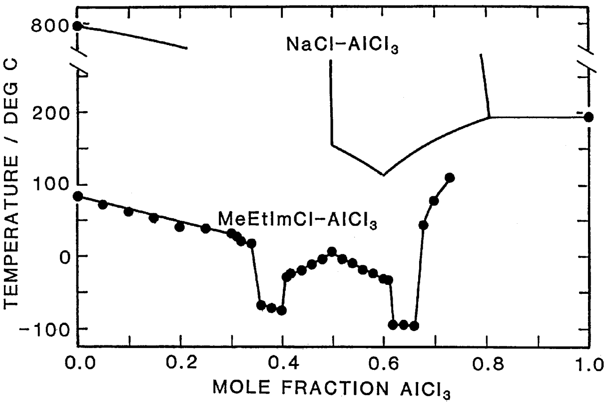


Fig. 10 Phase diagram of the 1-ethyl-3-methylimidazolium chloride–aluminium chloride salts compared to sodium chloride–aluminium chloride. The very low temperature data are actually glass transitions.

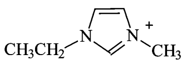
Fig. 11 Professor Kenneth E. Seddon (right) and the author (left) taken at a conference in Nova Scotia in 1996.

Water stable ionic liquids

The pyridinium- and the imidazolium-based chloroaluminate ionic liquids discussed above share the disadvantage of being reactive with water. Furthermore, a product of the reaction with water is corrosive HCl. This feature of chloroaluminates means that they must be handled with exclusion of moisture-laden atmosphere, usually in a glove box. This is not a major problem for the use of chloroaluminate ionic liquids in high-energy batteries, since such batteries are sealed from atmospheric contamination due to highly reactive electroactive ingredients. In 1990 Professor Mike Zaworotko (Fig. 12) took a sabbatical leave from St. Mary's University in Halifax. That year spent at

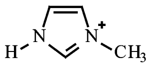
Fig. 12 Professor Michael Zaworotko of St. Mary's University, Halifax, Nova Scotia (now at the University of South Florida). Photo was taken in 1990 at the Air Force Academy.

the Air Force Academy introduced a new dimension to the growing field of ionic liquid solvents and electrolytes. His goal for that year was to prepare and characterize salts with dialkylimidazolium cations, but with water-stable anions. This was such an obviously useful idea that we marveled that nobody had tried to do this already. The preparation chemistry turned out to about as easy as the formation of the chloroaluminate salts, and could be done outside of the glove box. The new tetrafluoroborate, hexafluorophosphate, nitrate, sulfate and acetate salts, **15–19**, were first prepared by metathesis reactions of the dialkylimidazolium halide with the appropriate silver salt. They were stable (at least at room temperature) towards hydrolysis. [25] We thought of these salts as candidates for battery electrolytes, but they (and other similar salts) have proven more useful for other applications.



BF_4^-, PF_6^-, NO_3^-, CH_3COO^-, SO_4^{2-}
15 **16** **17** **18** **19**

One feature that we noticed about some of the crystallized ionic liquids (we did X-ray diffraction only on the salts that were solid at room temperature) was that some crystallized in non-centrosymmetric space groups. That implied that the salts might exhibit second order nonlinear optical properties. In a fortunate turn of events Joan Fuller (Fig. 13) came to the Air Force Academy just as Mike Zaworotko departed, and she spent several years extending the catalogue of water stable ionic liquids, discovering better ways to prepare them, and testing the solids for nonlinear optical properties. She made a large number of ionic liquids from the traditional dialkylimidazolium cations, plus a series of mono- and trialkylimidazoliums, **20–24**. She combined those cations with the water stable anions mentioned above (**15–19**) plus the additional series of mostly larger anions, **25–32**. This resulted in a huge array of new ionic liquids with anion sizes ranging from relatively small to very large. Some of these were published, [26] but many not.



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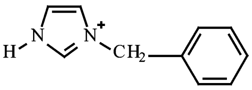

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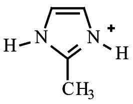

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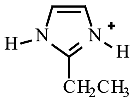

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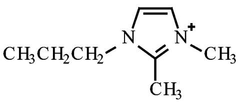

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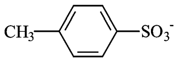
Br^- CN^- HSO_4^- IO_3^- $CF_3SO_3^-$
25 **26** **27** **28** **29**



$PhPO_3^-$ $^-O_2CCH(OH)CH(OH)CO_2^-$
30 **31** **32**

We never did lose sight of the potential usefulness of ionic liquids as battery electrolytes. In 1992 Richard Carlin took over leadership of the ionic liquids group at the Air Force Academy. (I remained nearby, but in a management position). Others in the group at that time were Joan Fuller (Fig. 13), Hugh DeLong and Paul Trulove (Fig. 14); all of who have continued to work in the ionic liquids field. Carlin and I had collaborated on the issue of reversible lithium deposition in the chloroaluminate ionic liquids while he was at the University of Alabama. This is obviously a topic of great interest for battery applications, because of the high energy density of the lithium electrode. On the face of it, one would not expect Li(I) to be reducible to Li metal in an electrolyte that contains Al(III), especially where the Al(III) is in very high concentration as the solvent and supporting electrolyte. Nevertheless, we found that when the ionic liquid is buffered at the Lewis neutrality point,[27] then Li (and even Na) could be electrodeposited.[28]

Lithium batteries with metallic lithium electrodes can store huge amounts of energy, but large sized batteries have fallen into disfavour due to the hazards involved with elemental Li and the difficulty in making a rechargeable cell. Lithium-ion rechargeable batteries are now the commercial favorites, although the military still uses metallic Li cells extensively. In Li-ion cells, the lithium is intercalated in a carbon matrix during the charging process, and then released by the de-intercalation followed by transport through a Li^+-conducting electrolyte to be intercalated in a chalcogenide matrix. Carlin and coworkers devised a similar battery cell where the component cations and anions of an ionic liquid are intercalated and deintercalated in carbon during charging and discharging. This dual intercalating molten electrolyte (DIME) battery concept uses the ionic liquid both as electrolyte and energy-storing electrode material.[29]

Fig. 13 Dr Joan Fuller as a University of Alabama graduate student pursuing her thesis research at the Air Force Academy in this *ca.* 1992 photo.

Fig. 14 Major (Dr) Hugh DeLong (upper), Dr Richard Carlin (middle), Lieutenant Colonel (Dr) Paul Trulove (lower). Photo was taken at a Gordon Research Conference in the mid 1990s.

Conclusion

This is a good place to stop the description of this particular line in the history of ionic liquids. The events recounted above take us to 1994. There are materials, events, processes, and most importantly people that were players in the history that I regret to have left out. This history is mainly from the point of view of events and people at the Air Force Academy, but progress in ionic liquids involved important contributions from many others. A partial list of people not mentioned here include Gery Stafford and G. Pedro Smith in the US; Tom Welton and Brian Ellis in UK, Keith Johnson in Canada, Michael Grätzel and Pierre Boñote in Switzerland; Yves Chauvin and Helene Olivier-Bourbigou in France; D. R. MacFarlane in Australia; and Y. Ito, N. Koura, and S. Takahashi in Japan. Since the Green Chemistry concept has caused an increased interest in ionic liquids, many other talented and productive researchers have entered the field. Their contributions will be in the next chapter on the impact of ionic liquids in Green Chemistry, to be written over the next few years.

Acknowledgements

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On the solubilization of water with ethanol in hydrophobic hexafluorophosphate ionic liquids

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The solubility of water in the hydrophobic 1-alkyl-3-methylimidazolium hexafluorophosphate (alkyl = butyl, hexyl, and octyl) ionic liquids, can be significantly increased in the presence of ethanol as a co-solute. 1-Hexyl-3-methylimidazolium hexafluorophosphate and 1-octyl-3-methylimidazolium hexafluorophosphate are completely miscible with ethanol, and immiscible with water, whereas 1-butyl-3-methylimidazolium hexafluorophosphate is totally miscible with aqueous ethanol only between 0.5–0.9 mole fraction ethanol at 25 °C. At higher and lower mole fraction of ethanol, the aqueous and IL components are only partially miscible and a biphasic system is obtained upon mixing equal volumes of the IL and aqueous ethanol. The observation of a large range of total miscibility between water and the IL in the three-component system has important implications for purifications and separations from IL.

*Dr Robin D. Rogers was born in Ft. Lauderdale, FL in 1957 and moved to Alabama in 1960. He obtained both his B.S. in Chemistry (1978, Summa Cum Laude) and his Ph.D. in Chemistry (1982) at The University of Alabama and is currently a Professor of Chemistry and Director of the Center for Green Manufacturing at UA. Dr Rogers' first faculty position was at Northern Illinois University (1982) where he was promoted through the ranks to full professor in 1994 and Presidential Research Professor in 1995. During this time, he worked closely with Argonne National Laboratory and was a faculty appointee there from 1993 to 1998. In 1996, he left Illinois to return to a full professorship at his alma mater. In 1998, he became the Director for The University of Alabama's Center for Green Manufacturing. Rogers holds three patents and has published over 480 papers on a diverse array of topics including structural chemistry, green separation science and technology, room temperature 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 has had an influential role in the expansion of interest and research in ionic liquid systems, his initial paper on ionic liquid/aqueous partitioning (*Chem. Commun.*, 1998, 1765) effectively kick-started interest in applying ionic liquids to clean separations. He has co-organized NATO ARW, and ACS symposia on Industrial Applications of Ionic Liquids. Rogers was the Editor of* Journal of Chemical Crystallography*, one of the Founding Editors of* Crystal Engineering*, and an Associate Editor for* Separation Science and Technology*. Recently Rogers was named Editor-in-Chief of the new ACS journal* Crystal Growth & Design *and serves on the Editorial Board of the ACS journal* Industrial and Engineering Chemistry Research.

Robin D. Rogers' Group at the University of Alabama

Green Context

Ionic liquids (IL) are among the most widely studied alternative solvents but much work remains to be done to achieve a better understanding of their physical properties. In particular, the solubility of different molecules in IL and the effects of co-solvents on these solubilities is critical both to their use as reaction media and to other possible applications including their use as azeotrope-breaking compounds for extractive distillation. In this paper it is shown that while various PF_6^- IL are only sparingly miscible with water, the addition of ethanol can significantly increase the water solubility and even lead to monophasic systems. The observation of regions of total miscibility in the three-component water–EtOH–IL system has important implications for purification and separations from IL.

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Introduction

Ionic liquids (IL) have been widely studied as solvents for electrochemical technologies[1–4] and most recently as clean, environmentally benign solvents for industrial chemical synthesis[5–8] and extraction processes[9–12] in Green Chemistry.[13–16] IL typically comprise of an organic cation and a weakly coordinating anion,[5] with the currently accepted general definition that ionic liquids (IL) exhibit no measurable vapor pressure and melt at, or below 100–150 °C.[16,17] We have examined the role of IL as replacements for volatile organic compounds (VOCs) in liquid/liquid separations,[18–20] particularly in aqueous–organic systems for extraction and purification applications. From the 'green' perspective, efficient separation and recovery of products from reaction systems, as well as the potential to recycle and reuse the reaction/separations media without generating secondary waste is of primary importance. For an IL based process, this can include the removal of reagents and products from the IL using clean extraction processes (for example, sc-CO_2 stripping, distillation, pervaporation) and also recovery and cleaning of IL from reaction vessels, columns and supports, *etc*.

Liquid/liquid separation processes operate on the basis that 'like dissolves like'. In a typical organic–aqueous two-phase extraction process, the less water-soluble the solute, the higher its affinity for the hydrophobic extracting (organic) phase. We have reported that organic solute partitioning in IL–water systems[9] shows a general correlation with the 1-octanol/water partition coefficient of the solute; more hydrophobic species tend to partition to the IL phase, whereas hydrophilic solutes remain in the aqueous phase. In these systems, the partitioning of ionizable solutes can be reversed according to the pH of the aqueous phase.[17]

Solvatochromatic studies[21–24] have shown that IL appear to have solvent characteristics similar to moderately polar organic solvents and have been compared to various alcohols and dipolar aprotic solvents. However, there are some inherent differences between IL and other solvents.[25] The solvent parameters determined for IL can vary significantly depending on the experimental probe used, and depend on the contributions from specific interactions between IL and solutes. Volume and hydrogen-bond acceptor terms appear to be most important to the overall solvating environment. In light of this, it is important to note that the hexafluorophosphate anion is a poor hydrogen-bond acceptor and consequently ethanol and water should not partition to the IL.

The solubility of tetrafluoroborate containing IL in water has been studied;[26,27] with increasing alkyl-chain length, the ionic liquids change from water miscible (hydrophilic) to immiscible (hydrophobic). In particular, Dullius *et al.*[27] have examined the variation in miscibility with temperature, showing that the miscibility curve is typical of a partially miscible two-component system and have identified the upper critical temperature for complete water/IL miscibility for $[C_4mim][BF_4]$. With increasing alkyl-chain length on the cation, the solubility of water in IL decreases irrespective of the anion present.

IL containing the hexafluorophosphate anion are commonly regarded as hydrophobic. The water content of saturated $[C_4mim][PF_6]$ has been variously reported as ranging from 1.2–2.3 wt %,[10,25,28,29] corresponding to a mole fraction between 0.16–0.27. For the IL samples used in this study, the water content of water-equilibrated $[C_4mim][PF_6]$ was found to be 1.2 wt% by Karl-Fischer titration. Spectroscopic studies have also identified the presence of the IL cation and anion at low concentrations in the aqueous phase. Friberg *et al.*[30] have studied the phase behavior of $[C_4mim][PF_6]$–water–nonionic surfactant mixtures and have highlighted the complexity of the co-miscibility/solvation profile in these systems and also noted that the IL exhibited only partial miscibility with hydrated ethanol.

Even in simplistic terms, an understanding of multi-component systems is fundamental to two-phase extraction processes, in order to determine the partitioning of the extracted component. Similarly, in practice, an aqueous component is almost always present in IL so that it is important to distinguish between the behavior of rigorously dried, ultra pure systems, and those that have been allowed to equilibrate with the local environment.[24,25] Specific interactions or a strong affinity of the IL for individual components within a mixture, for example as highlighted in our previous partitioning studies, could be used advantageously in order to facilitate differential separations. Of particular interest is the potential to use IL as an azeotrope-breaking component for extractive distillation in an analogous manner to the use of traditional inorganic salts.[31] There may be significant energy savings to be gained by adding the azeotrope breaker as a liquid salt rather than as a solid, which has to be dissolved. Moreover, azeotrope breaking occurs through selective interactions between the salt and one component of the mixture; IL compositions can be readily modified and may offer the flexibility to tune and optimize the separations processes.[18]

Initial observations, from partitioning studies, identified that $[C_4mim][PF_6]$ was completely miscible with aqueous ethanol between *ca.* 60–95 wt% ethanol, corresponding to 0.5–0.8 mole fraction of ethanol (χ_{EtOH})[32] whereas the two-component mixtures (IL–water and IL–ethanol) show only partial miscibility. In this study, we have surveyed the distribution of ethanol and water to the IL phase in three-component systems containing water, ethanol and the hydrophobic IL, $[C_4mim][PF_6]$, $[C_6mim][PF_6]$ and $[C_8mim][PF_6]$

Results and discussion

The hydrophobic IL, $[C_4mim][PF_6]$, $[C_6mim][PF_6]$ and $[C_8mim][PF_6]$ form biphasic mixtures with water. In this investigation, water was found to be soluble in $[C_4mim][PF_6]$ up to 1.2 wt% H_2O at 25 °C, the solubility decreasing with increasing alkyl-chain length on the IL. For $[C_6mim][PF_6]$ the limit of solubility was found to be 0.92 wt% H_2O and for $[C_8mim][PF_6]$, 0.47 wt% H_2O, these values representing the intrinsic saturated water content of 'water-equilibrated' IL. In reports by other researchers[28,29] and ourselves[10,17,25] the saturation point for water in these IL of up to 1.9, 1.2 and 0.92 wt%, respectively, have been reported at ambient temperatures. These weight percentages represent water contents as high as 0.5 molar for $[C_4mim][PF_6]$ and the variation in reported results between different groups cannot (at this point) be fully rationalized, however one possibility for increased water saturation may be the presence of hydrophilic contaminants. As we will show in this contribution, the presence of ethanol drastically increases the solubility of water in the IL. Other water soluble co-solvents, or hydrophilic anions (for example F^-, PO_4^{3-}, derived from IL contamination or degradation) may also contribute to an increased hydrophilicity.

At 25 °C, $[C_6mim][PF_6]$ and $[C_8mim][PF_6]$ were found to be totally miscible with ethanol in all proportions. In contrast, $[C_4mim][PF_6]$ is only partially miscible with ethanol and forms a mixture containing two phases, one IL-rich and one ethanol-rich, between *ca.* 10–95 wt% IL in ethanol.[32] The solubility limit of absolute ethanol in the $[C_4mim][PF_6]$ system was determined to be 10.1 wt%. Thus, for $[C_6mim][PF_6]$ and $[C_8mim][PF_6]$, the three-component mixtures are comprised of two mutually immiscible components (IL and water), both of which are soluble in the third component, and for $[C_4mim][PF_6]$, a mixture containing two immiscible components (water and ethanol), both of which are only partially miscible with the IL.

Triangular phase diagrams

Ternary mixtures of ethanol and water with the hydrophobic IL, [C_4mim][PF_6], [C_6mim][PF_6] and [C_8mim][PF_6] were investigated in order to determine the range of miscibility of the phases. The ternary phase diagrams are shown in Fig. 1(a)–(c) as weight ratios of the three components and in Fig. 1(d)–(f) from the initial mole fraction of the three components. The IL, [C_4mim][PF_6], is partially miscible with both pure deionized water and with pure ethanol at 25 °C. Regions of biphasic coexistence extend along the [C_4mim][PF_6]–H_2O and [C_4mim][PF_6]–ethanol axes, respectively. The solubility limit of absolute ethanol in the IL was determined to be 10.1 wt% and the solubility of water was 1.2 wt% corresponding to mole fractions of 0.41 and 0.16, respectively. The region of complete miscibility of the three components (water, ethanol and [C_4mim][PF_6]) is shown between the two binodal curves and extends from the EtOH–H_2O axis. The weight fraction diagram (Fig. 1(a)) shows that the IL is essentially immiscible with water and that only *ca.* 10 wt% of ethanol will dissolve in [C_4mim][PF_6]. However, when contacted with aqueous ethanol, containing between *ca.* 50–90 wt% ethanol, the IL is completely miscible.

The phase diagrams constructed for [C_6mim][PF_6] and [C_8mim][PF_6] with ethanol–water (shown as Fig. 1(b) and (c)) display a profile typical for three-component systems comprised of two miscible components, and one immiscible component. A monophasic domain extends along the two axes of co-miscibility (ethanol–water and ethanol–IL). The miscibility range of ethanol with the IL increases with increasing chain length. The presence of ethanol in the IL increases the miscibility of water, and a monophasic system can be obtained

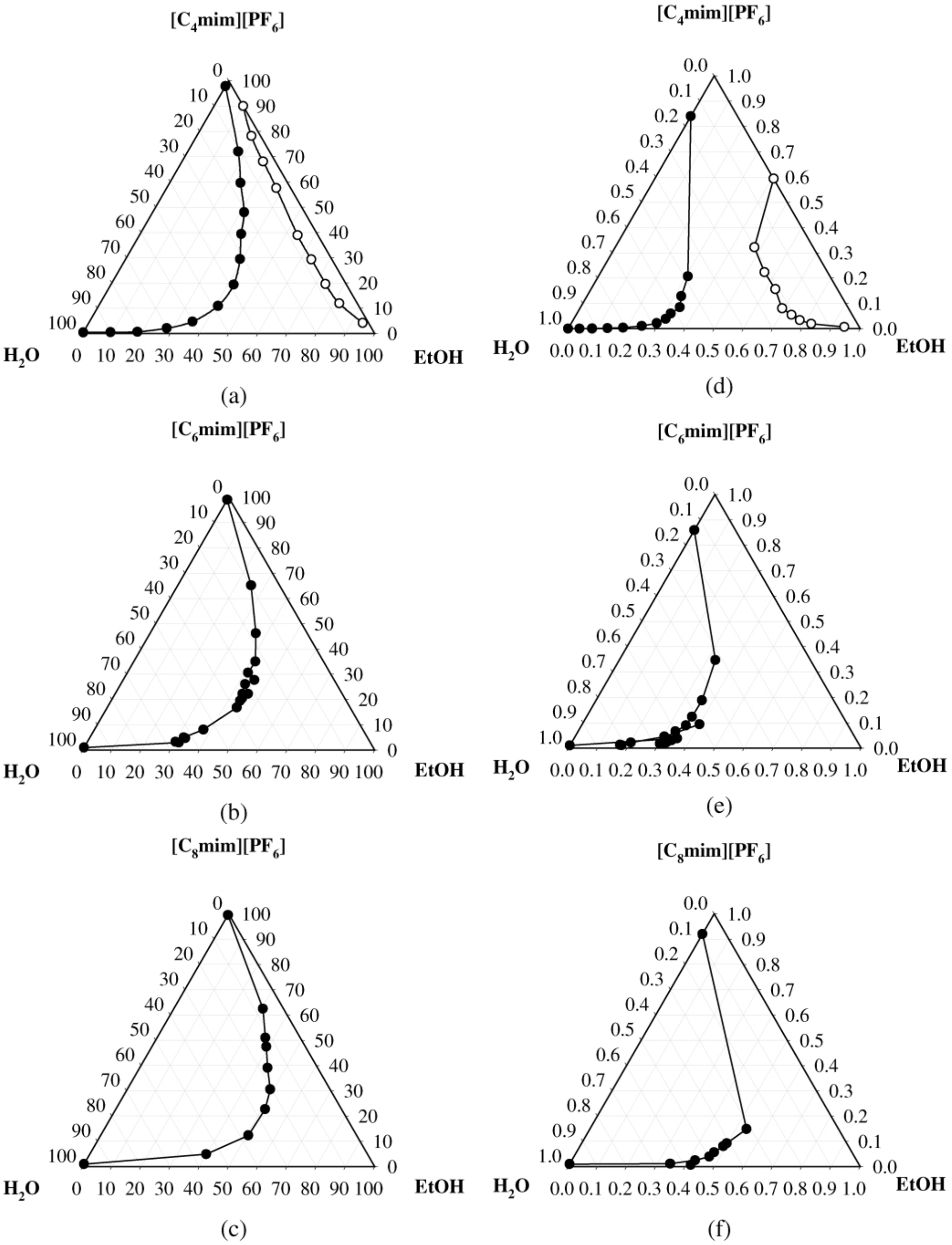

Fig. 1 Triangular phase diagrams for ternary compositions of [C_4mim][PF_6], [C_6mim][PF_6] and [C_8mim][PF_6] with ethanol and water plotted as initial wt% (1(a)–(c), left) and as mole fraction (1(d)–(f), right), respectively, determined at 25 °C. The region to the left of (●) is biphasic with water-rich and IL-rich phases; the region to the right of (○) is biphasic with ethanol-rich and IL-rich phases. The region extending from the ethanol-water axis to the IL apex is the monophasic composition containing all three components.

containing a large water component. With the increasing addition of water, a biphasic system containing IL-rich and aqueous-rich phases is produced. The biphasic region extends along the water–IL axis, and increases in area with increasing hydrophobicity of the ionic liquid, with the monophasic domain becoming less stable, the critical point moving to higher wt% ethanol.

The low miscibility of ethanol in [C$_4$mim][PF$_6$] appears to be anomalous, and that for all three IL systems, the miscibility of the IL with water can be significantly increased by the addition of a third component, in this case, ethanol. For example, in all three systems, a 1 : 1 : 1 mixture of the three components is completely miscible.

Distribution studies

To study the partitioning of ethanol and water to the IL in the biphasic systems, the distribution of ^{14}C-labeled ethanol in the IL and alcohol–water solution was determined[25] for a series of samples containing equal initial volumes of IL and aqueous ethanol. The distribution of ethanol between the IL and aqueous phases (D_{EtOH}), is given by the ratio of counts in the lower IL phase divided by the counts in the upper aqueous phases. The water content of the IL phase was determined by Karl-Fischer titration (results agree to within 10 ppm) in parallel experiments performed without addition of the radiotracer; results are given in Table 1 and shown graphically in Fig. 2(a) and (b). The equivolume mixtures of IL and aqueous ethanol components represent compositions approximately along the 60 wt% IL contour in the triangular phase diagrams (Fig. 1(a)–(c)). Equivolume experiments are comparable to those used for direct determination of distribution ratios by monitoring the activity of equal volumes of the two phases at equilibrium in other biphase systems.

In each of the three systems, the ethanol distribution (Fig. 2(a)), and wt% of water in the IL phase (Fig. 2(b)) increase with increasing ethanol mole fraction (χ_{EtOH}) in the initial aqueous phase in the biphasic regions from χ_{EtOH} = 0–0.5. For a given ethanol mole fraction, the distribution of ethanol and water content in the IL phase is greatest for [C$_4$mim][PF$_6$] and decreases with increasing cation size. As shown, from the triangular phase diagram, for [C$_4$mim][PF$_6$] between 0.5–0.9 mole fraction ethanol, the three components are totally miscible, forming a monophasic domain. For [C$_6$mim][PF$_6$] and [C$_8$mim][PF$_6$], the monophase boundary is approached when the ethanol:water mole fraction is 0.55 and 0.65, respectively. For each IL system, in the biphasic regions, the distribution of ethanol to the IL phase is less than 1, which indicates the preference of ethanol for the aqueous phase. The distribution ratios decrease with increasing alkyl-chain length on the IL cation, which corresponds to increasing lipophilicity and decreasing solvent polarity of the IL.

The initial distribution ratio for the ethanol tracer between [C$_4$mim][PF$_6$] and water is 0.16; this represents the distribution of ethanol at vanishingly small concentrations. Both the D_{EtOH} and water content increase linearly with χ_{EtOH} from 0–0.40, where a sharp rise in both is maintained until the miscibility region. At χ_{EtOH} = 0.90 a biphasic region is again observed and D_{EtOH} and water content decrease with addition of ethanol. Successive increases in the mole fraction of ethanol cause an increase in ethanol distribution ratios up to a maximum of 0.61 at 0.5 mole fraction of ethanol in water indicating the increase in ethanol partitioning to the IL phase. Between 0.4–0.5 mole fraction, the distribution of ethanol to [C$_4$mim][PF$_6$] and the water content of the IL increase dramatically, and between 0.5–0.9 mole fraction the system becomes monophasic, shown by the vertical lines in Fig. 2. Above 0.9 mole fraction, the system becomes biphasic again, thus allowing the measurement of the distribution ratios.

The distribution coefficient, D_{EtOH}, for ethanol to the IL is greatest for [C$_4$mim][PF$_6$] and decreases with increasing alkyl-chain length, but for all three IL the values are similar and are less than 1. This indicates that ethanol has a preference for the aqueous phase over the IL, an unsurprising observation considering that ethanol is hydrophilic and totally miscible with water whereas the IL are hydrophobic. Ethanol is more readily miscible with the more hydrophobic IL ([C$_6$mim][PF$_6$] and [C$_8$mim][PF$_6$]) as seen from complete miscibility along the EtOH–IL axis. The miscibility with [C$_4$mim][PF$_6$] increases with increasing temperature, an upper critical temperature for the 1 : 1 volume ethanol : IL biphasic–monophasic transition can be observed at approximately 55 °C;[33] above this temperature ethanol and [C$_4$mim][PF$_6$] are totally miscible. On cooling a monophasic 1 : 1 volume mixture of ethanol and [C$_6$mim][PF$_6$], the solution separates into a biphasic composition below room temperature at 17 °C. With [C$_8$mim][PF$_6$], a critical point was not found after cooling the monophasic solution to −10 °C in a freezer. On increasing alkyl-chain length from 4 to 8, miscibility of the IL with water decreases and miscibility with ethanol increases.

Co-solubility of water in the IL phase of the biphasic compositions increases with increasing mole fraction of ethanol. Fig. 2(b) for wt% water in the IL phase essentially mirrors the profile for D_{EtOH} in Fig. 2(a), this indicates the co-miscibility of the three components at high ethanol composition (towards the lower right corner of the phase diagrams in Fig. 1).

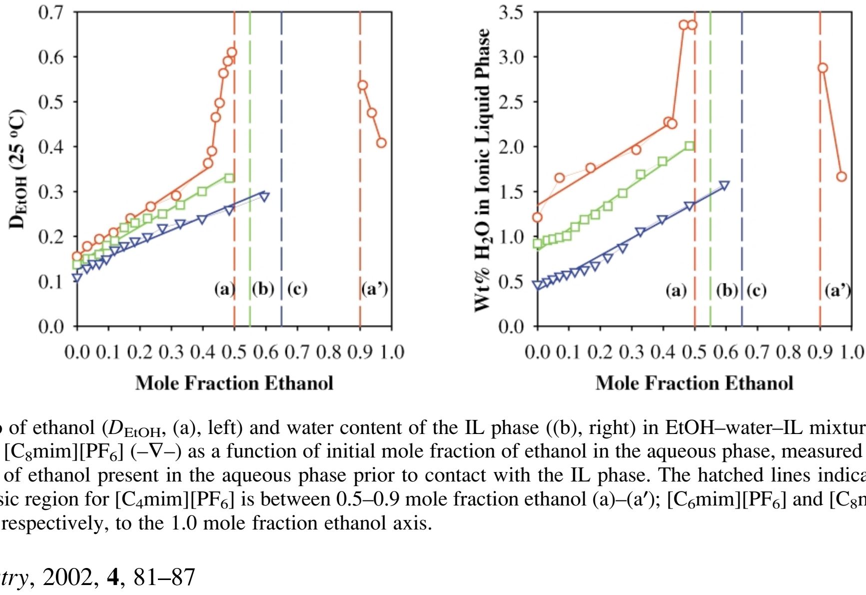

Fig. 2 Distribution ratio of ethanol (D_{EtOH}, (a), left) and water content of the IL phase ((b), right) in EtOH–water–IL mixtures for [C$_4$mim][PF$_6$] (–○–), [C$_6$mim][PF$_6$] (–□–) and [C$_8$mim][PF$_6$] (–∇–) as a function of initial mole fraction of ethanol in the aqueous phase, measured at 25 °C. The mole fraction ratios are for the amount of ethanol present in the aqueous phase prior to contact with the IL phase. The hatched lines indicate the biphasic–monophase boundaries, the monophasic region for [C$_4$mim][PF$_6$] is between 0.5–0.9 mole fraction ethanol (a)–(a′); [C$_6$mim][PF$_6$] and [C$_8$mim][PF$_6$] have monophasic regions from (b) and (c), respectively, to the 1.0 mole fraction ethanol axis.

Table 1 Distribution ratios for ethanol (D_{EtOH}) from an aqueous ethanolic solution to the IL [C$_4$mim][PF$_6$], [C$_6$mim][PF$_6$] or [C$_8$mim][PF$_6$], and water content of the IL phase on contacting with the aqueous phase compared to the initial composition of the aqueous phase, used to plot Fig. 2(a) and (b).

[C$_4$mim][PF$_6$]				[C$_6$mim][PF$_6$]				[C$_8$mim][PF$_6$]			
Initial wt% EtOH	χ_{EtOH}	D_{EtOH}	Wt% H$_2$O in IL layer	Initial wt% EtOH	χ_{EtOH}	D_{EtOH}	Wt% H$_2$O in IL layer	Initial wt% EtOH	χ_{EtOH}	D_{EtOH}	Wt% H$_2$O in IL layer
0.0	0.0	0.16	1.21	0.0	0.0	0.14	0.92	0.0	0.0	0.11	0.47
8.0	0.03	0.18		7.7	0.03	0.15	0.96	7.7	0.03	0.13	0.50
16.4	0.07	0.19	1.65	11.8	0.05	0.15	0.97	11.8	0.05	0.14	0.53
25.1	0.12	0.21		16.2	0.07	0.16	0.99	16.2	0.07	0.14	0.56
34.3	0.17	0.24	1.76	20.8	0.10	0.18	1.01	20.8	0.09	0.15	0.58
44.0	0.24	0.27		25.7	0.12	0.19	1.10	25.7	0.12	0.17	0.61
54.0	0.32	0.29	1.96	31.0	0.15	0.22	1.19	31.0	0.15	0.18	0.63
64.7	0.42	0.36	2.27	36.5	0.18	0.23	1.24	36.5	0.18	0.19	0.68
65.7	0.43	0.39	2.25	42.4	0.22	0.24	1.34	42.4	0.22	0.2	0.77
66.8	0.44	0.46		48.7	0.27	0.25	1.48	48.7	0.27	0.22	0.88
67.9	0.45	0.50		55.5	0.33	0.27	1.69	55.5	0.33	0.23	1.06
69.1	0.47	0.56	3.35	62.8	0.40	0.3	1.84	62.8	0.40	0.24	1.2
70.2	0.48	0.59		70.6	0.48	0.33	2.01	70.6	0.48	0.26	1.35
71.3	0.49	0.61	3.35					79.0	0.60	0.29	1.58
96.2	0.91	0.57	2.87								
97.5	0.94	0.48									
98.7	0.97	0.41	1.66								

The higher affinity of ethanol for [C$_4$mim][PF$_6$], combined with only limited miscibility, enhanced by the presence of water (to 1 : 1 mole fraction ethanol : water) seems to indicate that water and ethanol are solubilized together in the IL as an ethanol–water composite (hydrated ethanol). The structure and association in ethanol–water mixtures has been extensively studied[34] and it is generally accepted that at low mole fraction of ethanol ($\chi_{EtOH} < 0.2$), ethanol molecules cluster with the ethyl chains forming a hydrophobic core surrounded by water molecules in order to minimize hydrophobic-hydrophilic interactions. Between $0.2 < \chi_{EtOH} < 0.8$, a sandwich-type cluster is formed containing extended chains of hydrogen-bonded ethanol and water. The effects of salts and other additives on the partitioning and association of ethanol–water mixtures has been examined.[35–38] The phase behavior of the three component systems is then probably due to a size/shape complimentarity between free-volume cavities or void space in the IL[29] with water/ethanol clusters. This gives rise to the increased solubility of ethanol and water together, in [C$_4$mim][PF$_6$], and in the longer chain analogs at lower temperatures. The interactions that could occur between the water–ethanol clusters and the IL which may lead to the total miscibility region is not yet clear, but may allow ethanol and water to be dissolved together, while maintaining bulk ethanol–water hydrogen-bonding structure with only weak interactions between the alkyl-groups of the IL and the hydrophobic ethyl-substituents of the water–ethanol chains. A detailed study of the liquid structure in the homogeneous region was beyond the scope of this paper, but warrants further investigation.

Vapor composition

A comparison of the vapor phase above the [C$_4$mim][PF$_6$]–water–ethanol mixtures was made with that from ethanol–water mixtures containing the same equivalent mole fraction by SPME/GC in order to identify whether changes in composition could be observed that may be associated with a specific selective IL–water or IL–ethanol interactions. The results, as a function of ethanol/water mole fraction in the liquid for IL–ethanol–water and ethanol–water compositions, are shown in Fig. 3. The gas phase distribution of water and ethanol in the gas phase is not influenced by dissolution in the IL. In both the biphasic region (< 0.5 mole fraction of ethanol in the aqueous component) and in the monophasic region ($0.5 < \chi_{EtOH} < 0.9$), the vapor phase composition above the IL sample and above aqueous ethanol are the same.

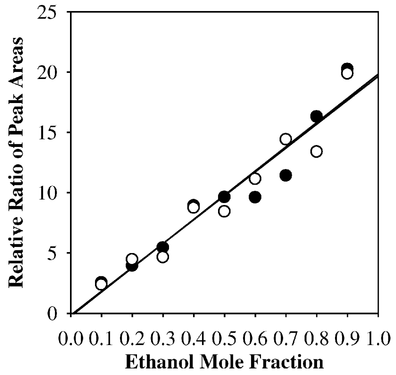

Fig. 3 Relative ethanol–water composition ratios in the vapor phase above ethanol–water (●) and ethanol–water–IL ternary compositions (○), determined from SPME/GC as a function of ethanol–water composition. Independent linear regressions of the two data sets give the same fit, shown by the solid line.

This indicates that for the [C$_4$mim][PF$_6$]–water–ethanol system, the formation of the monophasic regime occurs without a change in the vapor phase composition above the system. Similarly, the vapor composition from ethanol–water mixtures is not influenced by the addition of the IL, hence there appear to be no specific IL–ethanol or IL–water interactions in the system that are stronger than those between ethanol and water. This adds to our supposition that ethanol–water compositions solubilized in the IL are dissolved while maintaining intramolecular ethanol–water hydrogen-bonded structure. These results hint at complex underlying interactions in both phases. Of particular interest here, is the observation that biphasic separation of the components can be induced and controlled by changing position in the phase diagram.

There is a potential to change, and control the vapor phase composition above an IL through modification of the binding interactions between the IL and one, or more solutes. There are obvious applications here for separations processes to modify and improve distillation, evaporation and pervaporation process performance. In cases where the IL interacts much more strongly with one solute in a mixture, it might suggest that azeotropes could be broken and improved separations may be achieved. Indeed, it has been demonstrated that organic salts can be used as alternatives to inorganic salts to shift or break azeotropes,[39] and the choice of an IL azeotrope-breaker could have significant processing advantages over the use of solid, inorganic salts.

Conclusions

The hydrophobic IL [C$_4$mim][PF$_6$], [C$_6$mim][PF$_6$] and [C$_8$mim][PF$_6$] are only sparingly miscible with water. The addition of ethanol to biphasic IL-water mixtures increases the solubility of water (and ethanol) in the IL phase, and leads to monophasic systems where the IL, water and ethanol are totally miscible. The IL, [C$_6$mim][PF$_6$] and [C$_8$mim][PF$_6$], are totally miscible with ethanol in all proportions at 25 °C, whereas [C$_4$mim][PF$_6$] is only partially miscible with pure ethanol and forms a biphasic system between 10–95 wt% ethanol in IL. All three IL display partial miscibility with ethanol below the critical temperature, which is *ca.* 55 °C for [C$_4$mim][PF$_6$] and below 25 °C for [C$_6$mim][PF$_6$] and [C$_8$mim][PF$_6$].

The observation of regions of total miscibility in the three-component system containing water and hydrophobic IL has important implications for purification and separations from IL. In this study, we have shown the solubility of water in nominally hydrophobic IL can be drastically increased by the addition of a co-solute, in this case, ethanol. The presence of even small concentrations of water present in the IL may account for the variations in reported rheological properties of the IL. As shown here, the addition of a solute or combination of solutes dramatically affects the solution behavior of IL, highlighting the need to fully understand these systems and instances in which their solution chemistry may vary from that of traditional organic solvents. On a practical note, the results have importance in separations and reactions involving aqueous/IL two-phase systems where careful control of reagent and product concentrations may be needed to prevent homogenization, or in cleaning and recovery of IL from a reaction vessel or column without using volatile chlorinated organic solvents, by stripping out the IL with 50% aqueous ethanol, followed by dilution to phase shift to the biphasic region.

Experimental

HPF$_6$ was supplied by Ozark Fluorine Specialities (Tulsa, OK) and was used as received. All other reagents were at least 99% pure and were used as received from Aldrich (Milwaukee, WI). All aqueous solutions were prepared with deionized water that was purified with a Barnsted deionization system (Dubuque, IA) and polished to 18.3 MΩ cm. Ethanol partitioning experiments were performed using ^{14}C-labeled ethanol obtained from Sigma (St. Louis, MO) and analyzed using Ultima Gold scintillation cocktail (Packard Instrument, Downers Grove, IL).

The water content of each IL or its mixtures was determined by Karl-Fischer titration using a volumetric Aquastar Karl Fischer titrator (EM Science, Gibbstown, NJ) with Composite 5 solution as the titrant and anhydrous methanol as the solvent. Duplicate measurements were performed on each sample with results agreeing to within 5%. All measurements were made at 25 °C.

The IL, [C$_4$mim][PF$_6$], [C$_6$mim][PF$_6$] and [C$_8$mim][PF$_6$] were synthesized using previously published methods,[25] and were obtained as colorless liquids, dried *in vacuo* and characterized by ^{1}H/^{13}C NMR and UV–visible spectroscopy. Contacting samples of the IL with a dilute aqueous silver nitrate solution did not lead to clouding in the aqueous phase which would indicate the presence of chloride contamination. Samples were equilibrated with water prior to use by contacting with deionized water.

Initial ethanol–IL–water ternary phase diagrams were determined by direct observation of samples prepared with known composition.[40] Samples containing known ethanol/water weight composition were added to accurately measured samples of water-equilibrated [C$_n$mim][PF$_6$]. The mixtures were vortexed (2 min) followed by centrifuging (2 min) and the compositions were observed for clarity and turbidity (on the basis of previous work with these biphasic systems, the time allotted for vortexing and centrifuging was assumed to be sufficient to reach equilibrium). Additional points were then added to the phase diagram by cloud-point titration of samples containing known water–IL compositions with ethanol, and known ethanol–IL compositions with water.

Ethanol distribution ratios to the IL were determined by mixing 1 mL of IL and 1 mL of an aqueous phase followed by vortexing (2 min) and centrifuging (2000g, 2 min) to equilibrate the phases. Addition of the ^{14}C-ethanol tracer (*ca.* 0.005 μCi, 5 μL) was followed by two intervals of vortexing (2 min) and centrifuging (2000g, 2 min) to ensure that the phases were fully equilibrated and separated. Each tube was uncapped and 100 μL of each phase was removed for radiometric analysis.

A Hewlett Packard (Palo Alto, CA) HPG1800A GCD series gas chromatograph with electron ionization detection was used for SPME/GC determinations. For each experiment, equal volumes of the IL and aqueous phase were dispensed into a 7 mL headspace vial, covered with a black Viton septa, and crimped to form a closed system. Each system was equilibrated at room temperature. A carboxen/polydimethylsiloxane fiber was used to adsorb the vapor phase and was allowed to equilibrate for 5 minutes. The fiber was then inserted into the GC injection port for desorption of the vapors. The column was a 30 m × 0.25 mm DB-5 siloxane column with helium (1 mL min^{-1}) as the carrier gas. The inlet temperature was 240 °C, detection temperature was 280 °C, and the oven temperature was 30 °C. Both ethanol and water eluted in under a minute and the peaks were cleanly separated. The relative composition ratios of ethanol and water in the vapor phase composition was determined by measuring the relative peak areas in the detector signal for the ethanol and water components.

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Immobilisation of ionic liquids on solid supports

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A short summary of possible methods for the preparation of immobilised ionic liquids (ILs) is presented. The differences in the resulting heterogeneous catalysts are discussed and examples for the use of these catalysts in organic reactions are given. The different immobilised ionic liquids can be classified by their interaction with the support material. As will be shown, the ILs can be bound to a surface either by covalent bonds between silanol groups and the anion or the cation of the liquid, or without covalent bonds in the form of supported liquid phases (SLPs). In a few cases, the catalysts are prepared without actually using an ionic liquid at any step. Strictly speaking, these materials are not immobilised ionic liquids, but they are included here since they contain ionic complexes which show strong similarities to ionic liquids. In Friedel–Crafts alkylation reactions some of the novel catalysts show catalytic activities which are among the best to be found in literature.

Introduction

Early publications on ionic liquids concentrated on chloroaluminate liquids and their properties as liquid, acidic catalysts.[1–6] While a few researchers followed up on this,[7–9] most publications today can be found to be about the solvent properties of various second and third generation ILs, often in two-phase reactions. Nevertheless, the replacement of aluminium chloride as a catalyst for, *e.g.*, Friedel–Crafts reactions is a subject of high economical and ecological interest.

The work presented here shows different possibilities for the preparation of heterogeneous, acidic catalysts, either prepared from or based on the example of Lewis-acidic ionic liquids. The concept of "immobilised" or "heterogenised" liquids is well-known from supported liquid phase (SLP) catalysts.[10] As is the case there, the immobilisation process aims to transfer the desired catalytic properties of the liquids to a solid catalyst. The term "immobilised (ionic) liquids" used for the resulting catalysts therefore refers to the preparation procedure.

Compared to other well-known acid catalysts, *e.g.* silica-alumina or zeolites, immobilised ILs have some advantages. The most important advantage may be the easily tuneable acidity, but the possibilities given by the choice of support material and its properties, such as surface area and pore width, should not be neglected. Furthermore, by changing the length of side-chains of the inorganic cation, the hydro-philicity or -phobicity of the surface can be enhanced. In comparison to the pure ionic liquids, immobilised ionic liquids offer the additional features that they facilitate recovery of the catalyst and can be used in gas phase reactions. A few examples of immobilised ionic liquids can be found in literature, but these are limited to the use of support materials impregnated with pre-formed ionic liquids as catalysts for the alkylation of butene with isobutane.[11,12] All of the further research on this subject was carried out by our group during the last four years.

Our main interest was the preparation of new Lewis-acid catalysts for Friedel–Crafts reactions, therefore we concentrated on the corresponding ionic liquids. To simplify the distinction between the different materials, we introduced the term "Novel Lewis-Acid Catalysts" (NLACs). This refers to acid catalysts containing ionic complexes where either anion or cation is bonded covalently to a solid support.

Results and discussion

The immobilisation of ionic liquids can be carried out in different ways. This results in materials which can be classified

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Green Context

The heterogenisation of catalysts and reagents can offer important advantages in handling and in separation and reuse thus lowering the risks and hazards of a chemical process, as well as simplifying the work up procedure and avoiding waste products, all in keeping with the principles of Green Chemistry. Ionic liquids are most commonly thought of in the context of alternative "greener" solvents but they can also be designed to offer high activity, for example as acidic catalysts. Here, novel Lewis acid catalysts based on immobilised chloroaluminate ionic liquids are described, which combine the advantages of the liquids catalytic activity and heterogenisation. Different methods for preparing these materials are described and compared and their uses as Friedel–Crafts catalysts studied. ***JHC***

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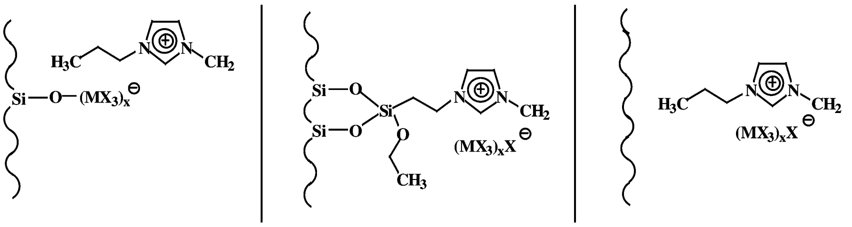


Scheme 1 Immobilisation of ionic liquids *via* the anion, the cation or as a supported liquid phase.

by the interaction between the ionic liquid or its components and the support material, as shown in Scheme 1.

Immobilisation *via* the anion: NLAC I

The easiest way for the preparation of an immobilised ionic liquid is the addition of a liquid to a solid support. In our group this was carried out by a method called "incipient wetness". This name generates from the experimental practice, where the ionic liquid is slowly added to the support material until the latter lost the appearance of a dry powder. Excess liquid was then removed by means of Soxhlet extraction. The material prepared by this method was denoted NLAC I.

The NLACs I were analysed by ICP-AES, CHN-analysis, XRD spectroscopy, DRIFT-IR and MAS NMR. Preferred carrier material was amorphous silica for the reasons of price and availability. Furthermore, it was found that it could contain chloroaluminate ionic liquids in comparatively high amounts, depending on the surface area of the silica. Table 1 shows a comparison of different support materials tested in the immobilisation of chloroaluminate ILs.

Analysis of the immobilised ILs by ^{29}Si MAS NMR showed the disappearance of Q^2 and Q^3 signals at −91 and −101 ppm. These signals are attributed to silicon atoms with one OR two, OH groups, respectively. We concluded, that during the immobilisation the formation of covalent bonds between the Lewis acid anions and silanol groups on the surface of the support takes place (see Scheme 2). This is further supported by the fact that HCl formation could be observed when adding ILs to the silica supports. Similar results were found for the immobilisation of $AlCl_3$ on silica as described in the literature.[13–15]

A drawback of this method was found when we tried to use structured support materials, such as zeolites or silica supports of the MCM family, as supports. As shown below for a 3A zeolite, the structure of the support is destroyed (see Fig. 1). This can be avoided by first impregnating the support material with aluminium chloride in a solvent with subsequent addition of an ionic liquid of low acidity. The highly acidic immobilised ionic liquid is then formed on the carrier by reaction between immobilised $AlCl_3$ and the ionic liquid.[16] Further examples for the destruction of zeolitic supports and a more detailed description of the two-step immobilisation developed to avoid this have been presented previously.[17,18]

Immobilisation *via* the cation: NLAC II

As described above, the immobilisation of ionic liquids by covalent bonds between the liquid's anions and silanol groups on the surface, while leading to acidic catalysts, has some disadvantages. The most important of these are the destruction of structured supports, the decrease of the IL's acidity, and, of course, the limitation to Lewis acid ionic liquids.

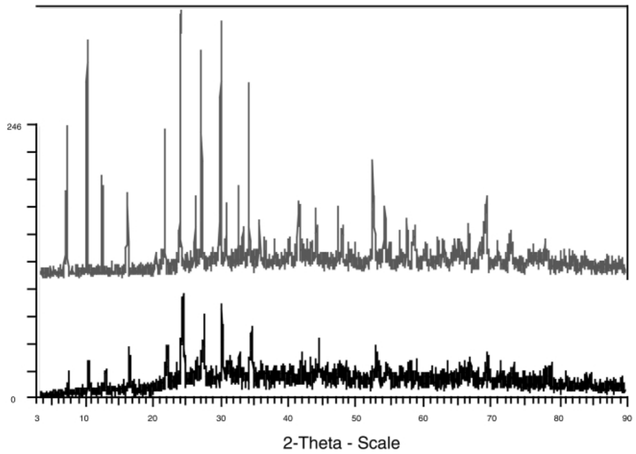


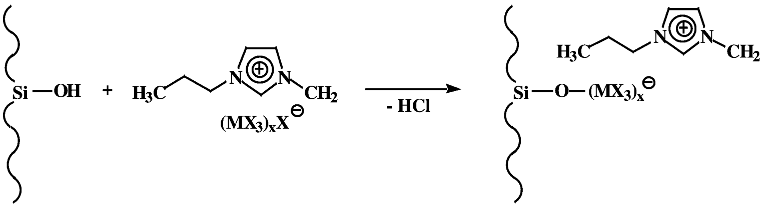
Fig. 1 XRD spectrum of a 3A zeolite before (top) and after (bottom) immobilisation of an chloroaluminate ionic liquid.

A way to avoid all of these problems was found in the new method described below. Instead of adding a pre-formed ionic liquid to a silica support material, in this method the organic halides which contain the cation of the ionic liquid are "grafted" to the surface of the support. In a second step the metal halide is added (see Scheme 3).

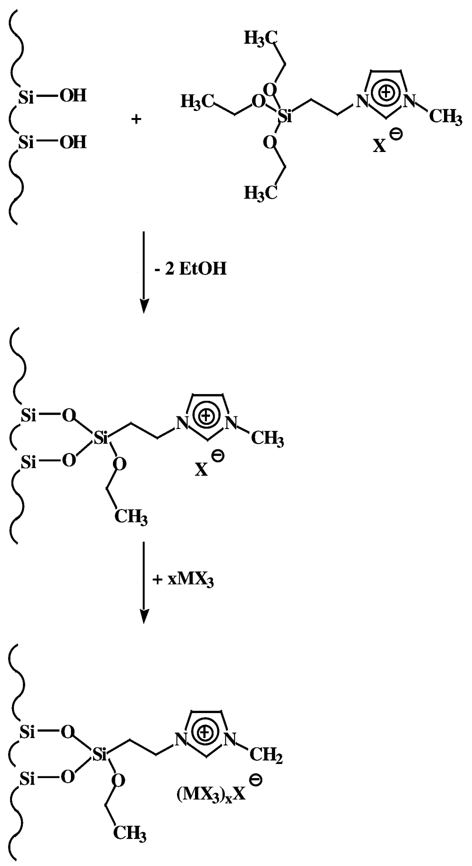
While the first step, the grafting of organic groups, is well-known from newer literature and was performed with organic bases previously,[19,20] this was the first time this method was used for the preparation of highly acidic ionic complexes. The

Table 1 wt% ionic liquid on different supports before and after extraction

Support	wt% IL before extraction	wt% IL after extraction
Nb_2O_5	22.1	0
TiO2	15.0	2.2
Na-Y	33.63	7.08
SiO_2, T350	38.9	11.9
SiO_2, D 11-10	64.6	15.9
SiO_2, HV 92/45	61.5	20.4
Pural SB	39.4	21.2
Al_2O_3, D 10-10	45.1	23.5
SiO_2, FK 700	78.8	35.4



Scheme 2 Immobilisation of ILs *via* the anion (incipient wetness method).



Scheme 3 Immobilisation *via* the cation (grafting method).

scheme of the grafting reaction shown below is simplified, as was shown by the group of Brunel and others in their research of these reactions.[21–24] We are well aware of the fact that the resulting solids are in fact not "immobilised ionic liquids", since ionic liquids do not participate in their synthesis, and therefore usually refer to these materials as "Novel Lewis-Acid Catalysts II" (NLACs II).

The new materials were examined by elemental analysis (ICP-AES and CHN), XRD, and MAS NMR after the grafting step and after addition of the $AlCl_3$. After reaction with aluminium chloride, ^{27}Al MAS NMR displays two sharp peaks (see Fig. 2).

The peak at −1.2 ppm, has been attributed to pure, unreacted, anhydrous $AlCl_3$ in keeping with Sato and Maciel,[15] while Xu *et al.* attributed the same peak to octahedrally coordinated Al.[25] A comparison with the ^{27}Al MAS NMR spectrum of the anhydrous $AlCl_3$ used in the reaction, which displayed a peak with the same shift and an identical distribution of spinning side bands, convinced us that Sato and Maciel's interpretation is correct. Of more interest is the peak at 102 ppm. The shift of this peak is identical with that of ^{27}Al MAS NMR spectra of pure chloroaluminate ILs. We considered this to be proof that a reaction between aluminium chloride and imidazolium chloride, corresponding to the formation of an ionic liquid, had taken place.

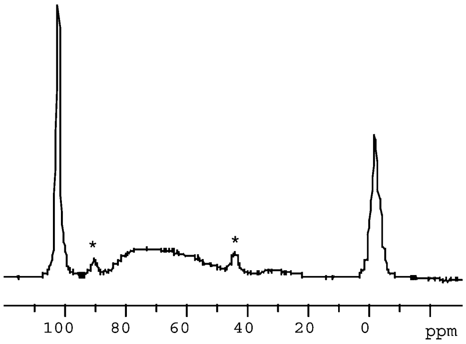


Fig. 2 ^{27}Al MAS NMR of a NLAC II. Asterisks mark spinning side bands.

Immobilisation *via* the cation: NLAC III

Alternatively, a support material containing the cationic groups can be prepared using the sol–gel method. Here, 1-(triethoxysilylpropyl)-3-methylimidazolium chloride is added to a mixture of a silicon source and a template from which a hexagonal mesoporous silica (HMS) is prepared. The resulting solid contains 1-propyl-3-methylimidazolium chloride groups bonded to surface silicon atoms. As with the NLACs II, addition of aluminium chloride leads to the formation of ionic complexes. These materials have been termed NLACs III (see Scheme 4).

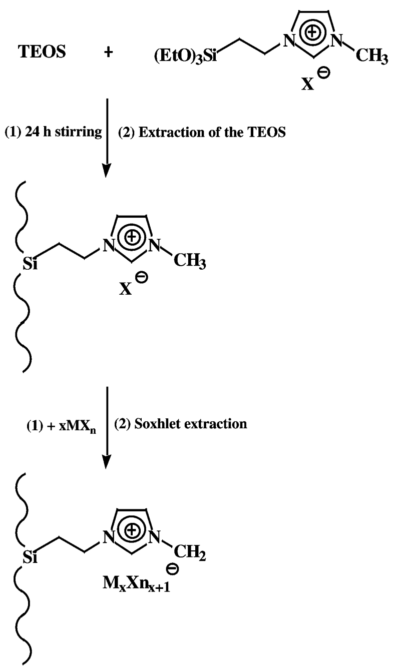
^{29}Si MAS NMR showed that the organically modified support contains a high number of Q^2 and Q^3 silanol groups. These can be expected to react with the $AlCl_3$ added in the second step, leading to less acidic chloroaluminate species. This was confirmed by ^{27}Al MAS NMR, which showed a close similarity to the corresponding spectrum of the NLAC I.

Alkylation reactions

The catalytic acticity of all NLACs in alkylation reactions was tested extensively. Selected examples are shown in Table 2.

All of the conversions presented here were calculated on the basis of the 1-alkene. Therefore, the isomerisation products of the 1-alkene were considered conversion as well. In this way, the isomerisation of the 1-alkene, which can be catalysed by weaker acids as well, can be observed and used to gain information on the acidity of the catalyst.

The low conversion found for the pure ionic liquids can be easily explained by the fact that under the reaction conditions chosen, the ionic liquid is nearly insoluble in benzene. Therefore, the reaction is actually a two-phase reaction. Optimisation of the reaction conditions, especially of the reactor, would be necessary to achieve a higher yield of



Scheme 4 Immobilisation *via* the cation (sol–gel method).

Table 2 Results for the alkylation of benzene with different olefins catalysed by NLACs; molar ratio benzene : olefin = 10 : 1

Catalyst	Olefin	T/°C	Time/h	Catalyst (wt%)	Olefin conversion (%)	Olefin isomers (%)	Sel. mono-alkylated (%)	Sel. heavier products (%)
Al-IL, pure	C_{12}=	80	1	6	4.5	86.7	13.3	0
SiO_2/NLAC I[a]	C_{12}=	80	1	6	99.4	0	99.7	0.3
SiO_2/NLAC II[b]	C_{12}=	80	1	6	92.3	22.3	76.2	1.5
MCM 41/NLAC II[b]	C_{12}=	80	1	6	100	12.6	85.6	1.8
MCM 41/NLAC III[c]	C_{12}=	80	1	6	74	17.8	82.2	0
SiO_2/NLAC I[a]	C_{12}=	20	1	1	10.9	7.7	89.9	2.3
SiO_2/NLAC II[b]	C_{12}=	20	1	1	46.8	7.6	90.7	1.8
MCM 41/NLAC II[2]	C_{12}=	20	1	1	92.9	0	92.3	7.7
SiO_2/NLAC I[a]	C_{12}=	20	2	1	35.2	19.7	80.3	0
SiO_2/NLAC I[a]	C_{10}=	20	2	1	34.1	7.1	89.6	3.3
SiO_2/NLAC I[a]	C_8=	20	2	1	44.9	0	96.5	3.5
SiO_2/NLAC I[a]	C_6=	20	2	1	45.3	0	73.8	26.2

[a] Incipient wetness method.[b] Grafted.[c] Sol–gel.

alkylation products. The NLAC I, on the other hand, displays a high catalytic activity at 100 °C. At 20 °C the conversion is strongly decreased, but the selectivity is still very high. Reactions using other olefins showed that the conversion increases with decreasing chain length. As Table 2 shows, the NLAC II is by far the most active catalyst. Even at room temperature complete conversion can be achieved within 1 hour, with very high selectivity to the preferred monoalkylated products. The NLAC III is far less active, as was predicted previously.

Experiments at different temperatures or molar ratios, and in various solvents led to results which correspond to those of similar reactions catalysed by pure $AlCl_3$ and will not be discussed here. The same was found for the distribution of product isomers, which is nearly identical to that of reactions catalysed by aluminium chloride, as has been reported previously.[26]

Supported liquid phase catalysts

In our search for a new, heterogeneous catalyst for the Friedel–Crafts acylation of various aromatic compounds, we found chloroferrate and chlorostannate ionic liquids (Fe-ILs and Sn-ILs) to have a far higher catalytic activity than the corresponding chloroaluminate ones (see Table 3)[27] In comparison to the chloroaluminate ILs, the Fe-ILs and Sn-ILs have a decreased Lewis-acidity and, in consequence, do not react with surface silanol groups of silica supports to the same extent. Therefore, silica-supported Fe- and Sn-ILs contain only up to 6 wt% of the catalytically active component and have a strong tendency towards leaching when used in liquid phase reactions. Since the iron chloride based ILs showed higher catalytic activity, the subsequent research concentrated on these.

Table 3 Results for the different acylation reactions catalysed by pure and immobilised ILs; 45 mmol aromatic compound/9 mmol acylating agent, catalyst amount: 0.2 mmol (pure ILs) or 100 mg (immobilised ILs)

Ionic liquid	Reaction	Conv. (%)	Sel. to main product (%)
Al-IL	Mesitylene + AcCl	68.05	98.08
	Anisole + Ac_2O	0.31	94.12
	m-Xylene + AcCl	3.52	96.35
	Toluene + AcCl	0	0
Sn-IL	Anisole + Ac_2O	2.48	90.41
	m-Xylene + AcCl	3.56	94.94
Fe-IL	Mesitylene + AcCl	94.74	94.9
	Anisole + Ac_2O	90.17	96.64
	m-Xylene + AcCl	33.80	79.39
	Toluene + AcCl	0.54	87.92
Fe-IL on MCM 41	Anisole + Ac_2O	6.54	100
	m-Xylene + AcCl	15.01	78.38
Fe-IL on charcoal	Anisole + Ac_2O	29.67	97.49
	m-Xylene + AcCl	18.39	76.00

The same leaching problems were observed when using activated charcoal as support material. In this case, no covalent bonds between ionic liquid and support can be formed, but the far higher surface area of the charcoal allows the immobilisation of correspondingly higher amounts of ionic liquids. As expected, using the resulting immobilised ionic liquids as catalysts for acylation reactions led to better conversions. The selectivity of the reaction was slightly decreased, but still in an acceptable range. Nevertheless, ICP-AES analysis of the product solution proved the presence of iron.

It was assumed that the leaching of these catalysts is caused by the formation of highly stable complexes between the metal halide anions and the aromatic compounds. The amount of leaching found by ICP-AES actually led to doubts regarding the reaction mechanism, since it could not be excluded that the reaction was catalysed exclusively by leached ionic liquid and therefore homogeneously. This was disproved when the reaction was carried out in the gas phase, where the catalysts led to a conversion in the range of 2–5% at a temperature of 250 °C and a WHSV of 1 h^{-1}.

Conclusion

In summary, it can be said that the Novel Lewis-Acid Catalysts (NLACs) presented here offer exciting new possibilities for the preparation of heterogeneous catalysts which contain many of the properties of ionic liquids. Work on this subject continues and is expected to deliver interesting new results.

The materials containing ionic liquids in form of a supported liquid phase are, due to the leaching of the active components, less suited for use in liquid phase reactions. Nevertheless, since they can be used in gas phase reactions, they might offer a cheap alternative to the NLACs for this special application.

Experimental

To ensure reaction conditions free of water, all experimental steps have to be carried out under an inert atmosphere. Prior to impregnation, the supports were calcined for 3 hours at 550 °C and stored under argon.

The imidazolium salts used for the preparation of the ionic liquids were kindly provided by Elementis Specialties, Durham. Aluminium and iron chloride were supplied by Merck AG. The silica support FK700 was kindly provided by Degussa-Hüls AG. 1-Methylimidazole, 3-chloropropyltriethoxysilane, diethyl ether, benzene, dodocene, undecane and dichloromethane were purchased from Fluka in 99% purity and used without further purification.

Preparation of the NLACs I

The immobilisation of the ionic liquids consisted in the addition of the AL-IL to the previously dried and calcined support (500 °C for 3 h and subsequently stored under argon) until its appearance changed from a dry to a wet powder. This supported ionic liquid was stirred overnight and the excess of AL-IL was extracted for 24 h with boiling dichloromethane in a Soxhlet extraction system. Conductivity measurements of the dichloromethane showed the extraction to be complete after 12 h at most, depending on the support used. The extracted catalyst was then dried under vacuum and stored in argon for its further use in the reaction.

Preparation of the NLACs II

The all-silica MCM-41 support was prepared according to the methods known from literature.[28,29] In a distillation apparatus, 3 g of the support were dispersed in dried toluene. After the addition of 1.5 g 1-(triethoxysilyl)propyl-3-methylimidazolium chloride the mixture was stirred at 90 °C for 16 h. In the following step, the solvent and the ethanol created in the grafting step were distilled off, the remaining solid dried under high vacuum and the excess of 1-(triethoxysilyl)propyl-3-methylimidazolium removed by 24 h extraction with boiling dichloromethane. The dried support was then added to a solution of 2 g $AlCl_3$ in toluene and left stirring for 3 hours at room temperature. After filtration, the excess of $AlCl_3$ was removed by extraction with boiling CH_2Cl_2 in an Soxhlet apparatus and the material was dried under reduced pressure.

Preparation of the NLACs III

In a solution of 50 ml ethanol and 50 ml H_2O 5.09 g of the template dodecylamine were dissolved. In a polypropylene autoclave TEOS and the organic triethoxysilyl compound were added separately but simultaneously to this solution. The solution was stirred for 18 h and then filtered. The template was removed from the remaining solid by a Soxhlet extraction with boiling ethanol.

The aluminium chloride was immobilised on the support materials as described for the NLACs II.

Preparation of the immobilised Fe-IL

In a round bottomed flask equipped with a magnetic stirrer and a gas inlet valve, an excess of ionic liquid was slowly added to the support. Either FK 700 amorphous silica, or granular activated charcoal supports were used. To ensure complete homogenisation, the mixture was left stirring overnight. The excess ionic liquid was removed by 24 h extraction with boiling dichloromethane in a Soxhlet apparatus. The catalyst was dried at 10 Pa and stored under argon.

Alkylation and acylation reactions

The batch reactor system consisted of a round-bottomed flask (slurry reactor) provided with a cooler, gas-inlet valve, and sampling exit. A magnetic stirrer equipped with a thermostat and a silicone oil bath were used to maintain the reaction temperature and ensure the homogeneity of reactants. The catalyst was weighed in the reactor and then the aromatic comound was added according to the proportion desired, followed by the addition of dodecene followed by acetyl chloride. Undecane was added as an internal standard to follow the reaction kinetics and to calculate the mass balance. Samples were taken periodically and analysed by gas chromatography in order to quantify conversion and selectivity of the reaction.

Reactions in the gas phase

The continuous gas phase reactor system consisted of a 1 m long coiled tube. The catalyst was introduced into the tube and stayed at the lower part. The reaction mixture was fed into the reactor and vaporised at the beginning of the tube. The reaction mixture was pumped by a peristaltic pump and a flow of dry nitrogen was used to carry the vaporised reactants through the reactor. The products were collected in a cooling trap from where samples were periodically withdrawn to follow the course of the reaction by GC.

Analytical methods

Solid state MAS-NMR measurements were carried out on a Bruker Avanza 500. X-Ray diffractometry (XRD) was performed on a D 5000 Instrument from Siemens, equipped with a copper tube FL Cu 4KE. FT-IR was performed on a Nicolet Protégé 460. For BET-measurements an ASAP 2000 machine from Micromeritics was used. The concentrations of Si and Al in the samples were determined by ICP-AES, using a Spectro-Flame D machine from Spectro. CHN analysis was performed on a Elementar Vario EL. GC analysis was done on a Siemens RGC 202, using a 30 m SE 54 column from Hewlett Packard.

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Epoxidation of electrophilic alkenes in ionic liquids

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A fast and efficient procedure is proposed for the epoxidation of electrophilic alkenes, the structures of which resemble the vitamin K class, in ionic liquids as solvents and using aqueous basic solutions of hydrogen peroxide as oxidant. Yields of epoxides ranging from very good to almost quantitative are observed for all the substrates analysed.

Introduction

Over recent years, one of the most imperative issue for chemists is the search of clean or green chemical transformations. In particular, waste minimisation/reduction is strongly recommended in order to achieve new attractive industrial processes. In general the use of volatile molecular solvents is one of the most significant sources of chemical waste in the fine chemicals and pharmaceuticals industry. Because of their peculiar properties ionic liquids (IL) have been proposed as novel and environmentally benign reaction media for organic synthesis. Selected examples include dimerization of alkenes,[1] Friedel–Craft reactions,[2] Diels–Alder cycloadditions,[3] hydrogenation reactions,[4] Heck C–C coupling reaction,[5] asymmetric epoxidation using chiral (salen)Mn complexes as catalysts[6] and bromination of double and triple bonds.[7] For an extensive collection of references, interested readers are referred to very recent reviews.[8–11]

It is of note that, with very few exceptions,[6,12–14] the exploitation of IL as solvents for oxidation reactions is still at an initial stage. A recent paper from Sheldon *et al.*[15] reports the epoxidation of cyclohexene in IL with a peracid formed through perhydrolysis carried out by *Candida antarctica* lipase. Yet, to the best of our knowledge, there are no references concerning the use of aqueous solutions of hydrogen peroxide as oxidants in the absence of metal catalysts.

Hydrogen peroxide has recently regained importance as an oxidant in both the industrial and academic community.[16] The main reasons are related to ‘regulatory forces causing the chemical industry to reduce, and in some instances eliminate, environmental pollution’, and to the fact that the chemical industry is now capable of employing H_2O_2 in a safer, more efficient and innovative manner.[16]

Here we present preliminary data on a fast and efficient procedure for epoxidation of electrophilic alkenes in ionic liquids as solvents by using an aqueous solution of hydrogen peroxide in the presence of base catalysis. With this procedure, which couples the use of a ‘green oxidant’ with ‘green solvents’, new routes for industrially appealing oxidations are envisaged.

Results and discussion

Epoxidation reactions were carried out at room temperature, or below, utilizing 1-butyl-3-methylimidazolium hexafluorophosphate [bmim][PF_6] (not miscible with water) and 1-butyl-

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Green Context

A combination of green techniques will often be required to effectively improve the environmental performance of chemical reactions. Here we see the successful combination of one of the newer and less environmentally threatening solvents with one of the safer and least wasteful oxidants. Epoxidations of electrophilic alkenes can be carried out using a mixture of an ionic liquid containing the substrate and aqueous hydrogen peroxide in the presence of a simple base such as sodium hydroxide. No competing hydrolysis reactions are observed and the products which are generally obtained in high yields with only small excesses of oxidant, are easily extracted using an immiscible solvents. *JHC*

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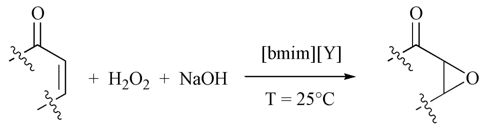
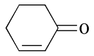
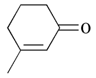
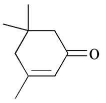
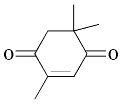
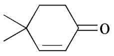
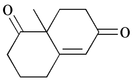
3-methylimidazolium tetrafluoroborate [bmim][BF_4], (hygroscopic) solvents. These ILs were chosen on the basis of their availability and stability in the presence of oxygen and water. All the substrates of choice are formally related to the structure of the vitamin K class,[17] prothrombogenic and antihemorrhagic derivatives. The vitamin K epoxides are also very important because of their higher stability to light as compared to the non-oxidized derivatives.

A typical reaction was carried out at 25 °C by dissolving 1 mmol of the substrate in 1 mL of the IL. The mixture was kept under vigorous stirring and 0.3 mL of a commercially available aqueous solution of H_2O_2 (30% w/v) 3 mmol, containing 2 mmol of NaOH, was subsequently added. The course of the reaction was monitored with GC analysis (see Experimental for details). Chromatographic, and in some cases ^1H NMR, comparison with epoxides obtained in the classical reaction carried out with H_2O_2/HO^- in water[17] was used to identify the products. The data are collected in Table 1.

Table 1 Room temperature base catalyzed oxidation of electrophilic alkenes with hydrogen peroxide in ionic liquids as solvents



No.	Substrate	[Y$^-$]	H_2O_2/ mmol	Time/min	Yield[a] (%)
1		[PF_6^-] [BF_4^-]	3 3	2 2	99 99
2		[BF_6^-] [BF_4^-]	3 3	2 2	99 97
3		[BF_6^-]	9[b]	180	80
4		[BF_6^-]	3	15	90
5		[BF_6^-]	3	60	99
6		[BF_6^-] [BF_4^-]	3 3	5 5	99 99

[a] No products other than epoxides were detected by GC analysis for all the substrates. In reactions 3 and 4 the substrate is the only other peak detected by GC.[b] Carried out by adding two additional subsequent portions of hydrogen peroxide.

Interestingly, with our procedure almost quantitative production of the epoxides is obtained, with the less hindered substrates, in the time required for the addition of a small excess of the oxidant. More substituted compounds require either longer reaction times or, as in the case of 3,5,5-trimethyl-2-cyclohexen-1-one (isophorone), the addition of a larger excess of H_2O_2 to complete the oxidation.

The epoxidation rate observed for the substrates reported in Table 1 with the procedure presented here , *i.e.* the use of ILs as solvents, can be compared with the reaction rate of the classical reactions performed in water.[18] Preliminary kinetic data indicate that the epoxidation rate observed in [bmim][PF_6], using 2-cyclohexen-1-one as a model alkene, is significantly higher than that obtained in water. A detailed kinetic analysis, actually underway in our laboratories, is clearly necessary for a more precise comparison of the rates, as well as for offering an explanation for the differences in reactivity observed with some hindered substrates.

Conclusions

In summary, the oxidation procedure presented above is characterised by several advantages with respect to classical methods for epoxidation of electrophilic alkenes. In particular, a new class of 'green solvents' and an environmentally benign and cheap oxidant are used. Complete consumption of the reactant is observed with small excesses of peroxide. An advantage over the epoxidation reactions carried out in aqueous systems is that no hydrolysis of the epoxides has been detected. Products are easily separated from the oxidation mixture by simple extraction with an immiscible solvent. Clearly a further improvement of the procedure can be evisaged on a large-scale system where the products may be either distilled from the reaction mixture or extracted with supercritical CO_2.

Experimental

In a standard epoxidation procedure, 1 mmol of the unsaturated compound was dissolved at room temperature in the ionic liquid (1 mL) and 0.3 mL of 30% aqueous hydrogen peroxide (3 mmol) containing sodium hydroxide (2 mmol) were subsequently added under vigorous stirring. The completion of the reaction was determined by controlling the entire consumption of the substrate *via* TLC. Products were then extracted at the end of the reaction by three subsequent additions of ethyl acetate (2 mL). The combined extracts were analyzed by GC using a Megadex DETTBS column. No products other than epoxides were observed with all substrates. The epoxides were identified by comparison with those obtained in the classical reaction carried out with H_2O_2/HO^- in water.[17] In the case of 2-cyclohexen-1-one and 3,5,5-trimethyl-2-cyclohexen-1-one (isophorone), the reactions were carried out on a larger scale (5.2 mmol) and the epoxides were isolated and identified on the basis of the ^1H NMR spectra of the crude extracts.

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The oxidation of alcohols in substituted imidazolium ionic liquids using ruthenium catalysts

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It has been demonstrated that ionic liquids based upon substituted imidazolium cations may be used as alternative solvent media for the selective oxidation of alcohols to aldehydes and ketones. The ruthenium catalyst tetrapropylammonium perruthenate has been used in conjunction with either *N*-methylmorpholine-*N′*-oxide or molecular oxygen as oxidants in two different catalytic systems. Benzylic alcohols are oxidized in good to excellent yields whereas aliphatic alcohols require far greater reaction times and give poor yields. The reaction products can be easily removed from the reaction mixture by extraction with diethyl ether.

Introduction

Ionic liquids are defined as compounds that are comprised entirely of ions and are liquids below 100 °C.[1] They exhibit a number of notable physical properties that may be exploited in synthetic processes. For instance, ionic liquids have negligible vapour pressures, allowing them to be used in high vacuum systems where distillation and/or sublimation techniques are employed to separate reaction products from the reaction mixture. The fact that ionic liquids do not evaporate lies at the heart of their claim to environmental benefit; with ionic liquids many of the containment issues surrounding the use of conventional organic solvents are circumvented.

Ionic liquids are good solvents for other salts and immiscible with many organic solvents. Thus organic reaction products can be easily extracted from ionic liquids containing charged catalysts or biphasic catalysis performed using them. The synthetic utility of ionic liquids has been reflected in the rapidly increasing volume of literature available. Reaction types successfully performed in ionic liquids include Diels–Alder,[2] Friedel–Crafts,[3] olefin hydrogenation,[4] hydroformylation,[5,6] oligomerization,[7] and Heck and Suzuki coupling reactions.[8,9]

The oxidation of primary alcohols to their aldehydes or carboxylic acids, and secondary alcohols to ketones are fundamental synthetic transformations. However, many oxidation processes rely upon environmentally damaging oxidants and have poor atom efficiencies. Thus, there is an increasing demand for oxidation processes that are catalytic and use environmentally benign oxidants, such as molecular oxygen and hydrogen peroxide.[10,11] It was therefore decided to pursue a line of research which would attempt to utilise such oxidants.

To date few oxidation processes have been performed in ionic liquids. Rhenium and manganese complexes have been used to epoxidize alkenes,[12,13] and nickel acetate to oxidize aromatic aldehydes.[14]

Tetrapropylammonium perruthenate ($\{[{}^{n}\mathrm{Pr}_4\mathrm{N}][\mathrm{RuO}_4]\}$, 'TPAP') in conjunction with *N*-methylmorpholine-*N′*-oxide as a co-oxidant, acts as a mild and selective catalyst for the oxidation of alcohols to aldehydes and ketones.[15,16] Reactions proceed rapidly with high turnover numbers, when performed in organic solvents and the presence of powdered molecular sieves.[17] TPAP is now commonly used in laboratory procedures and methods by which this catalyst may be supported and subsequently recycled have been developed.[18] TPAP was chosen as catalyst because it is well characterized, and comprises of an inorganic anion and large organic cation. It was expected that the catalyst would be immobilized in the ionic

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Tom Welton is a Senior Lecturer at Imperial College London. Having first arrived there in 1993 as the Lloyds of London Tercentenary Fellow he became a Lecturer two years later. Although he also has interests in other areas, Tom has worked with ionic liquids since his Ph. D. studies at the University of Sussex. Tom's group focus on understanding how the environment in which a reaction is occurring changes the observed reactivity. They study both stoichiometric and catalytic reactions and refer their results to detailed measurements of interactions between reacting species and their environments.

Green Context

Ionic liquids have attracted great attention as potentially green solvents for many organic reactions. Here, they are evaluated for oxidation reactions of alcohols, an area where progress must be made towards clean and selective oxidations. Perruthenate is used in conjunction with *N*-oxide as the oxidant. Alternatively, oxygen can be used, but Cu(I) and a diamine ligand must also be added. Conversions and yields are good and selectivities can also be very high. ***DJM***

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liquid and that organic substrates would be easily removed by conventional extraction techniques.

Results and discussion

It was observed that reaction yields were on occasion variable. Two aspects of the catalytic system were identified that could give rise to such variations: (i) the quality of the TPAP and (ii) the quality of the ionic liquid.

Although TPAP is at its most active when absolutely fresh, and activity is lost almost immediately, we have shown that there is minimal further loss between one and six days after synthesis, if stored at low temperatures (Table 1). Further to this, UV analysis of TPAP showed little change in either λ_{max} or extinction coefficient, even after one month. TPAP was therefore regularly synthesized and stored under N_2 at -18 °C.

We found that reactions performed in the same batch of ionic liquid gave consistent results. However, different yields of oxidation product have been obtained when using the same reaction conditions but a different batch of ionic liquid. These differences depend upon (i) the method used to prepare the ionic liquid and (ii) the batch of ionic liquid. Employing the following protocols for the synthesis of an ionic liquid has significantly reduced much of the variance observed in preliminary studies.

Table 1 Variation of reaction conditions for the oxidation of benzyl alcohol to benzaldehyde with NMO

Comment	% Conversion
1 g of powdered 4 Å molecular sieves added	70
No molecular sieves added	70
1 equiv. of water added	71
TPAP (1 day old)	70
TPAP (6 days old)	68

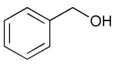
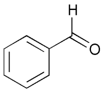
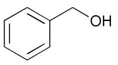
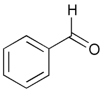
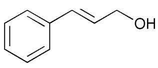
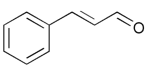
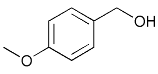
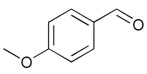
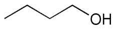
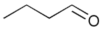
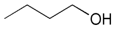
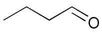
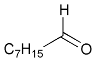
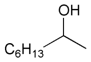
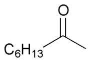
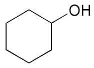
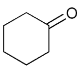
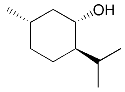
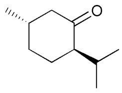
Preparation of ionic liquid

Good quality 1-butyl-3-methylimidazolium ($[bmim]^+$) based ionic liquids with the common anions; $[BF_4]^-$, $[PF_6]^-$, $[CF_3SO_3]^-$, $[CF_3CO_2]^-$ and $[(CF_3SO_2)_2N]^-$, are *always* free flowing, *colourless* liquids. Conversely, impure ionic liquids are frequently orange–yellow with variable viscosities. The source of the colouration is unknown, however, it has been observed that excessive heating during the synthesis of the imidazolium salt will cause increased colouring of the [bmim]Cl; colourless ionic liquids cannot be prepared from coloured [bmim]Cl. The colour is removed by multiple recrystallisations (see Experimental section). It should be noted that even a colourless ionic liquid is not necessarily pure.[19]

Depending upon the synthetic route used, either halide ions or acid may remain in the ionic liquid, which can have dramatic effects upon catalytic reactions later performed in them. To remove these impurities it is necessary to dissolve the ionic liquid in dichloromethane ('DCM') and wash this solution with water until the washings are halide free (determined by silver nitrate test) or pH neutral. After a final washing, the DCM is then removed *in vacuo*. It has been found that even when using these protocols the acid may still remain, *e.g.* $[bmim][CF_3SO_3]$, or be further generated *in situ*, as in the case of $[bmim][PF_6]$. It has been observed that the most significant fluctuations in the results arise from using ionic liquids prepared by the acid route. Thus, as halide salts have proved simpler to remove, the salt metathesis route has become our method of choice (compare entries 1 and 1a in Table 2).

Even with all due diligence the resultant ionic liquid is still frequently coloured. At this point any residual colour may be removed by passing the liquid through a short pad of acidic

Table 2 Oxidation of alcohols to aldehydes and ketones using TPAP and NMO stirring in $[bmim][BF_4]$ at room temperature with NMO

Entry	Alcohol	Product	% Conversion (2 h)[a]	% Conversion (24 h)	% Lit. value (*t*/h)[17]
1			70	89	80 (2)
1a[b]			59	—	80 (2)
2			59	97	91 (3)
3			71	95	68 (12)
4			24	—	95 (1)
4a[c]			43	—	—
5	C_8H_{17}—OH		35	43	—
6			48	56	—
7			48	46 (16 h)	100[d]
8			62	77	85 (1)

[a] *General reaction conditions*: TPAP (5 mol%) and NMO (3 mmol) predissolved in $[bmim][BF_4]$ (2 cm^3), alcohol (2 mmol), 1 atm N_2, 2 h stirring at room temperature. [b] $[bmim][BF_4]$ made *via* acid neutralization method. [c] Reaction sonicated for 1 h. [d] Reaction performed by author in DCM.

alumina (l = 10 mm) before use. In extreme cases it is sometimes necessary to stir the ionic liquid with activated charcoal for *ca.* 24 h before passing it through an alumina pad. It is then necessary to thoroughly dry the ionic liquid to the moisture level required, in this case by heating *in vacuo* at 70 °C for 24 h.

TPAP catalysed oxidations with NMO as co-oxidant

Investigations were initially conducted in the ionic liquid [bmim][BF_4]. This ionic liquid was chosen because it is stable to air and moisture, as well as being simple and inexpensive to prepare.[20] Control reactions were performed to verify that the ionic liquid was a benign participant in the process and did not itself oxidize the substrate, or in any other way react with it. Preliminary studies showed that unlike in molecular solvents, the addition of powdered molecular sieves did not enhance reaction yields or rates (Table 1).[17] Even the addition of one equivalent of water did not retard reaction rates nor was over-oxidation of the alcohol to the acid observed, unlike perruthenate in aqueous base.[17] Since [bmim][BF_4] mixes with water in all compositions this cannot be due to the lack of water in the solution. In a recent paper,[21] we have shown that the water in this ionic liquid is principally associated with the anions. Since perruthenate is an anionic species and one would expect it to be surrounded by cations, it may simply never come into contact with water at these levels in the ionic liquid.

Using the TPAP/NMO/[bmim][BF_4] system it was found that the oxidation of benzylic and allylic hydroxyl groups proceeded smoothly to give good yields within 2 h. In the case of entry 2 of Table 2 no double bond cleavage was observed and no other product of reaction detected, unlike perruthenate in aqueous base.[22] Reaction went to near completion for entries 2 and 3 in 24 h (Table 2). These results show that catalyst is still active even after extended reaction times. With the exception of entry 3 reaction rates are slower in [bmim][BF_4] than DCM (Table 2), it is possible that this result may simply be due to viscosity effects, [bmim][BF_4] and DCM have viscosities of 233 cP[23] and 0.4136 cP[24], respectively. Unactivated primary alcohols reacted sluggishly to give poor yields of aldehyde (entries 4 and 5, Table 2) and unreacted starting material. Unlike the benzylic alcohols, the aliphatic alcohols used for this investigation were immiscible with [bmim][BF_4]. Hence mass transport in these biphasic systems may have contributed to the low conversions seen. Indeed, it was found that for the oxidation of butan-1-ol to butyraldehyde, the yield could be boosted from 24% in 2 h to 43% in 1 h by sonicating (bath) the reaction mixture (entry 4a, Table 2) to increase the degree of mixing. The secondary alcohols cyclohexanol and menthol were also found to be immiscible with [bmim][BF_4], slow to oxidize, and gave moderate to fair final yields. Marked differences for the reaction between primary and secondary alcohols are not apparent, and as such it is not possible to determine whether the catalyst is sterically demanding, although it is often suggested that TPAP oxidations occur *via* ruthenate esters.[16]

TPAP catalysed oxidation using molecular oxygen as oxidant

A closely related system, which was first reported by Osborn and coworkers,[25] was also employed that uses molecular oxygen as oxidant and TPAP as catalyst, in conjunction with CuCl and/or 2-aminopyridine as co-catalysts. TPAP and molecular oxygen when used together were found to oxidize benzyl alcohol to benzaldehyde (as has already been demonstrated in conventional solvents),[26] however the yield of aldehyde obtained in 85 h was poor. In the same period of time no oxidation occurred using only molecular oxygen in the absence of the perruthenate catalyst. Conversions to the aldehyde were greatest when TPAP and molecular oxygen were used with CuCl, or 2-aminopyridine and CuCl (Tables 3 and 4).

Reactions were performed in the ionic liquid repeating Osborn's conditions (Table 4). Conversions were of a similar degree, so in order to determine the scope of the system further experiments were conducted that varied (i) the catalyst loading, (ii) the reaction temperature and (iii) reaction times. It was found that for benzylic alcohols good yields were obtained when operating at 60 °C and 5 mol% catalyst loading. Other studies showed that the most efficient rates of oxidation occurred when the oxygen was bubbled through the reaction mixture, rather than using air or oxygen blankets.[27] This result is in agreement with the finding that oxygen solubility in ionic liquids is low.[28]

Table 3 Oxidation of 4-trifluoromethybenzyl alcohol to 4-trifluoromethylbenzaldehyde in [bmim][$(CF_3SO_2)_2N$] stirring at 60 °C

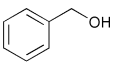
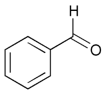
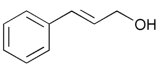
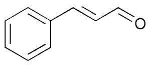
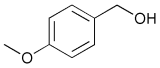
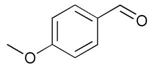
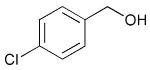
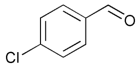
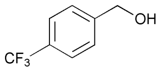
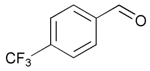
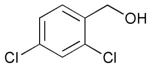
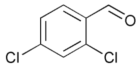
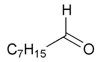
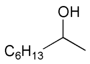
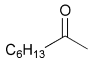
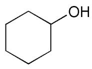
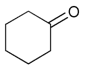
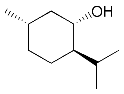
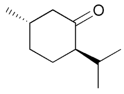
Reaction conditions	% Conversion
TPAP/O_2	34
TPAP/O_2/CuCl	>95
TPAP/O_2/2-aminopyridine	5
TPAP/O_2/CuCl/2-aminopyridine	40

TPAP/O_2/CuCl/2-aminopyridine system

Unlike the TPAP/NMO system the TPAP/O_2/CuCl/2-aminopyridine system is almost entirely selective towards benzylic alcohols. As with the NMO system, the alcohols in entries 2 and 3 are smoothly oxidized to the aldehyde in 24 h with no other products being observed (Table 4). The oxidation of benzyl alcohol does not go to completion and whilst benzyl alcohol remains at the end of the reaction a small amount of the condensation product of benzaldehyde and benzyl alcohol, benzoic acid benzyl ester, was also detected. Increasing the electronegativity of the substituent at the *para* position on the benzyl ring impeded reaction rates (compare entries 3–5). Within a 24 h period negligible oxidation of aliphatic alcohols and secondary alcohols is observed (*ca.* 3%, entries 7–10, Table 4) with a maximum conversion of 24% being observed for cyclohexanol in 40 h.

The presence of 1-butyl-3-methylimidazolidone and 1-butyl-3-methylimidazolidine-2,4,5-trione was observed by GCMS in the ether extracts for the oxidation of benzyl alcohol using the TPAP/O_2/CuCl/2-aminopyridine system. These compounds were not found before the oxidation process, hence oxidation of the ionic liquid is occurring. By deliberately trying to oxidize the ionic liquid in the absence of substrate it was still possible to detect them, but all attempts to isolate and quantify the amount of these compounds formed failed. However, if deprotonation at C2 of the imidazolium ring occurs in the reaction conditions then it is known that in the presence of O_2 and Cu(II), which is almost certainly present in our system, the azolone forms.[29] Although the mechanism for the formation of 1-butyl-3-methylimidazolidine-2,4,5-trione has not been investigated, the formation of the azolone leads to dearomatization of the ring and makes the double bond available for oxidation. Since this is a route to the decomposition of our solvent, we sought to prevent the formation of the azolone. Hence, reactions were performed using 1-butyl-2,3-dimethylimidazolium trifluoromethanesulfonimide ([bmmim][$(CF_3SO_2)_2N$]) to determine the affect of blocking the C2 position. The conversions were analogous to those observed for [bmim][$(CF_3SO_2)_2N$] and no apparent oxidation of the ionic liquid was detected.

Table 4 Oxidation of alcohols to aldehydes and ketones using TPAP/O_2/CuCl/2-aminopyridine and TPAP/O_2/CuCl systems in different solvents

			% Conversion in different solvents (24 h)					
Entry	Substrate	Product	DCM[a]	[bmim] [$(CF_3SO_2)_2N$][b]	[bmim] [$(CF_3SO_2)_2N$][c]	[bmim] [$(CF_3SO_2)_2N$][d]	[bmim] [$(CF_3SO_2)_2N$][e]	[bmmim] [$(CF_3SO_2)_2N$][f]
1			61 (21 h)	79	91	7	83	92
2			47 (29 h)	31	99	23	99	99
3			52 (23 h)	49	96	30	99	99
4			40 (26 h)	—	91	25	99	—
5			41 (26 h)	—	40	7	99	—
6			51 (25 h)	36	95	21	86	—
7	C_8H_{17}—OH		—	—	5 (40)	2	43	3
8			—	—	10 (40)	6	56	5
9			6 (39 h)	—	24 (40)	6	18	3
10			1 (72 h)	—	2 (40)	1[g]	6[g]	1

[a] Literature values, general reaction conditions: [$^nPr_4N$][RuO_4] (1 mol%), CuCl (1 mol%), 2-aminopyridine (5 mol%), 0.5 g of powdered molecular sieves, 1 atm molecular oxygen at 25 °C.[25] [b] [$^nPr_4N$][RuO_4] (1 mol%), CuCl (1 mol%), 2-aminopyridine (5 mol%), 1 atm molecular oxygen at 25 °C. [c] [$^nPr_4N$][RuO_4] (5 mol%), CuCl (5 mol%), 2-aminopyridine (25 mol%), 1 atm molecular oxygen at 25 °C. [d] [$^nPr_4N$][RuO_4] (1 mol%), CuCl (1 mol%), 1 atm molecular oxygen at 25 °C. [e] [$^nPr_4N$][RuO_4] (5 mol%), CuCl (5 mol%), 1 atm molecular oxygen at 60 °C. [f] [$^nPr_4N$][RuO_4] (5 mol%), CuCl (5 mol%), 2-aminopyridine (25 mol%), 1 atm molecular oxygen at 25 °C. [g] Menthol sublimed out of reaction mixture.

TPAP/O_2/CuCl system

It can be seen that for benzylic alcohols the conversions are comparable to those of the TPAP/O_2/CuCl/2-aminopyridine system (entries 1–5, Table 4). However, improved conversions are observed for aliphatic alcohols (entries 7 and 8, Table 4). This may be due to a change in the active catalyst or the solubility of the alcohols being altered. However, this system is clearly superior to the TPAP/O_2/CuCl/2-aminopyridine one as it does not require 2-aminopyridine.

Conclusion

In summary, it has been demonstrated that ionic liquids may be used as solvents for the oxidation of alcohols to aldehydes and ketones using TPAP as the source of metal catalyst. TPAP may be used in conjunction with CuCl and O_2 to quantitatively oxidize benzylic alcohols to their aldehydes. The reaction product can be easily extracted from the reaction mixture using diethyl ether.

Experimental

Reagents were purchased from Avocado Research Chemicals Ltd, Lancaster Synthesis Ltd and Aldrich. $RuCl_3 \cdot nH_2O$ was supplied by Johnson Matthey. Solvents were freshly distilled and dried by standard procedures (toluene over Na/benzophenone ketyl, MeCN and ethyl acetate over CaH_2, 1-chlorobutane over P_2O_5, and 1-methylimidazole and 1,2-dimethylimidazole from KOH). All manipulations were carried out under an atmosphere of dry nitrogen using standard Schlenk and cannula techniques, or in a dry box, unless specified otherwise. ^1H NMR spectra were recorded on a JEOL GSX-270 Fourier-transform NMR. NMR spectra were uncorrected for bulk magnetic susceptibility of the liquid. The mass spectrometry laboratories of the Department of Chemistry recorded GC-MS and FAB spectra. UV–VIS-spectrometry spectra were recorded using a Perkin Elmer Lambda 2 UV-VIS-Spectrophotometer. The spectra were run with the pure solvent in a matched reference cell. For analytical GC an Agilent 4890D Gas Chromatograph equipped with a flame ionisation detector (FID) and an HP-5 crossed linked 5% phenylmethyl siloxane column of length 10 m, diameter 0.53 mm and 1.5 μm film thickness, was used.

Preparation of 1-butyl-3-methylimidazolium chloride ([bmim]Cl)

Toluene (50 cm^3) was transferred *via* syringe to a three neck round bottom flask (500 cm^3) equipped with a reflux condenser and a magnetic stirrer. 1-Methylimidazole (100 cm^3, 1.25 mol, 1 equiv.) and 1-chlorobutane (143 cm^3, 1.37 mol, 1.1 equiv.) were added *via* cannula. The mixture was heated under a N_2 atmosphere at gentle reflux for 24 h. The mixture separated into two layers when cooled to room temperature, the top layer being toluene and the bottom layer an oil (the product). The flask was then placed in a freezer at −18 °C overnight, whence a white solid formed. The toluene was decanted under a stream of N_2. The white solid was recrystallized from the minimum amount of acetonitrile (*ca.* 75 cm^3). Aliquots of ethyl acetate were used to wash the salt and the resulting white precipitate was isolated by filtration using standard Schlenk techniques. The salt was then recrystallized in the same manner a second time. The product was dried in *vacuo* for 24 h to give the title compound as a white solid 203 g (1.16 mol, 93 %). ^{1}H NMR, δ_H (270 MHz, $CDCl_3$); 0.89 (3H, t, *J* 7.3 Hz, $\mathrm{NHCH_2CH_2CH_2C}H_3$), 1.30 (2H, m, $\mathrm{NCH_2CH_2C}H_2\mathrm{CH_3}$), 1.82 (2H, p, *J* 7.5 Hz, $\mathrm{NCH_2C}H_2\mathrm{CH_2CH_3}$), 4.05 (3H, s, NCH_3), 4.26 (2H, t, *J* 7.3 Hz, $\mathrm{NC}H_2\mathrm{CH_2CH_2CH_3}$), 7.40 (1H, m, C(5)H), 7.55 (1H, m, C(4)H), 10.54 (1H, s, C(2)H).[30] $^{13}C\{^1H\}$ NMR, δ_C (270 MHz, $CDCl_3$); 13.49 ($\mathrm{NHCH_2CH_2CH_2}C\mathrm{H_3}$), 19.51 ($\mathrm{NCH_2CH_2}C\mathrm{H_2CH_3}$), 32.21 ($\mathrm{NCH_2}C\mathrm{H_2CH_2CH_3}$), 36.60 ($NCH_3$), 49.82 ($\mathrm{N}C\mathrm{H_2CH_2CH_2CH_3}$), 121.94, 123.63 (C(5)H, C(4)H), 138.03 (C(2)H). *m/z* (FAB$^+$); 83 ($[C_4H_7N_2]^+$, 9%), 96 ($[C_5H_8N_2]^+$, 3%), 109 ($[C_6H_9N_2]^+$, 3%), 139 ([bmim]$^+$, 100%), 313 ({[bmim]$_2$Cl}$^+$, 17%).[31] *m/z* (FAB$^-$); 35 (Cl^-, 47%), 209 ({[bmim]Cl_2}$^-$, 100%), 383 ({[bmim]$_2Cl_3$}$^-$, 40%).

Preparation of 1-butyl-2,3-dimethylimidazolium chloride ([bmmim]Cl)

The same procedure was used as for [bmim]Cl. From 100 cm^3 (1.13 mol, 1 equiv.) of 1,2-dimethylimidazole and 130 cm^3 (1.24 mol, 1.1 equiv.) of 1-chlorobutane there was obtained the title compound as a white crystalline solid 199 g (1.05 mol, 93 %). ^{1}H NMR, δ_H (270 MHz, $CDCl_3$); 0.89 (3H, t, *J* 7.3 Hz, $\mathrm{NCH_2CH_2CH_2C}H_3$), 1.31 (2H, h, *J* 7.4 Hz, $\mathrm{NCH_2CH_2C}H_2\mathrm{CH_3}$), 1.74 (2H, m, $\mathrm{NCH_2C}H_2\mathrm{CH_2CH_3}$), 2.75 (3H, s, $\mathrm{NCC}H_3\mathrm{N}$), 3.98 (3H, s, NCH_3), 4.16 (2H, t, *J* 7.4 Hz, $\mathrm{NC}H_2\mathrm{CH_2CH_2CH_3}$), 7.49 (1H, d, *J* 1.98 Hz, C(5)H), 7.77 (1H, d, *J* 2.0 Hz, C(4)H). $^{13}C\{^1H\}$ NMR, δ_C (270 MHz, $CDCl_3$); 10.50 ($\mathrm{NHCH_2CH_2CH_2}C\mathrm{H_3}$), 13.51 ($\mathrm{NCH_2CH_2}C\mathrm{H_2CH_3}$), 19.55 ($\mathrm{NCH_2}C\mathrm{H_2CH_2CH_3}$), 31.83 ($NCH_3$), 35.92 ($\mathrm{N}C\mathrm{H_2CH_2CH_2CH_3}$), 48.65 ($\mathrm{NC}C\mathrm{H_3N}$), 121.32, 123.25 (C(5)H, C(4)H), 143.51 (C(2)H). *m/z* (FAB$^+$); 153 ([bmmim]$^+$, 100%), 123 ($[C_7H_{11}N_2]^+$, 3%), 110 ($[C_6H_{10}N_2]^+$, 3%), 97 ($[C_5H_9N_2]^+$, 10%).

Preparation of 1-butyl-3-methylimidazolium trifluoromethanesulfonimide ([bmim][$(CF_3SO_2)_2N$])

In a glove box [bmim]Cl (77.5 g, 0.44 mol, 1 equiv.) and Li[$(CF_3SO_2)_2N$] (132.1 g, 0.46 mol, 1.04 equiv.) were weighed into two three neck, round bottom flasks. At the bench the [bmim]Cl was dissolved in the minimum amount of water (*ca.* 35 cm^3) and to this rapidly stirring solution Li[$(CF_3SO_2)_2N$] was added (as this compound is very hygroscopic it was necessary to add it rapidly). A minimum amount of water was necessary to transfer residual salt into the reaction flask. DCM (*ca.* 80 cm^3) was added and the reaction mixture stirred at room temperature for 24 h. The DCM layer containing the product was washed with water until chloride free, as determined by silver nitrate test. The water washings were subsequently extracted with DCM (3 × 50 cm^3) and the DCM layers recombined. The DCM was removed *in vacuo* and the product passed through a short pad of acidic alumina (l = 10 mm). The final liquid was dried in *vacuo* at 70 °C for 24 h to give the title compound as a colourless liquid, 174 g (0.42 mol, 94%). ^{1}H NMR, δ_H(270 MHz, $CDCl_3$); 0.93 (3H, t, *J* 7.2 Hz, $\mathrm{NHCH_2CH_2CH_2C}H_3$), 1.34 (2H, m, $\mathrm{NCH_2CH_2C}H_2\mathrm{CH_3}$), 1.82 (2H, p, *J* 7.6 Hz, $\mathrm{NCH_2C}H_2\mathrm{CH_2CH_3}$), 3.92 (3H, s, NCH_3), 4.14 (2H, t, *J* 7.4 Hz, $\mathrm{NC}H_2\mathrm{CH_2CH_2CH_3}$), 7.29 (2H, m, C(5)H, C(4)H), 8.70 (1H, s, C(2)H).[30] ^{1}H NMR, δ_H (270 MHz, CD_3COCD_3, δ/ppm relative to TMS). $^{13}C\{^1H\}$ NMR, δ_C (270 MHz, CD_3COCD_3, δ/ppm relative to TMS); 12.27 ($\mathrm{NHCH_2CH_2CH_2}C\mathrm{H_3}$), 18.76 ($\mathrm{NCH_2CH_2}C\mathrm{H_2CH_3}$), 31.41 ($\mathrm{NCH_2}C\mathrm{H_2CH_2CH_3}$), 35.37 ($NCH_3$), 49.25 ($\mathrm{N}C\mathrm{H_2CH_2CH_2CH_3}$), 119.69 (2C, q, $^1J_{CF}$ 322 Hz, CF_3SO_2), 122.04, 123.29 (C(5)H, C(4)H), 135.83 (C(2)H). *m/z* (FAB$^+$); 83 ($[C_4H_7N_2]^+$, 9%), 96 ($[C_5H_8N_2]^+$, 3%), 109 ($[C_6H_9N_2]^+$, 3%), 139 ([bmim]$^+$, 100%), 558 ({[bmim]$_2$[$(CF_3SO_2)_2N$]}$^+$, 1%).[31] *m/z* (FAB$^-$); 147 ($[CF_3SO_2N]^-$, 5%), 280 ({$[CF_3SO_2]_2N$}$^-$, 100%). IR (neat) ν_{max}/cm^{-1}; 3157 (aromatic C–H str., s), 3122 (aromatic C–H str., s), 2967 ($\mathrm{NHCH_2CH_2CH_2C}H_3$ C–H str. asym., s), 2941 ($\mathrm{NC}H_2\mathrm{C}H_2\mathrm{C}H_2\mathrm{CH_3}$ C–H str. asym., m), 2880 ($\mathrm{NHCH_2CH_2CH_2C}H_3$ C–H str. sym., m), 1572 (aromatic C–C str., m), 1466 ($\mathrm{NHCH_2CH_2CH_2C}H_3$ C–H def., asym., m), 1351 (S–O str., s), 1190 (F–C–F str., s), 1138 (C–F str., s), 843 (aromatic C–H out of plane def., w).[32–34]

Preparation of 1-butyl-2,3-dimethylimidazolium trifluoromethanesulfonimide ([bmmim][$(CF_3SO_2)_2N$])

The same procedure was used as for [bmim][$(CF_3SO_2)_2N$]. Solvent volumes were scaled as necessary. From 33.16 g (0.176 mol, 1 equiv.) of [bmmim]Cl and 50.46 g (0.176 mol, 1 equiv.) of Li$(CF_3SO_2)_2N$ was obtained the title compound as a colourless liquid (61 g, 0.14 mol, 80%). ^{1}H NMR, δ_H (270 MHz, $CDCl_3$); 0.93 (3H, t, *J* 7.4 Hz, $\mathrm{NCH_2CH_2CH_2C}H_3$), 1.35 (2H, m, $\mathrm{NCH_2CH_2C}H_2\mathrm{CH_3}$), 1.75 (2H, m, $\mathrm{NCH_2C}H_2\mathrm{CH_2CH_3}$), 2.57 (3H, s, $\mathrm{NCC}H_3\mathrm{N}$), 3.77 (3H, s, $\mathrm{NC}H_3$), 4.02 (2H, t, *J* 7.4 Hz, $\mathrm{NC}H_2\mathrm{CH_2CH_2CH_3}$), 7.15 (1H, d, C(5)H), 7.18 (1H, d, C(4)H). $^{13}C\{^1H\}$ NMR δ_C (270 MHz, CD_3COCD_3, δ/ppm relative to TMS); 8.44 ($\mathrm{NHCH_2CH_2CH_2}C\mathrm{H_3}$), 12.49 ($\mathrm{NCH_2CH_2}C\mathrm{H_2CH_3}$), 18.82 ($\mathrm{NCH_2}C\mathrm{H_2CH_2CH_3}$), 31.10 ($NCH_3$), 34.23 ($\mathrm{N}C\mathrm{H_2CH_2CH_2CH_3}$), 47.88 ($\mathrm{NC}C\mathrm{H_3N}$), 119.59 (2C, q, $^1J_{CF}$ 321 Hz, CF_3SO_2), 120.49, 122.02 (C(5)H, C(4)H), 143.97 (C(2)H). $^{13}C\{^1H\}$ NMR, δ_C (270 MHz, $CDCl_3$); 9.60 ($\mathrm{NHCH_2CH_2CH_2}C\mathrm{H_3}$), 13.37 ($\mathrm{NCH_2CH_2}C\mathrm{H_2CH_3}$), 19.55 ($\mathrm{NCH_2}C\mathrm{H_2CH_2CH_3}$), 31.49 ($\mathrm{N}C\mathrm{H_3}$), 35.35 ($\mathrm{N}C\mathrm{H_2CH_2CH_2CH_3}$), 48.66 ($\mathrm{NC}C\mathrm{H_3N}$), 120.88, 122.58 (C(5)H, C(4)H), 143.82 (C(2)H). *m/z* (FAB$^+$); 97 ($[C_5H_9N_2]^+$, 7%), 110 ($[C_6H_{10}N_2]^+$, 5%), 123 ($[C_7H_{11}N_2]^+$, 4%), 153 ([bmmim]$^+$, 100%), 586 ({[bmmim][$(CF_3SO_2)_2N$]}$^+$, >1%). *m/z* (FAB$^-$); 280 ({$[CF_3SO_2]_2N$}$^-$, 100%), 147 ($[CF_3SO_2N]^-$, 5%). IR (neat) ν_{max}/cm^{-1}; 3187 (aromatic C–H str., s), 3151 (aromatic C–H str., m), 2968 ($\mathrm{NHCH_2CH_2CH_2C}H_3$ C–H str. asym., m), 2942 ($\mathrm{NC}H_2\mathrm{C}H_2\mathrm{C}H_2\mathrm{CH_3}$ C–H str. asym., m), 2880 ($\mathrm{NHCH_2CH_2CH_2C}H_3$ C–H str. sym., m), 1591 (aromatic C–C str., m), 1466 ($\mathrm{NHCH_2CH_2CH_2C}H_3$ C–H def., asym., m), 1352 (S–O str., s), 1193 (F–C–F str., s), 1137 (C–F str., s), 843 (aromatic C–H out of plane def., w).[32–34]

Preparation of 1-buty1-3-methylimidazolium tetrafluoroborate ([bmim][BF_4])

The same procedure was used as for [bmim][$(CF_3SO_2)_2N$]. Solvent volumes were scaled as necessary. From 130 g (0.75 mol, 1 equiv.) [bmim]Cl and 90 g (0.82 mol, 1.1 equiv.) sodium tetrafluoroborate, was obtained the title compound as a colourless liquid (128 g, 0.56 mol, 70%). ^{1}H NMR, δ_H (270 MHz, $CDCl_3$); 0.94 (3H, t, *J* 7.3 Hz, $\mathrm{NHCH_2CH_2CH_2C}H_3$), 1.35 (2H, m, $\mathrm{NCH_2CH_2C}H_2\mathrm{CH_3}$), 1.84 (2H, p, *J* 7.6 Hz, $\mathrm{NCH_2C}H_2\mathrm{CH_2CH_3}$), 3.94 (3H, s, NCH_3), 4.17 (2H, t, *J* 7.4 Hz, $\mathrm{NC}H_2\mathrm{CH_2CH_2CH_3}$), 7.27 (1H, s, C(5)H), 7.31 (1H, s, C(4)H), 8.81 (1H, s, C(2)H).[30] $^{13}C\{^1H\}$ NMR, δ_C (270 MHz, CD_3COCD_3, δ/ppm relative to TMS); 12.51 ($NHCH_2CH_2CH_2\mathit{C}H_3$), 18.72 ($NCH_2CH_2\mathit{C}H_2CH_3$), 31.38 ($NCH_2\mathit{C}H_2CH_2CH_3$), 35.26 ($NCH_3$), 48.85 ($N\mathit{C}H_2CH_2CH_2CH_3$), 121.90, 123.22 (C(5)H, C(4)H), 136.37 (C(2)H). *m*/*z* (FAB^+); 55 ($[C_3H_6N]^+$, 2%), 83 ($[C_4H_7N_2]^+$, 15%), 96 ($[C_5H_8N_2]^+$, 4%), 109 ($[C_6H_9N_2]^+$, 4%), 139 ($[bmim]^+$, 100%), 365 ($\{[bmim]_2[BF_4]\}^+$, 1%).[31] *m*/*z* (FAB^-); 19 (F^-, 83%), 87 ($[BF_4]^-$, 100%), 313 ($\{[bmim][BF_4]_2\}^-$, 10%). IR (neat) ν_{max}/cm^{-1}; 3162 (aromatic C–H str., m), 3121 (aromatic C–H str., m), 2965 ($NHCH_2CH_2CH_2C\mathit{H}_3$ C–H str. asym., m), 2939 ($NC\mathit{H}_2C\mathit{H}_2C\mathit{H}_2CH_3$ C–H str. asym., m), 2877 ($NHCH_2CH_2CH_2C\mathit{H}_3$ C–H str. sym., m), 1574 (aromatic C–C str., m), 1466 ($NHCH_2CH_2CH_2C\mathit{H}_3$ C–H def., asym., m), 1171 (aromatic C–H in plane def., m), 1059 (BF_4, ν_3, s, br.), 754 (BF_4, ν_1, m), 849 (aromatic C–H out of plane def., w).[32,33,35]

Synthesis of tetrapropylammonium perruthenate ($[^nPr_4N][RuO4]$)[36]

Anhydrous Na_2CO_3 (3.20 g, 30 mmol) and $NaBrO_3$ (12.00 g, 80 mmol) were dissolved in water (*ca*. 40 cm^3) and $RuCl_3.\mathit{n}H_2O$ (0.27 g, 1 mmol) pre-dissolved in water (20 cm^3) was added with stirring until the colour changed to yellow/green. $[^nPr_4][OH]$ (1 cm^3 of 1 mol dm^{-3}) was added with stirring and the deep moss green precipitate that formed extracted into DCM. The solution was dried over anhydrous $MgSO_4$ and concentrated in *vacuo* to give the title compound as a deep moss green solid 0.45 g (1.28 mmol, 99%). The solid was stored at −18 °C, mp 161 °C (decomp.). UV–VIS spectrum: λ_{max} (CH_2Cl_2)[nm(ε/dm^3 mol^{-1} cm^{-3})] 318 (1904), 384 (2261). IR (ν_{max}/cm^{-1}): 831 s ($\nu^{as}(RuO_4)$(lit.,[36] 836)). FAB^+ mass spectrum: $m/z = 186$ ($[^nPr_4N]^+$, 100%).

Typical oxidation procedure with NMO as co-oxidant

This general method was used for all reactions and different alcohols were used. The catalyst (5 mol%) was accurately weighed into a round bottom flask charged with ionic liquid (2 cm^3), the co-oxidant NMO (3 mmol, 1.5 equiv.) and a magnetic stirrer bar. The mixture was stirred until a homogeneous solution formed. The alcohol (2 mmol, 1 equiv.) was then added and the mixture stirred for 2 hours in an N_2 atmosphere. The product was extracted from the ionic liquid with Et_2O (3 × 2 cm^3) and analysed by GC.

Typical oxidation procedure with O_2 as co-oxidant

A round bottom flask (5 cm^3) was charged with TPAP (0.035 g, 5 mol% (with respect to substrate)) and a stir bar. The ionic liquid was then added (2 cm^3) followed by copper(I)chloride (0.010 g, 5 mol%) and 2-aminopyridine (0.047 g, 25 mol%). A suba-seal was placed in the neck of the flask and the flask placed in an oil bath thermostatted at the requisite temperature. The mixture was stirred thoroughly to give a black solution. A syringe was pierced through the suba-seal and placed well below the surface of the liquid. Oxygen was then bubbled through at a rate of approximately one bubble per second. The alcohol was added (2 mmol, 1 equiv.) in one portion to the reaction mixture by syringe through the suba-seal at $t = 0$. At the requisite times aliquots of the reaction mixture were removed and the alcohol and aldehyde extracted with Et_2O (3 × 2 cm^3). The ether/reaction product solution was then analysed by GC and GC-MS.

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Study of ligand and base effects on enantioselective allylation catalyzed by Pd(0) phosphine complexes in [bmim][PF_6] ionic liquid

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Enantioselective Pd-catalyzed allylic substitution of (*rac*)-(*E*)-1,3-diphenyl-3-acetoxyprop-1-ene with dimethyl malonate was studied in 3-butyl-1-methylimidazolium hexafluorophosphate ([bmim][PF_6]) as an ionic liquid. The reactions were catalyzed by Pd(0) complexes of three homochiral ferrocenylphosphine ligands, (*S*,*S*)-iPr-Phosferrox, (*S*,*R*)-iPr-Phosferrox, (*R*,*S*)-BCyPFA and (*R*)-BINAP. Potassium carbonate and bis(trimethylsilyl)acetamide (BSA)/AcOK were tested as the bases and simple optimization of the reaction procedure was performed. Experiments with other soft nucleophiles also were carried out under optimized conditions.

Introduction

Transition-metal complexes of homochiral ferrocenylphosphine ligands are very often used for homogeneous enantioselective reactions.[1,2] Asymmetric allylic substitution reactions of C-nucleophiles catalyzed by Pd(0) complexes of ferrocene ligands have been described by Hayashi *et al.*[3,4] Excellent ligands for allylic nucleophilic are ferrocenyl oxazolines having both central and planar chirality.[5,6] Nevertheless the application of homogeneous catalytic systems is limited due to complications with the catalyst recovery. Several methods such as immobilization of homochiral ferrocene ligands to carriers such as insoluble polymers,[7] silica gel,[8,9] mesoporous silica[10–12] or dendrimers[13–16] open the possibility for efficient recovery of the catalytic system.

In the last few years, room temperature ionic liquids have also been studied as an alternative for the most harmful solvents.[17–22] Ionic liquids are miscible with polar organic solvents such as lower alcohols and ethyl acetate but non-miscible with water on one side and less-polar organic solvents such as aliphatic or aromatic hydrocarbons, diethyl ether *etc.* on the other. From this point of view ionic liquids offer the potential for easy catalyst separation.

Xiao and coworkers described[23] palladium catalyzed allylation reactions in [bmim][BF_4] ionic solvent with the $Pd(OAc)_2$/PPh_3 catalytic system. It was found that a P : Pd molar ratio of 4 : 1 was optimal and products were obtained in good yields (54–91%). The same authors have published recently a study of the ligand effect on the course of palladium catalyzed allylation.[24] Simple achiral phosphines were employed and DBU was used as the base. Tris(cyclohexyl)- and tris(*tert*-butyl)-phosphines proved to be the best ligands and six different soft nucleophiles were tested.

In our recent paper,[25] we described a successful asymmetric Pd(0)-catalyzed allylation of (*rac*)-(*E*)-1,3-diphenyl-3-acetoxyprop-1-ene with dimethyl malonate (DMM); (*S*,*R*)-BPPFA and (*R*,*S*)-BPPFDEA were examined as the chiral ferrocenylphosphine ligands.

It is of interest to note that similar reactions were performed also in another non-typical solvent—water containing some surfactant.[26]

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Green Context

Enantioselective synthesis is becoming increasingly important as the value of more specific molecular activity is appreciated in pharmaceuticals and other application areas. The green chemistry benefits of this are readily apparent—more selective reactions and lower dosage, less toxic products. A much better understanding of the mechanism of the catalysis used in such reactions is necessary if we are to improve on the enantioselectivity. Here different ligands are studied and compared in the Pd(0)-catalysed allylation of dimethylmalonate. The reactions have additional green chemistry relevance in that they are carried out in ionic liquids—solvents with no volatility and therefore no emission problems. Some important conclusions are reached so as to help optimise these important reactions. *JHC*

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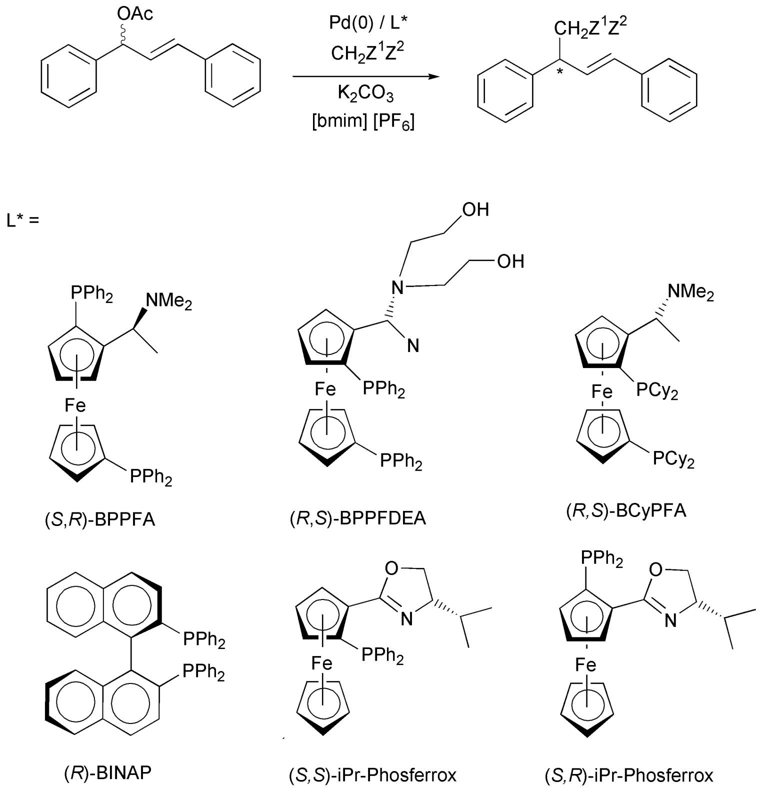
The main goal of this work was to examine several homochiral ferrocenylphosphine ligands for enantioselective Pd(0) catalyzed allylation of DMM and compare the results with those previously described. The second aim was to examine the effect of different bases and other reaction conditions such as temperature on the chemical yield and enantioselectivity of the reaction. We checked also the possibility to extend this reaction to other nucleophiles.

Results and discussion

Homochiral ferrocenylphosphine ligands, (*S*,*S*)-iPr-Phosferrox, (*S*,*R*)-iPr-Phosferrox, (*R*,*S*)-BCyPFA and (*R*)-BINAP were examined as ligands for enantioselective Pd(0)-catalyzed allylic substitution reactions of dimethyl malonate and (*rac*)-(*E*)-1,3-diphenyl-3-acetoxyprop-1-ene in 1-butyl-3-methylimidazolinium hexafluorophosphate ([bmim][PF_6]) as the solvent (Scheme 1).

The procedure developed by Xiao and coworkers[23] was used (2 mol% Pd; P:Pd ratio 4:1). The product was extracted into toluene, while the ionic solvent containing the catalytic system was washed with water and dissolved in ethyl acetate. This solution was dried over anhydrous sodium sulfate, solvent was evaporated and the catalytic system in the ionic liquid was used in subsequent reaction. The achieved results, isolated yields of product and its enantioselectivity, are given in Table 1.

Tested ligands (*S*,*S*)-iPr-Phosferrox, (*S*,*R*)-iPr-Phosferrox, (*R*,*S*)-BCyPFA were comparable or even better than (*S*,*R*)-BPPFA and (*R*,*S*)-BPPFDEA from the point of view of asymmetric induction, but were worse than (*R*,*S*)-BPPFDA in terms of yield. (*R*)-BINAP gave similar selectivity and yields as (*R*,*S*)-BPPFDEA. From our results it is seen that using bis(trimethylsilyl)acetamide (BSA)/AcOK as the base led to considerably higher yields than using K_2CO_3 as the base.



Scheme 1

Table 1 Pd-catalyzed allylic substitution of (*rac*)-(*E*)-1,3-diphenyl-3-acetoxyprop-1-ene with dimethyl malonate catalyzed by homochiral phosphine ligand/Pd(0) complexes in [bmim][PF_6] at room temperature

Ligand	Time/h	Yield (%)	Base	Ee (%) (config.)
(*S*,*R*)-BPPFA	24	62	K_2CO_3	40 (*R*)[4]
(*S*,*R*)-BPPFA	5	53	K_2CO_3	68 (*R*)[23]
(*R*,*S*)-BPPFDEA	15	81	K_2CO_3	74 (*S*)
(*S*,*S*)-iPr-Phosferrox	15	34	K_2CO_3	86 (*S*)
(*S*,*S*)-iPr-Phosferrox (1st reuse)	15	27	K_2CO_3	84 (*S*)
(*S*,*S*)-iPr-Phosferrox (2nd reuse)	15	16	K_2CO_3	78 (*S*)
(*S*,*S*)-iPr-Phosferrox	15	55	BSA/AcOK	68 (*S*)
(*S*,*S*)-iPr-Phosferrox (reused)	15	47	BSA/AcOK	66 (*S*)
(*S*,*R*)-iPr-Phosferrox	15	90	BSA/AcOK	58 (*S*)
(*S*,*R*)-iPr-Phosferrox (reused)	15	30	BSA/AcOK	56 (*S*)
(*R*,*S*)-BCyPFA	15	69	BSA/AcOK	56 (*S*)
(*R*,*S*)BCyPFA (reused)	15	25	BSA/AcOK	46 (*S*)
(*R*)-BINAP	5	36	BSA/AcOK	60 (*S*)
(*R*)-BINAP	15	78	BSA/AcOK	74 (*S*)
(*R*)-BINAP (reused)	15	15	BSA/AcOK	51 (*S*)

It is necessary to comment on our results from experiments with reused ionic liquid–catalyst systems. In all experiments, with the exception of (*R*)-BINAP, the enantiopurity of the products remained nearly unchanged. This is indirect evidence that the catalytic system was not changed, which is very important from an application point of view. A drop in the yields in experiments with reused ionic liquid–catalytic systems can be explained by the fact that only 1 ml of ionic liquid was used in our experiments. If during the extraction procedures *ca.* 0.1–0.2 ml of the ionic liquid was lost than this means that the next experiment was run with 10–20% lower amount of the catalyst. The exception was the experiment with (*R*)-BINAP, where the drop of the yield as well as selectivity were more prenounced. This suggests that the (*R*)-BINAP complex is more easily extracted out from ionic liquid during work-up.

It was intriguing to us that yields of the product were so low with (*S*,*S*)-iPr-Phosferrox as ligand and K_2CO_3 and therefore we decided to conduct a simple optimalization of this procedure. Results are given in Table 2.

Table 2 Attempts on optimization of Pd-catalyzed allylic substitution of (Rrac)-(RE)-1,3-diphenyl-3-acetoxyprop-1-ene with dimethyl malonate with (RS,*S*)-iPr-Phosferrox as the ligand and K_2CO_3 as the base

Time/h	Temp./°C	Yield (%)	Ee (%)
5	rt	31	92
15	rt	34	86
24	rt	38	62
15	0	10	87
5	40	83	88
15	40	86	90
15	40	65	76[a]
15	60	98	88

[a] Reused ionic liquid

From the results given in Table 2 it is seen that prolonging the reaction time at room temperature had practically no effect on the yields of the product, but had an undesirable effect on the ee value. Attempts to raise the ee by lowering the reaction temperature was also not effective. On the other hand a rise of the reaction temperature to 40 °C led to a considerably better yield without having any effect on the ee of the product. It is of interest to note that raising the reaction temperature to 60 °C resulted in practically a quantitative yield of the product with excellent ee.

From our experiments with other soft nucleophiles (Table 3) it is evident that our methodology is reasonably general and can be applied to several soft nucleophiles. Reasonable yields of the product were achieved with all of them with the exception of diethyl acetamidomalonate. Reactions proceed with a high asymmetric induction, but the ee of the reaction product with methyl cyanoacetate was not possible to determine by our methodology. An experiment with dimedone was also performed, but this was not a clean reaction, and a mixture of the products was detected by TLC.

Table 3 Pd-catalyzed allylic substitution of (Rrac)-(RE)-1,3-diphenyl-3-acetoxyprop-1-ene with different nucleophiles with (RS,*S*)-iPr-Fosferrox as ligand and K_2CO_3 as base (40 °C, 15 h)

Nucleophile	Yield (%)	Ratio of diastereomers	Ee (%)
Pentane-2,4-dione	44	—	56
Ethyl acetoacetate	56	1 : 1	81
Methyl cyanoacetate	85	1 : 1	Not determined
Diethyl acetamidomalonate	27	—	72

Experimental

^1H NMR (δ, ppm) spectra of samples were obtained for $CDCl_3$ solutions on a Varian Gemini 2000 spectrometer operating at 300 MHz frequency with tetramethylsilane as internal standard. Solvents were purified and dried according to known procedures. The ionic solvent [bmim][PF_6] was prepared as described.[27] Homochiral ferrocenylphosphine ligands, (*S*,*S*)-iPr-Phosferrox, (*S*,*R*)-iPr-Phosferrox, (*R*,*S*)-BCyPFA (*S*,*R*)-BPPFA and (*R*,*S*)-BPPFDEA were prepared according to the method of Richards and Hayashi.[28–30]

1-Phenyl-3-acetoxyprop-1-ene and (*rac*)-(*E*)-1,3-diphenyl-3-acetoxyprop-1-ene were prepared by acylation of appropriate alcohols with Ac_2O in diethyl ether under DMAP catalysis. $Pd_2(dba)_3{\cdot}CHCl_3$ was prepared according to published method.[31] The enantiomeric purity of the product was determined by ^1H NMR using chiral shift reagent Eu(hfc)$_3$.

General procedure for allylic substitution reaction of (*rac*)-(*E*)-1,3-diphenyl-3-acetoxyprop-1-ene and methylene active compounds in ionic solvent [bmim][PF_6]

$Pd_2(dba)_3{\cdot}CHCl_3$ (10.4 mg, 0.01 mmol, 2 mol% Pd) and ferrocenylphosphine ligand (0.04 mmol, 8 mol% P) were added to pre-dried [bmim][PF_6] (1 mL) and the resulting mixture was stirred at 80 °C under Ar-atmosphere for 20 min. Substrate (252 mg, 1 mmol), the appropriate methylene active compound (1.5 mmol) and K_2CO_3 (276 mg, 2 mmol) were added to the cooled reaction mixture. The reaction mixture was stirred at room temperature under Ar-atmosphere for 5 h. Toluene (2 mL) was added and mixture was vigorously stirred for 5 min, the separated toluene layer was collected and this procedure was repeated until no product was detected in the toluene layer (*ca.* 10 times). The combined toluene extracts were washed with water (20 mL), dried and solvent was evaporated. The residue was purified by chromatography on an SiO_2-column (30 g, 12.5% EtOAc–hexane). The product was obtained after evaporation of solvent as a clear colorless oil which crystallized in a freezer. The ionic liquid was washed twice with water (2 mL) and dissolved in EtOAc (10 mL), dried, solvent evaporated, dried at 40°C/1 mmHg during 3 h and stored under Ar-atmosphere in a freezer before reusing in next reaction.

All reaction products had physical constants and NMR spectra in accord with published data.[24,25]

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Solvation of small molecules in imidazolium ionic liquids: a simulation study

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Molecular dynamics simulations of a number of small molecules dissolved in dimethylimidazolium chloride at 400 K have been performed. The molecules chosen were water, methanol, dimethyl ether and propane, which have a range of properties from polar and hydrogen-bonding to non-polar. The local structure was analysed through ranked radial distribution functions and three dimensional probability functions, and the interaction energy with the anions and cations determined. The energetics and local structure show that the strongest interactions are hydrogen bonding to the chloride ion for water and methanol, while dimethyl ether and propane interact more strongly with the cation.

1 Introduction

Room temperature ionic liuqids are solvents with many potential applications, as they have vanishingly low vapour pressures and can be recycled after use in organic reactions. Many types of chemical reaction can be carried out successfully in these solvents, and solvent recovery and the work-up of products often depends on their relative solubility in different phases.[1] Thus it is important to understand the solvation properties of simple solutes in this unusual environment.

Atomistic simulation has proved to be a useful technique for helping to understand chemical reactivity and solvation properties in aqueous solutions and the aim of this work is to begin applying the same techniques to ionic liquids based on imidazolium cations. In this paper we report some solvation properties of a series of small molecules ranging from hydrogen-bonding (H_2O, MeOH), through a molecule with a dipole moment (Me_2O) to non-polar (Me_2CH_2) in dimethylimidazolium chloride (mmimCl). We have chosen dimethylimidazolium chloride for these initial studies as it is the simplest example of an ionic liquid based on substituted imidazolium salts and is the cheapest to model.

We find that the hydrogen-bonding solutes are strongly solvated, principally by forming hydrogen bonds with the chloride ion, while the non-hydrogen bonding solutes interact more strongly with the cation. This is shown from both energetics and local structure.

2 Molecular models and computational procedures

This section describes the technical details of the simulations. The results are presented and discussed in the following sections.

The cations and anions of the liquid were modelled as rigid charged molecules with fixed geometry. The intermolecular potentials were made up of two-body terms between atomic sites on each species. The methyl groups of both cations and solutes and the methylene group in propane were described by single sites (united atoms). The electrostatic part of the interaction was described by fixed point charges on each site (partial charges). The short range repulsion and dispersion interactions were also described by site–site interactions. Interactions between the molecular ions of the ionic liquid were taken from our earlier work[2] and have the form of partial charges on atomic sites with site–site Buckingham potentials for the short-range interactions. The solute–solvent short-range interactions were modelled using Lennard-Jones site–site interactions. The OPLS parameters of Jorgenson[3] were used

Green Context

While a considerable volume of literature has built up on the preparation and application of ionic liquids, relatively little work has gone into studying the behaviour of solutes in ionic liquids. Here simulation studies on the solvation of small molecules in some ionic liquids are reported. Specific interactions such as hydrogen bonding to the anion are identified. *JHC*

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except for water which was described by the spc/e model of Berendsen *et al.*[4] and the chloride ion where the parameters were taken from the work of Dang.[5] Cross terms were constructed using the Lorentz–Betholet rules. The partial charges on the solute sites were taken from the same sources and are given in Table 1. Molecular dynamics simulations[6] of one solute molecule, 192 cations and 192 anions were carried out using an adaptation of the DL_POLY program[7] at 400 K with a time step of 2 fs. The long range electrostatics was treated by the Ewald summation. The box size was set so that the average pressure was zero for the neat liquid and was not adjusted for these very dilute solutions. Calculations were carried out at 400 K where mmimCl is liquid. Long runs were needed to determine the interaction energies which were estimated from two or more indendent runs of 200 ps, 160 ps or 80 ps. The radial and probability distribution functions were found from the 200 ps runs.

We analysed the local structure in several ways. First we measured the direct solute–cation and solute–anion interaction energies and secondly we have examined the local environment around the solutes. One useful tool for the latter is the ranked radial distribution function introduced by Keyes.[8] To construct this type of distribution function for solvent sites of type S relative to a solute site M one takes each configuration, first ranks the atoms of the type S in order of their distance from the solute site concerned (M), and then constructs radial distribution functions in the standard way for the nearest atom, the second nearest atom, and so on. The total radial distribution function $g_{MS}(r)$ is the sum of all the ranked distribution functions. This gives one a very clear picture of the number of atoms in each shell and the tightness or looseness of the shell. The other tool that we have exploited is the construction of the three dimensional probability distribution functions for sites in the solvent molecules as seen from the solute molecule as introduced by and Svishchev and Kusalik.[9] These are difficult to display on a two dimensional diagram, and have the problem that they may look very different according to the limiting contour used for the display, but examining a series of such three dimensional plots using software which allows one to rotate the images proved to be instructive.

3 Solute–solvent interactions

3.1 Local structure

In order to find the local structure of the ionic liquid around the solute one must examine the radial distribution functions, the ranked radial distribution functions, and the three-dimensional probability functions as these give complementary information.

Table 1 Partial charges

Species	Atom	Charge
mmim$^+$	C_2	0.407
	N_1, N_3	−0.267
	C_4, C_5	0.105
	H_2	0.097
	H_4, H_5	0.094
	Me (united)	0.316
Cl^-	Cl	−1.000
H_2O	H	0.4238
H_2O	O	−0.8476
MeOH	H	0.4350
MeOH	O	−0.7000
MeOH	Me	0.2650
Me_2O	Me	+0.2900
Me_2O	O	−0.5800
Me_2CH_2	Me	0.000
Me_2CH_2	CH_2	0.000

Radial distribution functions are readily computed from simulations and give some information about the local environment of a given type of atom. For example, the radial distribution function $g_{OCl}(r)$ is proportional to the average probability density of chloride ions at distance r from oxygen atoms. Fig. 1 shows this function (narrow lines) for dilute solutions of each of the solutes in mmimCl. The graphs of $g_{OCl}(r)$ for methanol and water show unusually strong and distinct first peaks at about 3.2 Å. This means that there is a high probability of finding some chloride ions at this distance. Dimethyl ether and propane have no such nearby chloride ions. The average number of the nearby chloride ions can then be deduced from the ranked distribution functions shown in the same figure. The ranked functions show the contributions of the nearest neighbour, the next nearest neighbour, and so on to the radial distribution function. As the first peak in $g_{OCl}(r)$ for methanol is only due to the nearest neighbour, we deduce that exactly one chloride ion is very close to the methanol molecule. Similarly we deduce that there are two chloride ions very close to the water molecule from the fact that the two nearest neighbours contribute to the first peak of $g_{OCl}(r)$. Finally the preferred positions of these two chloride ions relative to the water molecule can be deduced from the three dimensional plots of the probability distribution functions shown in Fig. 2. In these plots the green regions near the OH protons are the places where the chloride ions are most likely to be found. Thus the combination of the ranked radial distribution functions and the three dimensional probability distribution shows that two chloride ions are strongly localised near the water molecule, accepting hydrogen bonds from its hydroxyl groups to form a $O(HCl^-)_2$ complex. A similar three-dimensional plot for the methanol molecule (not shown) shows that a single chloride ion is complexed to the methanol by hydrogen bond formation.

The arrangement of cations around the solutes is more diffuse. As the dimethylimidazolium ion is large, its position has been defined by three sites, the 'centre' site, the 'top' site

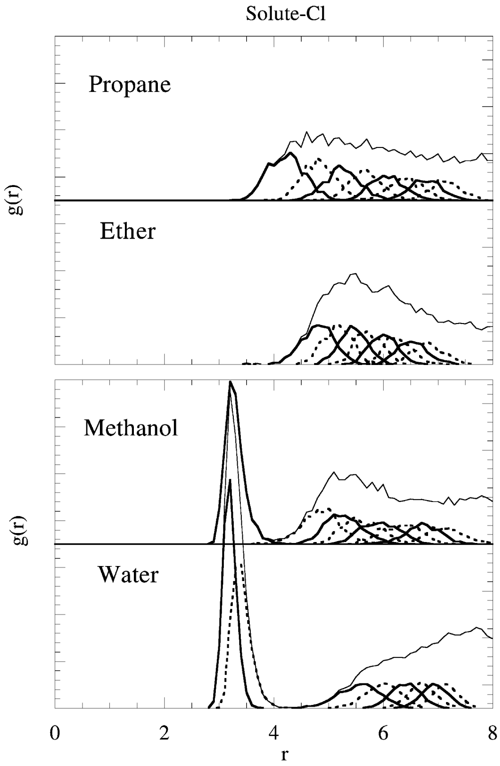

Fig. 1 Ranked radial distribution functions g_{SM} for the nearest eight chloride ions relative to the central sites (O or CH_2) of water, methanol, dimethyl ether and propane. The distributions of neighbours in ranking order are shown alternately with full and dashed lines. The total $g(r)$ is shown by a thin line. These graphs provide clear evidence that each hydroxyl group hydrogen-bonds with a separate chloride ion.

and the ‘bottom’ site. The positions of these sites are shown in Fig. 3. The ‘centre’ site is near the centre of the ring and is defined as the point half way between the nitrogen atoms. The ‘bottom’ site is on the proton attached to the C_2 ring carbon and the ‘top’ site is half way between the protons attached to carbon atoms 4 and 5. These three sites lie on the C_2 symmetry axis of the ring and can be used to find the preferred orientation of the $mmim^+$ ion relative to the solutes. The ranked distribution functions in Fig. 4 show that the ‘top’ site is closest to the water oxygen, but has an unusually broad distribution fluctuating from about 2.5 to 4 Å. Fifty percent of the time it is nearer than 3.3 Å. The black (‘top’ site), blue (‘centre’ site) and yellow (‘bottom’ site) regions in the three-dimensional distribution function in Fig. 2 show clearly that the nearest cation to the water molecule is strongly localised and is oriented by interaction with the chloride ions of the chloride–water complex.

The interaction of the cations with methanol is rather different. They are much less strongly localised and the preferred orientation relative to the solute is reversed. This can be seen in Fig. 4 which shows that there are usually two dimethylimidazolium ions whose ‘bottom’ sites are closer than 3.3 Å to the methanol oxygen atom. The closer of these sites is often as near as 2.5 Å from this oxygen. The three-dimensional plots (not shown) are messier than those for water, as the cations are not strongly localised but move around the methanol–chloride complex. The nearest imidazolium interacts with both the methanol oxygen and the hydrogen-bonded chloride ion, while the next nearest cation lies on the other side of the chloride ion. Both cations are oriented with their ‘bottom’ sites nearest to the methanol molecule (the reverse orientation to that found near water).

Fig. 5 shows the ranked distribution functions for the ‘top’ and ‘bottom’ sites on imidazolium relative to the central atoms of dimethyl ether and propane. The ranked distribution

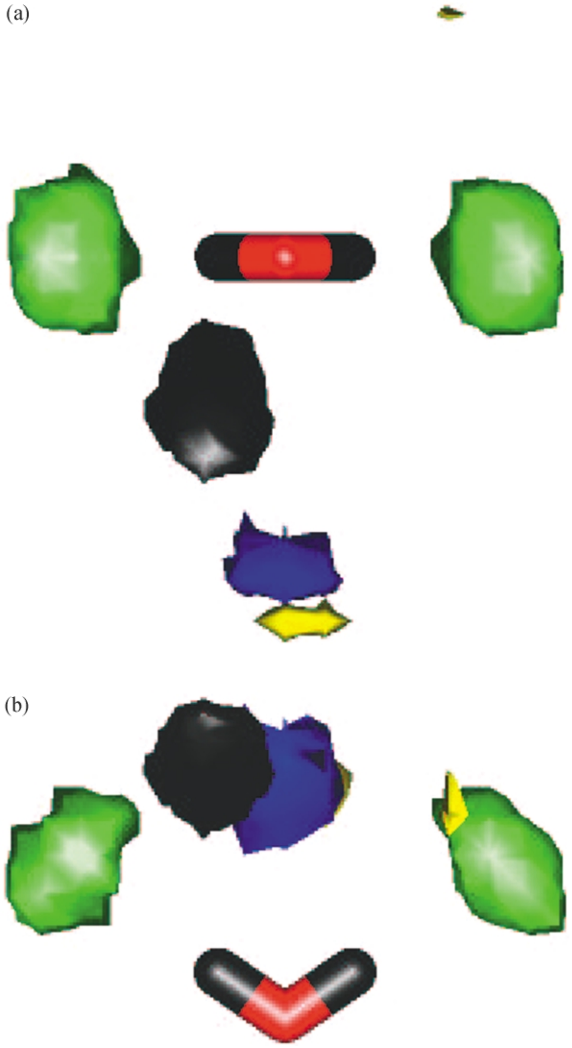

Fig. 2 Two views of the three dimensional probability distribution of ion sites relative to water in mmimCl. There is a high probability (> 20 times the average) of finding a chloride ion in the green regions and there is a medium probability (> 7 times the average) of finding the ‘centre’, ‘top’ and ‘bottom’ cation sites in the blue, black and yellow regions respectively; see text for definition of sites. The chloride ions are hydrogen bonded to the water OH groups and the imidazolium ion is oriented and localised between these chloride ions.

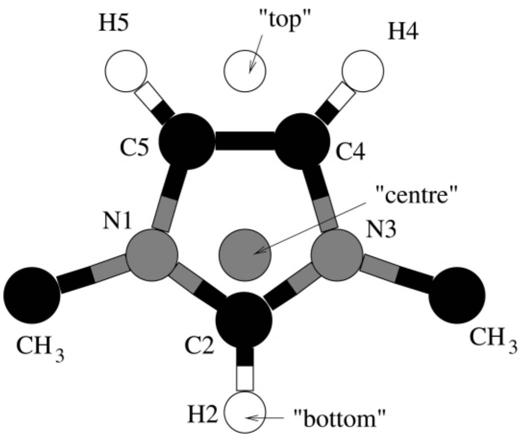

Fig. 3 Structure of the imidazolium ion showing the positions of the ‘top’ ‘centre’ and ‘bottom’ sites in the imidazolium ion.

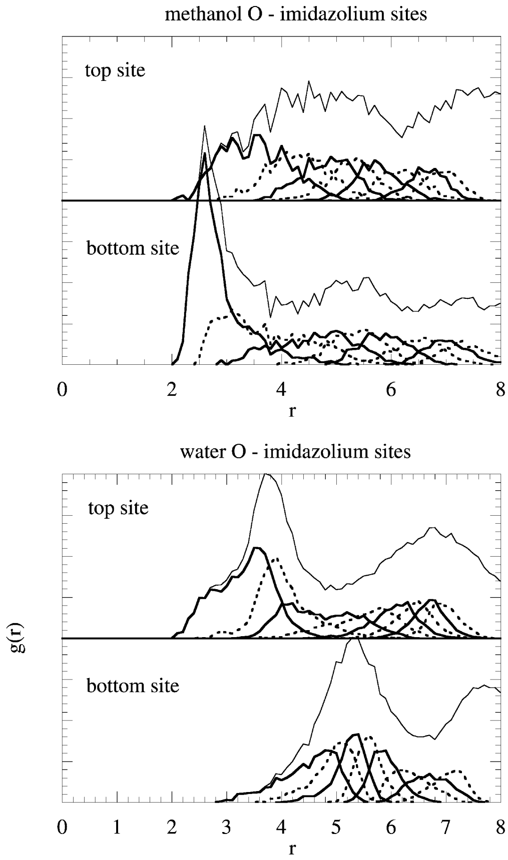

Fig. 4 Ranked radial distribution functions g_{SM} for ‘top’ and ‘bottom’ sites on the imidazolium ions relative to the oxygen atoms on the water and methanol molecules. The distributions of neighbours in ranking order are shown alternately with full and dashed lines. The total $g(r)$ is shown by a thin line. The positions of the sites are shown in Fig. 3.

functions for chloride ions relative to these solutes are shown in Fig. 1. For both solutes the nearest site is on a cation rather than on an anion. The individual ranked distribution functions are rather broad, showing that the local structure around the solute has considerable fluctuations and is not very well defined. The main differences between dimethyl ether and propane are that there is more preference for the nearest imidazolium ion to be oriented with its 'bottom' towards an ether molecule than a propane molecule, and secondly that the nearest imidazoloium ion is, on average, closer to a propane molecule than to a dimethyl ether molecule.

3.2 Energetics

Table 2 shows the interaction energies with cations, anions and their sum for the four solute molecules. The changes are consistent with the changes in local structure described in the previous section. As one traverses the series water, methanol, dimethyl ether and propane the following trends can be seen. First the interaction with the chloride becomes less favourable while the interaction with the dimethylimidazolium becomes more favourable, so that there is a comparatively small increase in the total interaction energy. Secondly the electrostatic (or Coulomb) contribution (which includes hydrogen bonding) is very large for water, about half the size for methanol and is still significant for dimethyl ether. This emphasises the importance of electrostatic forces in ionic liquids, both for molecules which form hydrogen bonds and for molecules with dipole moments. The magnitude of the solute–solvent interaction energy decreases by about 10 kJ mol^{-1} going from water to methanol and a further 10 kJ mol^{-1} going from methanol to dimethyl ether. Thus replacing an OH proton by a methyl group reduces the interaction energy by about 10 kJ mol^{-1}. The difference in interaction energy between the non-polar propane molecule and the similar-sized, but somewhat polar dimethyl ether molecule is larger at about 20 kJ mol^{-1}. These values are the average over the long runs that are necessary to sample the whole range of configurations that typify the liquid. Long runs are particularly necessary in ionic liquids as diffusion constants are slow[2] so that the local environment changes slowly. The errors in the calculation are shown in Table 2. These are the calculational uncertainties; there may also be systematic errors due to the difference between model molecules and true molecules. The values cannot at present be compared to experiment due to lack of experimental data. When data becomes available it must be recalled that the enthalpy of solution contains an additional term from the rearrangement energy of the solvent. However the trends in solvation enthalpies are likely to follow the trends of solvent–solute interactions energies for molecules of these types in a range of imidazolium ionic liquids.

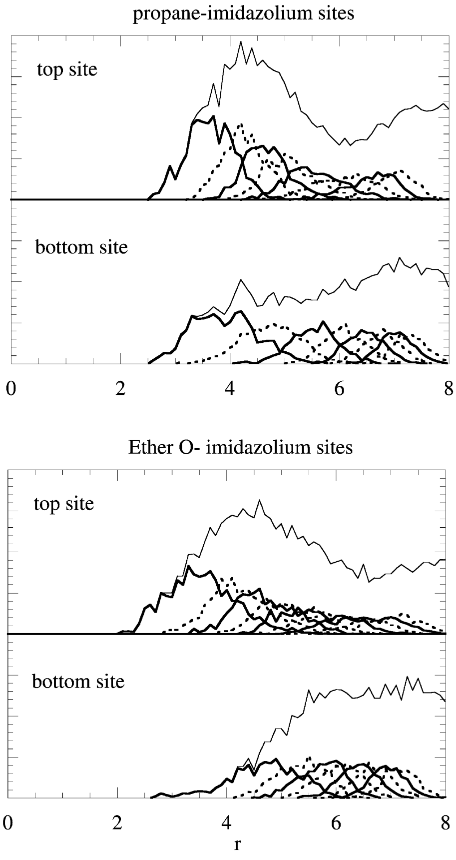

Fig. 5 Ranked radial distribution functions g_{SM} for 'top' and 'bottom' sites on the imidazolium ions relative to the central atoms of ether and propane molecules. The distributions of neighbours in ranking order are shown alternately with full and dashed lines. The total $g(r)$ is shown by a thin line. The positions of the sites are shown in Fig. 3.

Table 2 Interaction energies between solute molecules and solvent species in kJ mol^{-1}

Species (M)	M–mmim	M–Cl	Total	Coulomb
Me_2CH_2	−37 ± 1	−5.8 ± 0.5	−42 ± 5	0
Me_2O	−42 ± 5	−23 ± 3	−65 ± 5	−22 ± 1
MeOH	−26 ± 5	−46 ± 6	−72 ± 5	−52 ± 2
H_2O	−2 ± 10	−81 ± 7	−83 ± 7	−83 ± 2

Discussion

The solvation energetics and local structure around a solute are determined by the competition between the solute–solvent interaction and the interaction between the solvent ions, which is stronger than in most liquids due to the charged species. We find that the strongest solute–solvent interactions are hydrogen bonds between the solute and the anion and this dominates the solvation properties of solutes with hydroxyl groups. The local structure of the solvent around water and methanol can be thought of resulting from the formation of a water–chloride or methanol–chloride complex which then interacts with imidazolium ions. For dimethyl ether, which has no hydroxyl groups, interactions with the imidazolium ions become more important. These result in the oxygen atom being preferentially attracted to the side of the cation with two adjacent ring CH groups ('top' site). We predict that, because the chloride ions are highly localised by hydrogen bonding, the entropy of solvation is large and negative for water and decreases with the number of hydrogen bonds. However the structure-making due to the hydrogen bonding will be partly offset by structure-breaking of the structure of the neat liquid.

These simulations were carried out for a specific ionic liquid and a small sample of solutes in dilute solution. They show that it is possible to obtain information in spite of the fact that the ions diffuse abnormally slowly for a liquid.[2] Electrostatic interactions are particularly important in these solutions. We believe that the general trends for solvation of different types of molecule will carry over to ionic liquids with other relatively small cations and anions. For example we speculate that the solvation of solutes with hydroxyl groups will continue to be dominated by hydrogen bonding to the anions PF_6^- and BF_4^- as the local electric field near the fluorine atoms is still large. Lengthening the side chain on the imidazolium ring will certainly affect the local packing, but we predict that the main interactions of solutes with dipole moments such as dimethyl ether will be with the imidazolium ring as that is where the charge is located. In future we intend to extend the range of concentrations and solutes in our simulations and to use them measure solute chemical potentials.

Acknowledgements

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Thermodynamic properties of the ionic liquid 1-*n*-butyl-3-methylimidazolium hexafluorophosphate from Monte Carlo simulations

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We report results from the first molecular simulation study of 1-*n*-butyl-3-methylimidazolium hexafluorophosphate [bmim][PF_6], a widely studied ionic liquid. Monte Carlo simulations are carried out in the isothermal–isobaric (NPT) ensemble to calculate the molar volume, cohesive energy density, isothermal compressibility, cubic expansion coefficient and liquid structure as a function of temperature and pressure. A united atom forcefield is developed using a combination of *ab initio* calculations and literature parameter values. Calculated molar volumes are within 5% of experimental values, and a reasonable agreement is obtained between calculated and experimental values of the isothermal compressibility and cubic expansion coefficient. PF_6 anions are found to preferentially cluster in two favorable regions near the cation.

Introduction

Room temperature ionic liquids (ILs) are a class of organic salts that, in their pure state, are liquids at or near room temperature. Some of the more common air-stable ILs are composed of heterocyclic imidazolium or pyridinium cations having alkyl substituent groups and bulky anions such as $[PF_6]^-$, $[BF_4]^-$ or $[NO_3]^-$. Ionic liquids exhibit many interesting properties such as negligible vapor pressure, a low melting point, a large liquidus range and favorable solvation behavior. These properties can be altered to some extent by varying the anion, cation, or substituent groups on the cation. Due to their non-volatile nature and favorable solvation properties, ILs have been suggested as 'green' replacements for traditional volatile organic solvents.[1]

A host of different ILs have been synthesized[2–4] and used as a solvent for Diels–Alder, Heck, Friedel–Crafts and two-phase homogeneous catalytic reactions.[5–9] ILs have also been studied as a replacement for organic solvents in multiphase bioprocess operations.[10] One of the barriers preventing the adoption of ILs by industry is the dearth of physical property data for these compounds, as well as a general lack of fundamental understanding of how these properties depend on the chemical constitution of the IL. This situation is changing, as considerable effort has been expended to measure the density,[11] viscosity,[12] and miscibility of ILs with water[13] and organic solvents.[14]

An excellent review of these properties for ILs based on alkylimidazolium cations and fluoroanions has recently been made available.[15] Various thermal properties of imidazolium salts have also been reported,[16] and a few studies have focused on measuring the local fluid structure of ILs. NMR studies have indicated a possible hydrogen bonding between the cation and the anion in 1-*n*-butyl-3-methylimidazolium tetrafluoroborate [bmim][BF_4][17] and X-ray diffraction studies have yielded information on the organization of IL crystals.[18,19] Neutron diffraction experiments have been conducted to determine the liquid structure of moisture-sensitive chloride-based imidazolium salts such as imidazolium chloride–HCl and imidazolium

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Green Context

While ionic liquids are widely researched as non-volatile reaction media, there is relatively little work on the study of their physical properties. The general lack of understanding on structure–property relationships in particular is hampering their uptake as solvents by industry. Fortunately, these shortfalls are now more generally appreciated and articles such as this one are improving the situation. Detailed studies of molecular simulations of the ionic liquid [bmim][PF_6] are reported. There is good agreement between experimental and calculated properties which adds credibility to the calculations. Some of the interesting conclusions are the observation of long range ordering and the association between the anion and one of the imidazolium ring carbons. ***JHC***

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chloride–$AlCl_3$.[20] Preliminary neutron scattering experiments have been conducted on water stable ILs.[21]

The thermophysical properties of ILs can also be studied through the use of molecular simulation. In this approach, a detailed geometric and energetic model of the fluid is constructed at the atomistic level. Millions of different conformations of the system are generated through use of an appropriate numerical technique. The thermophysical properties of the model system are computed by application of statistical mechanical formalisms to the atomic trajectories. This approach is now commonly used to compute the properties of organic liquids,[22] aqueous and ionic systems,[23] and solids.[24] The methods enable quantitative prediction of thermophysical properties from molecular-level information, and also lead to a better fundamental understanding of the way in which these properties depend upon molecular energetics and architecture. To our knowledge, Lynden-Bell and co-workers have carried out the only molecular simulation study of a water-stable IL.[25] They simulated dimethylimidazolium and ethylmethylimidazolium salts using a rigid model for the cation and anion. They computed crystal structures, potential energies, densities, diffusivities and local liquid structures for these species.

In the present study, we use a Monte Carlo technique to simulate 1-*n*-butyl-3-methylimidazolium hexafluorophosphate [bmim][PF_6]. We report the interatomic potential model used for the simulations and compare calculated values of the molar volume, cohesive energy density, isothermal compressibility, and cubic expansion coefficient against experimental data measured in our laboratory.[11] We also determine the local structure of the liquid *via* radial distribution functions and a probability distribution plot.

Forcefield

The success of a molecular simulation method in accurately predicting thermophysical properties depends on the quality of the inter- and intra-molecular potential functions used in modeling the fluid. These potential functions are collectively referred to as the forcefield. Eqn. (1) gives the functional form of the forcefield used in this work

$$v_{tot} = 1/2\sum_{ij}\left[4\varepsilon_{ij}\left(\left(\frac{\sigma_{ij}}{r_{ij}}\right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}}\right)^{6}\right) + \frac{q_i q_j}{r_{ij}}\right] + v(\phi) \qquad (1)$$

where v_{tot} refers to the total energy of the system. The non-bonded portion of the forcefield consists of Lennard-Jones and Coulombic terms that account for dispersion and electrostatic interactions. The sum extends over all the interaction sites i and j on different molecules or those within the same molecule separated by more than three bonds. The Lennard-Jones collision diameter and energy well depth are given by σ and ε, respectively. The last term in eqn. (1), $v(\phi)$, accounts for the torsional potential governing the four rotatable dihedral angles associated with the butyl group on the cation. This energy is given by the following Fourier series

$$v(\phi) = v_0 + \frac{v_1}{2}(1+\cos(\phi)) + \frac{v_2}{2}(1-\cos(2\phi)) + \frac{v_3}{2}(1+\cos(3\phi)) \qquad (2)$$

where ϕ is the torsion angle and v_1,v_2 and v_3 are the Fourier coefficients. The parameters for eqns. (1) and (2) were determined in the following manner.

First, *ab initio* calculations were carried out on an isolated cation and anion using Gaussian 98©[26] at the restricted Hartree-Fock (RHF)/6-31G* level to determine the minimum geometry of the [bmim] cation (Fig. 1) and the anion. Partial charges on each atom were derived by fitting to the electrostatic potentials at points selected according to the CHELPG scheme.[27] The total partial charge on the cation and anion were forced to be +1 and −1, respectively. The Cartesian coordinates of the optimized geometry of the [bmim] cation are reported in Table 1. Next, a united atom (UA) approximation was adopted for the carbon atoms and the PF_6 anion (Fig. 2). In this approach, each carbon atom and the hydrogen atoms bonded to it are represented as a single site located at the center of the carbon atom. A partial charge equal to the sum of the calculated charges on the carbon and hydrogen atoms was assigned to the united atom center. In the same way, the fluorine atoms in the anion were subsumed into the phosphorus atom, yielding a single interaction site for each anion with partial charge of −1. The UA approximation was adopted mainly to reduce computational costs. All bond lengths and angles were fixed at the optimized values obtained from the quantum calculation, as were the dihedral angles within the imidazolium ring. The Lennard-Jones interaction parameters for the butyl and methyl chain carbons were taken from the optimized potentials for liquid simulations united atom (OPLS-UA) force field.[28] An all-atom version of this forcefield (OPLS-AA) contains parameters for nitrogen and carbon in imidazole.[29] The OPLS-AA

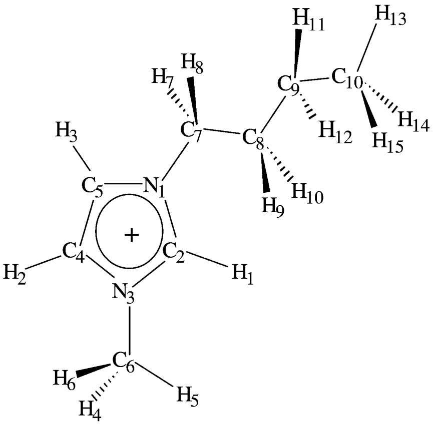

Fig. 1 All atom representation of [bmim]$^+$.

Table 1 Cartesian coordinates of the optimized geometry of [bmim] in Angstrom

Atom	*x*	*y*	*z*	Atom	*x*	*y*	*z*
N_1	0.494	0.183	0.466	C_2	1.414	−0.745	0.325
N_3	2.518	−0.211	−0.15	C_4	1.035	1.382	0.057
C_5	2.298	1.138	−0.325	C_6	3.771	−0.916	−0.437
C_7	−0.889	−0.026	0.943	C_8	−1.904	−0.006	−0.197
C_9	−3.33	−0.219	0.318	C_{10}	−4.361	−0.202	−0.809
H_1	1.285	−1.779	0.563	H_2	0.478	2.293	0.081
H_3	3.055	1.791	−0.699	H_4	4.011	−0.805	−1.483
H_5	4.561	−0.504	0.173	H_6	3.645	−1.962	−0.204
H_7	−1.089	0.748	1.671	H_8	−0.9	−0.975	1.463
H_9	−1.841	0.944	−0.721	H_{10}	−1.648	−0.78	−0.915
H_{11}	−3.386	−1.167	0.847	H_{12}	−3.572	0.554	1.043
H_{13}	−5.36	−0.356	−0.416	H_{14}	−4.355	0.747	−1.335
H_{15}	−4.166	−0.988	−1.533				

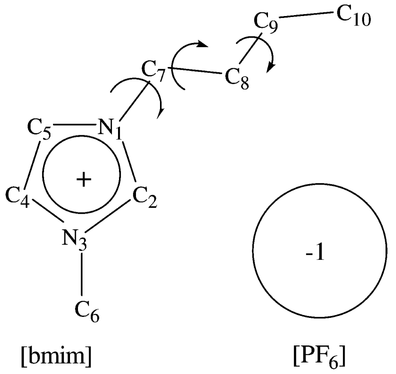

Fig. 2 United atom (UA) representation of [bmim]$^+$ and [PF$_6$]$^-$.

imidazole nitrogen Lennard-Jones parameters were adopted for imidazolium nitrogen, while the carbon atom parameters in the ring were determined by scaling the OPLS-AA all-atom parameters of the carbon in imidazole by the ratio of the sp^2 UA carbon parameters to those for AA carbon. A crude estimate of the anion collision diameter was obtained by scaling the literature value for SF$_6$[30] by the ratio of the molecular radii of PF$_6$ and SF$_6$ obtained from gas phase quantum calculations, while the energy well depth was set equal to the literature value for SF$_6$.[30] Unlike pair interaction parameters were obtained by using a geometric mean combining rule such that $\sigma_{ij} = (\sigma_{ii}\sigma_{jj})^{1/2}$ and $\varepsilon_{ij} = (\varepsilon_{ii}\varepsilon_{jj})^{1/2}$. A listing of all the Lennard-Jones parameters and partial charges is given in Table 2. Table 3 lists the flexible torsion angles in the system, along with the Fourier coefficients for each of the dihedral angles.

Table 2 Forcefield parameters used in this work

Atom	σ_{ii}/Å	ε/kJ mol^{-1}	q_i/e
N$_1$	3.250	0.710	0.071
N$_3$	3.250	0.710	0.133
C$_2$	3.880	0.443	0.229
C$_4$	3.880	0.443	0.041
C$_5$	3.880	0.443	0.096
C$_6$	3.775	0.865	0.217
C$_7$	3.905	0.493	0.024
C$_8$	3.905	0.493	0.118
C$_9$	3.905	0.493	0.118
C$_{10}$	3.905	0.732	−0.047
PF$_6$	4.720	1.668	−1.000

Table 3 Torsional parameters for the rotatable dihedral angles

Dihedral angle	V_0/kJ mol^{-1}	V_1/kJ mol^{-1}	V_2/kJ mol^{-1}	V_3/kJ mol^{-1}
C$_7$–C$_8$–C$_9$–C$_{10}$	0.00	5.89	−1.13	13.17[a]
N$_1$–C$_7$–C$_8$–C$_9$	0.00	11.41	0.96	2.05[b]
C$_2$–N$_1$–C$_7$–C$_8$	0.00	−5.85	−1.80	0.00[c]
C$_5$–N$_1$–C$_7$–C$_8$	0.00	−5.85	−1.80	0.00[c]

[a] OPLS-UA parameters for *n*-alkane. [b] OPLS-AA parameters for *n*-ethylformamide. [c] OPLS-AA parameters for ammonium ion.

One of the objectives of this work is to determine whether the thermophysical properties of ionic liquids can be modeled accurately using standard potential parameters with little modification. This is important, given the fact that very little data exists on ionic liquids at the present time. Given enough experimental data, it is usually possible to adjust forcefield parameters to match experimental data, but this luxury does not exist with ionic liquids. Thus this study, in which all forcefield parameters were set prior to the start of the simulations with no subsequent adjustments, serves as a test of the predictive capability of molecular simulation in determining the thermophysical properties of ionic liquids.

Simulation details

The simulations were carried out in the isobaric–isothermal (NPT) ensemble using a Monte Carlo technique. A total of 192 cations and 192 anions were simulated in a cubic simulation cell with standard periodic boundary conditions. Initial configurations were generated by randomly inserting a cation–anion pair into the simulation box, after which the system was relaxed by performing a few hundred Monte Carlo cycles. A cycle refers to N moves, where N is the number of ions currently in the system. During this initial equilibration phase, only three types of Monte Carlo moves were performed: translation of an ion center-of-mass (COM); rotation about a randomly chosen axis through the cation COM; and dihedral angle rotations of one of the torsion angles in the butyl chain. The boldness of each move was adjusted during this phase so that roughly 50% of the moves were accepted. This insertion–relaxation process was repeated until all the ions were added to the system. The initial simulation box volume was chosen such that the starting density was equal to the experimental density at the state point of interest. Once all the ions were added to the system, the entire system was equilibrated for 10 000 cycles. During this equilibration phase (and the subsequent production run), two other moves were used in addition to the three moves mentioned above. A volume change was attempted once every two cycles. This move allowed the density to vary in order to maintain pressure at the desired value. The maximum size of the volume change was adjusted to achieve roughly 35% acceptance. Finally, a combined displacement move was used, in which cation–anion pairs are moved together. This move is similar in spirit to a cluster move proposed earlier.[31] This move was used to improve the sampling efficiency of the method, given the difficulty of independently moving ions that are strongly associating. Standard Metropolis acceptance rules were used for each of the moves.[32]

Well-equilibrated systems were used as starting configurations for the final production runs. These runs consisted of two sets of 5000 Monte Carlo cycles. Spherical potential truncation was employed at half of the simulation box length for dispersion interactions, and long range corrections[32] were applied beyond the cutoff distance. A hard inner cutoff was also used such that a move bringing two interactions sites closer than 1 Å was immediately rejected. Long range electrostatic interactions were handled by the Ewald summation method with the permittivity of the surrounding medium set equal to that of vacuum ($\varepsilon_s = 1$).

Results and discussion

Local fluid structure, molar volume, cohesive energy density, isothermal compressibility and cubic expansion coefficient of [bmim] [PF$_6$] were computed at ten different state points. Five of the state points were at atmospheric pressure (0.98×10^5 Pa), with temperatures ranging from 298 to 343 K. The remaining five state points were at 323 K and pressures ranging from 0.98×10^5 to 2028×10^5 Pa. These state points were chosen because experimental data is available against which the simulation results can be compared.[11]

Cohesive energy density

Cohesive energy density is defined as[33]

$$c = \frac{\Delta \nu^{vap}}{\nu^{l}} \tag{3}$$

where $\Delta \nu^{\text{vap}}$ refers to the energy change upon complete vaporization of the liquid to the ideal gas state at the same temperature and v^l is the liquid molar volume. In a simulation, the former quantity was determined by computing the average internal energy in the liquid and gas phases. Liquid phase energies were calculated during the course of the liquid simulations. Ideal gas energies were computed by simulating a pair of [bmim] and [PF_6] ions in a cubic simulation box of length 1000 Å. Translational, rotational and dihedral moves were implemented to obtain the gas phase average energies. It was observed that the cohesive energy density, over the entire temperature and pressure range, remained relatively constant at around 170 cal cm^{-3}. This value may be compared with those of hydrocarbons such as hexadecane and naphthalene for which the cohesive energy densities are 64.0 and 98.0 cal cm^{-3}, respectively.[34] The high cohesive energy density, due in large part to strong electrostatic interactions between ions, helps explain the low volatility of this IL.

Molar volume

Molar volumes of the pure IL were computed as a function of pressure and temperature by setting the simulated temperature and pressure equal to that at the experimental state points and computing the resulting molar volume. In Fig. 3, molar volumes computed as a function of pressure at 323 K are compared against experimental values. The lines are fits to the Tait equation.[35] The Tait equation, in terms of molar volume is

$$V = V_0 - V_0 C \ln\left(\frac{B+P}{B+P_0}\right) \qquad (4)$$

where V_0 the molar volume at a reference pressure P_0, chosen to be 0.98 × 10^5 Pa in this case. The constants B and C are optimized to obtain best fit with the isothermal molar volume data. Fig. 4 shows the simulation predictions for molar volume as a function of temperature at atmospheric pressure where lines are the linear fits to the data. Results are also given in Tables 4 and 5. In all cases, the simulations predict molar volumes that are roughly 3–5% less than experimentally obtained values. This level of agreement is remarkably good, considering that the calculations are entirely predictive (*i.e.* no adjustments have been made to the parameters to match experimental data). The disagreement with experiment is likely due to two effects. First, the UA representation used here may enable the cations and anions to pack more efficiently than would be the case with a 'rougher' all-atom forcefield. Second, the values of the Lennard-Jones parameters may be in error. In particular, the collision diameter of the anion may be slightly too small, which would tend to cause the molar volume to be too small. This is supported by the fact that in preliminary calculations (not shown here) a slight increase in the Lennard-Jones s parameter for the PF_6 anion increased the molar volume of the system by roughly 5%. Nevertheless, the good degree of agreement between calculated and experimental molar volumes over a wide range of temperatures and pressures indicates that the forcefield used in this work is reasonable and should provide insight into the liquid state properties of this IL. It was thus used without further adjustment to compute additional thermophysical properties for the IL.

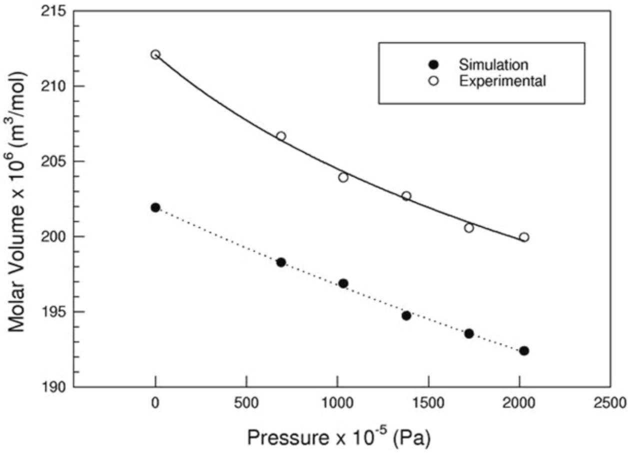

Fig. 3 Comparison of experimental and predicted molar volumes of [bmim][PF_6] from 0.98 × 10^5 to 2028 × 10^5 Pa at 323 K. Lines are fits to the Tait equation.

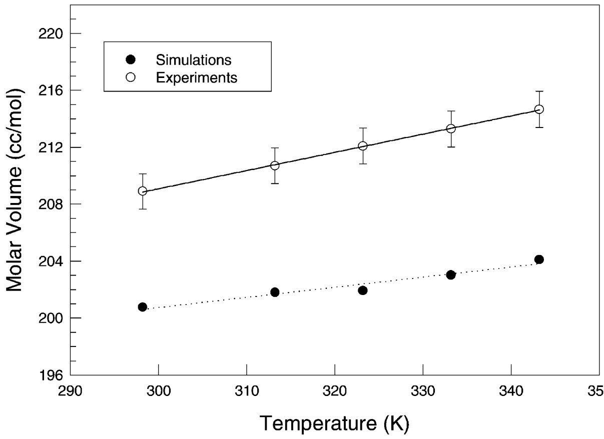

Fig. 4 Comparison of experimental and predicted molar volumes of [bmim][PF_6] from 298 to 343 K at 0.98 × 10^5 Pa. Linear fits to the data are also shown.

Table 4 Comparison of molar volume predictions with experimental results for pressure ranging from 0.98 × 10^5 to 2028 × 10^5 Pa at 323 K.

10^{-5} Pressure/Pa	10^6 V_{sim}/ m^3 mol^{-1}	10^6 V_{exp}/ m^3 mol^{-1}	Deviation (%)
0.98	201.98 ± 0.3	212.1 ± 1.3	−4.78
691	198.3 ± 0.6	207.0 ± 2.0	−4.05
1035	196.9 ± 0.3	204.0 ± 2.0	−3.45
1380	194.72 ± 0.07	203.0 ± 2.0	−3.92
1725	193.5 ± 0.5	201.0 ± 2.0	−3.5
2028	192.39 ± 0.08	200.0 ± 2.0	−3.77

Table 5 Comparison of molar volume predictions with experimental results from 298 to 343 K at atmospheric pressure

Temperature/K	10^6 V_{sim}/ m^3 mol^{-1}	10^6 V_{exp}/ m^3 mol^{-1}	Deviation (%)
298	200.8 ± 0.4	208.9 ± 1.2	−3.89
313	201.8 ± 0.30	210.7 ± 1.3	−4.22
323	201.9 ± 0.3	212.1 ± 1.3	−4.79
333	203.0 ± 0.6	213.3 ± 1.3	−4.84
343	204.1 ± 0.3	214.7 ± 1.3	−4.91

Cubic expansion coefficient (α_P)

The degree to which the density of a fluid changes with temperature at constant pressure is quantified by the cubic expansion coefficient, defined as

$$\alpha_P = \frac{1}{V}\left(\frac{\partial V}{\partial T}\right)_P \qquad (5)$$

where V is molar volume and P is pressure. The cubic expansion coefficient can be estimated using eqn. (5) by carrying out a series of simulations at constant pressure but different temperatures. Since the volume changes linearly with temperature, a_P can be calculated directly from a linear fit to the data (Fig. 4).

Alternatively, a_P can be computed by monitoring the fluctuations in volume and enthalpy that occur during an NPT simulation. Formally, this is written as

$$\alpha_P = \frac{1}{\langle V \rangle k_B T^2}(\langle VH \rangle - \langle V \rangle \langle H \rangle) \tag{6}$$

where H is enthalpy and $\langle\,\rangle$ denotes an ensemble average. The a_P computed using these two approaches are plotted in Fig. 5 and are compared with the experimental results. It is observed that a_P remains relatively constant over the entire temperature range, in good agreement with the experiments. Cubic expansion coefficients computed using the fluctuation formula are slightly lower than what is obtained from a linear fit to the simulation molar volumes, but are generally consistent. In all cases, the simulations predict expansion coefficients that are lower than the experimental values by about a factor of two. This may indicate that the interactions among the various ions in the model system are stronger than those present in the actual system. Derivative quantities such as the expansion coefficients are notorious for being more difficult to predict from simulation than densities. Given this and the fact that the trend with temperature is captured well, it appears that the model again does a reasonably good job of predicting IL properties (Table 6).

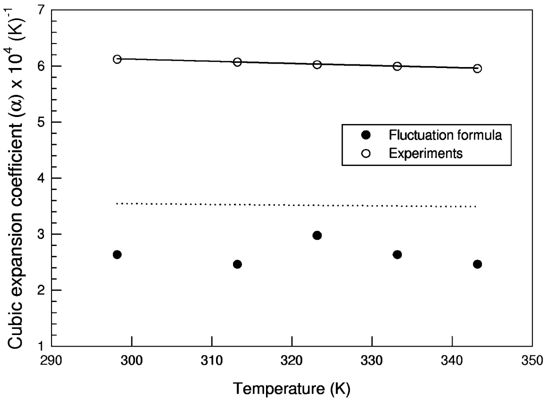

Fig. 5 Cubic expansion coefficient of [bmim][PF$_6$] from 298 to 343 K at 0.98 × 10^5 Pa. The dashed line was obtained from a linear fit to simulated densities.

Table 6 Comparison of cubic expansion coefficient using different methods as a function of temperature from 298 to 343 K

Temperature/K	$10^4\ \alpha_{\exp}{}^a$/K^{-1}	$10^4\ \alpha_{\text{sim}}{}^b$/K^{-1}	$10^4\ \alpha_{\text{fit}}{}^c$/K^{-1}
298	6.11 ± 0.04	2.630 ± 0.012	3.52 ± 0.07
313	6.06 ± 0.04	2.460 ± 0.011	3.50 ± 0.07
323	6.02 ± 0.04	2.970 ± 0.016	3.50 ± 0.07
333	5.99 ± 0.04	2.630 ± 0.200	3.48 ± 0.07
343	5.94 ± 0.04	2.460 ± 0.011	3.46 ± 0.07

[a] Experimentally obtained.[11] [b] Fluctuation formula (eqn. (6)). [c] Linear fit of simulation molar volumes.

Isothermal compressibility (κ_T)

The change in molar volume with pressure at a given temperature can be quantified by the isothermal compressibility κ_T.

$$\kappa_T = -\frac{1}{V}\left(\frac{\partial V}{\partial P}\right)_T \tag{7}$$

In a simulation, this quantity is estimated in one of two ways. Molar volumes are computed for a number of isothermal simulations at varying pressure, and κ_T is estimated by fitting the Tait equation (eqn. (4)) to the predicted molar volumes and using eqn. (7). Alternatively, fluctuations in system volume can be monitored under constant pressure and temperature conditions, and κ_T calculated as

$$\kappa_T = \frac{\langle V^2 \rangle - \langle V \rangle^2}{k_B T \langle V \rangle} \tag{8}$$

Fig. 6 shows a comparison of isothermal compressibilities determined from eqns. (7) and (8) for [bmim][PF$_6$] with experimental data. The model system is less compressible than the actual IL at low pressures, but as the pressure is increased the difference between the simulations and experimental results decreases. Overall, the simulations predict a decrease in volume of 5.8% in going from atmospheric pressure to 2028 × 10^5 Pa (Fig. 3), in excellent agreement with experimental values that show a decrease in molar volume of ~5.7% over the same pressure range. A possible reason the model performs better at high pressure than low pressure has to do with the united atom approximation. As mentioned above, the united atom model smoothes out the surface of the molecules, enabling more efficient packing than exists in the real system at low pressure. As the pressure is increased, however, the IL tends to acquire its closest packing volume, at which point [bmim][PF$_6$] attains a nearly constant isothermal compressibility and the agreement with simulations becomes very good (Table 7).

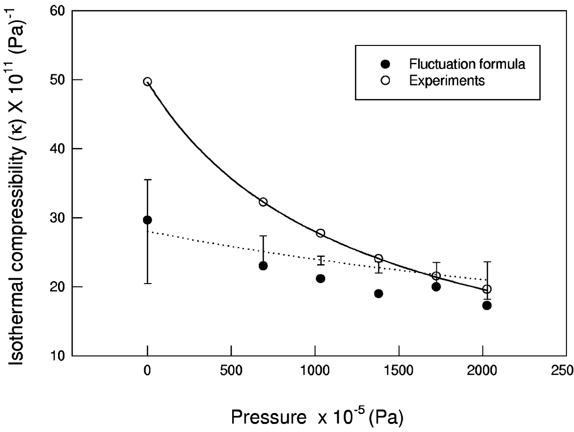

Fig. 6 Isothermal compressibility of [bmim][PF$_6$] from 0.98 × 10^5 to 2028 × 10^5 Pa at 323 K. Lines are obtained using Tait equation fits.

Table 7 Comparison of isothermal compressibility for pressures ranging from 0.98 × 10^5 to 2028 × 10^5 Pa at 323 K.

10^{-5} Pressure/Pa	$10^{11}\ \kappa_{\exp}{}^a$/Pa^{-1}	$10^{11}\ \kappa_{\text{sim}}{}^b$/Pa^{-1}	$10^{11}\ \kappa_{\text{fit}}{}^c$/Pa^{-1}
0.98	49.6 ± 0.48	29.6 ± 0.30	29.2 ± 7.5
691	32.3 ± 0.31	23.0 ± 0.20	25.0 ± 2.3
1035	27.7 ± 0.27	21.2 ± 0.20	23.6 ± 0.6
1380	24.0 ± 0.23	19.0 ± 0.07	22.5 ± 0.8
1725	21.5 ± 0.30	20.0 ± 0.20	21.7 ± 1.8
2028	19.6 ± 0.19	17.2 ± 0.03	20.9 ± 2.7

[a] Experimentally obtained.[11] [b] Fluctuation formula (eqn. (8)). [c] Derived from Tait equation fit (eqn. (4)).

Molecular structure

One of the more important fundamental questions concerning ionic liquids has to do with the fluid structure. X-Ray studies have shown that IL solids form ordered, layered structures.[18] Very little is known about the local structure of the liquid. The good agreement between experimental pressure–volume–temperature properties and those obtained by simulations provides reasonable confidence that the actual local fluid structure of the IL should be in good accord with that determined from simulations. One particularly useful means of reporting fluid structure is *via* the radial distribution function, $g(r)$, which gives the probability of finding a pair of atoms separated by a distance r, relative to the probability expected for a completely random distribution at the same density. Thus $g(r) = 1$ indicates no order (a random distribution), while $g(r) > 1$ indicates a local ordering and $g(r) < 1$ indicates a depletion at a given separation r. Fig. 7 shows the cation–cation, anion–anion and cation–anion center-of-mass radial distribution function (RDF) at 298 K and 0.98×10^5 Pa. RDFs at other state points are qualitatively very similar and are not shown here. It is observed that cation–anion pairs tend to order in a first solvation shell at a separation of about 4 Å. Subsequent cation–anion solvation shells occur at 10 and 17 Å. Long range order persists even out beyond 20 Å, as evidenced by the fact that $g(r)$ still shows oscillations. Such long range order is not observed for non-polar liquids, but is expected here, given the strong Coulombic interactions in the system. Peaks in $g(r)$ due to anion–anion and cation–cation ordering occur at roughly 8 and 13 Å. These peaks are the result of secondary order induced by the cation–anion pairs. The anion–anion peak is sharper than the cation–cation peaks because the center-of-mass provides a better description of the location of the anion than it does for the bulky cation.

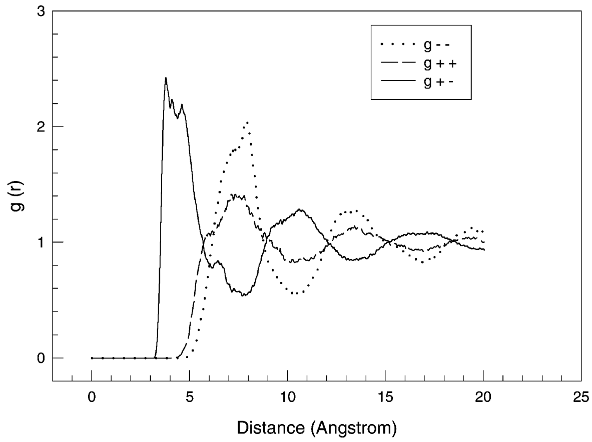

Fig. 7 Center of mass (COM) radial distribution of [bmim][PF$_6$] at T = 298.2 K and P = 0.98×10^5 Pa.

Further insight into the local fluid structure can be gained by examining the three dimensional probability plot (Fig. 8) of anions around the cation. The highest probability is found around the C$_2$ carbon atom, both below and above the plane of the imidazole ring. The C$_2$ carbon atom is the center of the largest positive charge on the anion, so it is not surprising that this is where the anion localizes. This result is consistent with *ab initio* calculations performed in our group, which suggest that the lowest energy conformations consist of close association between the C$_2$ carbon and the anion. It is also observed that there are regions around C$_4$ and C$_5$ carbons along with the C$_6$ carbon where anions are located. These four distinct regions offer a good explanation for different peaks observed in the first solvent shells of the cation–anion RDF. The three dimensional probability plot also reveals useful insights into the location of the butyl chain. The butyl chain rotates freely in space excluding some of the volume in which anions could reside. A very similar distribution of anions was also observed in the simulations of dimethylimidazolium hexafluorophosphate.[25]

Conclusion

Results of molecular simulations of the IL [bmim][PF$_6$] are reported. A united atom molecular forcefield is developed for the ionic liquid, using a mixture of *ab initio* calculations and parameters obtained from the literature. The forcefield was not adjusted to match any experimental data. The agreement between experimental and calculated values of the molar volume, isothermal compressibility and cubic expansion coefficient is good, although simulated molar volumes are roughly 5% less than experimental values. Expansion coefficients and compressibilities are also slightly lower than experiment. Discrepancies between the simulations and experiment are attributed to the simplified nature of the united atom model and the use of non-optimized potentials. Local liquid structure is also reported in the form of centers-of-mass radial distribution functions for cation–anion, anion–anion and cation–cation pairs. Long range ordering (beyond 20 Å) is observed, and the anion tends to associate with the C$_2$ carbon atom of the imidazolium ring.

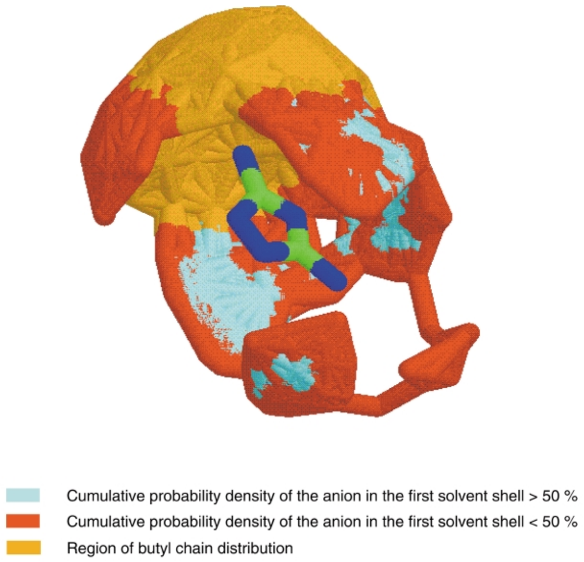

Fig. 8 Probability density plot of [PF$_6$]$^-$ and location of butyl chain around [bmim]$^+$. Blue indicates regions in the first solvation shell where the cumulative probability of finding the anion is greater than 50%, while red indicates the remaining regions in the first solvation shell where there is a finite probability of finding an anion. The gold color indicates regions where the butyl chain end is found.

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Selective catalytic oxidation of benzyl alcohol and alkylbenzenes in ionic liquids

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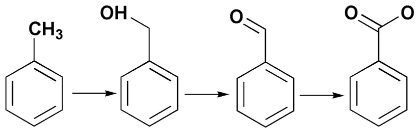
Industrially performed catalytic oxidation reactions often suffer from drawbacks such as poor conversion and selectivity due to over-oxidation, corrosive reaction media, lack of solvent and catalyst recycling, and negative environmental impact due to evaporation of the solvents. In order to provide a methodology that addresses these problems, ionic liquids have been investigated as reaction media. For the example of the oxidation of benzyl alcohol to benzaldehyde (dehydrogenation), it was shown that the palladium metal catalysed oxidation can be brought about, leading to better TOFs than those observed in dimethyl sulfoxide, with the added advantage of facile catalyst and solvent recycling. It was found that the selectivity to benzaldehyde is strongly dependent on the level of chloride ion, which leads to the formation of dibenzyl ether. Secondly, the amount of water present in the ionic liquid determines the extent of benzoic acid formation. Interestingly, ionic liquids are able to deactivate the water formed in the oxidation of benzyl alcohol and thus prevent it from further reaction to benzoic acid. The oxidation of toluene and ethylbenzene showed that the introduction of oxygen into the molecule is feasible using the same methodology.

The selective catalytic oxidation of hydrocarbons, such as toluene, to their respective aldehydes is a major challenge for industry. Such reactions are frequently performed at very low conversion rates in order to avoid the formation of carboxylic acids, and, if performed in the gaseous phase, decomposition to carbon dioxide.[1] These over-oxidations occur due to the large activation energy required to bring about the first step in the oxidation reaction, *e.g.* the formal removal of a hydrogen atom from the methyl group of toluene, which is greater than those for the subsequent oxidation steps. Therefore, if the energy is introduced thermally, the oxidation proceeds directly to benzoic acid or carbon dioxide. Another problem of conventional oxidation is that, if performed in the liquid phase, ethanoic acid is often used as a solvent with a transition metal catalyst, commonly cobalt-based. This mixture is corrosive and requires laborious separation from the products; in fact, catalyst recycling is often not feasible.[2,3]

Since the discovery of second-generation ionic liquids in 1992,[4] these novel media have been extensively investigated as solvents, and in particular for catalysis. Although ionic liquids have been used, *inter alia*, for transition metal catalysed hydroformylation, hydrogenation, Heck and Suzuki reactions, hydrodimerisation, hydroesterification, and various coupling reactions,[5-8] very few chemical catalytic oxidations have been reported in the literature,[9,10] with the notable exception of the epoxidation reactions recently published.[11–13] Some of the advantages of using ionic liquids in catalytic reactions are connected with the lack of a measurable vapour pressure: products can be easily distilled out of the reaction mixture and the impact on the environment and operating personnel is dramatically reduced. In addition, due to the great choice of different ionic liquids, the solvent properties may be tuned to suit a particular application (*e.g.* selectivity, yield, degree of solubility of products and substrates, *etc.*). In order to investigate such oxidation reactions in ionic liquids, the selective oxidation of toluene to benzaldehyde was selected as a model reaction (Scheme 1).

Benzaldehyde is an interesting target molecule, since it is easily over-oxidised to benzoic acid, as mentioned above; therefore, the formation of benzoic acid is a direct measure of the selectivity of the protocol. Moreover, since the oxidation of toluene proceeds *via* benzyl alcohol, the latter can be used to study the factors that influence the selectivity for benzaldehyde under less drastic conditions. Therefore, the concept of this study was firstly to investigate if a transition metal catalysed



Scheme 1 Stepwise oxidation of toluene to benzoic acid, *via* benzyl alcohol and benzaldehyde

Green Context

The use of ionic liquids (ILs) as non-volatile media in which to carry out transition metal catalysed organic processes is a rapidly growing field. Oxidation reactions have been relatively little studied in these solvents, however. It is clear that improvements both in rate of partial oxidation of benzyl alcohol and ease of isolation of benzaldehyde occur when the reaction is carried out in ILs instead of DMSO. The replacement of DMSO as a reaction solvent is an important development, given its toxicity. Although the reaction is not optimised, the ability to recycle the catalyst/IL system is demonstrated, and evidence for some deactivation of the water by-product is presented. The oxidation of aryl alkyl compounds occurred less readily, but once again preliminary results using ILs indicate that a usable partial oxidation reaction might be developed. ***CMG***

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selective oxidation would be at all possible in an ionic liquid, using benzyl alcohol as a substrate. The second step encompassed a thorough investigation of the factors that influence the selectivity to benzaldehyde, before the methodology was applied to the oxidation of alkylbenzenes.

In 1998, Peterson and Larock reported a very successful homogeneous method for the liquid phase oxidation of primary and secondary alcohols.[14] These authors used palladium(II) ethanoate in dimethyl sulfoxide, under 1 atm of dioxygen at 80 °C. The oxidation of alcohols under these conditions has several advantages: (i) the oxidation of alcohols with transition metal catalysts in the presence of dioxygen produces only water as by-product. (ii) Over-oxidation to the carboxylic acids did not occur. (iii) Palladium(II) ethanoate is relatively cheap, non-toxic and readily available. The synthesis of expensive ligands is not necessary. (iv) Dioxygen is a very inexpensive oxidant.

However, some disadvantages remain, which are in particular connected to the use of dimethyl sulfoxide. (i) Dimethyl sulfoxide (dmso) is toxic, and difficult to quantitatively remove from the product. (ii) The recycling of the catalyst and solvent is not feasible.

In order to provide a cleaner process, and investigate possible effects of the ionic liquid upon selectivity, the above-mentioned protocol was adapted to ionic liquids.

In a preliminary study, it was investigated whether the oxidation of benzyl alcohol could be brought about in an ionic liquid, using the principal method of Peterson and Larock[14] (1 mmol benzyl alcohol; 1 cm^3 dmso; 5 mol% $Pd(O_2CMe)_2$; 1 atm O_2; 80 °C), but replacing dmso with the ionic liquid 1-butyl-2,3-dimethylimidazolium tetrafluoroborate ([C$_4$dmim][BF$_4$]).† The reaction in dmso proceeded to 90% conversion within 48 h, giving a TOF‡ of 0.4. In the ionic liquid however, the same conversion was achieved after only 15 h, which corresponds to a TOF of 1.2. This comparative study demonstrates that [C$_4$dmim][BF$_4$] could indeed be used as a substitute for dmso. Moreover, the TOF is increased by a factor of 3. This result prompted us to investigate the effect of the nature of the ionic liquids in more detail.

The influence of an ionic liquid on transition metal catalysed reactions is dependent on the nature of its constituent anions and cations. First, the coordinative ability of the anion will determine whether it plays a role in the formation of the catalytic species or whether it has little influence. Thus, if palladium(II) ethanoate is dissolved in a halide-containing ionic liquids such as [C$_6$mim]Cl, a homogeneous solution results, which stays homogeneous upon addition of the alcoholic substrate at 1 atm of dioxygen and 80 °C. On the other hand, in ionic liquids with poorly coordinating anions, such as tetrafluoroborate, precipitation of palladium metal occurs§ under otherwise identical conditions (see Fig. 1). Thus, the reaction in such ionic liquids proceeds, unlike when carried out in dmso, by a heterogeneous mechanism.

Secondly, the cation may have an influence on the prevalent palladium species: in presence of a base, *e.g.* ethanoate, [C$_n$mim]$^+$-based ionic liquids are able to formally form a carbene by proton abstraction, which has been demonstrated to be a very stable ligand on palladium.[15,16] The possibility of carbene-formation can be greatly reduced by substituting the acidic 2-H proton of the imidazolium cation for a methyl group in the ionic liquid, or by using pyridinium-based cations.

Table 1 shows that the reaction in [C$_6$mim]Cl is not selective. The formation of dibenzyl ether is due to the generation of $[PdCl_4]^{2-}$ *in situ*;¶ when the preformed salt [C$_4$mim]$_2$[PdCl$_4$] was used in [C$_4$mim][BF$_4$], similar amounts of dibenzyl ether were obtained (compare Table 1, entries 1 and 2). This finding indicates that the reaction is strongly sensitive to the presence of small amounts of chloride (*e.g.* from the preparation of the ionic liquid), confirming the importance of determining the chloride content of each batch of ionic liquid used. It is interesting to note that not only palladium metal, but also $[PdCl_4]^{2-}$, is able to catalyse the oxidation, indicating that at least two different mechanisms are possible for the oxidation.

The occurrence of benzoic acid (Table 1, entry 1) can be explained with another property of halide-based ionic liquids: such ionic liquids are strongly hygroscopic, and the presence of water brings about the over-oxidation (*vide infra*). On the other hand, the analogous bromide ionic liquid (see Table 1, entry 3), does not give any reaction at all, again showing the influence of the anion upon the catalytically active palladium species. Table 1, entries 4 and 5 show that, because of their similar TOF values, both [C$_4$mim][BF$_4$] (TOF = 1.5) and [C$_4$dmim][BF$_4$] (TOF = 1.2) can be used to bring about the selective oxidation to benzaldehyde.‡ It is therefore likely that carbene formation in

Fig. 1 Palladium metal suspension occurring in [C$_4$mim][BF$_4$] upon addition of benzyl alcohol at 80 °C.

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† *Experimental*: $Pd(O_2CMe)_2$ was dissolved in the ionic liquid, and benzyl alcohol added. A Pasteur-pipette was inserted into the reaction mixture, which was connected to a line carrying pre-dried dioxygen. The reaction vessel was immersed in an oil-bath and stirred *via* a magnetic follower while being heated to 80 °C. At higher temperatures, benzaldehyde evaporated and was overoxidised in the gas phase. The work-up was performed by extraction with diethyl ether, although benzaldehyde may be quantitatively distilled out of the reaction mixture. For the recycling experiments (see Fig. 3), the same procedure as described above was employed (10 cm^3 [C$_4$mim][BF$_4$], 9.2 mmol benzyl alcohol, 4.8 mol% $Pd(O_2CMe)_2$, 80 °C, time indicated in Fig. 3). After the removal of the product by extraction with diethyl ether, the residual ionic liquid–catalyst mixture was placed *in vacuo* for 1 h at room temperature. 9.2 mmol benzyl alcohol was added to this mixture, and the vessel connected to the oxygen line, and heated to 80 °C, for the time indicated. Analysis of the ether extract was performed on a Perkin Elmer AutoSystem XL gas chromatograph, which was equipped with an Rtx®-5 column and an FID detector. The water content of each batch of ionic liquid used in oxidation reactions was determined by Karl–Fischer titration. Only ionic liquids with a water-content of < 500 ppm for water-immiscible ionic liquids, and < 1000 ppm for the halide ionic liquids were used. The chloride-content of each batch used in transition metal catalysed reaction was determined *via* a chloride-selective electrode, and was typically < 0.025 (mol Cl$^-$) kg^{-1}.

‡ TOF (turnover frequency), calculated as (mol benzaldehyde) (mol metal)$^{-1}$ h^{-1}.

§ The black precipitate from such a reaction was analysed by X-ray powder diffraction and identified as palladium metal by comparison with a known sample. The precipitation is quantitative ($> 10^{-4}$ M) as determined by EXAFS.

¶ The formation of dibenzyl ether occurs both in presence of chloride, or (in the absence of chloride) at very low substrate/catalyst ratios. This finding is the topic of a forthcoming publication.

Table 1 Conversion to benzaldehyde in different ionic liquids, at 80 °C and 1 atm O_2

	Ionic liquid	V_{IL}/cm^3	Benzyl alcohol/ mmol	$Pd(OAc)_2$/ mol%[a]	*t*/h	Conversion (%)[b] Benzaldehyde	Benzoic acid	Dibenzyl ether
1	$[C_6mim]Cl$	3	19.4	0.5	28	12.8	5.2	10.8
2	$[C_4mim][BF_4]$	3	9.7	0.9[c]	18	13.4	0	12.7
3	$[C_4mim]Br$	2	1.8	2.8	23	0	0	0
4	$[C_4mim][BF_4]$	2	1.8	2.8	23	100	0	0
5	$[C_4dmim][BF_4]$	1	1.0	5.0	15	90	0	0

[a] With respect to benzyl alcohol. [b] Residual percentages correspond to unreacted benzyl alcohol. [c] Preformed $[C_4mim]_2[PdCl_4]$ was used.

$[C_4mim][BF_4]$ does not take place under the specified conditions, or that it does not have an impact.

The effect of water on the selectivity was investigated by a set of four reactions, in which the concentration of water was varied (Table 2, Fig. 2).

The water-content of the ionic liquid used in this experiment was analysed by Karl–Fischer titration, and found to be 0.1 wt%. The total amount of water present in Table 2, experiment 1 was calculated from the density[17] of $[C_4mim][BF_4]$ (1.2077 g cm^{-3} at 20 °C). In the 2 cm^3 of ionic liquid used, 2.4 mg (0.133 mmol) water are present. In the experiments, 1 mmol benzyl alcohol was oxidised, which would give 1 mmol of water in the case of quantitative conversion. Although there was a slight excess of water (with respect to benzaldehyde) present in the system, no over-oxidation to benzoic acid occurred. It appears as if the ionic liquid protects the benzaldehyde formed from further oxidation.

When water (0.5 cm^3) was added to the ionic liquid (1.5 cm^3), a total of 30 mmol of water are present. The small amounts of water initially present in the ionic liquid can be neglected here. In Table 2, experiments 2, 3 and 4, more water is present than ionic liquid. These reaction mixtures are thus not ionic liquid solutions, but aqueous solutions containing dissolved ionic liquid. Considering this and the fact that there is at least thirty times more water than benzyl alcohol present, 4% of the over-oxidation-product benzoic acid (Table 2, experiment 2) is insignificant. The reaction in water, in contrast, produces benzoic acid only under the same reaction conditions.

The presence of water has a strong effect on the selectivity of the oxidation of benzyl alcohol to benzaldehyde. Additionally, Table 2 and Fig. 2 show that increasing amounts of water increase the rate of oxidation. This study indicates that it is of utmost importance that the water content of the reaction medium is monitored. Since in oxidation reactions with dioxygen, equimolar amounts of water are formed, this point has to be addressed if the ionic liquid–catalyst system is to be recycled, as Fig. 3 shows: a $[C_4mim][BF_4]$/palladium metal suspension was recycled for four runs. For the first three runs, benzaldehyde was selectively obtained. The rate of reaction appears to fluctuate, which might be due to slight changes in the reaction temperature or stirring rate. More importantly, in the fourth run, only benzoic acid is formed, and the system is not selective any more. After the removal of the benzoic acid, the residual ionic liquid–catalyst mixture was dried *in vacuo* at 80 °C for 5 h. When reused in the subsequent reaction, again only benzaldehyde was obtained; the selectivity was regained.

This study demonstrates that the catalyst and ionic liquid may be reused for at least five recycles. From time to time, the system should be dried prior to further use, in order to remove water that accumulates either as reaction by-product or by absorption of moisture from the atmosphere during the work-up. This drying process was attempted by adding molecular sieves to a moist ionic liquid. The method was however not effective; it resulted in the decomposition of the molecular sieve. Therefore, drying is recommended at elevated temperatures (70 °C) for 24 h under reduced pressure.

It can be concluded from this study that the ionic liquid is responsible for the selectivity of the oxidation of benzyl alcohol to benzaldehyde. The amounts of water produced in the reaction are insignificant in terms of selectivity, as long as there is an excess of ionic liquid present. It would be interesting to investigate how much water may be deactivated per ion pair of ionic liquid.‖

Table 2 Benzoic acid formation as a function of water content[a]

Experiment	1	2	3	4
Water/cm^3	0	0.5	1.0	2.0
$[C_4mim][BF_4]$/cm^3	2	1.5	1.0	0
Water (vol%)	0	25	50	100
Water (mol%)[b]	0	77.7	91.3	100
Benzyl alcohol (%)	81.4	69.7	26.0	0
Benzaldehyde (%)	18.6	26.0	17.1	1.5
Benzoic acid (%)	0	4.3	56.9	98.5

[a] *Reaction conditions*: 1 mmol benzyl alcohol; 5 mol% palladium(II) ethanoate; 80 °C; 1 atm O_2, 14 h. [b] Mol% relates to the mol of water present in the water/ionic liquid solution.

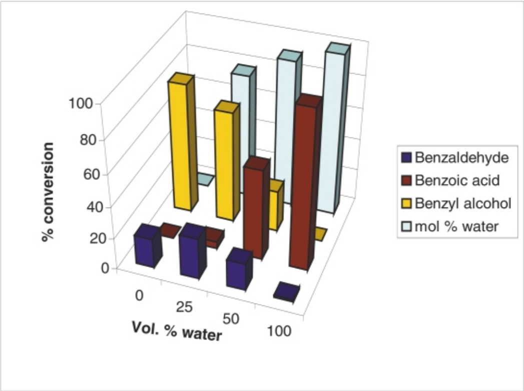

Fig. 2 The effect of water on selectivity.

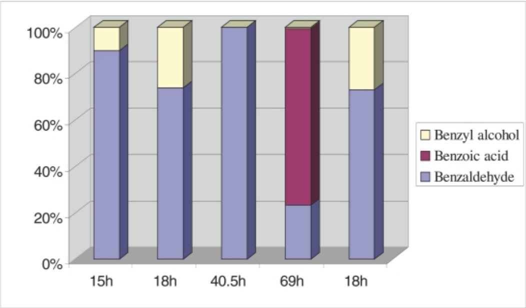

Fig. 3 Recycling of a $[C_4mim][BF_4]$/palladium metal suspension in the oxidation of benzyl alcohol.

‖ Recently, Cammarata *et al*. found that in moist $[C_4mim][BF_4]$ and similar ionic liquids, ‘water molecules are not associated into clusters or pools of water.’ Instead, each hydrogen atom of the water molecule is involved in hydrogen bonding to a discreet anion, yielding a 2 : 1 complex of water.[18]

This deactivation of water prompted us to investigate the oxidation of alkylbenzenes. It was thought that if benzaldehyde was stabilized against over-oxidation in an ionic liquid, it might be possible to introduce the large amount of activation energy required to abstract the methyl hydrogen of toluene.

Preliminary experiments with toluene in [C$_4$dmim][BF$_4$] and [C$_4$mim][BF$_4$], with Pd(O$_2$CMe)$_2$ (9 mol%) at 10 atm O$_2$ and 80 °C, showed that the maximum conversion achieved was only 4.5% benzyl alcohol and 1% benzaldehyde within 24 h. Likewise, if Co(acac)$_2$ (0.8 mol%; acacH = pentane-2,4-dione) was used under otherwise similar conditions, the maximum conversion to benzaldehyde was only 4.7% after 48 h.** Although the conversions are quite low, and the reaction conditions not optimised (*e.g.* for pressure and temperature), it is exciting to note that the introduction of oxygen, catalysed by a transition metal, is indeed feasible in an ionic liquid! It is also interesting that no benzoic acid was formed, although in conventional solvents, benzoic acid is produced. For example, the Snia Viscosa process operates at 165 °C and under 10 atm of air in presence of a homogeneous cobalt catalyst in ethanoic acid.[19] Under these batch conditions, only benzoic acid is formed. On the other hand, the selectivity to benzaldehyde is improved, if a continuous process is used, in which the conversion per pass is kept low.[1]

Ethylbenzene, on the other hand, is more reactive in oxidations than toluene, since the abstraction of a hydrogen atom from a secondary carbon requires less energy. Additionally, since the target molecule is a ketone, the over-oxidation to the carboxylic acid is only possible under very harsh conditions.

Table 3 shows the results obtained for the Co(acac)$_2$ catalysed oxidation of ethylbenzene. No reaction took place at temperatures under 80 °C, even in the presence of perfluorohexane, which has been used to concentrate the dissolved dioxygen.†† However, in the presence of perfluorohexane at 80 °C, acetophenone is formed in 25% yield within 24 h at 1 atm of O$_2$ in [C$_6$dmim][BF$_4$], and this yield could be raised to 91% total oxidation products at 10 atm of O$_2$ (Table 3, entry 3). It appears surprising that the main product in entry 3 is the intermediate alcohol, although the high pressure should drive the reaction towards acetophenone. 1-Phenylethanol is rarely observed (and, even then, only as by-product in small quantities) in commonly used solvents.[21] This phenomenon also occurred in the oxidation of toluene at 10 atm in presence of Pd(O$_2$CMe)$_2$, and is being further investigated.‡‡

As in the oxidation of alcohols, the analogous [C$_6$dmim]Br (Entry 4) did inhibit the reaction, although in conventional solvents (*e.g.* in ethanoic acid), bromide is added to increase the reaction rate.[22,23]

After having demonstrated that the ionic liquid [C$_6$dmim][BF$_4$] could be used as a solvent in the cobalt(II) catalysed oxidation of ethylbenzene, the effect of perfluorohexane and Co(acac)$_2$ was investigated in more detail. The experiments were conducted in absence of ionic liquid, in order to exclude any effects which could possibly arise due to the presence of ionic liquid. Table 4 shows the results obtained.

Table 4 The catalytic effects in the oxidation of ethylbenzene (8.2 mmol) in the absence of solvent

	[cat.] (mol%)[a]	O$_2$/atm	T/°C	t/h	Yield[c]
1	0	1	80	24	0
2	0	1[b]	80	24	9.8% 1-phenylethanol 15% acetophenone
3	1.0	1	80	24	34.6% acetophenone
4	1.0	1[b]	80	24	55.6% acetophenone

[a] With respect to ethylbenzene. [b] 0.4 cm^3 perfluorohexane added. [c] Residual percentages correspond to unreacted starting material.

Entry 1 of Table 4 shows that ethylbenzene is not autoxidised by 1 atm of dioxygen at 80 °C. However, the addition of perfluorohexane brought about the oxidation to acetophenone and 1-phenylethanol, even in the absence of a transition metal catalyst (Table 4, entry 2).

On the other hand, in *absence* of perfluorohexane and *presence* of cobalt(II) catalyst precursor, the reaction proceeded under otherwise similar reaction conditions to yield acetophenone as the sole product (Table 4, entry 3). The highest yields were obtained if both, perfluorohexane and cobalt(II) were used in conjunction (Table 4, entry 4). These results indicate that the oxidation of ethylbenzene is dependent on the dioxygen concentration in the reaction mixture. It appears that there are two different mechanisms that may be employed to achieve the oxidation of ethylbenzene.

It was found that the work-up of the reaction-mixtures containing the transition metal catalyst without ionic liquid solvent was difficult: the separation of the catalyst from the substrate/product mixture could not be performed quantitatively, thus resulting in a yellow crude product. This finding indicates small amounts of catalyst in the product phase. On the other hand, all the crude product/substrate mixtures obtained by extraction with diethyl ether (or distillation) from the reactions in ionic liquids were colourless. This observation implies that the leaching is reduced, if not avoided, when using ionic liquids as solvents.

In conclusion, this study has shown that transition metal catalysed oxidations can be carried out in ionic liquids. It was found, for the oxidation of benzyl alcohol, that better reaction rates can be achieved than when dmso is used as solvent. Furthermore, the recycling of the catalyst and solvent has been demonstrated. The selectivity is dependent on two factors: firstly, in the presence of chloride, a homogeneous system results due to the formation of [PdCl$_4$]$^{2-}$, which causes the formation of dibenzyl ether as a side-product. This is a significant finding, as it stresses the importance of determining the chloride content of an ionic liquid; since many ionic liquids are made from halide precursors, care must be taken to ensure its quantitative removal. Secondly, the selectivity of the benzyl alcohol oxidation is dependent on the water content of the ionic liquid. Although the presence of water increases the rate of

Table 3 Oxidation of ethylbenzene (1 cm^3, 8.2 mmol) to acetophenone with Co(acac)$_2$ (1.0 mol%) in 2 cm^3 of ionic liquid

	Solvent	[O$_2$]/atm	T/°C	t/h	Yield[b]
1	[C$_6$dmim][BF$_4$]	1[a]	80	12	5.8% acetophenone
2	[C$_6$dmim][BF$_4$]	1[a]	80	24	25% acetophenone
3	[C$_6$dmim][BF$_4$]	10[a]	80	24	68.5% 1-phenylethanol, 22.6% acetophenone
4	[C$_6$dmim]Br	1[a]	90	24	0

[a] 0.4 cm^3 perfluorohexane added. [b] Residual percentages correspond to unreacted starting material.

** No oxidation of the ionic liquid occurred with either Co(acac)$_2$ or Pd(O$_2$CMe)$_2$ at 10 atm O$_2$, 80 °C within 3 days.

†† Fluorous phases are known to increase the dioxygen concentration.[20]

‡‡ 1-Phenylethanol can be quantitatively and selectively oxidized to acetophenone using the same methodology as for the oxidation of benzyl alcohol, in the presence of palladium metal, at 1 atm and at 80 °C. The oxidation of 1-phenylethanol and other alcohols is the subject of a forthcoming publication.

oxidation, an excess of water leads to an over-oxidation to benzoic acid. Since water is produced in the oxidation reaction, it should be removed regularly by heating to 70 °C *in vacuo*. This will restore the selectivity of the palladium metal catalyst.

The study of the oxidation of toluene and ethylbenzene showed that the introduction of oxygen (as opposed to dehydrogenation) is also feasible using this concept. Although the oxidation of toluene is not yet fully investigated, and gives low conversions, the oxidation of ethylbenzene yields acetophenone in satisfying yields, which compare well with results in conventionally used solvent systems.[24,25] Due to the possibility of recycling the solvent and catalyst, the ionic liquid processes provide a greener scenario.

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Indium and tin-mediated allylation in ionic liquids

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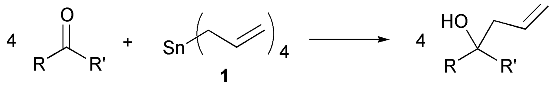
The first report of the use of indium metal and allyl bromide for the allylation of aldehydes and ketones in ionic liquids is given in this paper. The homoallylic alcohol products are obtained in high yields on reaction at room temperature using stoichiometric quantities of indium. Initial results gained using a catalytic system of indium, manganese and TMSCl are also reported. The effect of ionic liquid solvents on the stereochemical selectivity of allylation of 2-methoxycyclohexanone and benzoin methyl ether has been investigated, showing a higher selectivity towards the chelation-controlled mechanism in ionic liquids than in conventional solvents such as water and THF. Using tetraallyltin as the allylating agent, the same reaction occurs with modest improvements in stereoselectivity compared with conventional solvents. The addition of 5 mol% $Sc(OTf)_3$, however, results in a large increase in both reaction rate and selectivity, and permits the isolation of high yields of product *via* a simple workup procedure. The ionic liquid/$Sc(OTf)_3$ mixture may also easily be recycled with good maintenance of yield and stereoselectivity.

1. Introduction

Room temperature ionic liquids (RTILs) are finding many applications, but most notably as solvents in organic synthesis, and as media for biphasic catalysis. A wide range of C–C bond forming processes has been investigated, and these are well summarised in a number of recent review articles.[1] From a green chemistry perspective, ionic liquids possess a number of interesting features, most notably that they lack any measurable vapour pressure, thus reducing the degree of harmful emissions compared with conventional organic solvents. Furthermore, ionic liquids have been shown to be efficient media for the immobilisation of transition metal based catalysts,[2] Lewis acids,[3] and enzymes.[4] In comparison, however, the use of main group metals and their compounds in ionic liquids has been relatively little studied.

The allylation of carbonyl compounds to produce homoallylic alcohols is a useful organic transformation, which has attracted considerable attention in recent years.[5] A common method is the use of metal–allyl complexes, and a number of authors have reported the use of tetraallyltin (**1**) for allylation under very mild conditions (Scheme 1).[6] This reagent is more reactive and more atom efficient than the trialkylallyltin and dialkyldiallyltin reagents often employed for allylation, as all four organic groups are transferred in the course of the reaction. We have recently reported that the allylation of aldehydes using **1** proceeds very efficiently in RTILs, with the organic products isolated *via* extraction of the RTIL phase with diethyl ether. This protocol allows simple isolation of very pure products from the tin-containing by-products, accompanied by easy reuse of the solvent and removal of Sn(IV) containing residues.[7] The



Scheme 1

Green Context

Efficient Barbier type allyl-coupling reactions are significant in organic synthesis and the current paper demonstrates the possible use of ionic liquids in this field. *In situ* generation of the reactive organotin and organoindium species and the emerging evidence that the reactions can be performed catalytically show potential, though the cost of indium reagents may prove to be prohibitive and toxicity concerns with reagents are still a concern. *RDR*

Dr Charles Gordon graduated from the University of Oxford with a BA (Hons.) in Chemistry in 1988. He then carried out his Ph.D. research at the University of Nottingham under the supervision of Professor Jim Turner and Professor Martyn Poliakoff, studying organometallic intermediates and principally employing the technique of matrix isolation. In 1992 he took up a Royal Society European Exchange Scheme postdoctoral fellowship at the University of Wrzburg in Germany, working with Professor Ulrich Schubert on organometallic synthesis. In 1993 he moved to a European Network funded postdoctoral position at Dublin City University, working with Dr Conor Long on the photochemistry of transition metal sandwich complexes. Then, in May 1995 he moved to his final postdoctoral position at the Queen's University of Belfast, working with Professor Ken Seddon where he established his interest in ionic liquids. In January 1997 Dr. Gordon took up his current position at the University of Strathclyde, initially as a temporary lecturer, and from January 1999–December 2001 as a BP/Royal Society of Edinburgh Research Fellow. His research interests chiefly cover the area of ionic liquids covering both the properties of these exciting materials, and their application as solvents for environmentally friendly chemistry.

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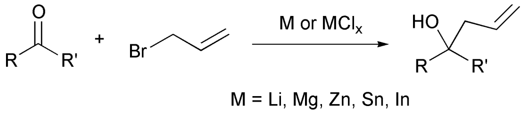
allylation of Weinreb amides in RTILs has also been reported using the same reaction protocol.[8] The method is somewhat limited, however, by the relatively high cost of **1**, as well as the potential problems with the toxicity of organotin compounds.[9]

Allylation may also be accomplished by generation of the allylating agent *in situ* by the reaction of allyl halides with a range of main group metals or their halides, in a transformation commonly known as the Barbier reaction (Scheme 2).[10] This process has the advantage that prior synthesis of the metal–allyl complex is unecessary. The first examples of the Barbier reaction involved the use of magnesium and lithium, although in recent years other metals such as zinc and tin have also been applied successfully. Recently there has been much interest in the use of metallic indium to mediate the allylation of carbonyls[11] and imines.[12] Whereas many other metals require elevated temperatures, catalysts, ultrasound or microwave initiation in order to gain reasonable yields with more unreactive substrates such as ketones,[10] most reactions using indium may be carried out at room temperature and without external assistance. The high activity of indium towards such reactions has been attributed to the low first ionisation potential of the metal.[11]



Scheme 2

Many different solvents have been used with indium, most notably water.[13] Although the reaction occurs efficiently in aqueous systems, the In(0) is oxidised to In(III) at the end of the reaction, thus preventing its easy reuse.[14] In these reactions, indium is generally added to the reaction mixture in a 1 : 1 stoichiometric ratio with the carbonyl substrate, and the inability to recycle the metal, combined with its cost, means that the reaction cannot be economically scaled up. More recently, methods have been developed involving the use of catalytic quantities of indium powder together with manganese powder and chlorotrimethylsilane (TMSCl).[15] This method gives reasonable yields, but requires the use of organic solvents owing to the water sensitivity of the TMSCl.

In this paper we report the use of RTILs as solvents for the indium-mediated allylation of a range of aldehydes and ketones. This is the first time that reactions involving metallic indium have been reported in RTILs. The majority of the work involves the use of stoichiometric quantities of indium, although initial results of an investigation of catalytic processes are reported. Where appropriate the results gained are compared with those obtained in conventional solvents. We also report an extension of our investigations into the use of **1** for the allylation of ketones in RTILs, including the effect on both rate and stereoselectivity of the addition of a Lewis acid catalyst.

2. Results and discussion

Indium-mediated allylation reactions

In our first studies we investigated the allylation of benzaldehyde with allyl bromide in RTILs containing stoichiometric quantities of indium, followed by extraction of the products with diethyl ether. As isolation of the products requires the hydrolysis of an indium alkoxide intermediate, although distilled diethyl ether was used in the extraction step, the separation was not carried out under nitrogen to allow equilibration of the system with atmospheric water. The RTILs used were [bmim][BF$_4$], [bmim][PF$_6$] and [bmim][Tf$_2$N] (bmim = 1-butyl-3-methylimidazolium, Tf = CF$_3$SO$_2$). In the [BF$_4$]$^-$ and [PF$_6$]$^-$ salts the desired homoallylic alcohol was formed with good levels of conversion, as monitored by ^{1}H NMR spectroscopy, but with variable isolated yields. In general, yields were lower with the more viscous [bmim][PF$_6$]. When the solvent was [bmim][Tf$_2$N], however, the isolated yields were extremely poor. As a result, [bmim][BF$_4$] was used in all subsequent experiments. The results obtained for the allylation of a series of aldehydes and ketones in [bmim][BF$_4$] using a simple diethyl ether extraction (method A) are shown in Table 1. Here, it can clearly be seen that the reaction proceeds to completion for most substrates studied, although as stated above the isolated yields were disappointing compared with those previously reported in conventional solvents. At the end of all reactions, the indium metal looked largely unchanged compared with the start of the reaction, being present as a grey or slightly brown powder. Most importantly, there was little evidence for the formation of white In(OH)$_3$.

Compared with equivalent reactions using **1**,[7] however, the products isolated were relatively impure, and contained considerable amounts of unidentified impurities that were variable from reaction to reaction. As the reactions appeared still to contain large amounts of apparently unreacted indium, attempts were made to recycle the In/RTIL mixtures. Successive reactions gave steadily decreasing conversions and yields of homoallylic alcohol, although clearly some degree of recycling is possible using this system.

One possible explanation for the relatively low isolated yields was that the indium alkoxide intermediates were not being fully hydrolysed to release the homoallylic alcohol in the workup step. An alternative protocol was therefore instituted where the reaction mixture was quenched with water at the end of the reaction, before the products were extracted with diethyl ether (method B in Table 1). In this case, at the end of the reaction the majority of the indium was present as the white hydroxide rather than the grey powder observed in the 'dry' system. As can be seen in Table 1, this approach resulted in much better isolated yields of homoallylic alcohol for all substrates except acetophenone. In general, the yields obtained were roughly comparable with those in conventional solvents with the

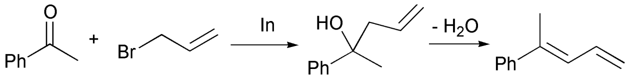
Table 1 Yields obtained on the reaction of a range of carbonyl compounds with allyl bromide and indium metal in [bmim][BF$_4$] at 30 °C

Entry	Substrate	Time/h	Method A[a] Yield[c] (conversion)[d](%)	Time/h	Method B[b] Yield[c] (conversion)[d](%)
1	Benzaldehyde	16	67 (100)	16	92 (100)
2	Pentanal	5	43 (100)	16	79 (100)
3	Acetophenone	5	62 (80)	16	55 (64)[e]
4	Cycloheptanone	—	—	16	53 (60)
5	2-Methoxycyclohexanone	16	59 (70)	16	83 (100)
6	Benzaldehyde	16	—	16	37 (81)[f]

[a] Method A: the products were extracted with Et$_2$O (5 × 5 mL), the extracts were combined, and the solvent was removed *in vacuo*. Where necessary, the crude product was purified by column chromatography. [b] Method B: at the end of the reaction, the mixture was quenched with 5 mL deionised water. The water–ionic liquid mixture was then extracted with Et$_2$O (5 × 5 mL), the extracts were combined and dried over MgSO$_4$, and the solvent was then removed *in vacuo*. Where necessary, the products were purified by column chromatography. [c] Isolated yield. [d] Assessed by ^{1}H NMR. [e] Isolated yield consisted of 39% 2-phenylpent-4-en-2-ol and 16% 4-phenylpenta-1,3-diene. [f] Reaction carried out using 0.1 equiv. In, 2 equiv. Mn and 2 equiv. TMSCl.

aldehydes and 2-methoxycyclohexanone giving complete conversion and excellent isolated yields (Table 1, entries 1, 2 and 5). The results with acetophenone and cycloheptanone showed that the system was less active towards unactivated ketones, as was expected. The purity of products obtained was also markedly superior to the earlier workup route, with unreacted starting material being the only impurity in cases where the reaction did not proceed to completion, again with the exception of acetophenone, as will be discussed below.

The best combination of yield and purity was obtained using a substrate:allyl bromide:indium ratio of 1 : 1.5 : 1 Further investigation revealed that after each reaction a small amount of metallic indium remained in the form of a small ingot. The mass of this generally corresponded to *ca*. 20% of the mass of indium powder initially added to the reaction. In the case of acetophenone, two products were formed, notably the expected 2-phenylpent-4-en-2-ol in 39% yield, and (*E*)-4-phenylpenta-1,3-diene in 16% yield formed by dehydration of the tertiary alcohol product (Scheme 3). The ^{1}H NMR spectrum indicated that complete (*E*) selectivity was observed in this reaction.[16] The latter product was not observed following the earlier reaction protocol without the aqueous quench, and is not reported when the reaction is carried out in organic solvents or water.

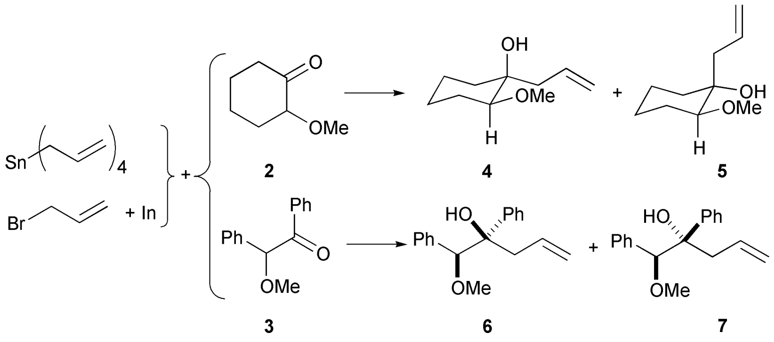


Scheme 3

Stereochemical investigations

The allylation of 2-methoxycyclohexanone (**2**) and benzoin methyl ether (**3**) using **1** was studied both with and without Lewis acids. The rates of allylation reactions have previously been shown to be enhanced by the presence of both Lewis[5b] and mineral acids.[6a] Both **2** and **3** are more reactive than most ketones with regard to allylation reactions, owing to the participation of the oxygen atom of the α-methoxy group. The presence of this group also allows the formation of two diastereoisomeric products in each case (Scheme 4). Products **4** and **6** are formed *via* chelation control, whereas products **5** and **7** are formed *via* a non-chelation mechanism.[17,18] It should be noted that products **4–7** are formed as racemic mixtures of the two possible enantiomers under the conditions described in this paper.

Previous work has shown that allylation of **2** and **3** using **1** may be accomplished in reasonable yields in toluene and methanol, although longer reaction times and higher temperatures are required using the former solvent.[17] In general the chelation-controlled product **4** predominated, although the stereoselectivity obtained was relatively low, and for the allylation of **2** in toluene with **1**, the non-chelation product **5** predominated. The allylation of **2** in [bmim][PF$_6$] and [bmim][BF$_4$] gave reasonable conversions at room temperature (see Table 2, entries 1 and 2), and levels of selectivity towards **4** that were higher than those observed in methanol (Table 2, entry 7) or toluene.[17] The proportions of **4** and **5** were quantified from integrals of ^{1}H NMR signals at 3.01 and 3.08 ppm respectively, corresponding to the H-atom at the 2-position on the cyclohexane ring. Perhaps surprisingly, the same reaction in aqueous solution gave both low yields and selectivity (Table 2, entry 6). The addition of 5 mol% Sc(OTf)$_3$ resulted in a great enhancement in both reaction rate and selectivity towards the chelation controlled product **4**, however. This Lewis acid was chosen as it had been shown previously to be very active in RTILs for Friedel–Crafts alkylation,[19] Claisen rearrangement,[20] and Diels–Alder reactions.[3a,21] Sc(OTf)$_3$ has also been reported to be an active catalyst for the formation of homallylic amines from the reaction of **1** and benzoylhydrazones.[22] In the case of



Scheme 4

Table 2 Results gained on allylation of 2-methoxycyclohexanone[a]

Entry	Allylating agent	Solvent	Time/h	Yield[b] (%)	Ratio **4** : **5**[c]
1	**1**	[bmim][BF$_4$]	16	70	3.9 : 1
2	**1**	[bmim][PF$_6$]	16	51	2.3 : 1
3	**1**	[bmim][PF$_6$] + 5 mol% Sc(OTf)$_3$	16	75	15 : 1
4	**1**	Recycle of run 3	2.5	94	19 : 1
5	**1**	Recycle of run 4	1	80	16 : 1
6	**1**	H$_2$O	16	39	1.4 : 1
7[d]	**1**	MeOH	3	95	1.8 : 1
8	In/allyl bromide	[bmim][BF$_4$] (30 °C)	16	83	18.6 : 1
9[e]	In/allyl bromide	H$_2$O (25 °C)	—[f]	95	12.5 : 1
10[e]	In/allyl bromide	THF–H$_2$O 1 : 1 (25 °C)	—[f]	93	14.1 : 1
11	In/Mn/TMSCl/allyl bromide	[bmim][BF$_4$] (30 °C)	16	37 (81)[g]	6.1 : 1

[a] All reactions carried out at 20 °C except where noted. [b] Isolated yield. [c] Calculated using relative peak integrals from ^{1}H NMR. [d] Taken from reference 14 [e] Taken from reference 15. [f] Reaction time not given in reference. [g] % Conversion in parenthesis.

the reaction with 2-methoxycyclohexanone, the selectivity for the *cis*-product was increased to 15 : 1 (Table 2, entry 3). Furthermore, neither selectivity and reactivity were decreased when the RTIL/Sc(OTf)$_3$ mixture was recycled (Table 2, entries 4 and 5). Over three cycles, excellent yields were obtained, and the products were isolated in extremely pure form (uncontaminated by any starting material or RTIL) simply by extraction of the reaction mixture with Et$_2$O, followed by filtration of the extracts through a plug of cotton wool. It was not necessary to clean the ionic liquid between runs. The impressive rate enhancement was illustrated by the fact that an excellent yield was obtained after a reaction time of only one hour on the third cycle of the reaction.

Similarly, the reaction of **3** with **1** occurred in excellent selectivity of 9 : 1 towards the chelation control product **6** in [bmim][PF$_6$] (Table 3, entry 1). This compared favourably with the results reported for the same reaction in toluene (4 : 1) and methanol (3 : 1).[17] The reaction did not proceed to completion however, resulting in a yield of only 55%. When 5 mol% Sc(OTf)$_3$ was added to the reaction mixture, however, the rate of reaction was clearly enhanced as effectively quantitative isolated yields of product were obtained, and an increase in stereoselectivity to 19.8 : 1 in favour of **6** was observed. As with the reactions of **2**, the IL/Sc(OTf)$_3$ system proved extremely easy to recycle as shown in Table 3, entries 2–4. Yields were not diminished over three reaction cycles, although the stereoselectivity did appear to decrease somewhat on the third reaction cycle.

As indicated in the previous section, the allylation reaction may potentially be carried out using indium and allyl bromide. It has been reported that the transformation **2** → **4** occurs with excellent stereoselectivity in a range of conventional solvents, for example 12.5 : 1 in water and 12.2 : 1 in THF.[18] We investigated the allylation of **2** and **3** in [bmim][BF$_4$] in order to gain an idea of how the reaction yields and stereoselectivity would be influenced by the ionic liquid environment. As was the case for the In-mediated reactions discussed in the previous section, the best results were obtained when the reactions were quenched with water at the end of the reaction, and these results are presented in Table 2 (entries 8–10). As can be seen, excellent yields were obtained for the allylation of **2**, and the stereoselectivity of 18.6 : 1 in favour of **4** was slightly superior to that reported previously for reactions in water and water/THF mixtures.[18] Surprisingly, however, the allylation of **3** did not proceed in [bmim][BF$_4$] under these conditions. Since the reaction has been reported to occur successfully in THF,[15] the reason for this unreactivity is currently unclear.

Finally, we have investigated the possibility of carrying out allylation in the presence of a catalytic quantity of indium. A recent report has described the use of 0.1 equivalents of indium, combined with 5 equivalents each of manganese powder (as reductant) and TMSCl (to trap the alkoxide species).[15] This reaction gave yields equivalent to those obtained using stoichiometric quantities of indium, and was generally carried out in solvents such as THF, with the products isolated following an aqueous workup procedure. Attempts to carry out the allylation of **2** using the above protocol in [bmim][BF$_4$] resulted in the isolation of products containing large quantities of an unidentified impurity. A repeat of the reaction using a smaller quantity of manganese and TMSCl (2 equiv. of each), however, resulted in the isolation of the desired products in good purity, with an overall conversion of 81%, although the isolated yield of product was disappointingly low at 37% (Table 2, entry 15). The isomer ratio **4** : **5** was also slightly lower than that observed for the stoichiometric reaction at 6.1 : 1. We are confident that both yields and conversion can be raised to acceptable levels by optimisation of the reaction conditions, and will report the results of these investigations in due course.

Table 3 Results gained on allylation of benzoin methyl ether[a]

Entry	Allylating agent	Solvent	Time/h	Yield[b] (%)	Ratio **6** : **7**[c]
1	**1**	[bmim][PF$_6$]	16	55 (77)[d]	9 : 1
2	**1**	[bmim][PF$_6$] + 5 mol% Sc(OTf)$_3$	16	95	19.8 : 1
3	**1**	Recycle of run 2	16	97	18.2 : 1
4	**1**	Recycle of run 3	16	98	7.8 : 1

[a] All reactions carried out at 20 °C. [b] Isolated yield. [c] Calculated using relative peak integrals from ^{1}H NMR. [d] % Conversion in parenthesis.

3. Conclusions

We have demonstrated that the allylation of carbonyl compounds may be achieved in high yields in RTILs using both tetraallyltin and an indium/allyl bromide mixture. This is the first report of the use of indium metal for synthetic chemistry in RTILs. Although the indium system does not currently display significant advantages over similar reactions in conventional solvents, there is evidence that the reaction does not require a full stoichiometric equivalent of indium. Furthermore, the results show that the relatively high viscosity of the RTILs used here does not result in a significant lowering of reaction rate compared with conventional organic solvents or water. We have also demonstrated that the allylation reaction can be carried out using catalytic quantities of indium using manganese and TMSCl. Excellent levels of stereoselectivity are obtained in the allylation of 2-methoxycyclohexanone using indium and allyl bromide. In the case of the tetraallyltin system, a large enhancement in both rate and stereoselectivity of allylation of both 2-methoxyhexanone and benzoin methyl ether was achieved when the reaction was carried out in the presence of Sc(OTf)$_3$, and it was shown that the Lewis acid could be recycled with no loss in yield or selectivity. We are currently investigating the allylation of other less reactive substrates and are developing the use of catalytic quantities of indium for this reaction, and will report our results in due course.

4. Experimental

Materials

1-Methylimidazole, bromobutane, ammonium tetrafluoroborate, allyl bromide, benzaldehyde, pentanal, cycloheptanone, acetophenone, 2-methoxycyclohexanone, chlorotrimethylsilane, tetraallyltin, indium powder (100 mesh) and scandium triflate were purchased from Aldrich. All were used as received, except for benzaldehyde, pentanal and allyl bromide, which were distilled, 1-methylimidazole, which was distilled from potassium hydroxide, and 1-bromobutane, which was washed with concentrated sulfuric acid and water, and then distilled from phosphorus pentoxide prior to use. Benzoin methyl ether (Avocado), manganese powder (Johnson Matthey), HBF$_4$ (Fisons Scientific Equipment) and HPF$_6$ (Fluorochem) were used as received.

Spectroscopy

NMR spectra were recorded in CDCl$_3$ solution on a Bruker DPX 400 MHz FT NMR spectrometer. Infrared spectra were recorded on a Nicolet 400D FTIR spectrometer.

Synthesis

[bmim]Br was prepared by the reaction of 1-methylimidazole with 1-bromobutane following literature procedures.[23] [bmim][PF_6] was prepared by the reaction of [bmim]Br with 70 wt% HPF_6 solution following the method of Huddleston *et al*.[24] [bmim][BF_4] was prepared by the reaction of an aqueous solution of [bmim]Br with either 50 wt% HBF_4 solution or an aqueous solution of NH_4BF_4, following the method of Lancaster *et al*.[25]

General procedure for the reaction of aldehydes and ketones with allyl bromide in the presence of indium. Allyl bromide (1.5 mmol) and indium powder (1 mmol) were added to 2.5 mL [bmim][BF_4] or [bmim][PF_6] and stirred for a few minutes. The carbonyl compound (1 mmol) was then added, and the reaction vessel was sealed and stirred at 30 °C for 16 h. At the end of the reaction, different methods were employed for the workup. Method A: the products were extracted with Et_2O (5 × 5 mL), the extracts were combined, and the solvent was removed *in vacuo*. Where necessary, the crude product was purified by column chromatography. Method B: at the end of the reaction, the mixture was quenched with 5 mL deionised water. The water–ionic liquid mixture was then extracted with Et_2O (5 × 5 mL), the extracts were combined and dried over $MgSO_4$, and the solvent was then removed *in vacuo*. Where necessary, the products were purified by column chromatography.

General procedure for the reaction of 2-methoxycyclohexanone and benzoin methyl ether with tetraallyltin. The ketone (1 mmol) and (where appropriate) 25 mg $Sc(OTf)_3$ (0.05 mmol) were dissolved in 2.5 mL [bmim][PF_6], and the mixture was stirred until any solids were fully dissolved. When $Sc(OTf)_3$ was present the mixture took on a pale pink colour. Tetraallyltin (70 mg, 0.25 mmol) was then added to the reaction mixture. After stirring at 20 °C for the appropriate time (generally 16 h, except where otherwise noted), the organic products were extracted with Et_2O (5 × 2 mL). The combined extracts were filtered through a pad of cotton wool, and the solvent was removed *in vacuo*. When recycling of the solvent mixture was required, any remaining Et_2O was removed by evaporation, and the RTIL/$Sc(OTf)_3$ mixture was then used as found.

Procedure for the allylation of 2-methoxycyclohexanone in the presence of indium, manganese and TMSCl. Indium powder (0.2 mmol), allyl bromide (3 mmol) and manganese powder (4 mmol) were stirred for 15 min in 4 mL [bmim][BF_4]. Chlorotrimethylsilane (4 mmol) and 2-methoxycyclohexanone (2 mmol) were then added to the mixture, which was stirred at 30 °C for 16 h. Over this time the colour changed from black to grey, and finally to a white slurry. Water (4 mL) was added dropwise, and the product was then extracted with diethyl ether (5 × 5 mL). The extract was passed through a pad of $MgSO_4$, neutral silica and Kieselguhr, dried over $MgSO_4$, and the solvent was then removed *in vacuo*.

Characterisation of products. The products were characterised by ^1H NMR and IR spectra and comparison with literature values: 1-phenylbut-3-en-1-ol,[26] 2-phenylpent-4-en-2-ol,[27] 4-phenylpenta-1,3-diene,[16] oct-1-en-4-ol,[26] 1-(2-propenyl)cycloheptanol,[28] (1*S*,2*S*)-1-allyl-2-methoxycyclohexan-1-ol (**4**),[17] (1*R*,2*S*)-1-allyl-2-methoxycyclohexan-1-ol (**5**),[17] (1*S*,2*R*)-methoxy-1,2-diphenylpent-4-en-2-ol (**6**)[17] and (1*S*,2*S*)-1-methoxy-1,2-diphenylpent-4-en-2-ol (**7**).[17]

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Friedel–Crafts acylation reactions using metal triflates in ionic liquid

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Aromatic electrophilic substitution reactions such as benzoylation and acetylation catalysed by metal triflates have been conducted in an ionic liquid, [bmim][BF_4] (bmim = 1-butyl-3-methylimidazolium). $Cu(OTf)_2$ (OTf = trifluoromethanesulfonate) was found to be the most efficient catalyst used, affording quantitative conversion of benzoyl chloride and anisole to methoxybenzophenone within 1 h and with an *ortho*/*para* product ratio (*o*/*p*) of 4/96. The same reaction performed in the molecular solvents CH_3CN and CH_2ClCH_2Cl gave lower 1 h conversions of 64 and 73%, respectively, and a reduced *o*/*p* regioselectivity of 7/93 in both cases. The scope and limitations of the reaction and recyclability of the ionic liquid/catalyst system are presented.

Introduction

Ionic liquids, which are entirely composed of ions, can provide an ideal medium for reactions that involve reactive ionic intermediates.[1] Indeed, in our recent work on palladium-catalysed C–C coupling reactions in imidazolium ionic liquids, we have complemented the steadily growing family of reactions in which ionic liquids can promote unprecedented selectivities and enhanced reaction rates and such alternations could at least partly be attributed to the increased ability of ionic liquids to stabilise charged intermediates compared with conventional molecular solvents.[2] Consequently, our attention turned to Lewis acidic metal ion catalysed Friedel–Crafts reactions and the potential advantage of ionic liquids to immobilise such catalysts and stabilise the intermediary cations.

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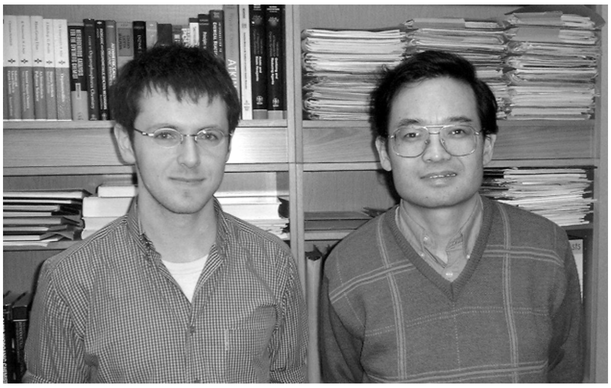

J. Ross **J. Xiao**

Activation of C–H bonds, *via* aromatic Friedel–Crafts reactions, is an important means of adding functionality to simple carbon compounds and as such, is of great importance to many sectors of chemistry.[3] In a typical Friedel–Crafts acylation reaction, an aromatic compound undergoes electrophilic substitution with an acylating agent in the presence of an acid catalyst (Lewis or Brønsted) to afford a ketone. However, when using the common Lewis acid catalyst, $AlCl_3$, a stable adduct compound is formed between the catalyst and the carbonyl oxygen of the ketone product. Thus, an over stoichiometric excess of $AlCl_3$ is required to achieve complete reaction.[3] Copious quantities of inorganic waste materials are produced invoking associated environmental and economic impedimenta.

One of the earliest examples of catalytic reactions performed in room temperature ionic liquids were Friedel–Crafts reactions. The ionic liquid [emim]Cl–$AlCl_3$ (emim = 1-ethyl-3-methylimidazolium) was shown to demonstrate catalytic activity in Friedel–Crafts acylations and alkylations, amongst other reactions, acting both as catalyst and as solvent.[4] Recently, Seddon has reported the Friedel–Crafts acylation of both activated and deactivated aromatics to proceed at ambient and subambient temperatures in [emim]Cl–$AlCl_3$, affording ketone products in high yield and regioselectivity in very short reaction times.[5] Using the analogous [emim]I–$AlCl_3$ ionic liquid, Singer and coworkers have demonstrated the applicability of these solvent

Green Context

Friedel–Crafts acylation reactions represent one of the greatest challenges to green chemistry. Traditional methods generally employ large quantities of hazardous soluble Lewis acids, which are destroyed on work-up giving poor resource utilisation and large volumes of waste. For this reason new research aimed at more efficient and environmentally benign reactor systems is important. Here it is shown that relatively small amounts of metal triflates can catalyse some acylations reactions in ionic liquid solvents. Copper triflate is particularly effective. Unfortunately the reactions reported are limited to highly activated substrates but at least some value with these new systems is evident.
JHC

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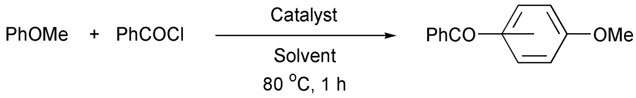
systems to promote the acylation of organometallic compounds, with the ionic liquid again serving both as solvent and as active catalyst.[6] More recently, Song *et al*. have shown that Friedel–Crafts alkylation of aromatics with simple alkenes can readily be performed, using $Sc(OTf)_3$ as catalyst in imidazolium ionic liquids such as $[bmim][PF_6]$, which are easier to handle and are recyclable together with the catalyst.[7]

In conventional molecular solvents, $Sc(OTf)_3$ and a number of other Lewis acidic metal compounds have already proven to be attractive catalysts for Friedel–Crafts alkylation as well as acylation reactions and complete conversion to product can sometimes be achieved with catalyst concentrations < 1 mol%.[8] In addition, their stability in aqueous phases makes them recyclable as active catalysts. Of particular note is that the activities of some of the catalysts such as $Sc(OTf)_3$ and $In(OTf)_3$ can significantly be enhanced by the addition of $LiClO_4$, which accelerates the reaction probably by helping the formation of reactive ionic species.[9] The aim of the present work was to demonstrate the feasibility of Friedel–Crafts acylation catalysed by metal Lewis acids that are easily available and require no special caution to handle. In so doing, we anticipated that the ionic nature of the imidazolium ionic liquids could facilitate the reaction by providing stabilisation of reactive charged intermediates.

Results and discussion

Four commercially available metal triflates were chosen for the study of Friedel–Crafts acylation reactions in $[bmim][BF_4]$, namely $Cu(OTf)_2$, $Zn(OTf)_2$, $Sn(OTf)_2$ and $Sc(OTf)_3$. The benzoylation of anisole was used as a test reaction to compare the catalytic ability of each metal triflate in turn. In a typical reaction, a mixture of benzoyl chloride (1 mmol) and anisole (5 mmol) was added to a mixture of catalyst (0.1 mmol) immobilised in $[bmim][BF_4]$. The reaction was performed at 80 °C under an atmosphere of dry argon. All four catalysts used provided 100% conversion of the benzoyl chloride to product after overnight reaction. However, $Cu(OTf)_2$ demonstrated the greatest activity of the four catalysts tested, affording quantitative conversion within 1 h, while $Zn(OTf)_2$ and $Sn(OTf)_2$ displayed moderately reduced activity, affording 1 h conversions of 87 and 74%, respectively, as evidenced by ^1H NMR and GC analysis of the crude product (Table 1). $Sc(OTf)_3$ was least active, producing a 1 h conversion of only 10%. This is somewhat surprising. Catalyst solubility was not a factor since both $Cu(OTf)_2$ and $Sc(OTf)_3$ are highly soluble in $[bmim][BF_4]$ under the reaction conditions employed. In addition a previous study revealed that $Cu(OTf)_2$ and $Sc(OTf)_3$ behave similarly in acylaminoalkylation and Friedel–Crafts alkylation in CH_2Cl_2.[8e] Interestingly, we found that addition of CF_3CO_2H (0.5 mmol) increased the activity of the $Sc(OTf)_3$ catalysed reaction in $[bmim][BF_4]$, improving the 1 h conversion from 10 to 47% with concomitant increase in regioselectivity from an *o*/*p* ratio of 16/84 to 6/94. However, no reaction occurred when CF_3CO_2H was used in the absence of $Sc(OTf)_3$, indicating that CF_3CO_2H is not catalysing the reaction but merely facilitating the $Sc(OTf)_3$ catalysed reaction as an additive. Hence, the established ease of recycle of $Sc(OTf)_3$,[7,8] coupled with the means of increasing its catalytic performance as demonstrated here, may compensate for its lower activity compared with $Cu(OTf)_2$ in $[bmim][BF_4]$. $Cu(OTf)_2$ is also one of the most regioselective catalysts, as can be judged by the *o*/*p* ratios in Table 1. The benzoylation of anisole was also attempted in the presence of other copper catalysts such as $CuCl_2{\cdot}2H_2O$ and $Cu(OAc)_2{\cdot}H_2O$ in the $[bmim][BF_4]$ solvent. Both reactions failed to reach completion after 44 h, affording only 60 and 76% conversions, respectively, although $CuCl_2{\cdot}2H_2O$ showed greater catalytic activity in $[bmim][BF_4]$ than in conventional solvents. $CuCl_2{\cdot}2H_2O$ and $Cu(OAc)_2{\cdot}H_2O$ were observed to be less soluble in $[bmim][BF_4]$ than was $Cu(OTf)_2$. Thus the enhanced performance of the latter as catalyst in $[bmim][BF_4]$ can be attributed both to favourable electronic properties and to increased solubility. Metal halides have been shown to be effective Lewis acids in the benzoylation of 2-methoxynaphthalene at higher temperature in $PhNO_2$.[8c] In establishing a standard reaction protocol, the benzoylation of anisole was also performed at various temperatures in $[bmim][BF_4]$. The reaction became slower at lower temperature and no reaction occurred at room temperature.

Table 1 Benzoylation of anisole catalysed by metal triflates in $[bmim][BF_4]$ and molecular solvents[a]



Entry	Catalyst	Solvent	Conversion (%)[b]	*o*/*p*[c]
1	$Cu(OTf)_2$	$[bmim][BF_4]$	100	4/96
2	$Zn(OTf)_2$	$[bmim][BF_4]$	87	4/96
3	$Sn(OTf)_2$	$[bmim][BF_4]$	74	25/75
4	$Sc(OTf)_3$	$[bmim][BF_4]$	10	16/84
5	$Cu(OTf)_2$	CH_3CN	64	7/93
6	$Zn(OTf)_2$	CH_3CN	82	8/92
7	$Sn(OTf)_2$	CH_3CN	80	7/93
8	$Sc(OTf)_3$	CH_3CN	53	9/91
9	$Cu(OTf)_2$	CH_2ClCH_2Cl	73	7/93
10	$Zn(OTf)_2$	CH_2ClCH_2Cl	45	2/98
11	$Sn(OTf)_2$	CH_2ClCH_2Cl	86	5/95
12	$Sc(OTf)_3$	CH_2ClCH_2Cl	57	5/95

[a] Ratio of anisole/benzoyl chloride = 5/1. [b] Conversion of benzoyl chloride, measured by ^1H NMR. [c] *ortho*/*para* Ratio measured by GC.

The reactivity and regioselectivity of $Cu(OTf)_2$ as catalyst in the benzoylation of anisole in $[bmim][BF_4]$ compares favourably with those observed in molecular solvents. Thus, in $[bmim][BF_4]$, ketone was obtained quantitatively within 1 h with an *o*/*p* ratio of 4/96. In contrast, in CH_3CN and CH_2ClCH_2Cl, lower conversions and *o*/*p* ratios were obtained (Table 1), and the reaction performed in excess anisole required a much longer time to complete and led to two ketones with an *o*/*p* ratio of 10/90.[10] However, for the other three catalysts, the results with the ionic liquid compare less favourably than those with the conventional solvents.

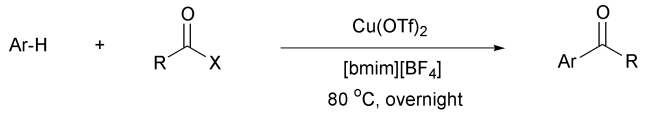
Due to its greater activity and ready availability, $Cu(OTf)_2$ was subsequently used to catalyse a range of Friedel–Crafts acylation reactions in $[bmim][BF_4]$. Whilst most reactions involving acyl halides went to completion within 1 h, all the reactions were performed overnight, due to slower acylation with related anhydrides (*vide infra*). Under such conditions GC and ^1H NMR analysis of the crude mixture showed a complete reaction for all the acylating agents. The ketone product was extracted with organic solvents. The results are summarised in Table 2. The benzoylation of anisole derivatives furnished the ketones with good to excellent isolated yields (Table 2, entries 1–4). The benzoylation of 3,5-dimethylanisole preferentially afforded the less hindered *ortho*-substituted product with an isomer distribution similar to that observed in conventional solvents (Table 2, entry 2).[11] The benzoylation of the bulkier aromatic-substituted anisole derivative 2-methoxynaphthalene in $[bmim][BF_4]$ produced 2-methoxy-1-naphthyl phenyl ketone exclusively (entry 3). This product is the kinetic product and, when formed under conventional reaction conditions, often undergoes isomerisation to give a mixture including 6-methoxy-2-naphthyl phenyl ketone, a precursor in the synthesis of Naproxen.[8c] In $[bmim][BF_4]$, isomerisation to this thermodynamically more stable product was not observed even after prolonged reaction, reminiscent of the acetylation of naphthylene, where the thermodynamically unfavoured 1-isomer was predominantly obtained and the product did not rearrange when heated.[5] Intriguingly, the benzoylation of 2-methoxybiphenyl affords the substitution product 2-(2-methoxyphenyl)benzophenone exclusively in [bmim][BF_4], whereas benzoylation occurring exclusively in the position *para* to the methoxy group is reported in the literature (entry 4).[12] Acetylation of anisole proceeded equally well, affording the *para* isomer as the only product detectable with GC (Table 2, entry 5).

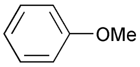
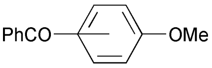
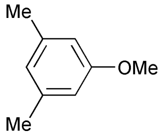
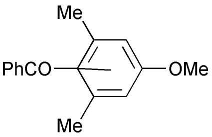
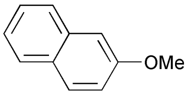
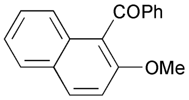
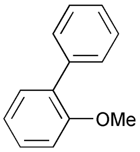
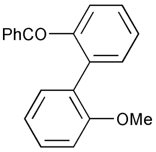
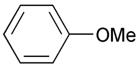
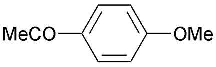
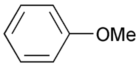
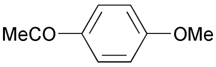
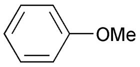
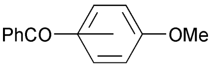
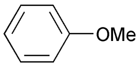
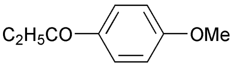
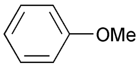
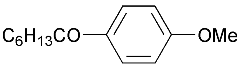
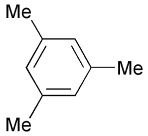
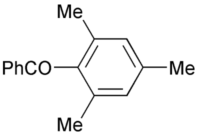
Thus far, 10 mol% Cu(OTf)$_2$ had been used to catalyse the benzoylation of anisole in [bmim][BF_4], which is the most common catalyst loading found in the literature.[8a,b,e–g,10] Attempting to lower the amount of added catalyst, this reaction was conducted sequentially in the presence of 5 mol% and then 1 mol% Cu(OTf)$_2$. Reducing the amount of added catalyst from 10 mol% to 5 mol% did not alter the 1 h conversion, which was quantitative. However, further lowering to 1 mol% slowed the reaction noticeably; hence there was no detectable conversion after 1 h and only 84% conversion after 20 h.

The handling of acyl chlorides is generally disagreeable and as such their anhydride analogues were also investigated.[13] Under conditions similar to those for the chlorides, acetic anhydride, benzoic anhydride and even the much more hydrophobic heptanoic anhydride all underwent complete reactions with anisole, yielding the *para* isomers as the only or predominant product, albeit with moderate isolated yields (Table 2, entries 6–9). Worthy of note is the apparent difference between the Friedel–Crafts reactions of anhydrides and acyl chlorides in [bmim][BF_4]. Thus, ^{1}H NMR monitoring of the reaction of acetic anhydride with anisole showed only 19% conversion to ketone after 1 h, whereas quantitative conversion was observed, within the same time period, when the anhydride was replaced with acetyl chloride. Comparative to the above example, replacing benzoyl chloride with benzoic anhydride in the reaction with anisole decreased the 1 h conversion from 100% to less than 10%, although similar regioselectivities were achieved for both reactions (Table 2). In common solvents such as CH_2ClCH_2Cl and CH_3CN, the same reaction catalysed by Cu(OTf)$_2$ was similarly slow. Faster reactions were achieved only when excess anhydride was used as both the acylating agent and solvent.[10]

The low activity of Cu(OTf)$_2$ towards anhydrides is related to its behaviour in the ionic liquids. Unlike the reaction involving the acyl halides, the acylation by anhydrides in [bmim][BF_4] was always accompanied with immediate and ultimately quantitative formation of a pale blue precipitate, identified as

Table 2 Cu(OTf)$_2$ catalysed acylation of aromatic compounds in [bmim][BF_4][a]



Entry	Ar-H	RC(O)X	ArC(O)R	Yield (%)[b]	*o*/*p*[c]
1		PhCOCl		81	4/96
2		PhCOCl		91	63/37[d]
3		PhCOCl		72	
4		PhCOCl		65	
5		MeCOCl		87	
6		Ac$_2$O		48	
7		(PhCO)$_2$O		46	6/94[d]
8		(C_2H_5CO)$_2$O		55	
9		($C_6H_{13}CO$)$_2$O		58	
10		PhCOCl		53	

[a] For general reaction conditions, see Experimental. [b] Isolated yields. 100% *para* product unless stated otherwise. [c] *ortho*/*para* %Ratio by GC. [d] *ortho*/*para* With respect to OMe.

$Cu(OAc)_2{\cdot}H_2O$ by NMR, elemental analysis and comparison with an authentic sample, when using acetic anhydride. The formation of $Cu(OAc)_2{\cdot}H_2O$ in [bmim][BF_4] is caused by the trace amounts of water found in such hygroscopic ionic liquids and is driven by the insolubility of this resulting neutral species in the ionic liquid. The end result is lowering of the concentration of active Cu(II) species and thus the activity of the reaction in the ionic liquid. Consistent with this, when the [bmim][BF_4]/catalyst system was further dried by stirring in the presence of activated 4Å molecular sieves for 3 h prior to the addition of acetic anhydride and anisole, the acetylation reaction was faster, affording a complete conversion to 4′-methoxyacetophenone after 1 h. Such trace amounts of water appear to be inconsequential towards the reactions of acyl halides in the same medium, probably due to differing behaviours of HCl and AcOH generated in the chloride and anhydride reactions in [bmim][BF_4] (*vide infra*).

The Friedel–Crafts benzoylation reaction in [bmim][BF_4] was also extended to a series of toluene derivatives using $Cu(OTf)_2$. The benzoylation of mesitylene led to quantitative conversion to product after overnight reaction (Table 2, entry 10). But the similar reaction with the less reactive toluene only afforded a 26% conversion, although with a high selectivity (*o*/*p* = 3/97), suggesting that Cu(II) is not acidic enough to generate highly reactive acylium ions, which could be formed by exchange of the chloride with triflate ion and by donor–acceptor interaction between the carbonyl oxygen and Cu(II).[8g]

Attempts were made to recycle the solvent/catalyst system. The benzoylation of anisole with benzoyl chloride under the conditions similar to those for Table 2 was run for three cycles, furnishing the methoxy substituted benzophenones with 86, 79 and 65% isolated yields, respectively, and an *o*/*p* ratio of 4/96 for all runs. The product was extracted with Et_2O; a second reaction was initiated after simple decanting of the organic layer and drying under vacuum for 30 min. It is thought that a gradual accumulation of HCl, possibly leading to formation of an increasing amount of $CuCl_2$, is responsible for the deactivation of the solvent/catalyst system towards subsequent reactions. Evidence for HCl formation is in detecting an acidic gas (pH ~ 2) emitted during the reaction. Dense white fumes were formed upon exposure of this acidic gas to concentrated ammonia solution, indicative of NH_4Cl.

As might be expected from previous studies,[3] under the same reaction conditions used for forming C–C bonds, C–N and C–O bonds were readily formed and in high isolated yields. Thus, phenol and *m*-cresol formed their respective esters, and aniline formed benzanilide, with benzoyl chloride. Reaction with benzyl alcohol also proceeded but was not quantitative (Table 3).

Conclusions

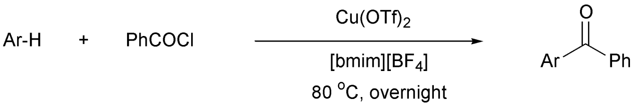
In summary, the feasibility of metal triflates as Lewis acids for Friedel–Crafts acylations in an imidazolium ionic liquid has been demonstrated. Using $Cu(OTf)_2$ as catalyst, greater regioselectivities and enhanced rates of reaction can be achieved in [bmim][BF_4] compared with conventional solvent conditions for the Friedel–Crafts acylation of activated aromatic compounds. But deactivated aromatics and acylation by anhydrides give less satisfactory results. Recycling of the solvent/catalyst system was demonstrated when using $Cu(OTf)_2$. The faster rates associated with the copper catalyst could result from enhanced Lewis acidity of Cu(II) and/or easier generation of charged cations in the ionic liquid. However, the accelerating effect of ionic liquids, if any, varies with catalysts used, as exemplified by the other three triflates studied. The involvement of an active copper *N*-heterocyclic carbene species is less likely; the strong σ-donating capability of such a ligand would significantly reduce the Lewis acidity of Cu(II).[14,15] The difference between ionic liquids and conventional molecular solvents is further highlighted by the easy precipitation of neutral $Cu(OAc)_2{\cdot}H_2O$ by anhydrides in [bmim][BF_4] but not in solvents such as CH_2ClCH_2Cl and CH_3CN. The insolubility of this Cu(II) species, which shows negligible activity towards the acylation of anisole using acetic anhydride in [bmim][BF_4], is an additional driving force toward the degradation of $Cu(OTf)_2$ not observed in solvents such as CH_2ClCH_2Cl and CH_3CN, showing that the physical and chemical properties of ionic liquids need to be more fully understood before their full potential can be realised.

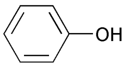
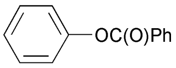
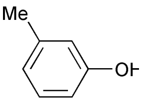
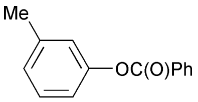
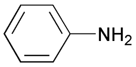
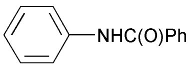
Experimental

All reactions were carried out in oven-dried glassware under an atmosphere of dry argon. [bmim][BF_4] was prepared according to a published procedure, vacuum-dried and stored under an atmosphere of dry argon.[16] Anisole and toluene were freshly distilled from calcium hydride under dinitrogen immediately prior to use. All other chemicals were purchased from commercial suppliers and were used as received. Reaction progress was monitored by ^{1}H NMR and GC analysis; [bmim][BF_4] was removed by passing the reaction sample through a pad of silica gel and flushing with solvent. Alternatively, ^{1}H NMR analyses of samples containing [bmim][BF_4] were run in acetone-d_6. Products were purified by chromatographic separation. Characterisation of ketone products was *via* NMR, C/H analysis, melting points (where appropriate) and MS with reference to literature values.

A typical reaction procedure is given for the acylation by acyl chlorides. A round-bottomed flask was charged with $Cu(OTf)_2$ (36.2 mg, 0.1 mmol). After drying under vacuum for 1 h with stirring and flushing several times with dry argon, [bmim][BF_4] (2 ml) was added. The mixture was stirred at 80 °C for 10 min until homogenous. After cooling to ambient temperature, benzoyl chloride (0.141 g, 1 mmol) and anisole (0.541 g, 5 mmol) were added. The reaction was stirred at 80 °C under an atmosphere of dry argon. Upon completion of the reaction, the organics were extracted with Et_2O. When recycling the solvent/catalyst system, fresh acylating agent and aromatic were added following prior drying of the solvent/catalyst system for 30 min at 80 °C under vacuum. The combined organic extracts were washed with water, aqueous $NaHCO_3$ and brine. After removing the solvent, the product was purified by flash chromatographic separation (eluent: light petroleum (bp 40–60 °C)/ethyl acetate = 10/1). Selected analytic data are given for the following compounds.

Table 3 C–O and C–N bond formation under Friedel–Crafts conditions in [bmim][BF_4][a]



Entry	Ar–H	Product	Yield, (%)[b]
1			67
2			86
3			81

[a] Reaction conditions were the same as those for the benzoylation of anisole. [b] Isolated yields.

4-Methoxybenzophenone[8a]

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.78 (s, OCH_3, 3H), 6.90 (d, J = 8.9 Hz, 3-/5-H, 2H), 7.41 (m, 3′-/5′-H, 2H), 7.50 (m, 4′-H, 1H), 7.72 (d, J = 6.9 Hz, 2′-/6′-H, 2H), 7.78 (d, J = 8.9 Hz, 2-/6-H, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 55.89, 113.95, 128.58, 130.12, 130.55, 132.28, 132.96, 138.68, 163.62, 195.96; Anal. Calc. for $C_{14}H_{12}O_2$: C, 79.26; H, 5.66. Found: C, 79.28; H, 5.66%.

2-Methoxy-4,6-dimethylbenzophenone/4-methoxy-2,6-dimethylbenzophenone[11]

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.10 (s, 4-CH_3 and 2-/6-CH_3), 2.35 (s, 6-CH_3), 3.61 (s, OCH_3), 3.74 (s, OCH_3), 6.61 (m, 3-/5-H), 7.35–7.60 (m), 7.75–7.85 (m); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 19.32, 22.10, 55.94, 112.06, 113.43, 128.92, 129.73, 129.79, 132.79, 133.63, 133.94, 138.05, 138.11, 200.83; Anal. Calc. for $C_{16}H_{16}O_2$: C, 80.01; H, 6.73. Found: C, 80.29; H, 6.98%.

2-Methoxy-1-naphthyl phenyl ketone[8c]

Mp 122–123 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.82 (s, 3H), 7.33–7.44 (m, 5H), 7.49–7.58 (m, 2H), 7.83–7.87 (m, 3H), 7.96 (d, J = 9.0 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 56.54, 113.09, 122.92, 124.05, 124.09, 127.39, 128.11, 128.28, 128.57, 128.77, 129.62, 131.17, 131.69, 133.47, 137.91, 154.07, 197.79; Anal. Calc. for $C_{18}H_{14}O_2$: C, 82.45; H, 5.38. Found: C, 82.37; H, 5.38%.

2-(2-Methoxyphenyl)benzophenone[12]

Mp 94–96 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.85 (s, OCH_3, 3H), 7.01 (d, J = 8.6 Hz, 1H), 7.25–7.55 (m, 8H), 7.76–7.87 (m, 4H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 56.22, 110.92, 127.78, 128.49, 128.63, 129.93, 130.14, 130.68, 131.01, 132.13, 132.32, 133.61, 137.90, 138.67, 160.52, 195.94; Anal. Calc. for $C_{20}H_{16}O_2$: C, 83.34; H, 5.59. Found: C, 83.17; H, 5.59%.

1-(4-Methoxyphenyl)ethanone[8a]

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.56 (s, CH_3, 3H), 3.88 (s, OCH_3, 3H), 6.94 (d, J = 8.9 Hz, 3-/5-H, 2H), 7.94 (d, J = 8.9 Hz, 2-/6-H, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 26.64, 55.81, 114.07, 114.34, 130.78, 130.94, 131.22, 163.88, 197.06; Anal. Calc. for $C_9H_{10}O_2$: C, 71.98; H, 6.73. Found: C, 71.90; H, 6.77%.

1-(4-Methoxyphenyl)propan-1-one[17]

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.20 (t, J = 7.7 Hz, CH_3, 3H), 2.95 (q, J = 7.7 Hz, CH_2, 2H), 3.85 (s, OCH_3, 3H), 6.94 (m, 2H), 7.96 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 8.82, 31.79, 55.82, 113.73, 114.04, 130.38, 130.60, 130.88, 163.68, 199.94; Anal. Calc. for $C_{10}H_{12}O_2$: C, 73.14; H, 7.38. Found: C, 73.42; H, 7.43%.

1-(4-Methoxyphenyl)heptan-1-one[18]

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.90 (br, CH_3, 3 H), 1.32 (m, CH_2, 6H), 1.72 (m, CH_2, 2H), 2.91 (br, CH_2, 2H), 3.88 (s, OCH_3, 3H), 6.93 (d, J = 8.8 Hz, 3-/5-H, 2H), 7.95 (d, J = 8.8 Hz, 2-/6-H, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 14.45, 22.94, 25.00, 29.51, 32.08, 38.72, 55.84, 114.04, 130.58, 130.71, 163.68, 199.71; Anal. Calc. for $C_{14}H_{20}O_2$: C, 76.31; H, 9.17. Found: C, 76.49; H, 9.22%.

2,4,6-Trimethyl-benzophenone:[19]

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.08 (s, CH_3, 6H), 2.32 (s, CH_3, 3H), 6.89 (s, CH, 2H), 7.42 (m, 3′-/5′-H, 2H), 7.56 (m, 4′-H, 1H,), 7.81 (d, J = 7.2 Hz, 2′-/6′-H, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 19.74, 21.53, 129.02, 129.19, 129.61, 133.89, 134.63, 137.39, 138.08, 138.88, 201.05; Anal. Calc. for $C_{16}H_{16}O$: C, 85.67; H, 7.20. Found: C, 85.57; H, 7.26.

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Hydrogensulfate and tetrakis(hydrogensulfato)borate ionic liquids: synthesis and catalytic application in highly Brønsted-acidic systems for Friedel–Crafts alkylation

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Hydrogensulfate and tetrakis(hydrogensulfato)borate ionic liquids have been synthesised and characterised. These ionic liquids are halogen-free, available from cheap raw materials and easy to prepare. They have been used as additives to sulfuric acid in the Friedel–Crafts-alkylation of benzene with 1-decene. The results clearly demonstrate an interplay of acidity and solubility effects caused by the ionic liquid additive. In some cases, low amounts of ionic liquid additive result in a dramatic improvement of product yield.

Introduction

Transformations catalysed by highly acidic and superacidic (stronger Brønsted-acidic than 100% sulfuric acid) catalysts are among the most important reactions in industrial chemistry. Refinery alkylation, alkane isomerisation and functionalisation reactions of aromatic compounds (alkylation, carbonylation, acylation, isomerisation) are typical examples.

However, many of these reactions using mineral acids or classical superacidic systems can not be regarded as environmentally benign. Often, hazardous, volatile acids are involved (*e.g.* HF). In other cases, the acid has to be used in stoichiometric or even in over-stoichiometric ratio to the feedstock. Hereby, a lot of waste is produced *e.g.* during the hydrolysis for product isolation. Other restrictions originate from the physico-chemical properties of the commonly used acidic systems. Especially, insufficient solubility of the substrates in the liquid acid is a common limitation.

Peter Wasserscheid was born in 1970 in Würzburg. He studied chemistry at the RWTH Aachen and received his PhD in 1998 in the group of Professor Keim with a dissertation on Ni-catalyzed C–C linkage reactions in ionic liquids. At present he is carrying out his Habilitation at the Institute für Technische Chemie und Makromolekulare Chemie at the RWTH Aachen and is working on further applications of ionic liquids in synthetic and catalytic reactions. His scientific abilities were recognized at an early stage when he was awarded the DECHEMA Student prize for excellent performance in study and diploma work and the Friedrich–Wilhelm prize from the RWTH Aachen. Recently, he received the 'Carl-Zerbe-Preis' of the DGMK and the 'Max Buchner-Forschungspreis 2000' of DECHEMA. Peter Wasserscheid is author of ca. 40 publications and patents.

Ionic liquids are low melting (< 100 °C) salts which represent a new class of non-molecular, ionic solvents.[1–3] Highly Brønsted acidic ionic liquids have been known since 1989 when Smith *et al.* described ionic liquids obtained from the reaction of an acidic chloroaluminate melt and HCl to be superacidic. For example, Smith *et al.* determined quantitatively the acidity of the system 1-ethyl-3-methylimidazolium ([EMIM])Cl/$AlCl_3$/HCl (see eqn. (1)).[4]

$$HCl + Al_2Cl_7^- \rightleftharpoons [H]^+_{non\text{-}solvated} + 2\ AlCl_4^- \qquad (1)$$

In general, there are many good reasons to study ionic liquids as alternative Brønsted-acids in acid catalysed reactions. Besides the engineering advantage of their non-volatile nature, the investigation of new biphasic reactions with an ionic catalyst phase is of special interest. Here, the possibility to adjust solubility properties by different cation/anion combinations allows a systematic optimisation of the biphasic reaction, *e.g.* with regard to product selectivity. Attractive options to improve selectivity in multiphase reactions derive from the preferential solubility of only one reactant in the catalyst solvent or from the *in situ* extraction of reaction intermediates out of the catalyst layer. Finally, the ionic liquid may be in some applications a superior solvent for the acidic species. In these cases, significant enhancement of catalyst activity and stability should be possible.

Acidic ionic liquids were used as reaction media for Friedel–Crafts reactions as early as 1976.[5] Systematic investigations into Friedel–Crafts alkylation of benzene with short–chain alkyl halides were published in 1986 by Wilkes and coworkers.[6] The alkylation of benzene with alkenes in acidic imidazolium chloroaluminate melts is the subject of a patent from BP Chemicals from 1994.[7] As advantages over the reaction with

Green Context

This article describes some interesting new additions to the family of ionic liquids. They are halogen-free, available from cheap raw materials and easy to prepare. The first catalytic applications of these metals in highly Bronsted-acidic systems are reported. As additives their effects on acidity and solubility are clear and give dramatic improvements in product yields in alkylation reactions. ***JHC***

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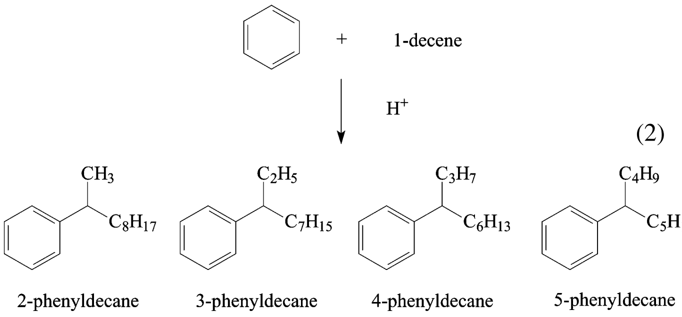
aluminum trichloride in organic solvents, claims are made regarding the easy isolation of the product, the practically total reusability of the liquid catalyst and the better selectivity to the alkylated products. Later, Akzo Nobel claimed that acidic chloroaluminate melts with trialkylammonium ions can be applied in the same manner as much cheaper alternatives to the imidazolium based systems.[8] In more recent times Hölderich and coworkers described Friedel–Crafts alkylation reactions with acidic chloroaluminate systems that have been immobilised on different supports.[9] Finally, a Brønsted superacidic medium obtained by reaction of an acidic chloroaluminate melt with HCl was used as catalyst for the alkylation of benzene with dodecene by Qiao and Deng.[10]

However, highly acidic systems based on chloroaluminate ionic liquids have some serious limitations. They are extremely oxophilic thus forming adducts with C–O functionalities and reacting irreversibly with traces of water to form HCl and Al-oxides. Therefore, our aim was to develop highly acidic, non-chloroaluminate systems.

In the present paper, we report the synthesis of hydrogensulfate and tetrakis(hydrogensulfato)borate ionic liquids. Moreover, we describe the first catalytic application of these melts in highly Brønsted acidic systems. For the catalytic evaluation, the Friedel–Crafts alkylation of benzene with 1-decene (see eqn. (2)) was chosen as model reaction for several reasons. (a) The reaction is of significant technical interest since monoalkylbenzenes with alkyl chains of 10–14 C-atoms are important intermediates for the production of alkylbenzenesulfonates. These are widely used as biodegradable, anionic detergents in commercial washing powder. Sulfuric acid is one of the technically used catalysts for this reaction;[11] (b) the reaction is an ideal starting point for future investigations of Friedel–Crafts alkylations with functionalised aromatic compounds. Obviously, this future goal makes the application of non-chloroaluminate systems particularly interesting. (c) The reaction proceeds in biphasic reaction mode with all ionic liquid systems under investigation thus offering a simple way for catalyst recovery and recycling.



(2)

Experimental

General remarks

All reactions were carried out under argon unless otherwise noted. Benzene and 1-decene were distilled from sodium. Octane and tetradecane were dried over molecular sieves 4Å. Sulfuric acid, 100%, was purchased from Merck. Other solvents were dried according to common methods and distilled under argon.[12] Gas chromatography was carried out on a Siemens Sichromat 3 with a 50 m Pona HP-FS column, equipped with a Hewlett Packard 3359 integrator. Octane and tetradecane were used as internal standards.

NMR spectra were recorded on a 300 MHz Bruker spectrometer in $CDCl_3$ or CD_3CN and calibrated with tetramethylsilane (TMS) as the internal reference.

Synthesis of the acidic ionic liquid systems

The synthesis of ionic liquids of general type [cation][HSO_4] has been first described in the patent literature.[13]

1-Butyl-3-methylimidazolium sulfate [bmim]$_2$[SO_4]. [bmim]$_2$[SO_4] was prepared from [bmim][Cl][14] by anion exchange over the ion exchange resin Amberlyst A27 (sulfate form) in water. The aqueous [bmim]$_2$[SO_4] solution was evaporated and the wet residue was dissolved in acetonitrile. The acetonitrile solution was dried by azeotropic removal of water at the rotatory evaporator. This procedure was repeated three times until the residue showed no solubility in acetonitrile. The reaction mixture was filtered under argon and washed twice with acetonitrile. The white, chloride free crystalline powder was dried from traces of water by evaporation in high vacuum at 50 °C over night (80% yield, mp.185–190 °C). $\delta_H(D_2O)$ 0.91 (t, *J* 7.5 Hz, 3H), 1.24–1.37 (m, 2H), 1.79–1.89 (m, 2H), 3.89 (s, 3H), 4.19 (t, *J* 6.9 Hz, 2H), 7.43 (m, 1H), 7.47 (m, 1H), 8.72 (s, 1H); $\delta_C(CD_3OD)$ 13.8, 20.5, 33.2 , 36.5, 50.5, 123.4, 124.9, 137.9.

1-Butyl-3-methylimidazolium hydrogensulfate [bmim][HSO_4][13]. A stoichiometric amount of neat sulfuric acid was added to 1-butyl-3-methylimidazolium sulfate and stirred for at least 2 h at 50 °C to obtain an almost colourless, viscous melt which crystallised after few hours (mp 29–32°C). $\delta_H(CD_3CN)$ 0.91 (t, *J* 7.3 Hz, 3H), 1.25–1.37 (m, 2H), 1.76–1.86 (m, 2H), 3.88 (s, 3H), 4.18 (t, *J* 7.3 Hz, 2H), 7.45 (m, 1H), 7.47 (m, 1H), 8.94 (s, 1H), 10.09 (s, 1H); $\delta_C(CD_3CN)$ 13.8, 20.0, 32.7, 36.8, 50.1, 123.2, 124.6, 137.8.

1-Octyl-3-methylimidazolium hydrogensulfate [omim][HSO_4]. 1.0 eq [omim][$(CF_3SO_2)_2N$] (prepared in analogy to a method described by Grätzel and coworkers[15]) and 0.95 equiv. [NBu_4][HSO_4] were dissolved in water (mass ratio water/salts = 2) and extracted twice with the same amount of dichloromethane. Again 0.05 equiv. [omim][$(CF_3SO_2)_2N$] were added. The solution was vigorously shaken and again extracted twice with dichloromethane. The aqueous phase was evaporated at the rotatory evaporator. The residue was diluted three times with dichloromethane and evaporated for azeotropic removal of water. The yellow, highly viscous liquid was dried from traces of water in high vacuum at 50 °C over night. It crystallised very slowly overnight (95% yield, mp 38–39°C). $\delta_H(CDCl_3)$ 0.85 (t, *J* 6.6 Hz, 3H), 1.17–1.34 (m, 10 H), 1.75–1.90 (m, 2H), 3.98 (s, 3H), 4.23 (t, *J* 7.4 Hz, 2H), 7.35 (s, 1H), 7.54 (s, 1H), 9.22 (s, 1H), 10.24 (s, 1H); $\delta_C(CDCl_3)$ 14.1, 22.6, 26.3, 29.0, 29.1, 30.2, 31.7, 36.4, 49.9, 137.2, 121.9, 123.9.

1-Butyl-3-methylimidazolium bis(trifluoromethanesulfonato)amide [bmim][$(CF_3SO_2)_2N$][15]. To a solution of [bmim] Cl[14] in water lithium bis(trifluoromethanesulfonato)amide was added in small excess. The solution was extracted with dichloromethane and the layers were separated. The organic layer was washed three times with water, dried over molecular sieve and evaporated in high vacuum. [bmim][Tf_2N] was obtained as a colourless liquid of low viscosity in 95% yield. $\delta_H(CDCl_3)$ 0.95 (t, *J* 7.3 Hz, 3H), 1.30–1.43 (m, 2H), 1.80–1.90 (m, 2H), 3.92 (s, 3H), 4.17 (t, *J* 7.3 Hz, 2H), 7.36 (m, 1H), 7.38 (m, 1H), 8.64 (s, 1H); $\delta_C(CDCl_3)$ 13.2, 19.4, 32.0 , 36.3, 50.0, 120.0 (q, *J* 321.1 Hz), 122.6, 123.9, 135.9; $\delta_F(CDCl_3)$ −79.8.

1-Octyl-3-methylimidazolium bis(trifluoromethanesulfonato)amide [omim][$(CF_3SO_2)_2N$]. The synthesis of 1-octyl-3-methylimidazolium bis(trifluoromethanesulfonato)amide was in analogy to the preparation of 1-butyl-3-methylimidazolium bis(trifluoromethanesulfonato)amide according to Grätzel and coworkers[15] Instead of [bmim][Cl] 1-octyl-3-methylimidazolium ([omim]) chloride[16] was used to obtain a yellow liquid of low viscosity (96% yield). δ_H($CDCl_3$) 0.87 (t, *J* 6.6 Hz, 3H), 1.20–1.36 (m, 10H), 1.78–1.92 (m, 2H), 3.93 (s, 3H), 4.15 (t, *J* 7.3 Hz, 2H), 7.32–7.36 (m, 2H), 8.70 (s, 1H); δ_C($CDCl_3$) 14.0, 22.6, 26.1, 28.8, 28.9, 30.1, 31.6, 36.3, 50.2, 119.8 (q, *J* 321.1 Hz), 122.3, 123.8, 135.9; δ_F($CDCl_3$) −79.6.

Boron trihydrogensulfate $B(HSO_4)_3$[17]. SO_3 was condensed into a glass autoclave at −78 °C. The boron acid $B(OH)_3$ was added in stoichiometric amount at one time and the autoclave was closed immediately. The mixture was allowed to warm up and after a violent reaction a clear, colourless liquid was obtained. A few minutes later the solution became viscous and was stirred 15 h at 100 °C. The $B(HSO_4)_3$ has the consistency of wax and hardens after a few days.

1-Butyl-3-methylimidazolium tetrakis(hydrogensulfato)borate [bmim][$B(HSO_4)_4$)]. [bmim]$_2$[SO_4], sulfuric acid and boron trihydrogensulfate were added in the same stoichiometric amounts and stirred for 3 h at 50 °C to yield a slightly yellow liquid of high viscosity. δ_H(neat substance, C_6D_6, coaxial NMR tube) 0.82 (br, 3H), 1,25 (br, 2H), 1.76 (br, 2H), 3.81 (br, 3H), 4.07 (br, 2H), 7.24 (br, 1H), 7.26 (br, 1H), 8.23 (br, 1H), 10.70 (br, 4H); δ_C(neat substance, C_6D_6 coaxial NMR tube) 13.0, 19.1, 31.6, 36.0, 49.7, 122.5, 123.9, 135.3.

1-Octyl-3-methylimidazolium tetrakis(hydrogensulfato)borate [omim][$B(HSO_4)_4$)]. [omim][$B(HSO_4)_4$] was prepared by adding a stoichiometric amount of [omim][HSO_4] to $B(HSO_4)_3$. The very viscous, reddish-brown liquid was used for the catalysis in an *in situ* system without further characterisation.

Catalytic experiments

All alkylation experiments were carried out in Schlenk tubes under argon with 15 mm PTFE stirring bars. The ionic liquid was stirred for 10 min with sulfuric acid at room temperature before the organic solution was added to give a biphasic reaction mixture. The molar ratio of benzene to 1-decene was 5 : 1. The amount of the standards octane and tetradecane were 8 mass% each. The standard alkylation reactions were carried out at 50 °C for 1 h with a mass ratio of 1-decene to sulfuric acid of 2 : 1. The reaction was stopped after 1 h by stirring the solution for 2 min in an ice-bath. After a further 2 min during which the solution separated into two phases, a sample of the organic layer was taken. The sample was neutralised over dried Amberlyst A21 (weakly basic anion exchange resin, free base form) by shaking for 30 min in the same amount of acetone. The remainder of the reaction solution was quenched with a 1 : 1 mixture of water and acetone and stirred vigorously for 1 min. The organic layer was dried over molecular sieves 4Å. Both samples were analysed by gas chromatography.

The standard reaction conditions were selected to obtain with neat sulfuric acid as catalyst (without ionic liquid additive) a monoalkylbenzene yield of 40.8%. This allowed to determine both activating and deactivating effects caused by the added ionic liquids.

Results and discussion

Benzene alkylation using Brønsted acidic ionic liquids of general type H_2SO_4/[cation][HSO_4]

In a first set of experiments ionic liquids of the general type [cation][HSO_4] were tested as additives to sulfuric acid for the catalytic benzene alkylation with 1-decene. The biphasic reactions were carried out under standard conditions. The results with two different cations and different amounts of added ionic liquid are illustrated in Fig. 1.

The experiments reveal a significant dependence of the catalytic reactivity on the cation of the ionic liquid. With added [bmim][HSO_4] a continuous drop in catalytic activity is observed. In contrast, added [omim][HSO_4] results at low concentration (< 12 mol%) in a clear enhancement of activity. These results can be interpreted taking into account both acidity and solubility effects of the ionic liquid additive.

From the autoprotolysis equilibrium of pure sulfuric acid, it is clear that the addition of a hydrogensulfate salt to 100% sulfuric acid should reduce the concentration of the most acidic species [H_3SO_4]$^+$. For this reason the overall acidity of the H_2SO_4/[cation][HSO_4] mixture is lower then the acidity of 100% sulfuric acid alone. Interestingly, in the case of [omim][HSO_4] this effect is overcompensated at low ionic liquid concentration by a phase-transfer effect of the added ionic liquid. Very probably the higher 1-decene solubility of the ionic liquid modified catalyst layer accounts for this effect. In this context it is noteworthy that the selectivity to monoalkylbenzene was found to be higher than 97% in all cases.

These first experiments already demonstrate two general features of a hydrogensulfate ionic liquid additive to a sulfuric acid catalyst: on the one hand, the chance to moderate in a defined manner the catalyst's acidity by proper choice of the sulfuric acid to hydrogensulfate ionic liquid ratio; on the other, the possibility to adjust the solubility of the feedstock in the acidic layer by variation of the cation of the ionic liquid and again by choice of the sulfuric acid to hydrogensulfate ionic liquid ratio.

Brønsted acidic ionic liquids of general type H_2SO_4/[cation][$B(HSO_4)_4$]

Encouraged by these interesting results we dedicated a second set of experiments to investigate the influence of the anion of the ionic liquid. Here we pursued the concept to test anions which should combine the following properties: (a) very low basicity in order to maintain or even enhance the acidity of the acidic mixture with sulfuric acid; (b) high tolerance towards substrates with *e.g.* hydroxy or carbonyl functions in order to use the developed system in future work for the alkylation of functionalised aromatic compounds.

In this context we synthesised, for the first time, ionic liquids with the anion [$B(HSO_4)_4$]$^-$. The idea that ionic liquids with this anion could generate highly acidic systems came to our

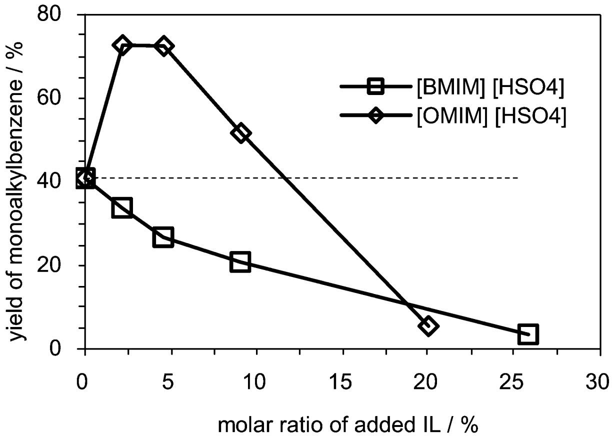


Fig. 1 Effect of the amount of added ionic liquid and influence of the cation of the ionic liquid on the Friedel–Crafts alkylation of benzene with 1-decene using H_2SO_4/[cation][HSO_4] as acidic catalyst system.

minds when we recognised a certain analogy with the well-known chloroaluminate ionic liquids. In the latter case, the Lewis acid $AlCl_3$ is added to a chloride melt to create the less coordinating, less basic anion $[AlCl_4]^-$. In a comparable way the anion $[B(HSO_4)_4]^-$ can be regarded as the product of a reaction between $[HSO_4]^-$ and the Lewis-acid $[B(HSO_4)_3]$. Ionic liquids with the $[B(HSO_4)_4]^-$ anion are very easily obtained by mixing a hydrogensulfate ionic liquid with boron acid and SO_3 in the correct stoichiometry or by reaction of equimolar amounts of an sulfate ionic liquid with sulfuric acid and $[B(HSO_4)_3]$.

As shown in Fig. 2, [bmim]$[B(HSO_4)_4]$ proved to be a very suitable ionic liquid additive to sulfuric acid for the alkylation of benzene. While ionic liquids with identical cation and $[HSO_4]^-$ and $[(CF_3SO_2)_2N]^-$ showed a continuous drop in catalytic activity with increasing molar amount of added ionic liquid, the catalytic mixtures with [bmim]$[B(HSO_4)_4]$ displayed even higher catalytic activity at ionic liquid addition of up to 30 mol%! Again, the selectivity to monoalkylbenzene was $>97\%$ in all cases.

In order to take maximum advantage of the ionic liquid additive we tried to combine, in a third set of experiments, the observed cation and anion effects. For this purpose, we synthesised [omim]$[B(HSO_4)_4]$ which should combine low basicity with enhanced solubility for the 1-decene feedstock in the catalytic layer. In fact, using this ionic liquid as an additive to sulfuric acid, excellent yields of monoalkylbenzene were obtained. With an addition of only 2.2 mol% of [omim]$[B(HSO_4)_4]$ we could increase the catalytic activity of the acidic layer by almost 90% (in comparison to neat sulfuric acid!) The catalytic results are presented in Fig. 3. As in the experiments before the selectivity to monoalkylbenzene was $>97\%$ in all cases with added ionic liquid (the monoalkylbenzene selectivity was found to be only around 95% with the $[B(HSO_4)_3]$ additive).

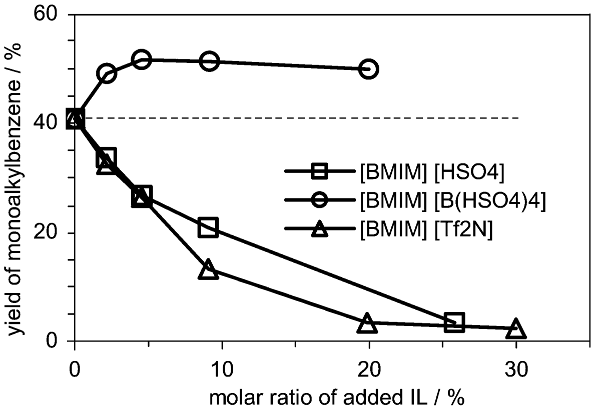


Fig. 2 Effect of the amount of added ionic liquid and influence of the anion of the ionic liquid on the Friedel–Crafts alkylation of benzene with 1-decene using H_2SO_4/[bmim][A] as acidic catalyst systems; $[Tf_2N] = [(CF_3SO_2)_2N]$.

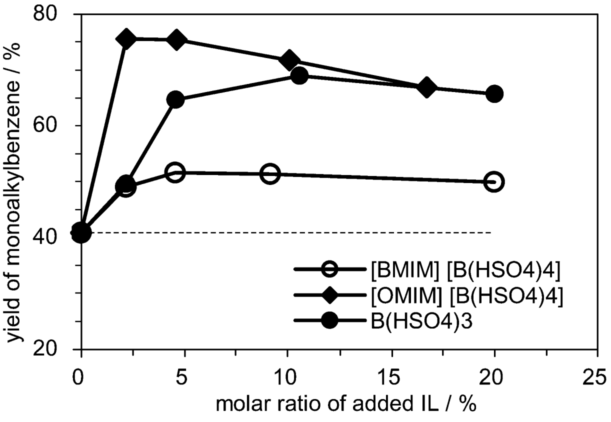


Fig. 3 Effect of the amount of added ionic liquid and influence of the cation of the ionic liquid on the Friedel–Crafts alkylation of benzene with 1-decene using H_2SO_4/[cation]$[B(HSO_4)_4]$ as the acidic catalyst system.

Again, the influence of the different additives is related to an interplay of acidity and solubility effects. The lower product yield with added [bmim]$[B(HSO_4)_4]$ *cf.* added [omim]$[B(HSO_4)_4]$ can be understood as result of the higher 1-decene solubility in the catalytic layer in the latter case. Since the acidity of the catalytic protons is believed to be mainly dependent on the basicity of the anions of the melt, no major acidity change is expected upon variation of the cation. Interestingly, the acidic layer obtained by adding low amounts of [omim]$[B(HSO_4)_4]$ yields even more monoalkylbenzene than the same molar addition of the Lewis-acid $[B(HSO_4)_3]$. The latter should have a significant effect on the Brønsted-acidity of the catalytic mixture due to complexation of $[HSO_4]^-$ to $[B(HSO_4)_4]^-$. This clearly demonstrates that the effect of added [omim]$[B(HSO_4)_4]$ can not uniquely be explained by enhanced proton acidity.

Regioselectivity of the alkylation reaction

In benzene alkylation with 1-decene several regioisomers are produced (as already shown in eqn. (2)). While 1-phenyldecane is scarcely detectable for mechanistic reasons, 2-phenyldecane is the alkylation product of benzene with 1-decene. However, 3-, 4- and 5-phenyldecane are obtained to a significant extent due to the fast isomerisation of 1-decene to the internal decenes by the acidic catalyst system. Hence, the regioselectivity obtained with different catalysts can be regarded as an indicator for the rate of catalytic 1-decene isomerisation *vs.* rate of aromatic alkylation.

In Table 1, the selectivity to 2-phenyldecane is presented for different acidic catalysts described above. In order to allow a proper comparison, only the regioselectivity of those reactions that showed very similar yields of monoalkylbenzene are compared.

Obviously, the use of different sulfuric acid + additive mixtures can significantly influence the distribution of regioisomers depending on the nature of the additive and depending on the acid/additive ratio (comparison of entries a and b, c and d, e and f). These results can be interpreted taking into account the different effects of each additive on the acidity of the melt as well as its solubility properties. From these results we conclude that the amount of 2-phenyl isomer in the monoalkylbenzene product decreases to a larger extent with an additive that leads to high proton acidity. However, more of the 2-phenyl isomer is found in the monoalkylbenzene product when an additive is used that mainly works as a good phase transfer catalyst but clearly reduces the acidity of the protons. Interestingly, with neat sulfuric acid as catalyst only 33% of 2-phenyldecane was obtained in the monoalkylated products at only 40.8% yield of

Table 1 Regioselectivity of benzene alkylation with sulfuric acid + additive; formation of 2-phenyldecane (2-PD) as a function of added ionic liquid or Lewis-acid at comparable monoalkylbenzene yields

Entry	Additive (mol%)	Yield of monoalkylbenzene (%)	Selectivity (1,8-product) (%)
a	$B(HSO_4)_3$ (20.2)	65.7	37
b	[omim]$[B(HSO_4)_4]$ (16.72)	66.8	40
c	[bmim]$[B(HSO_4)_4]$ (9.16)	51.3	35
d	[omim]$[HSO_4]$ (9.07)	51.7	41
e	[bmim]$[HSO_4]$ (25.80)	3.5	41
f	[bmim]$[(CF_3SO_2)_2N]$ (19.87)	3.4	57

phenyldecanes. By use of the developed ionic liquid additives it is therefore possible to create catalytic systems which combine lower isomerisation activity with higher alkylation activity (at least in comparison to neat sulfuric acid). Consequently, higher yields of the technically desired 2-phenylalkyl product would be possible in a potential technical application of the ionic liquid modified sulfuric acid catalyst.

Conclusion

The use of ionic liquids in highly Brønsted-acidic catalysts has so far been limited to chloroaluminate systems. However, chloroaluminate ionic liquids have a number of serious limitations, namely their irreversible destruction by moisture and their lack of tolerance to functionalities in the substrates. From the results of this publication we conclude that hydrogensulfate and tetrakis(hydrogensulfato)borate ionic liquids are highly interesting additives to mineral acids to form new, highly Brønsted-acidic catalysts. These ionic liquids are halogen-free, available from cheap raw materials and easy to prepare.

The first catalytic application of these systems in the biphasic alkylation of benzene with 1-decene revealed a number of very interesting features. For example, we found that *e.g.* mixtures of sulfuric acid with only 2.2 mol% of [omim][$B(HSO_4)_4$] ionic liquid yielded 90% more monoalkylbenzene product than the neat sulfuric acid catalyst under identical reaction conditions. This and related results are explained by an interplay of solubility and acidity effects caused by the ionic liquid additive. The acidity of the catalyst can be fine-tuned by choice of the amount of ionic liquid additive and by choice of its anion. In the same way the solubility properties of the catalytic layer for the substrates can be adjusted by a suitable choice of the ions of the ionic liquid and again by the amount of added ionic liquid. Finally, the use of the ionic liquid additives provides a very general tool to optimise the biphasic reaction system. For example, modification of the density of liquid acidic catalysts should be possible by ionic liquid additives, so enabling faster phase separation and easier recovery of the acidic catalyst layer.

In future work, we will investigate the alkylation of functionalised aromatic compounds and other proton catalysed reactions where tuneable acidity, tuneable solubility and reduced volatility of the acidic catalyst may be of interest.

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In situ XAFS investigation of palladium species present during the Heck reaction in room temperature ionic liquids

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The Heck reaction, performed in room temperature ionic liquids, has been studied by *in situ* XAFS, which indicates that palladium clusters of 0.8–1.6 nm diameter are the main species present during reaction.

Introduction

There is an increasing awareness of the environmental and economic costs associated with conventional media in synthetic industrial chemical processes. Ionic liquids possess many desirable properties which alleviate some of the environmental issues such as no effective vapour pressure, and good solubilities for a wide range of inorganic, organic and polymeric materials (high solubility implying small reactor volumes). In addition, with many combinations of anions and cations available, ionic liquids can be tailored to suit specific needs of reactions. Hence, there is significant interest in using them as replacements for conventional organic solvents. Room temperature ionic liquids have already been shown to perform a range of reactions, which have been reviewed extensively recently.[1]

The formation of C–C bonds using the Heck reaction is of major importance in organic chemistry and is widely used industrially. The Heck reaction has been studied extensively using a variety of catalysts and solvent systems and has recently been reviewed.[2] In the vast majority of reactions, palladium complexes and salts catalyse the reaction of aromatic halides with olefins. Although many studies have been performed, there are few investigations on the recyclability of the catalyst, which is problematic using conventional organic solvents due to the precipitation of palladium black at the end of the reaction. Recently, the Heck reaction has been reported to proceed efficiently in room temperature ionic liquids,[3–6] as has the closely related Suzuki cross coupling reaction,[7] with the added advantage that they enable recycle of the catalyst. To date, however, only two attempts have been made to characterise the possible catalytic species present during reaction.[5,6]

This paper presents the first *in situ* study of the Heck reaction in ionic liquids. Using an *in situ* cell,[8] X-ray absorption fine structure (XAFS) has been used to examine palladium species formed when palladium ethanoate is dissolved in various ionic liquids both in the presence and absence of PPh_3 as well as reagents. The reaction was followed at various temperatures, and the time variation of the palladium species found in solution was related to reaction kinetic data. The ionic liquids studied were based on the 1-alkyl-3-methylimidazolium, *N*-alkylpyridinium and tetraalkylammonium salts.

Chris Hardacre was born in Buckinghamshire, UK, in March 1969. He read Natural Science at the University of Cambridge and, following graduation in 1990, stayed in Cambridge to do a PhD with Dr R. M. Lambert on 'Surface Chemistry and Catalysis of novel Pt/CeO$_2$ systems. He graduated in 1994 and became a SERC reasearch fellow and a research fellow of Emmanuel College, Cambridge. In April 1995, he was appointed to a lectureship in Physical Chemistry at the Queens's University of Belfast. He is a member of the catalysis research group within the School of Chemistry and is one of the academic supervisors within QUILL. His current interests lie in two main areas, namely, understanding heterogeneously catalysed processes and their application in fine chemical synthesis and the use of synchrotron radiation to probe the structure of ionic liquids and understand reactions performed in them.

Results and discussion

On dissolution of palladium ethanoate at 80 °C in 1-butyl-3-methylimidazolium ([C$_4$mim]$^+$) and *N*-butylpyridinium ([C$_4$py]$^+$) hexafluorophosphate and tetrafluoroborate ionic liquids, and triethylhexylammonium bis(trifluoromethanesulfonyl)imide ([N$_{6222}$][NTf$_2$]), a gradual change from ethanoate coordination to the formation of palladium metal is observed. Using [C$_4$mim][PF$_6$] as an example, the XAFS data and pseudo-

Green Context

Ionic liquids are very attractive as alternative reaction media for greener chemical reactions. They have no vapour pressure and can be tailored to suit various applications. Recently it has been shown that these are suitable media for carrying out the important C–C bond forming Heck reactions. This paper progresses these studies by showing the nature of the catalytic species to be metal clusters. Importantly the stability effect of the solvent on the metal cluster allows recyclability and simple product separation enabling an overall reduction in the number of process steps and an increase in the atom efficiency of the whole process.
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radial distribution functions for the dissolved palladium ethanoate is shown in Fig. 1 and the bond distances, Debye–Waller factors and coordination numbers used in modelling the spectra are summarised in Table 1. Changing the anion to chloride, however, prevented the formation of the metal in both imidazolium and pyridinium ionic liquids. In [C_6mim]Cl, the XAFS was consistent with the formation of a bis-carbene complex, where the imidazolium ring is coordinated to the metal centre at the C(2) position on the ring. Similar bis-carbene complexes have been observed by NMR on dissolving Pd$(OAc)_2$ in [C_4mim]Br upon thermal[5] and ultrasound treatment.[6] In [C_4py]$^+$ and [C_6py]$^+$ chloride ionic liquids and in 1,2-dimethyl-3-hexylimidazolium chloride ([C_6mmim]Cl) , *i.e.* where the C(2) position is protected by a methyl group, only $[PdCl_4]^{2-}$ was observed. Fig. 2 shows examples of the XAFS data and pseudo-radial distribution functions for dissolved palladium ethanoate in chloride based ionic liquids and the parameters used in modelling the spectra are summarised in Table 2.

The Heck reaction is commonly performed with the addition of a Group 15 ligand additive such as triphenylphosphine. XAFS was also taken of the systems described above but in the presence of PPh_3. Fig. 1 and 2 also show the effect of the presence of triphenylphosphine on palladium ethanoate dissolved in [C_4mim][PF_6] and chloride based ionic liquids. For all ionic liquids containing chloride, only a small change was observed in the XAFS data. In [C_6mim]Cl, the bis-carbene was still present without change, however for the [C_4py]Cl, [C_6py]Cl and [C_6mmim]Cl ionic liquids, the amplitude of XAFS oscillations decreased slightly as did the intensity of the peak at 2.3 Å in the pseudo-radial distribution function. Although, in the latter three ionic liquids, the data can still be

Table 1 Structural parameters from the fitted XAFS spectra from palladium ethanoate in [C_4mim][PF_6] (A) without and (B) with triphenylphosphine at 80 °C and (C) in the presence of triphenylphosphine and reagents at 50 °C for 20 min.

Reaction medium	Shell/atom	Shell distance/Å	Coordination number	Debye–Waller factor/Å^2	Fit factor (%)
A	1 O	2.02	1.0	0.011	22.8
	2 Pd	2.73	6.1	0.013	
	3 C/O	3.06	2.0	0.002	
	4 Pd	3.10	0.5	0.003	
	5 Pd	3.85	3.0	0.020	
	6 Pd	4.76	12.0	0.022	
B	1 O	1.95	0.6	0.016	23.0
	2 P	2.26	0.9	0.013	
	3 Pd	2.71	3.4	0.015	
	4 C/O	3.10	1.2	0.004	
	5 Pd	3.82	1.7	0.017	
	6 Pd	4.73	6.7	0.028	
C	1 O	1.98	1.0	0.020	19.2
	2 P	2.27	2.4	0.018	
	3 Pd	2.72	1.1	0.015	
	4 C/O	3.10	2.0	0.003	
	5 Pd	3.73	0.6	0.009	

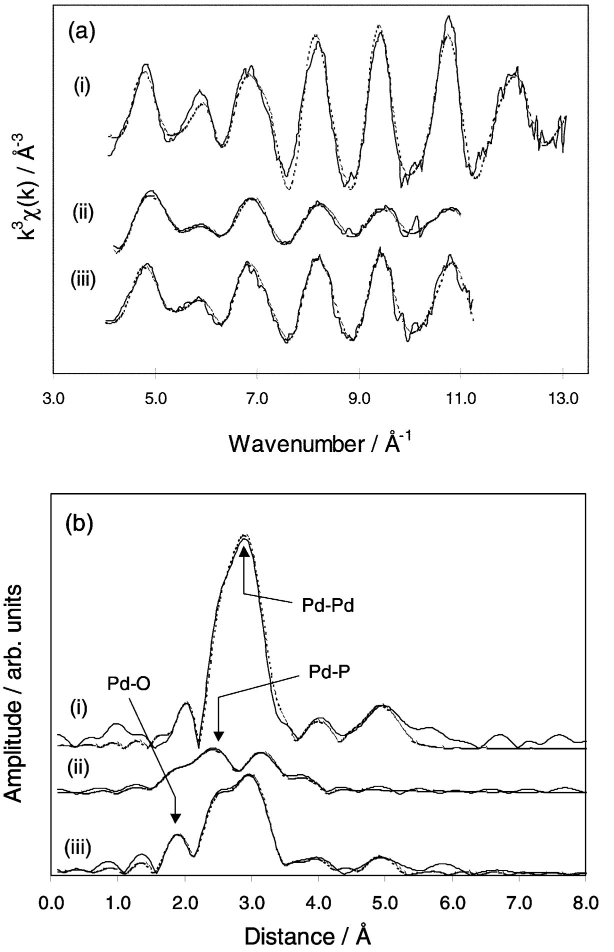

Fig. 1 Comparison of the experimental (solid line) and fitted (dashed line) (a) XAFS and (b) pseudo-radial distribution functions from palladium ethanoate in [C_4mim][PF_6] (i) without and (ii) with triphenylphosphine at 80 °C and (iii) in the presence of triphenylphosphine and reagents at 50 °C for 20 min. The parameters used to model the experimental data are summarised in Table 1.

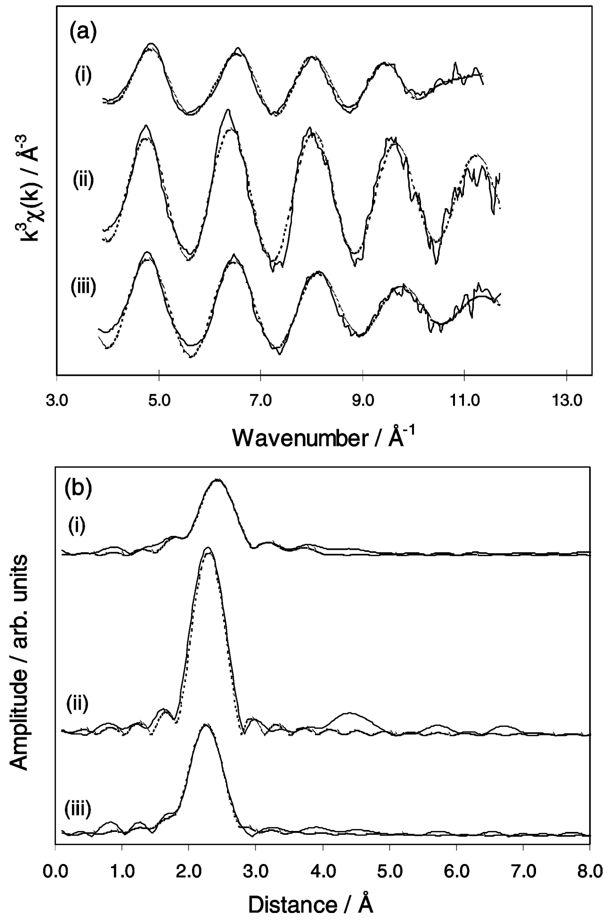

Fig. 2 Comparison of the experimental (solid line) and fitted (dashed line) (a) XAFS and (b) pseudo-radial distribution functions from palladium ethanoate dissolved in (i) [C_6mim]Cl and (ii) [C_4py]Cl without triphenylphosphine and in (iii) [C_6mmim]Cl in the presence of triphenylphosphine at 80 °C. The parameters used to model the experimental data are summarised in Table 2.

Table 2 Structural parameters from the fitted XAFS spectra from palladium ethanoate dissolved in [C_6mim]Cl (A) and [C_4py]Cl (B) without triphenylphosphine and in [C_6mim]Cl (C) in the presence of triphenylphosphine at 80 °C

Reaction medium	Shell/atom	Shell distance /Å	Coordination number	Debye–Waller factor/Å^2	Fit factor (%)
A	1 C	2.05	2.0	0.012	22.6
	2 Cl	2.34	2.0	0.010	
	3 N	2.97	4.0	0.008	
	4 C	3.32	4.0	0.026	
B	1 Cl	2.33	4	0.008	24.9
C	1 P	2.34	2	0.015	21.8
	2 Cl	2.94	2	0.016	

modelled by $[PdCl_4]^{2-}$, a significantly better fit is obtained by incorporating two triphenylphosphine coordinating to the metal centre. In the $[BF_4]^-$, $[PF_6]^-$ and $[NTf_2]^-$ ionic liquids studied, the change in the XAFS data is much more dramatic. A large decrease in the Pd–Pd coordination and the appearance of the peak associated with triphenylphosphine coordination is observed. The XAFS following dissolution in [C_4mim][PF_6] at 80 °C for 20 min in the presence of triphenylphosphine, was fitted to a composition of 20% palladium metal, and the remaining 80% coordinated to ethanoate (25%) and triphenylphosphine (55%). In comparison, without triphenylphosphine, dissolution resulted in 80% palladium metal and only 20% coordinated to ethanoate.

In the presence of the reagents, iodobenzene and butyl acrylate, little change was observed in the species generated. Again no palladium metal was formed on dissolution of palladium ethanoate in [C_6mim]Cl, with or without triphenylphosphine whereas for bis(trifluoromethanesulfonyl)imide, tetrafluoroborate and hexafluorophosphate anions, palladium was formed. In the presence of the reagents, the formation of palladium was found to be quicker than in the absence of reagents. For example, at 50 °C, palladium ethanoate in [C_4mim][PF_6] in the presence of triphenylphosphine and reagents shows 50% metal after only 15 min whereas even at elevated temperature (*e.g.* 80 °C) only 20% metal is shown without reagents present, as described above. This can be seen clearly in the pseudo-radial distribution functions of the XAFS shown in Fig. 1 to enable direct comparison with the species found without reagents present. It should be noted that in all cases the reaction system is found to be recyclable without significant loss in activity, with the exception of [C_6mim]Cl, in which the reaction was found not to work.

Where full transformation of the palladium to the metal was observed, the XAFS data was analysed in order to estimate the average diameter of the metal clusters formed. Assuming that the metal cluster was spherical, and using the geometrical relationship between the number of neighbouring atoms in the first four coordination shells and the average particle size derived by Borowski,[9] a minimum is found in the fits on varying the particle size. In all cases, the cluster diameter was found to lie between 0.8 and 1.6 nm. Table 3 summarises the diameters of the particles and the XAFS fits obtained for the ionic liquid systems studied.

Table 3 Palladium cluster size after 1 hour reaction of iodobenzene and butylacrylate at 100 °C using palladium ethanoate in a range of ionic liquids with and without triphenylphosphine.

Ionic liquid	Cluster size/nm	Fit factor (%)
[C_4mim][PF_6]	1.3	20.5
[C_4mim][PF_6]/PPh_3	0.8	25.5
[C_4Py][BF_4]	1.6	23.9
[C_4Py][BF_4]/PPh_3	1.1	21.3
[N_{6222}][NTf_2]	1.0	27.4

The average size of the metal clusters varies according to the media in which they are formed. The presence of PPh_3 results in metal clusters that are at least 25% smaller in size than those formed in the absence of PPh_3. The tetraalkylammonium system produced colloids that fell between the sizes of those formed in the two PPh_3 systems studied even though in this case no additive was present.

The gradual formation of palladium observed in the XAFS may explain the reaction kinetics observed. Fig. 3 shows the time variation of the Heck reaction of iodobenzene and butylacrylate to *trans*-butylcinnamate at 50 °C in [C_4mim][PF_6]. Clearly an induction period is seen which is increased in the presence of PPh_3. Similar induction periods are observed for all the ionic liquids studied. On heating the system without reagents for the length of the induction period, the induction period is reduced significantly and in many cases is eliminated. With increasing temperature the induction period observed decreases, and above 70 °C, little induction period is observed. Although triphenylphosphine increases the induction period and decreases the reaction rate, unsurprisingly, systems containing PPh_3 were found to be more stable with respect to palladium black formation, and showed better recyclability than those without. For example, in [C_4mim][PF_6], little palladium black was observed in triphenylphosphine containing systems even after three reactions. It was found however, that in [N_{6222}][NTf_2] the palladium showed similar stability without the need for triphenylphosphine. It is interesting to note that both the triphenylphosphine stabilised and [N_{6222}][NTf_2] systems had the smallest cluster size as determined by XAFS. The cluster size in each of these cases was unchanged, even after prolonged heating.

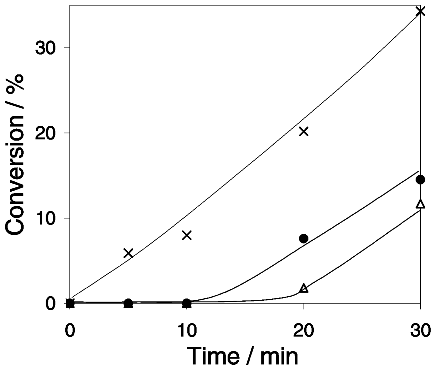

Fig. 3 Conversion *vs.* time for the reaction of iodobenzene and butylacrylate at 50 °C using palladium ethanoate with triphenylphosphine predissolved in [C_4mim][PF_6] at 80 °C for (a) 20 min (×) (b) 5 min (△) and (c) 5 min and left at 50 °C for 30 min (●).

The formation of palladium metal clusters stabilized by molten salts is not a new concept, nor is their use in the Heck reaction. For example, tetraalkylammonium salts have been studied extensively as a stabiliser for chemical/electrochemically produced transition metal clusters.[10] Isolated palladium clusters, dissolved in conventional organic solvents, have proved effective for the Heck reaction,[11,12] however, other types of stabilising agents, such as polystyrene-*b*-poly-4-vinyl pyridine micelles, have proved superior[13] due to thermal stability and recyclability.[12]

The formation of palladium clusters within the Heck reaction has been reported previously. Reetz and Westermann showed that palladium clusters were formed during a Heck reaction in conventional organic media, and identified them using TEM.[14] As in the present research, an induction period was observed and showed a correlation between cluster formation and the initiation of the reaction. The TEM results indicated that the cluster diameter was approximately 1.6 nm. Recently, Deshmukh *et al* also used TEM to show the presence of 1 nm diameter palladium clusters , after a successful Heck reaction using ultrasound at 30 °C in 1,3-dibutylimidazolium bromide and tetrafluoroborate based ionic liquids.[6]

In conclusion, palladium clusters of diameters between 0.8–1.6 nm can be formed in various ionic liquids, the size and stability of which vary according to the system in which they are present. The kinetics of the Heck reaction in ionic liquids shows an induction period below 70 °C, which may be related to the formation of palladium metal. Indeed it is found that if the metal is preformed prior to reaction, the induction period is decreased substantially. The stabilising effect of the ionic liquid on the palladium clusters allows complete recyclability and simple product separation without the incorporation of palladium in the product or the loss of catalyst from the reaction medium. The overall effect is a reduction in the number of separation steps required and an increase in the atom efficiency of the whole process.

Experimental

The XAFS spectra were recorded at the Synchrotron Radiation Source at Daresbury using station 9.2 equipped with a double crystal Si(220) monochromator on the Pd K edge. Typical operating conditions were 2 GeV at a beam current of 160–240 mA. Scans were collected and averaged using EXCALIB, this was also used to convert the raw data into energy *vs.* absorption data. EXBROOK was used to remove the background. The pre-edge background was fitted *via* two quadratic functions before and after the edge jump, whilst the post-edge background was fitted using a cubic-spline method. The analysis of the XAFS data was performed using EXCURV98[15] on the raw XAFS data without Fourier filtering, using the curved wave theory, with the calculated phaseshifts and backscattering amplitudes from experimentally determined data on known standards. The data reported here is of *in situ* XAFS taken on solutions mixed with graphite to enable good contact between the reagents and the ionic liquid/catalyst system, since they are immiscible at the temperatures stated. In order to calculate the percentages, the fitted coordination numbers were used assuming the only species present were $Pd(OAc)_2$, $Pd(PPh_3)_4$ and palladium metal clusters with an average diameter of 1.0 nm.

The preparation of the ionic liquids was performed according to standard literature procedures[16] and all other reagents were obtained from Aldrich and used as supplied. The Heck reaction was performed using ionic liquid (1.05×10^{-2} mol), palladium ethanoate (0.1 mmol) and triphenylphosphine (0.2 mmol), heated with stirring at 80 °C for 20 min and allowed to cool to 50 °C. Triethylamine (7.5 mmol), iodobenzene (5.0 mmol), and butyl acrylate (12.5 mmol) was then added to the cooled ionic liquid solution of the catalyst. Samples were taken every 5 min and analysed by GC-FID. Drying the ionic liquid had little effect on the kinetics observed. Following reactions in the XAFS cell, the systems were analysed and showed comparable conversion (within 5%) to those performed in the laboratory. In each case the products were extracted with diethyl ether prior to analysis.

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Alternating copolymerisation of styrene and carbon monoxide in ionic liquids

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Room temperature ionic liquids have been used as solvents for the palladium-catalysed copolymerisation of styrene and carbon monoxide. The behaviour of various ionic liquids, the nature and concentration of palladium catalyst, and the reusability of the catalyst–ionic liquid system are discussed. The effects of cation, anion and alkyl chain length of the ionic liquids on the reaction are also addressed. The yield of the polyketone in the ionic liquid systems is enhanced over conventional solvents studied under similar conditions.

Introduction

Room temperature ionic liquids have emerged as promising alternative media for the replacement of conventional organic solvents.[1] There is a phenomenal growth in the development of new ionic liquid systems, in our fundamental understanding of their behaviour,[2] and in their applications for a range of reactions.[3,4] Whereas the practical applications of the first generation ionic liquids (chloroaluminates) are limited due to their water-sensitive nature,[5] the second generation (neutral) ionic liquids exhibit a wide range of thermal stability, water tolerance, and coordinating ability, and have been found active in many industrially important organic transformations,[6] for example, alkylations,[7] C–C bond coupling,[8–10] and polymerisation.[11,12] Ionic liquids have also been used for gas–liquid reactions for example, hydrogenation,[13] hydroformylation,[14] and alkoxycarbonylation.[15]

Using conventional organic solvents, such as methanol, carbonylation of olefins using palladium catalysts offers perfect alternating copolymers, polyketones.[16] In particular, ethylene- and styrene-based polyketones are of specific interest due to their excellent mechanical properties[17] and piezo-, pyro-, as well as ferro-electric properties.[18] The possibility of induction of a chiral centre makes polyketones a useful class of materials for chromatographic and membrane separation/purification of optically-active substances. Further, polyketones possess biodegradable and photodegradable properties.[18] Thus, alternating copolymerisation of olefins and carbon monoxide has attracted much attention and been the subject of recent review articles.[19,20] What apparently hinders the commercial exploitation of these materials is a process that can offer high yields whilst employing a stable, reusable catalyst system.

Milani *et al.* reported that $[Pd(bipy)_2][PF_6]_2$ (bipy = 2,2′-bipyridine) was a highly active catalyst for styrene copolymerisation with CO, in methanol or trifluoroethanol.[21] High productivity of polyketone [*ca.* 17.4 kg (g Pd)$^{-1}$] was obtained in 48 h, with 32 ppm palladium contamination in the resultant polyketone. We decided to study this reaction in non-volatile ionic liquids, specifically to achieve better or equal yields and to minimise the decomposition and hence prevent the loss of palladium during the polymerisation. Here we report our preliminary results on the preparation of polyketone *via* alternating carbonylation of styrene and carbon monoxide, using $[Pd(bipy)_2][PF_6]_2$ in an ionic liquid media. The performance of various ionic liquids, the effect of reaction parameters and the reusability of ionic liquid-catalyst system are highlighted.

Results and discussion

Table 1 shows the yields of polyketone [reported as turnover number, TON, (g polyketone) (g Pd)$^{-1}$ h^{-1} obtained in various ionic liquids. From Table 1 it is evident that type of cation, the alkyl chain length and the anion govern both the yield and the catalytic activity. For both pyridinium and imidazolium based ionic liquids, the yield is found to decrease in the order $[NTf_2]^-$ > $[PF_6]^-$ > $[BF_4]^-$. From Table 1, entries 2, 3, 7, 8 and 9, one can generalise that hydrophobic ionic liquids are more suitable for this reaction. This effect of anions in ionic liquids has also been observed in the carbonylation of aryl halides[22] and in the hydrogenation of dienes.[23] Recently, Rogers and coworkers.[24] have studied a series of ionic liquids and have found out that the anionic component of the ionic liquids affect the physical properties of ionic liquids to a large extent. The type of cation also affected the yield of polyketone. Comparison of the activity in pyridinium, imidazolium, quaternary nitrogen- and phosphonium-based bistrifylamide ionic liquids show that the

Green Context

The alternating copolymerisation of olefins and carbon monoxide is of considerable interest with the resulting materials having many interesting and useful properties. Unfortunately, their exploitation has been hindered by the lack of an effective reusable catalyst system. Here it is shown that ionic liquids can be used as solvents for the synthesis of polyketones and the catalyst–solvent system can be recycled with no significant loss in activity or in changes in the properties of the polymer ***JHC***

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Table 1 Screening of ionic liquids for styrene copolymersation with carbon monoxide

Entry	Ionic liquid[a]	Viscosity/cP 20 °C	80 °C	Weight of polyketone/g	TON[b]	M_w[c]	M_n[c]	M_w/M_n[c]
1	$[C_4Py][NTf_2]$	Solid	9.9	1.0	168	16300	6940	2.3
2	$[C_6Py][NTf_2]$	53.8	5.9	1.9	320	31050	14100	2.2
3	$[C_6Py][BF_4]$	240.9	15.7	0.8[d]	134	—	—	—
4	$[C_8Py][NTf_2]$	134.4	13.5	2.0[d]	355	9720	4840	2.0
5	$[C_{10}Py][NTf_2]$	160.1	15.0	1.5[d]	240	4800	3390	1.4
6	$[C_{16}Py][NTf_2]$	Solid	29.4	1.0[d]	168	—	—	—
7	$[C_6mim][NTf_2]$	87.3	10.5	1.0	168	—	—	—
8	$[C_6mim][PF_6]$	690	37.6	0.8[d]	134	6200	4750	1.3
9	$[C_6mim][BF_4]$	314	22.6	0.5[d]	64	—	—	—
10	$[NC_{6,2,2,2}][NTf_2]$	22.2	1.6	0.4	67	—		
11	$[PC_{6,6,6,14}][NTf_2]$	165	14.1	0.02[d]	36	—	—	—

[a] Abbreviations used: *e.g.* $[C_4Py]$ is *N*-butylpyridinium, $[C_{16}Py]$ is *N*-hexadecylpyridinium, $[C_6mim]$ is 1-hexyl-3-methylimidazolium, $[NC_{6,2,2,2}]$ is hexyltriethylammonium, $[PC_{6,6,6,14}]$ is tri(*n*-hexyl)tetradecylphosphonium and $[NTf_2]$ is bis(trifluoromethylsulfonyl)amide. *Reaction conditions*: styrene 8 cm³, mol ratio styrene/Pd = 10000, ionic liquid = 1 cm³, mol ratio benzoquinone/Pd = 250, 80 °C, P_{CO} = 10 atm., 8 h. [b] (TON) Turnover number defined as g polymer (g Pd)$^{-1}$ h^{-1}. [c] M_w is the weight average molecular weight, M_n is the number average molecular weight, the ratio M_w/M_n is referred as 'polydispersity', expressed relative to a polystyrene equivalent. [d] Pd leaching in the polyketone.

Table 2 Comparison of Ionic liquids with molecular solvents in copolymerisation of styrene and carbon monoxide[a]

Solvent	Weight of polyketone/g	TON[b]	M_w	M_n	M_w/M_n
$[C_6Py][NTf_2]$	0.25	416	11800	7480	1.6
Trifluoroethanol	0.05[c]	90	—	—	—
Methanol	0.005[c]	9	6300	4100	1.5
$[C_6Py][NTf_2]$–methanol (1 cm³ each)	0.08[c]	160	3250	2370	1.4

[a] *Reaction conditions*: styrene = 3.5 cm³, mol ratio styrene/Pd = 100 000, mol ratio benzoquinone/Pd = 5, 60 °C, P_{CO} = 40 atm, duration 24 h, solvent = 1 cm³. [b] (TON) Turnover number defined as g polyketone (g Pd)$^{-1}$ h^{-1}. [c] Pd leaching in the polyketone.

polyketone yield also decreases in the similar order. The length of alkyl chain was found to have a significant effect on the reactivity and recyclability of the system. In $[C_nPy][NTf_2]$ ionic liquids, the yield was found to increase from *n* = 4 to 10. However, for *n* = 8, 10 and 18, the polymer formed was found to be grey in colour, indicating the inclusion of palladium, *via* the decomposition of the catalyst, in the polymer. Similarly, the effect of alkyl chain length was also observed by Farve *et al.* during their study on hydroformylation of 1-hexene.[25] Higher solubility of 1-hexene was observed at increasing alkyl chain length. The success of the copolymerisation of olefins and CO would largely depend upon the ease of CO diffusion from the gaseous phase into the liquid phase. The mass transfer would be effective in ionic liquids of low viscosity. This trend is clearly observed in both imidazolium- and pyridium-based ionic liquids.

On the basis of the results obtained from the screening of ionic liquids, styrene copolymerisation with CO in $[C_6Py][NTf_2]$ was compared with conventional solvents like methanol and trifluoroethanol. The results are presented in Table 2. Using methanol as a solvent, a polyketone sample in lower yield and of lower molecular weight was obtained. When equal volumes of $[C_6Py][NTf_2]$ and methanol were used, polyketone with the lowest molecular weight was obtained. This suggests that the reaction proceeds *via* a different mechanism in ionic liquid, and in methanol. The study of mechanistic aspects of this reaction in ionic liquids is underway. Initial experiments using high temperature NMR spectroscopy and L-SIMS (liquid secondary ion mass spectrometry) failed to indicate any apparent interaction between the catalyst and ionic liquid.

In the ionic liquid, the yield of polyketone was found to be higher without any measurable palladium leaching (by ICP analysis). Better stabilisation of catalytic species has also been observed by Waffenschmidt and Wasserscheid during platinum catalysed hydroformylation of 1-octene in $[bmim][SnCl_3]$[26] and in biphasic oligomerisation of ethane in $[bmim][PF_6]$ using cationic nickel complexes.[27]

Using $[C_6Py][NTf_2]$, the copolymerisation reaction was investigated to study the effect of various reaction parameters (Table 3 and Fig. 1). An increase in the reaction temperature (from 20 to 100 °C), resulted in the remarkable increase in activity and molecular weight. The turnover number at *ca.* 46 g polyketone (g Pd)$^{-1}$ h^{-1} at 20 °C increased to 1235 g of polyketone (g Pd)$^{-1}$ h^{-1} at 100 °C (Fig. 1). At 80 °C, polyketone samples with satisfactory yield and molecular weight were obtained. These results are in accordance with the previous reports on olefin copolymerisation.[21] Higher partial pressure of CO, on the other hand, had an adverse effect on the productivity. The yield of polyketone increased when the partial pressure of CO was increased from 1 to 10 atm, but further increase in the pressure resulted a significant reduction of the yield and molecular weight (Table 3, entries 1 and 8). These results are in agreement with those of Rix *et al.* who reported the inhibitory role of CO in ethylene carbonylation.[28] At lower catalyst concentration (mol ratio styrene/Pd = 100 000) a turnover number of 1332 g polyketone (g Pd)$^{-1}$ h^{-1} was obtained. Upon increasing the catalyst concentration ten-fold (mol ratio styrene/Pd 10 000) the turnover number decreased by a factor of four; however the overall yield increased by more than two-fold (Table 3, entries 1–3). Further increase in catalyst concentration resulted in decomposition of palladium catalyst and precipitation of palladium in the polyketone formed.

Even in the absence of any oxidant (*viz.* 1,4-benzoquinone), the reaction does take place. However, the material was obtained in lower yield and with catalyst decomposition. Addition of an excess benzoquinone prevented catalyst decomposition and in turn high molecular weights were obtained (Table 3, entries 4–8).

The volume of ionic liquid was also observed to affect the productivity of the reaction. Increasing the volume of ionic liquid from 1 to 4 cm³, caused the yield of polyketone to increase ten-fold. This may be due to increased stabilisation of the charged catalytically active species in the charged ionic liquid compared with the covalent styrene component. Further increase in the volume of ionic liquid dramatically reduced the yield of polyketone. This may simply be the result of dilution, however, Peng and Deng[29] also observed the adverse effect of increased volume of ionic liquid, during Beckmann rearrangement of ketoximes.

Table 3 Effect of reaction parameters[a]

Entry	P_{CO}/atm	Mol ratio styrene/Pd	Mol ratio Pd/BQ	Volume ratio styrene/IL	Weight of polyketone/g	TON[b]	M_w	M_n	M_w/M_n
1	10	100 000	250	8	0.80	1332	16150	13300	1.9
2	10	20 000	250	8	1.40	467	—	—	—
3	10	10 000	250	8	1.90	320	31050	14100	2.2
4	10	100 000	0	8	0.02[c]	46	25500	13100	2.0
5	10	100 000	5	8	0.37	851	22800	12200	1.9
6	10	100 000	25	8	0.43	989	49300	25600	1.9
7	10	100 000	100	8	0.63	1449	53500	21600	2.5
8	40	100 000	250	8	0.14	320	8480	4320	2.0
9	40	100 000	250	4	0.54	1235	12100	7140	1.7
10	40	100 000	250	2	1.40	3201	7810	4680	1.7
11	40	100 000	250	1.3	0.55	1241	10500	6030	1.7
12	40	100 000	250	1	0.18	412	12500	7150	1.8

[a] *Reaction conditions*: styrene = 8 cm^3, 80 °C, duration 8 h, ionic liquid used was [C_6Py][NTf_2]. [b] (TON) Turnover number defined as g polyketone (g Pd)$^{-1}$ h^{-1}. [c] Pd leaching in the polyketone.

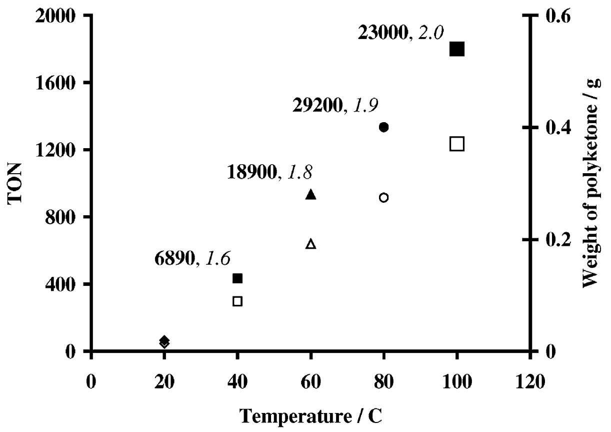

Fig. 1 Effect of reaction temperature on the yield of polyketone (filled symbols) and on the turnover number (open symbols). The values near each point represent M_w (in bold) and M_w/M_n (in italics). *Reaction conditions*: styrene 8 = cm^3, mol ratio styrene/Pd = 100 000, mol ratio benzoquinone/Pd = 250, [C_6Py][NTf_2] = 1 cm^3, P_{CO} = 1 atm., 8 h. Turnover number (TON) defined as g polyketone (g Pd)$^{-1}$ h^{-1}.

Thus, at this stage, we could achieve polyketone productivity up to 24 kg of polymer (g Pd)$^{-1}$ under following conditions. Mol ratio styrene/Pd = 100 000; volume ratio styrene/ionic liquid = 2; mol ratio benzoquinone/Pd = 250; P_{CO} = 40 bar; 80 °C, 8 h. Work on optimisation continues in our laboratory.

After the polymer separation and removal of hydroquinone by extraction or by vacuum distillation, ionic liquid containing catalysts were reused for the reactions without further purification. For at least after four successive recycles, no significant drop on either the yield or the quality of the polyketone was observed (Fig. 2). Polyketone samples of similar molecular weight and polydispersity were obtained.

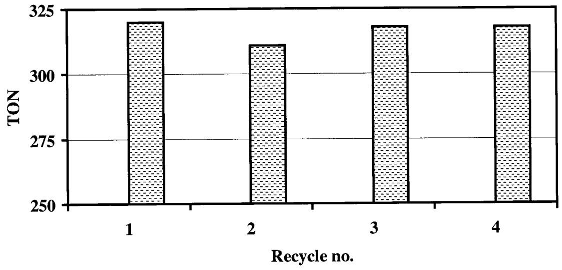

Fig. 2 Recyclability of ionic liquid-catalyst system. *Reaction conditions*: refer to Table 1. (TON) Turnover number defined as g polyketone (g Pd)$^{-1}$ h^{-1}

Conclusions

Ionic liquids can be used as solvents for the synthesis of polyketones. Increased yield of the polymer, ease of product separation, and recyclability of the ionic liquid-catalyst system (with negligible catalyst leaching) show the advantage of this system over the conventional organic solvents commonly used for this reaction.

Experimental

Styrene, 2,2′-bipyridine, 1,4-benzoquinone were obtained from Aldrich and used as received. The catalyst [Pd(bipy)$_2$][PF_6]$_2$ was prepared and characterized according to the procedure explained by Milani *et al.*[21] However, in the present preparation, 60 wt% aqueous solution of HPF_6 (Aldrich) was used instead of instead of [NH_4][PF_6]. The details of ionic liquid preparation can be found elsewhere.[30,31]

A typical reaction was carried out in following manner: A mixture of ionic liquid (1 cm^3), styrene (70 mmol), benzoquinone (0.185 mmol), palladium catalyst [Pd(bipy)$_2$](PF_6)$_2$] (7 × 10^{-4} mmol) otherwise stated was placed in a stainless steel jacketed glass reactor (30 cm^3); Baskerville reactors, UK. The reactor was then pressurised at the desired pressure with carbon monoxide and the reactor temperature was raised to 80 °C for 8 h. The solid polymer product was precipitated on addition of methanol (5 cm^3) and separated by filtration. The product was characterized by FT-IR (1695 cm^{-1}, CO group); elemental analysis (calc. C 81.79, H 6.10; found 81.62, H 6.05%), Thermal analysis (melting point 275 °C) and by ^{13}C NMR (1,1,1,3,3,3-hexafluoro-2-propanol–$CDCl_3$,7/3 v/v, 27 °C), δ 210.8 (CO), 136.4 (Ph-C_{ipso}), 129.9, 128.9, 128.5 (Ph-$C_{o,m,p}$), 54.7 (CHCH_2), 43.5 (CH$C$$H_2$). Molecular weight ($M_w$ = 31050, M_n = 14100, polydispersity = 2.2) were obtained by gel permeation chromatography (carried out at Rapra Technology Limited, UK) and is expressed in terms of 'polystyrene equivalents' using a 50/50 w/w mixture of trichlorobenzene and phenol at 115 °C. It was also possible to obtain the polyketone material with narrow polydispersity (*ca.* 1.6) by further increasing the volume of ionic liquid, which also resulted in lowering the molecular weight (M_w = 7000, M_n = 4355) of the polyketone.

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Biocatalysis in ionic liquids

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This review describes the recent developments of enzymatic catalysis in ionic liquids, reporting the use of different biocatalysts in organic synthesis. Several ionic liquids appear as an alternative to conventional organic solvents, providing comparable or higher rates and, in some cases, improved enantioselectivity.

Introduction

Ionic liquids are receiving increasing attention as solvents for organic synthesis in general and catalytic processes in particular.[1,2] This interest stems from their potential as 'green' solvents.† Their non-volatile character and thermal stability makes them potentially attractive alternatives for environmen-

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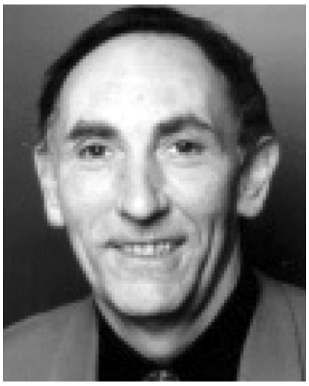
† We note, however, that there is very little known with regard to their degradability and aquatic toxicity.

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

Rute Madeira Lau (1974) studied chemical engineering (specialisation in biotechnology) at the Instituto Superior Tcnico (Lisbon, Portugal). She did her diploma work in the Biocatalysis and Organic Chemistry group at the Delft University of Technology (1997). After a short stay in industry (DSM Gist), she moved back to the Delft University where she started her PhD research in 1999 under the supervision of Prof. Roger Sheldon and Dr. Fred van Rantwijk. The topic of her research is the application of lipases in non-aqueous media, with special attention to the performance of these enzymes in ionic liquids.

Menno J. Sorgedrager (1975) studied biotechnology at the Delft University of Technology. His graduate work was carried out in the group of Prof. Roger Sheldon (Biocatalysis and Organic Chemistry) where he studied the behaviour of lipases in ionic liquids. In 2001 he started his PhD research on the application of aldolases engineered by directed evolution.

Fred van Rantwijk (1943) studied organic chemistry at the Delft University of Technology where he remained as a staff member. He received his PhD in 1980, for work under the guidance of Professor H. van Bekkum. Since the late 1980s he has been working on the application of enzymes in organic synthesis. His particular research interests are the use of enzymes in non-natural reactions, enzyme immobilization, and transformations using multi-enzyme systems.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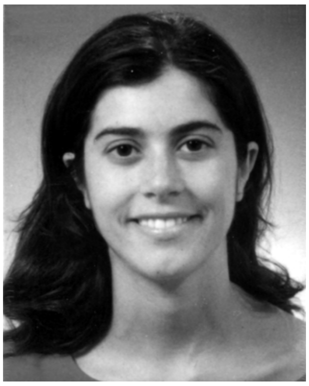
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Fred van Rantwijk

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tally unattractive volatile organic solvents, notably chlorinated hydrocarbons. Moreover, their hydrophobicity/hydrophilicity can be tuned by appropriate modification of the cation or anion, which has earned them the accolade 'designer solvents'.[3] Depending on their structure, they can be immiscible with water or, *e.g.* alkanes, which renders them useful for performing catalytic reactions in biphasic media, thus facilitating catalyst recovery and recycling. Most studies have involved the use of 1,3-dialkylimidazolium salts, *e.g.* 1-butyl-3-methylimidazolium tetrafluoroborate, [bmim][BF_4] and hexafluorophosphate, [bmim][PF_6] which are miscible and immiscible with water, respectively (see Fig. 1).

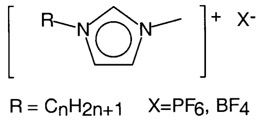
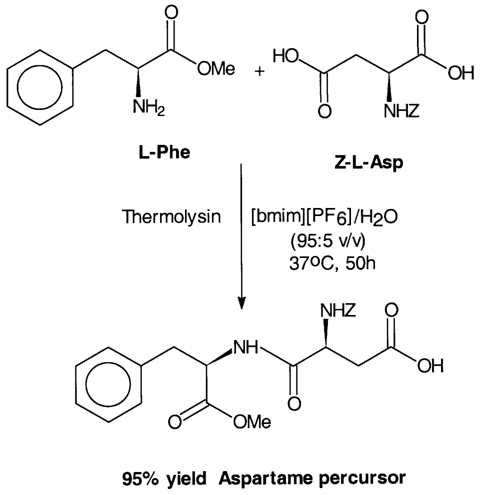


Fig. 1 Structures of ionic liquids based on methylimidazolium salts.

Recently, the use of ionic liquids as reaction media has been extended to biocatalytic processes. Lye and coworkers[4] reported the use of a biphasic [bmim][PF_6]/H_2O medium for the conversion of 1,3-dicyanobenzene to 3-cyanobenzamide and 3-cyanobenzoic acid catalysed by whole cells of *Rhodococcus* R312. The ionic liquid acts as a reservoir for the substrate and product, thereby decreasing substrate and product inhibition observed in water, and, hence, increasing the catalyst productivity. Replacement of toluene by [bmim][PF_6] as the second phase was beneficial as the latter caused less damage to the microbial cells. Similarly, 1-octyl-3-methylimidazolium hexafluorophosphate, [omim][PF_6] was used to enhance the recovery of *n*-butanol from a fermentation broth.[5] In process extraction of *n*-butanol into the ionic liquid phase followed by recovery from the ionic liquid by pervaporation constitutes an attractive alternative to conventional, energy intensive separation from water by distillation.

The feasibility of using isolated enzymes in ionic liquid media has also been demonstrated. Erbeldinger and coworkers[6] reported the thermolysin-catalysed synthesis of Z-aspartame in [bmim][PF_6]/H_2O (95/5, v/v) as shown in eqn. (1).



(1)

Green Context

The use of enzymes for many reactions is hampered by the need for an aqueous environment, which can lead to side-reactions and other problems. Organic solvents can sometimes be used, but often with significant reduction in efficiency. This short review summarises recent work which indicates that ionic liquids are promising as media for these transformations, allowing high levels of efficiency, good solubility and no volatility ***DJM***

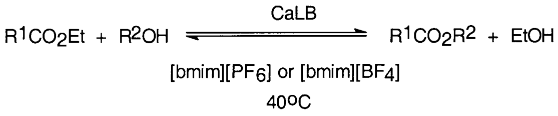
Reaction rates were comparable to those observed in ethyl acetate/H_2O and the enzyme displayed a higher stability in the ionic liquid medium. It was furthermore shown that the small amount of thermolysin (3.2 mg ml^{-1}) that dissolved in the ionic liquid was not active.

The above mentioned examples all involve biocatalysis in ionic liquid–water mixtures. We were interested to ascertain whether or not an enzyme could function in a water free ionic liquid. We chose lipases for our study since these robust enzymes are known to perform well in essentially anhydrous organic media.

Results and discussion

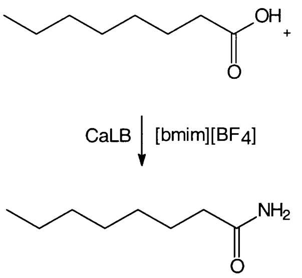
Lipases in ionic liquids

We showed that *Candida antarctica* lipase B (CaLB), either as the free enzyme (SP525) or in an immobilised form (Novozym 435), is able to catalyse a variety of transformations in [bmim][BF_4] or [bmim][PF_6] in the absence of added water[7] (the ionic liquid was stored over P_2O_5 and the enzyme was essentially anhydrous). For example, transesterifications (eqn. (2)) proceeded with rates comparable to those observed in *tert*-butyl alcohol, a commonly employed solvent for such transformations. The immobilised enzyme (Novozym 435) gave higher rates than the free enzyme (SP525) suspended in the ionic liquid. This is consistent with the generally observed higher reactivity of the immobilised lipase, compared to the free enzyme, in organic media.[8]



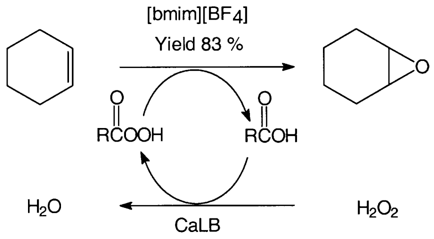
$$R^1CO_2Et + R^2OH \underset{\substack{[bmim][PF_6] \text{ or } [bmim][BF_4] \\ 40^oC}}{\overset{CaLB}{\rightleftharpoons}} R^1CO_2R^2 + EtOH \tag{2}$$

We previously showed[9] that CaLB-catalysed ammoniolysis of carboxylic esters to the corresponding amides occurs smoothly under mild conditions. Primary fatty acid amides, for example, are important commodities that are conventionally prepared by reaction of the ester with ammonia under forcing conditions of temperature and pressure.[10] Heijnen and coworkers[11] subsequently showed that CaLB-catalysed ammoniolysis of carboxylic acids is feasible, albeit with very long reaction times using ammonium carbamate in methyl isobutyl ketone. Hence, we were interested to see if improvements could be achieved in ionic liquid media. Indeed, we found that the reaction of octanoic acid with ammonia (eqn. (3)) in the presence of Novozym 435 at 40 °C in [bmim][BF_4], proceeded to complete conversion in 4 days,[7] compared to 90–100% conversion in 17 days using ammonium carbamate in methylisobutylketone.[11]



(3)

Peroxycarboxylic acids are commonly used oxidants in (industrial) organic synthesis. However, increasing restrictions, with regard to their handling, transport and storage, are making their use prohibitive. Hence, methods for their *in situ* generation constitute an attractive alternative. It has previously been shown[12] that this is feasible *via* lipase-catalysed perhydrolysis of the corresponding carboxylic acid. We have now shown that this reaction can be performed in an ionic liquid.[7] For example, the epoxidation of cyclohexene by peroctanoic acid, generated *in situ* by Novozym 435-catalysed reaction of octanoic acid with commercially available 60% aqueous hydrogen peroxide in [bmim][BF_4], afforded cyclohexene oxide in 83% yield in 24 h (eqn. (4)). For comparison, a yield of 93% was observed in 24 h in acetonitrile, which was previously shown to be the optimum organic solvent for the reaction.[13]



(4)

Enantioselectivity

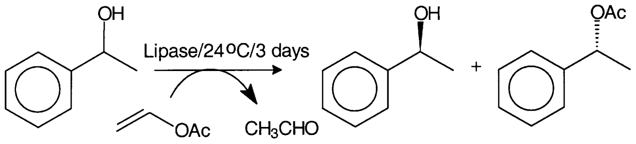
Recently, several groups have investigated lipase-catalysed transesterifications of chiral substrates in ionic liquids. A primary aim of these studies was to ascertain the effect of ionic liquid media on the enantioselectivities of these transformations. For example, Kragl and coworkers[14] investigated the kinetic resolution of 1-phenylethanol (Table 1 eqn. (5)) with nine different lipases in ten different ionic liquids.

Good activities and, in many cases, improved enantioselectivities were observed compared with the same reaction in methyl *tert*-butyl ether (MTBE). CaLB generally gave the best results and some lipases, *e.g. Candida rugosa* lipase and *Thermomyces lanuginosus* lipase, showed almost no activity. The rates and/or enantioselectivities were dependent on both the anion and the alkyl group in the 1-methyl-3-alkylimidazolium cation. In general, the best results were observed in [bmim][CF_3SO_3], [bmim][$(CF_3SO_2)_2N$] and [omim][PF_6]. Surprisingly, virtually no reaction ($<5\%$ conversion) was observed in [bmim][BF_4] and [bmim][PF_6], which is contradictory to what we and others (see later) have observed.

The same resolution of 1-phenylethanol using lipase from *Pseudomonas cepacia* in several [BF_4] ionic liquids was studied by Kazlauskas and coworkers.[15] They observed that the purification step used in the synthesis of ionic liquid is an important factor in order to obtain higher conversion rates. The use of unpurified ionic liquids resulted in reaction rates at least two to five times slower than in toluene, while after purification of the ionic liquid by method A (addition of silver tetrafluoroborate, removal of silver halide precipitate by filtration, followed by chromatography on silica gel) or B (filtration through silica gel plug, wash with saturated aqueous sodium carbonate) reaction rates increased to a value similar to that in an organic solvent or even higher. The addition of sodium carbonate also gave a dramatic increase in reaction rate. This was attributed to the removal of silver ions and neutralization of acidic impurities in the ionic liquid, which adversely affected enzymatic catalysis.

Itoh and coworkers[16] similarly observed that the rate of the transesterification of a chiral allylic alcohol (Table 2, eqn. (6)) was strongly dependent on the nature of the anion in [bmim][X]. In contrast, only a minor effect on the enantioselectivity was observed. We note, however, that the enantioselectivity was

Table 1 Lipase mediated enantioselective acylation of 1-phenylethanol



(5)

Comparison of various lipases[14]

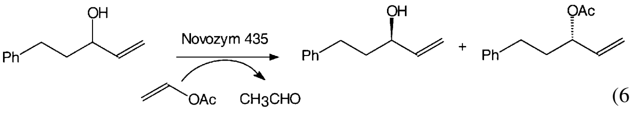
Solvent	CaLB Conv (%)	CaLB ee (%)	*Pseudomonas cepacia* sp Conv (%)	*Pseudomonas cepacia* sp ee (%)	*Alcaligenes* sp. Conv (%)	*Alcaligenes* sp. ee (%)
MTBE	43	>98	53	84	98	0
[bmim][PF_6]	<5	—	0	—	44	77
[bmim][BF_4]	<5	—	7	53	60	81
[hmim][BF_4]	10	>98	0	—	68	14
[omim][BF_4]	41	>98	<5	—	50	>98
[bmim][CF_3SO_3]	50	>98	50	>98	70	82
[bmim][$(CF_3SO_2)_2N$]	50	>98	47	>98	89	15

Effects of additives and purification[15]

Solvent	Purification	Additive	Conv. after 24 h (%)	*E*
Toluene	None	None	44	>200
DMSO	None	None	0	—
[bmim][BF_4]	None	None	7.8	>200
[bmim][BF_4]	A	None	13	>200
[bmim][BF_4]	B	None	36	>200
[bmim][BF_4]	B	$AgBF_4$	0	—
[pmim][BF_4]	None	None	0	—
[pmim][BF_4]	A	None	39	>200
[moemim][BF_4]	A	None	0	—
[moemim][BF_4]	B	None	42	>200
[bpyr][BF_4]	A	$NaHCO_3$	0	—
[bpyr][BF_4]	A	Na_2CO_3	32	>200

bmim = Butylmethylimidazolium; hmim = hexylmethylimidazolium; omim = octylmethylimidazolium; pmim = propylmethylimidazolium; moemim = methoxyethanemethylimidazolium; bpyr = *N*-butylpyridinium

Table 2 Lipase mediated enantioselective acylation of 5-phenyl-1-penten-3-ol



(6)

Solvent	Time/h	Yield (%)	Ee (%)	Rate	*E*
Pr^i_2O	3	45	> 99	17	> 1000
[bmim][PF_6]	5	49	> 99	9.4	> 580
[bmim][BF_4]	3.5	44	> 99	14	> 640
[bmim][TFA]	48	19	91	0.25	227
[bmim][OTf]	24	34	> 99	1.8	> 450
[bmim][SbF_6]	48	31	> 99	0.8	> 360

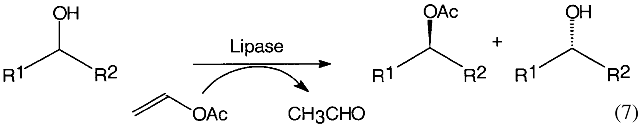
very high ($E > 200$) in all cases which makes it difficult to observe differences. The best results were obtained in [bmim][BF_4] and [bmim][PF_6], in contrast to the results reported (see above) for reaction 5. A comparison of different lipases in [bmim][PF_6] revealed that Novozym 435 gave the highest rate, followed by lipases from *Alcaligenes* sp. and *Pseudomonas cepacia* (PCL) while those from *Candida rugosa* and porcine liver exhibited no activity. It was further shown that the product could be extracted with ether and the ionic liquid, [bmim][PF_6], containing the suspended enzyme, could be recycled (although the activity decreased dramatically after the second recycle).

Kim and coworkers[17] studied the transesterification of several chiral alcohols (Table 3, eqn. (7)) catalysed by CaLB and PCL in [emim][BF_4] and [bmim][PF_6]. Markedly enhanced enantioselectivities were observed compared with the same reactions performed in toluene or THF.

Solubility and stability of enzymes in ionic liquids

The above described results clearly show that enzymes are able to perform in ionic liquid media, even in the absence of water. From both a practical and a theoretical viewpoint it was of interest to ascertain the stabilities of enzymes, in various formulations, in ionic liquids versus (molecular) organic solvents. We were also interested to see if enzymes would dissolve in ionic liquids and retain their activity in dissolved form. To this end we examined the CaLB-catalysed transesterification of racemic phenylglycine methyl ester with ethanol (eqn. (8)).[18] This reaction is not very enantioselective ($E = 7$ in t-BuOH), which was one of the reasons for choosing it.

Table 3 Lipase mediated enantioselective acylation of secondary alcohols



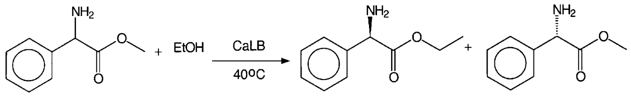
(7)

R^1	R^2	Lipase	Solvent	*E*
CH_3	$PhCH_2CH_2$	CaLB	THF	141
			Toluene	207
			[emim][BF_4]	648
			[bmim]PF_6]	> 967
CH_3	$PhCH_2O$-$COCH_2$	CaLB	THF	26
			Toluene	187
			[emim][BF_4]	651
			[bmim]PF_6]	155
CH_2Cl	Ph	PCL	THF	56
			Toluene	158
			[emim][BF_4]	183
			[bmim]PF_6]	> 450
CH_2Cl	$PhOCH_2$	PCL	THF	150
			Toluene	85
			[emim][BF_4]	172
			[bmim]PF_6]	> 1000

The reaction was studied with four different formulations of CaLB: free enzyme (SP525), immobilised on a support (Nov435), crosslinked enzyme crystals (CLECs)[19] and crosslinked enzyme aggregates (CLEAs).[20] As shown in Table 4 the reaction rates in [bmim][PF_6] and [bmim][CF_3SO_3] were comparable to those observed in *tert*-butanol. In contrast, no reaction (< 5% conversion) was observed in [bmim][NO_3], [bmim][lactate], [emim][$EtSO_4$] and [$EtNH_3$][NO_3]. We observed similar results in the transesterification of ethyl butyrate with *n*-butanol in the same solvents. Interestingly, the free enzyme (SP525) dissolved in the ionic liquids in which no activity was observed. However, dissolution as such does not explain the lack of activity since the immobilised preparations were also inactive in these solvents. The ionic liquids in which low activities are observed contain more strongly coordinating anions: lactate, nitrate and ethylsulfate. We suggest that a plausible explanation for this is that coordination of these anions to the enzyme surface, be it in the free or immobilised form, causes conformational changes in the enzyme, leading to a loss of activity.

We studied the effect of dissolving enzymes in ionic liquids on their subsequent hydrolytic activity. CaLB lipase was dissolved in [bmim][NO_3], [bmim][lactate], [emim][$EtSO_4$]

Table 4 Transesterification of phenylglycine methyl ester with ethanol by different preparations of CaLB



(8)

	Novozym 435		SP525		CLEA		CLEC	
Solvent/CaLB prepar ation	Conv. after 24 h (%)	*E*	Conv. after 24 h (%)	*E*	Conv. after 24 h (%)	*E*	Conv. after 24 h (%)	*E*
[bmim][BF_4]	42	1	36	9	24	9	50	2
[bmim][PF_6]	39	1	32	9	47	4	40	1
[bmim][OTf]	41	1	44	3	—	—	44	1
Bu^tOH	46	1	40	4	52	7	50	1
[bmim][NO_3]	< 5	—	< 5	—	< 5	—	< 5	—
[bmim][Lactate]	< 5	—	—	—	—	—	—	—
[emim][$EtSO_4$]	< 5	—	—	—	—	—	—	—
[$EtNH_3$][NO_3]	< 5	—	< 5	—	< 5	—	—	—

and $[EtNH_3][NO_3]$ and the solution allowed to stand for 24 h at 40 °C. The solution was then diluted with a large excess of water forming an homogeneous system and the activity of the enzyme was determined in the hydrolysis of triacetin. In all cases we observed a substantial recovery of activity, varying from 33% in $[EtNH_3][NO_3]$ to 73% in $[bmim][NO_3]$. Taken together with the observed lack of transesterification in these solvents (see earlier) these results suggest that the enzyme denatures (unfolds) on dissolving in the ionic liquid and that on the addition of water it refolds into its active form. It is known[21] that denaturated enzymes are able to refold when put into an aqueous medium. An alternative explanation is that the loss of activity on dissolution is caused by strong coordination of the anions to the enzyme (see above). Investigations are underway, *e.g.* using circular dichroism, to confirm whether or not the enzyme unfolds on dissolution in an ionic liquid and on methods to stabilise the enzyme in solution.

It is also evident from Table 4 that both the nature of the ionic liquid and the form of the enzyme have an influence on the enantioselectivity of the reaction. However, the enantioselectivity was modest at best ($E = 9$) and the hoped-for dramatic improvements were not observed.

Thermal stability of CaLB in ionic liquids

We studied the thermal stability of different CaLB preparations by suspending them in an organic solvent or $[bmim][PF_6]$, allowing the mixture to stand at 80 °C and taking aliquots at various time intervals and measuring the residual activity, after dilution with water, in triacetin hydrolysis.

Incubation of free enzyme (SP 525) in $[bmim][PF_6]$ at 80 °C resulted in an increase in activity. After an incubation time of 20 h, the maximum activity found was 120% of the activity of the native untreated enzyme. This activity value did not decrease up to an incubation time of 100 h, while in Bu^tOH a nearly linear deactivation in time was observed. Incubation of Novozym 435 in $[bmim][PF_6]$ at 80 °C showed a maximum activity of 350% compared to the activity of the untreated SP 435 after an incubation time of 40 h. After 5 days this preparation still exhibited 210% of the initial activity. Here again, incubation in Bu^tOH showed a linear deactivation in time. Recently, Iborra and coworkers[22] have similarly reported a stabilising effect of ionic liquids on CaLB. Interestingly, they found that the half-life of the enzyme was three orders of magnitude greater when it was incubated in the presence *versus* in the absence of the substrate. In their study experiments were performed in the presence of 2% (v/v) water.

In contrast to the results obtained with free CaLB and Novozyme 435, no stabilising effect was observed when a CLEC or CLEA from CaLB was incubated in $[bmim][PF_6]$ at 80 °C. A decrease in activity was observed in both the ionic liquid and *tert*-butyl alcohol which was comparable to that found for CaLB and Novozyme 435 in *tert*-butyl alcohol. The stabilising effect of the ionic liquid on the free and supported enzyme possibly results from a protecting action of a coating of ionic liquid on the microenvironment (hydration layer) of the enzyme. The reason for the lack of a stabilising effect on the CLEA and CLEC preparations is not clear and forms the subject of further investigations.

Concluding remarks & future prospects

As the preceding discussion hopefully has shown, performing biocatalytic conversions in ionic liquids can be beneficial with regard to activity, (enantio)selectivity and stability. Indeed, the use of enzymes in ionic liquids opens up new possibilities for non-aqueous enzymology. Ionic liquids could have added benefits for performing biotransformations with highly polar substrates, *e.g.* carbohydrates[23] and amino acids, which are sparingly soluble in most organic solvents. We are currently investigating the scope with regard to type of enzyme and biotransformation and the origins of the observed dependence of activity and stability of the enzyme on the structure (both cation and anion) of the ionic liquid and will report our results in due course.

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An investigation of the radiochemical stability of ionic liquids

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Ionic liquids have been considered for their potential applications within the nuclear fuel cycle. If ionic liquids are to be successful in their application as solvents for highly radioactive materials in any future process, there will be a requirement for them to be robust to high radiation doses. A preliminary assessment of the radiation stability of 1,3-dialkylimidazolium cation based ionic liquids containing nitrate and chloride anions has been performed. The results of radiolysis studies are reported, in which the samples were exposed to alpha radiation from a tandem Van der Graaff generator, beta radiation from a linear accelerator and gamma radiation from cobalt 60 sources. These results suggest that their stability is similar to that of benzene and that they are much more stable than mixtures of tributylphosphate and odourless kerosene under similar irradiation conditions. The radiolysis of 1,3-dialkylimidazolium cation based ionic liquids reflects their combination of the properties of a salt, an alkane and an aromatic. They appear to be relatively radiation resistant and there is certainly no major decomposition of the organic component.

Introduction

Volatile organic compounds (VOCs) have been linked to several air pollution problems including smog, ozone depletion and groundwater contamination.[1] VOCs are commonly used by industry as solvents in chemical processes. In the nuclear industry, for example, odourless kerosene is used in processing spent nuclear fuel. The relatively low boiling points of VOCs aid their removal after the process but hamper their quantitative recovery and make storage difficult. Due to their low vapour pressures, organic salts with relatively low melting points, often referred to in the literature as ionic liquids,† are currently being investigated as replacements for VOCs in an increasing number of chemical processes. The large number of reviews covering the field of ionic liquids[2] is evidence of the increasing academic and industrial interest on the subject of ionic liquids. The editorial comments at the beginning of this special issue of *Green Chemistry* provide a contextual overview of ionic liquids, no more need be said concerning the general background of ionic liquids.

There is a long and well-established history of the use of molten salts in the nuclear industry, and extensive reviews of this field (such as that of uranium oxides in molten salts by Griffiths and Volkovich)[3] exist elsewhere. The possibility of

Green Context

The use of ionic liquids in a range of processes is dependent upon a thorough understanding of their physical propeties and stability under appropriate conditions. One potential application is in the nuclear fuel cycle. Results presented here indicate that dialkylimidazolium based ionic liquids have relatively good stability, better than that of some potential solvents in this application. The provision of such data is important if novel solvent systems are to be considered for such applications. ***DJM***

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† In this report, the term 'ionic liquid' refers solely to organic salts with melting points below 100 °C. Such materials have been given a variety of names in the literature, *e.g.*, liquid organic salts, ambient (or room) temperature molten salts, nonaqueous ionic liquids, or ionic fluids. The 1-alkyl-3-methylimidazolium ionic liquids under investigation in this report will be referred to as [C$_n$mim]X where n is the number of carbons in the 1-alkyl group and X is either chloride or nitrate.

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applying ionic liquids to processes in the nuclear fuel cycle has also been the subject of much investigation, including recent work from our laboratories that has led to the publication of a series of patents concerned with using ionic liquids in nuclear fuel reprocessing and molten salt waste treatment.[4] Beginning with the work of Hitchcock *et al.*,[5a] the electrochemical and spectrochemical behaviour of dioxouranium(VI) species in chloroaluminate room temperature ionic liquids have been investigated.[5] Costa *et al.*[5e] recently compared the dioxouranium(VI) and dioxoplutonium(VI) chemical and electrochemical systems in acidic chloroaluminate ionic liquids and presented arguments for the potential use of ionic liquids throughout the nuclear industry. It has been demonstrated that room temperature ionic liquids can be used for solvent extraction of metal species from aqueous media;[6] this is an area of great significance to the nuclear industry which currently uses solvent extraction in the PUREX process for reprocessing spent nuclear fuel.[7] Critical mass calculations carried out by Harmon *et al.*, on two plutonium metal/ionic liquid mixtures have recently been published.[8]

If ionic liquids are to be successful in their application as solvents for highly radioactive materials in any future process, there will be a requirement for them to be robust to high radiation doses: that is, they must not undergo significant degradation due to radiolysis upon exposure to high radiation doses. A benchmark of comparison would be the solutions of tributylphosphate in odorless kerosene (TBP/OK) currently used in the Purex process for reprocessing spent nuclear fuel. Radiolysis of TBP is known to produce radiolysis products that interfere with the Purex process.

Experiments to assess the radiation stability of ionic liquids are challenging to design. The ionic liquids should be subjected to a high radiation dose, whilst avoiding any localised heating of the samples. The samples during and after irradiation must be able to be subjected to analytical techniques, so for ease of handling should not be contaminated with radioactive materials. Analytical techniques should be sufficiently sensitive to detect any radiolysis products and their concentrations.

The initial interaction of gamma, beta and alpha radiation with chemical systems is by ionisation [eqn. (1)] and excitation (eqn. (2)).

$$R \rightarrow R^+ + e^- \tag{1}$$

$$R \rightarrow R^* \tag{2}$$

Ionisation may be followed by geminate recombination [eqn. (3)] to give more excited states or by ion dissociation [eqn. (4)].

$$R^+ + e^- \rightarrow R^* \tag{3}$$

$$R^+ \rightarrow R^{\cdot +} + H^{\cdot} \tag{4}$$

A range of recombination and hydrogen abstraction processes can follow these reactions. In general aromatic compounds are more stable than non-aromatic, because the aromatic ring can absorb energy and relax non-dissociatively. Furthermore, mixtures of aromatic and non-aromatic compounds tend to show less decomposition of the non-aromatic component than would be expected from its concentration because of energy transfer to the aromatic compound.

Typically, H_2 is found as a radiolysis product from irradiated organics [eqn. (5)].

$$RH + H^{\cdot} \rightarrow R^{\cdot} + H_2 \tag{5}$$

It is impossible to generalise about the results from alkanes and aromatics, but typically[9] alkanes give rise to hydrogen yields [$G(H_2)$] of about 5–6 molecules per 100 eV. A comparison of alkanes with benzene [$G(H_2)$ = 0.04 molecules per 100 eV],[9] substituted benzenes [$G(H_2)$ = 0.1–0.2 molecules per 100 eV][7] and a nitrogen heterocyclic compound such as imidazole [$G(H_2)$ = 0.03 molecules per 100 eV][10] demonstrates the stabilising effect of aromaticity upon a molecules tendency to undergo radiolysis. It is believed that the aromatic nature of [$C_n$mim]X ionic liquids will make them highly resistant to radiolysis.

Ionic liquids have recently been used in two different investigations involving radiolysis. Behar *et al.*,[11] subjected the [C_4mim][PF_6] and [C_4mim][BF_4] ionic liquids to beta irradiation in order to study the reaction kinetics of the [CCl_3O_2]$^{\cdot}$ radical. Their report showed spectroscopic evidence of the formation of the [C_4mim]$^{\cdot}$ and [C_4mim]$^{\cdot 2+}$ radicals upon beta irradiation in the neat ionic liquids. Marcinek *et al.*,[12] exposed a number of ionic liquids to beta irradiation to study their use as media for generation and characterisation of radical species. However, these samples were either aqueous solutions or cryogenic glassy samples, never the neat ionic liquids. They also report the formation of the [C_4mim]$^{\cdot}$ radical and comment upon the ability of ionic liquids to stabilise radical ions.

Results and discussion

All of the ionic liquids tested for radiation stability were subjected to a radiation dose of 400 kGy. This was the radiation dose used in recent radiation stability tests of TBP/OK mixtures recently carried out for BNFL. This dose was used so a comparative study could be made, as it is known that significant degradation occurs to TBP/OK mixtures at this dosage, and there was an attempt to produce degradation products at measurable levels. ^{1}H and ^{13}C NMR spectroscopy was used to analyse all samples which underwent radiation stability tests. Spectra recorded before and after testing were compared to determine if any radiolysis had occurred. It should be noted that NMR spectroscopy is unable to identify if conversion is below 1%. However, this was sufficient for comparison with a solution of TBP/OK which underwent up to 15% conversion under similar conditions. The ionic liquids tested included 1-butyl-3-methylimidazolium nitrate [C_4mim][NO_3], 1-ethyl-3-methylimidazolium chloride [C_2mim]Cl and 1-hexyl-3-methylimidazolium chloride [C_6mim]Cl.

Gamma irradiation test results

At the J. J. Thomson Irradiation Laboratory, four samples each of [C_2mim]Cl and [C_4mim][NO_3] sealed in glass ampoules were exposed to total doses and at dose rates as shown in Table 1. NMR spectra recorded prior to and after irradiation were compared. The comparison showed no discernible changes in the spectra following irradiation, indicating that less than 1% of the samples underwent radiolysis in each case. All samples and the glass ampoules showed considerable darkening following irradiation; the darkening of both the samples and the ampoules was observably more intense with increasing dose. No evidence of the formation of insoluble material was found.

A more detailed analysis of the changes in the UV absorption spectrum and a chemical analysis of the ionic liquids following irradiation was carried out at AEA Technology. Results of the spectral changes occurring during the gamma irradiation of [C_6mim]Cl (Fig. 1) and [C_4mim][NO_3] (Fig. 2) show some

Table 1 Gamma irradiation tests

Batch number[a]	Dose rate/ Gy h^{-1}	Irradiation time/h	Dose/kGy
1	10	200.8	2.008
2	400	25.2	10.08
3	400	250.1	100.0
4	1000	400.0	400.0

[a] Each batch consisted of a sealed glass ampoule of [C_2mim]Cl and a sealed glass ampoule containing [C_4mim][NO_3].

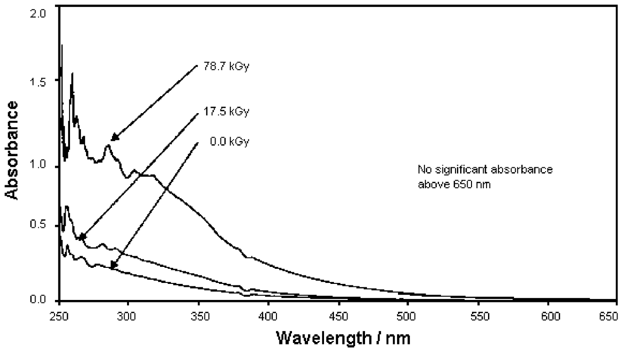

Fig. 1 Effect of gamma irradiation on the absorbance UV/vis spectrum of [C$_6$mim]Cl.

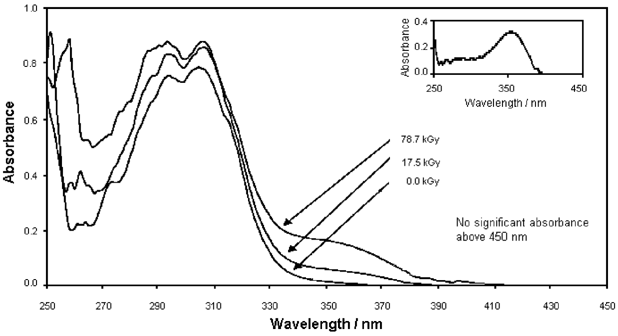

Fig. 2 Effect of gamma irradiation on the absorbance UV/vis spectrum of [C$_6$mim][NO$_3$]. Inset: Absorbance spectrum for NaNO$_2$ in H$_2$O, 0.014 mol l^{-1}.

changes as irradiation proceeds. In both cases this amounts to an absorbance increase with dose which correlates to the observed darkening reported above. For the chloride ionic liquid, this absorbance increase affects the entire spectra below 540 nm whereas for the nitrate ionic liquid the absorbance increase is limited mainly to a broad region around 350 nm. The appearance of the broad shoulder at 350 nm is an indication of the formation of the [NO$_2$]$^-$ anion; the spectrum of an aqueous solution of NaNO$_2$ (Fig. 2, inset) has a broad peak around 360 nm.

The pH values of samples diluted with water (dilution factor of approximately 25) are shown in Table 2. Only small changes were observed. The diluted solutions of [C$_4$mim][NO$_3$] tended to become slightly more acidic following gamma irradiation, whereas the solutions of [C$_6$mim]Cl became slightly more basic. From the results of [NO$_2$]$^-$ anion analysis (Table 3) it can be seen that gamma irradiation led to an almost linear increase of the concentration of [NO$_2$]$^-$, from no [NO$_2$]$^-$ present in the sample prior to irradiation to a concentration of 1.4 × 10^{-2} mol l^{-1} after a dose of 90 kGy.

Table 2 Changes in pH with gamma irradiation time

	Dose /kGy	pH[a]	[H$^+$]/mol l^{-1}
[C$_4$mim][NO$_3$]	0	7.24	5.75 × 10^{-8}
	1.3	7.21	6.16 × 10^{-8}
	18	7.12	7.56 × 10^{-8}
	79	7.08	8.32 × 10^{-8}
[C$_6$mim]Cl	0	6.00	10.0 × 10^{-7}
	18	6.30	5.01 × 10^{-7}
	79	6.34	4.57 × 10^{-7}

[a] The pH of diluted aqueous samples of [C$_6$mim]Cl and [C$_4$mim][NO$_3$] diluted in H$_2$O with a dilution factor of approximately 25.

Table 3 Changes in nitrite concentration with gamma irradiation time

Dose /kGy	[NO$_2$]$^-$ /mol l^{-1}[a]
0	<4.0 × 10^{-5}[b]
1.3	6.5 × 10^{-4}
18	4.0 × 10^{-3}
79	1.4 × 10^{-2}

[a] The concentration of [NO$_2$]$^-$ of diluted aqueous samples of [C$_4$mim][NO$_3$] with a dilution factor of approximately 25. [b] Below the limit of detection.

Beta irradiation test results

Using the 10 diode multi-wavelength detection system, irradiation of the neat sample of [C$_4$mim][NO$_3$] with a 0.1 μs pulse (10 Gy) showed an immediate transient absorption in the UV spectrum extending from around 400 to 770 nm. Strong absorption of light by the sample below 400 nm prevented interrogation of this region of the spectrum. Although the transient absorption decreased steadily from 400 to 770 nm, light absorption by the sample at the low wavelength end of the spectrum meant that the best signals for analysis were obtained around 480 nm. The immediate absorption was followed by some indication of a fast decay (ns), a longer-lived growth (μs) and a final transient decaying to zero concentration with a first order kinetics (ms). At 480 nm (Fig. 3) the final decay rate constant was 848 s^{-1} corresponding to a half-life of 0.82 ms.

Spectra of the ms decay process were recorded at various times after the pulse. Using the 10 diode multi-wavelength detector a spectrum from 400 to 770 nm was obtained using only two separate pulses, each on a fresh sample. The spectra recorded were comparable at all times. Similarly, the kinetics were comparable at all wavelengths.

The experiment was repeated at shorter timescales for the μs growth (Fig. 4). At 536 nm a first order fit was obtained for the growth with a rate constant of 3.39 × 10^4 s^{-1} and a half-life of 20 μs. Spectra were recorded from 400 to 770 nm at times varying form 2 to 60 μs after the pulse; again, the spectra recorded were very similar at all times and the kinetics were similar at all wavelengths.

Typical results for the single wavelength detection experiments are shown in Table 4. Transient absorption was observed at three different timescales after the pulse. Immediate formation of an absorbing species was followed by a decay in the ns timescale, a growth in the μs timescale and a decay in the ms timescale. In all cases there was no absorption after 4 ms. No longer-lived or permanent absorption was observed in the spectral region studied.

The results for observations of the ns decay process show no difference in samples which were nitrogen saturated, air

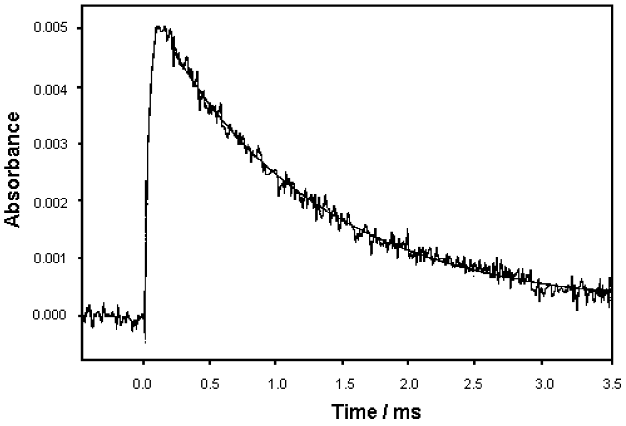

Fig. 3 UV/vis absorbance of [C$_4$mim][NO$_3$] at 478 nm following a beta irradiation pulse (0.1 μs) at t = 0 s.

Table 4 Spectral analysis of gamma irradiation tests

Process type	Sparge gas	Wavelength/nm	I_0/mV	k/s^{-1}	$t_{1/2}{}^a$/s
ns Decay	N_2	512	512	5.62×10^6	1.23×10^{-7}
	Air	480	330	5.65×10^6	1.23×10^{-7}
	O_2	480	305	5.62×10^6	1.23×10^{-7}
μs Growth	N_2	530	5020	3.20×10^4	2.20×10^{-5}
	Air	530	4935	6.25×10^4	1.11×10^{-5}
ms Decay	N_2	480	4885	n/a	n/a
	Air	480	4780	1.03×10^3	6.70×10^{-4}

[a] The pH of diluted aqueous samples of [C_6mim]Cl and [C_4mim][NO_3] diluted in H_2O with a dilution factor of approximately 25.

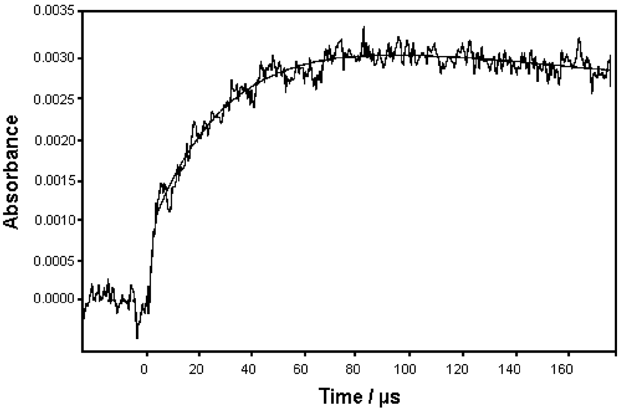

Fig. 4 UV/vis absorbance of [C_4mim][NO_3] at 536 nm following a beta irradiation pulse (0.1 μs) at t = 0 s.

saturated or oxygen saturated. The half-lives for the decay are 123 ns in each case. The lack of effect of oxygen suggests that species formed are unlikely to be in a triplet excited state.

The results for observations of the μs growth process show no observable difference between the nitrogen saturated and air saturated samples. The half-lives for the growth as measured by first order kinetic analysis are 14 and 11 μs, respectively, showing little, if any, effect caused by the presence of oxygen. half-life values of 22 and 19 μs, respectively, were obtained when traces were re-analysed using a consecutive first order kinetic fitting routine which corrects for the subsequent decay of the species.

Observations of the ms decay process also show no discernible effect due to the presence of oxygen and the results for the nitrogen saturated and air saturated samples are similar. The single pulse experiments were in agreement giving a first order decay with an average half-life of about 0.70 ms.

After 100 pulses (1 kGy per pulse) at 1 pulse s^{-1} analysis of the decay profile showed significant deviation from simple first order kinetics. Hence, the consecutive first order kinetic fitting routine was employed and this yielded half-life values of 100 μs and 0.91 ms for the fast and slow components of the decay, respectively. This experiment was repeated with a 5 min wait after the first 100 pulses. The half-lives were essentially the same suggesting no reaction between the transient and some very long-lived (at least 5 min) species produced in the first 100 pulse irradiation. A further 500 pulses, giving 600 in total (6 kGy) were added and the respective half-lives were 87 μs and 0.93 ms. Although these half-life values are prone to some error due to the relatively poor signal to noise ratio and should be interpreted with some caution, the fact that repeated radiolysis of the sample does not result in a change from simple exponential to bi-exponential decay kinetics is indicative of an accumulation of some radiolysis products(s).

A repeat of the single shot experiment on a nitrogen saturated sample (half-life = 0.70 ms) shows an enhanced reaction rate in the presence of 20% nitric acid, giving a half-life of 290 μs. When saturated with oxygen in the presence of 20% nitric acid the reaction rate is even faster with a half-life of 141 μs. This is potentially good news in that the presence of nitric acid (or water) and air enhances the decay of the transient. If this transient species was part of the degradation mechanism for the solvent, then nitric acid, water and oxygen could stabilize the solvent.

An experiment was carried out to compare the electron irradiation with gamma radiolysis. Approximately 2 ml of the nitrogen saturated sample was irradiated in a sealed glass tube using 2500 150 Gy pulses (total dose = 400 kGy) of 5 μs duration at a repetition rate of 1 Hz. The rate was low to minimize the temperature rise; the maximum temperature recorded was 62 °C. ^{1}H NMR analysis of the sample prior to and after irradiation show no discernable differences, indicating radiolysis of less than 1% of the sample. No evidence of the formation of insoluble material was observed.

Alpha irradiation test results

A typical spectrum obtained from mass spectrometry measurements on the helium sparge gas during irradiation of the materials is shown in Fig. 5. The only significant peaks are from H_2O, H_2, O_2 and CO_2. No discernable peaks from organic fragments were found. The only peak which changed during radiolysis was a small increase in the yield of H_2 from irradiated [C_6mim]Cl. In the final irradiation the mass spectrometer was set up to measure H_2 and He continuously and their yields were measured as a function of $^4He^{2+}$ current. Fig. 6 demonstrates that this was definitely a radiation induced chemical change as the yield of H_2 was increased directly with the increase in $^4He^{2+}$ current. The yield of H_2 [$G(H_2)$] for [C_6mim]Cl is equivalent to 0.72 molecules per 100 eV taking the sensitivity of the mass spectrometer as 68% for H_2 compared with He. For [C_4mim][NO_3], $G(H_2)$ = 0.65 molecules per 100 eV.

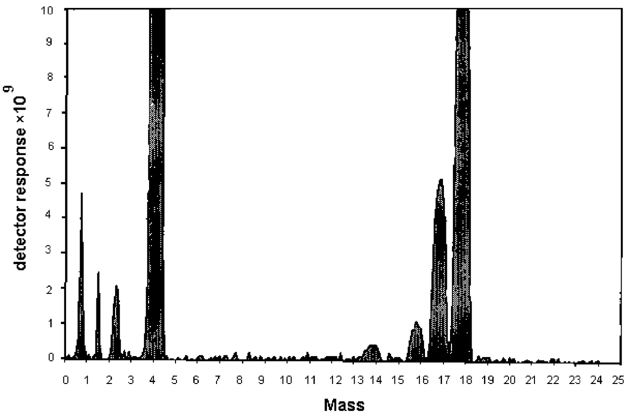

Fig. 5 Mass spectrum obtained from the sampled helium gas sparged through [C_6mim]Cl undergoing alpha particle irradiation.

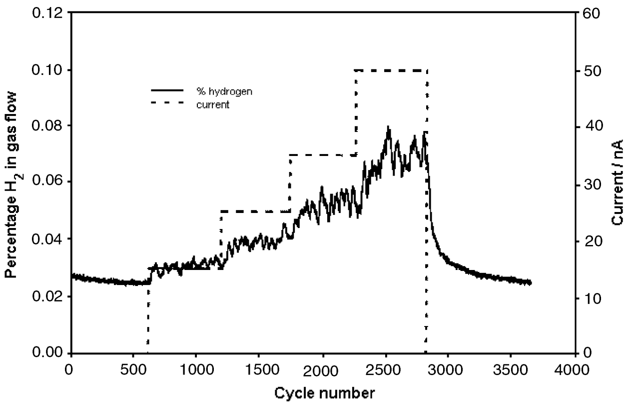

Fig. 6 Output of hydrogen (solid line) as measured by mass spectrometry and its dependence upon the increase of the $^4He^{2+}$ current (dashed line).

Discussion

Ionic liquids can be viewed as consisting of three components: an anion, a charged methylimidazolium cation, and a neutral alkyl side chain. Table 5 shows the fraction of energy one could expect to be deposited in the three components based upon their relative masses. Despite their complexity, the radiolytic mechanisms described in the Introduction may be expected to apply to the ionic liquids noting that the aromatic ring would be a good electron receptor. If the hydrogen atom at the 2 position in the imidazolium ring is labile, then any decomposition of the imidazolium cation is likely to lead to either H^+ cation or $H^\cdot$ radical leaving to form the carbene. The H^+ may add to the tertiary amines to form quaternary compounds or possibly react with the anion and could subsequently be hydrated by water. Reactions involving ionization of the imidazolium ring or excitation may lead to formation of the carbene, which could result in a UV/vis absorbing species. Average bond energies (Table 6) suggest that Cl^-, NO_3^- and $H^\cdot$ can abstract $H^\cdot$ from the organic cation. The radiation chemistry of some related compounds has been measured including alkanes,[9] aromatics,[9] a wide range of nitrogen heterocycles,[10] $NaNO_3$ as the solid and as a molten salt[13] and nitric acid.[14]

Radiolysis mechanisms in [C$_n$mim]Cl ionic liquids may be relatively simple depending on the behaviour of the Cl^- anion. A suggested mechanism consists of the following six possible reactions: (1) ionisation of Cl^- would form $Cl^\cdot$ and e^- which may be followed by geminate recombinations to reform Cl^- or neutralization by reaction of e^- with the positively charged imidazolium cation. (2) Ionisation of the imidazolium cation would almost certainly give an excited neutral imidazole radical with a higher ionisation potential than Cl^- so charge transfer would occur to give an excited neutral imidazole radical and $Cl^\cdot$. (3) Electrons formed in the ionisation processes could be captured by the imidazolium ring to form a neutral imidazole radical. (4) $Cl^\cdot$ could react with the neutral imidazole radical to yield the starting materials Cl^- and the imidazolium cation. (5) $Cl^\cdot$ could abstract a hydrogen atom from the alkyl substituent since the bond energies are favourable (see Table 6). If this happened the resulting organic radical could then undergo a number of processes such as dimerisation or abstraction of a hydrogen atom from the imidazole ring or alkyl side chain. These processes would lead to a build up of HCl. (6) $Cl^\cdot$ could react with Cl^- to form the radical anion $Cl_2^{\cdot -}$ which would not oxidize the imidazolium cation by hydrogen abstraction but would most probably only react with the electron adduct to give Cl^-.

The result of these processes would be expected to be very little decomposition. In irradiation conditions involving high dose-rates, $Cl^\cdot$ recombination may occur to form Cl_2 along with formation of a dimer from the radical adduct of the imidazole ring, unless it is sterically hindered. The Cl_2 would act as an electron scavenger and oxidize further electron capture products at the aromatic ring. If step (5) is dominant then HCl should build up; this is not indicated by the results of the pH analysis carried out on aqueous solutions of [C$_6$mim]Cl following irradiation, which showed the solution to become more alkaline as irradiation was carried out.

Assuming all the H_2 arises from the alkyl side chain in [C$_6$mim]Cl, then the value of $G(H_2) = 0.72$ molecules per 100 eV determined for this ionic liquid would be equivalent to $G(H_2) = 1.7$ molecules per 100 eV for the alkyl side chain alone. This value is lower than the values of $G(H_2)$ reported for alkanes (5–6 molecules per 100 eV) but consistent with the prediction that the aromatic ring serves to inhibit radiolysis of the alkyl side chain. If the lower value is due to energy transfer, presumably this process would be more efficient the shorter the alkyl chain.

The radiolysis of [C$_n$mim][NO$_3$] ionic liquids will be different to [C$_n$mim]Cl ionic liquids, but similar mechanisms may apply. $[NO_3]^-$ is a good electron acceptor and would form $[NO_3]^{2-}$ which may abstract hydrogen from the organic cation to form $[HNO_3]^-$ (*i.e.*, NO_2 and $[OH]^-$). $[NO_3]^-$ would also have a relatively low ionisation potential and so would neutralise any radical cations to form $[NO_3]^\cdot$ which would react with $[NO_3]^{2-}$, the net result being no decomposition. However, the range of possible oxidation states of nitrogen makes the behaviour of $[NO_3]^-$ a more complex process than the equivalent behaviour of Cl^-. $[NO_3]^-$ may react rapidly with $H^\cdot$, the precursor to H_2 in irradiated organic compounds, to suppress the observed $G(H_2)$. $[NO_3]^-$ may also absorb energy directly to form $[NO_2]^-$ and $O(^3P)$. $O(^3P)$ may be expected to react with $[NO_3]^-$ to form $[NO_2]^-$ and O_2, although other reactions may occur in the presence of organic compounds: most studies have involved aqueous nitrate[13] or molten alkali[14] nitrate solutions and none are known on organic nitrate salts. However, the radiolysis of molten alkali nitrate salts[13] and nitric acid[14] are both known to give rise to $[NO_2]^-$ and O_2.

The radiolysis of the [C$_2$mim]X family of ionic liquids reflects their combination of the properties of a salt, an alkane and an aromatic. They appear to be relatively radiation resistant

Table 6 Relative bond energies

Bond	Bond energy/kJ mol^{-1}
H–Cl	432
H–C	413
H–H	436
H–NO$_3$	466

Table 5 Fraction of energy theoretically deposited on ionic liquid component parts based on the relative mass of each component part

	Anion		*N*-Methylimidazole		Alkyl chain	
Ionic liquid	RAM/g mol^{-1}	Fraction	RAM/g mol^{-1}	Fraction	RAM/g mol^{-1}	Fraction
[C$_4$mim][NO$_3$]	62	0.31	82	0.41	57	0.28
[C$_6$mim]Cl	35.5	0.18	82	0.40	85	0.42

and there is certainly no major decomposition of the organic component.

Experimental

Ionic liquids

The methods for preparing [C_2mim]Cl, [C_6mim]Cl and [C_4mim][NO_3] have been previously reported.[15] Gamma irradiation tests were carried out on [C_2mim]Cl, [C_6mim]Cl and [C_4mim][NO_3]. Beta irradiation tests were carried out on [C_4mim][NO_3]. Alpha irradiation test were carried out on [C_6mim]Cl. In all cases, ^{1}H NMR spectra of the test materials were recorded at Queen's University Belfast using a Bruker Advance DRX 500 NMR spectrometer prior to and following irradiation tests.

Gamma irradiation tests

Gamma radiation tests were performed at the J. J. Thomson Irradiation Laboratory, Royal Military College of Science, Shrivenham, UK. The Cobalt 60 Gamma Facility was used as the gamma source. The ionic liquids were subjected to four different doses of gamma irradiation using three different dose rates, up to a maximum dose of 400 kGy. Dosimetry was performed by a N. E. Technology Ionex 2500/3 Ion Chamber dose rate meter calibrated and traceable to NPL Standard.

Gamma irradiation tests were also carried out at AEA Technology in Harwell using a cobalt 60 source. A sample of liquid contained in a glass ampoule was positioned in the centre of a cavity into which an annular cobalt 60 source was lowered which was situated around the sample. The dose rate was measured by Fricke dosimetry. Samples of the irradiated ionic liquids were diluted with water (dilution factor approximately 25). The pH of the aqueous solutions was measured with a Philips PW9240 pH meter using a Phillips CE1 electrode. The UV/vis spectra of the diluted samples were measured using an Hitachi U-3000 spectrophotometer with 1 cm path length cells. In the case of [C_4mim][NO_3] the diluted samples were also analysed for the presence of the [NO_2]$^-$ anion using an ion selective electrode.

Beta irradiation tests

Beta irradiation was carried out on a Vickers 10 MeV electron linear accelerator (Linac) at the Christie Hospital's Paterson Institute for Cancer Research in conjunction with the pulse radiolysis system. The 10 MeV linear accelerator is capable of generating pulses of 5 ns to 5 μs duration and can be operated in either single shot mode or repetitive mode at rates of 1 to 50 Hz.[16] The dose per pulse was calibrated using a Fricke dosimeter. A 0.1 μs pulse gave a dose of 10 Gy and a 5 μs pulse gave a dose of 160 Gy.

Time-resolved adsorption spectrophotometry measurements were carried out in a 25 mm quartz capillary cell (0.1 ml) using either a photomultiplier detector system[17] or a 10 diode multi-wavelength detection system.[18] Fast (ns) transient studies were performed using a Si diode based system and a pulsed analyzing light source.[19] The digitized data was transferred to a PC for kinetic and spectral analysis.

10–15 ml samples of [C_2mim][NO_3] were de-aerated for a minimum of 30 min using high purity nitrogen. The sample was transferred to the Linac without exposure to air. Samples were pushed through the quartz cell under nitrogen pressure, again without exposure to air. It is possible to carry out this procedure remotely and after each irradiation pulse. Samples were also irradiated without de-aeration (air saturated) and saturated with oxygen.

Alpha irradiation tests

$^4He^{2+}$ ion irradiations were carried out using a Tandem Van de Graaff accelerator. The sample was positioned at the end of a beam line (Fig. 7) in a glass vessel (Fig. 8). The beam excited the beam line through a 50 μm thick aluminium vacuum window and an approximately 1 cm air gap before entering the target vessel. The vessel had a 25 μm thick titanium window to allow penetration of the $^4He^{2+}$ ions into the liquid. The beam of 15.2 MeV $^4He^{2+}$ ions from the Van de Graaff accelerator was calculated to enter the liquid with an energy of 6 MeV.

Dosimetry was by charge collection using a rhodium–platinum alloy wire connected to a Brookhaven current integrator, the dose from this measurement was compared to the dose on a Faraday cup and a tantalum plate inserted after the vacuum window. There was a facility to scatter a fraction of the beam onto a particle detector using a rotating beam scatterer in order to provide a secondary on-line dosimetry but this was unsuccessful in Run 2. The sample was stirred continuously although because of its viscosity this was not particularly effective. The range of 6 MeV $^4He^{2+}$ would be approximately 35 μm (based on Mylar 34 μm, PTFE 29 μm and Polythene 46 μm). A helium sparge of 25 ml min^{-1} was used to remove volatile products and transfer them to a mass spectrometer.

The irradiation vessel was wrapped with a nichrome wire heater to heat the vessel to 80 °C. Temperature was monitored and controlled by two thermocouples in a pocket in the glass vessel. Currents in the range of 10–50 μA were used, which is

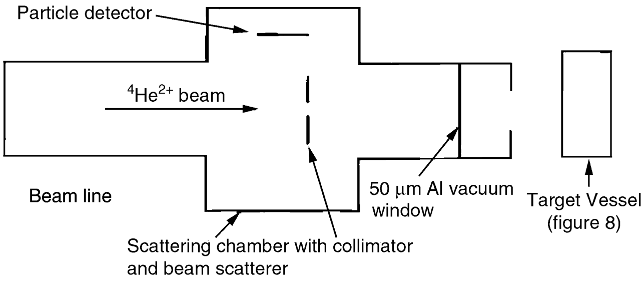

Fig. 7 Schematic of beam line for irradiation.

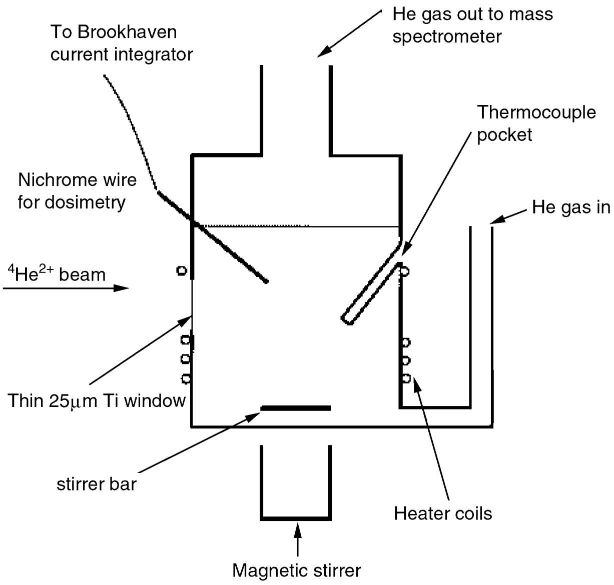

Fig. 8 Schematic of irradiation vessel.

equivalent to approximately 1–5 Mrad h^{-1} in 10 ml liquid, although local dose rates would have been much greater.

The mass spectrometer, a VG Instruments micromass with Sprectascan software, was calibrated by passing He gas at the same flow rate as used in the irradiations through an electrolysis cell containing 10% H_2SO_4. The hydrogen concentration was measured for a range of currents provided by a Keithley Instruments microamp current source.

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Esterification reactions in ionic liquids. The efficient synthesis of ferrocenyl esters in the ionic liquids [bmim][BF_4] and [bmim][PF_6]

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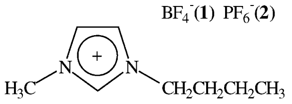
The synthesis of ferrocenyl esters has been achieved using the DCC/DMAP protocol in the ambient temperature ionic liquids 1-butyl-3-methylimidazonium tetrafluoroborate ([bmim][BF_4]) and 1-butyl-3-methylimidazonium hexafluorophosphate ([bmim][PF_6]). Yields are very high and efficient recycling of solvent was achieved.

Introduction

The synthesis of the ester functional group using the DCC/DMAP methodology is widely popular in organic synthesis.[1] It allows for the introduction of the ester functional group under mild conditions and without the use of air-sensitive acid chlorides. The protocol has found widespread use in our group in the synthesis of liquid crystal molecules.[2] The usual solvent for carrying out this type of reaction is anhydrous dichloromethane. With the current desire to avoid the use of chlorinated molecular solvents in chemistry, we decided to investigate the use of potentially cleaner solvents, namely 1-butyl-3-methylimidazonium tetrafluoroborate [bmim][BF_4] **1** and 1-butyl-3-methylimidazonium hexafluorophosphate [bmim][PF_6] **2** for DCC/DMAP promoted esterifications.



Ionic liquids, especially imidazonium salts, are currently receiving a lot of attention in chemistry and have already proved to be useful solvents in organic synthesis. Some of the reactions already successfully carried out in imidazonium salts include Diels–Alder,[3] Wittig,[4] the Suzuki cross-coupling,[5] Heck,[6] oxidations,[7] reductions,[8] and hydrogenations.[9]

Results and discussion

The results of the reactions of ferrocenemonocarboxylic acid with a range of substituted phenols in the presence of DCC/DMAP and ionic liquid ([bmim][BF_4] or [bmim][PF_6]) are provided in Table 1. The isolated yields of the ester products are in all cases very good. Small quantities of unreacted ferrocenemonocarboxylic acid were also isolated. One of the primary aims of our study was to investigate the recycling of the ionic liquid and this is clearly important in the context of economic feasibility and sustainable development.

The reaction of ferrocenemonocarboxylic acid and 4-methoxyphenol in [bmim][BF_4] in the presence of DCC/DMAP was repeated in the same batch of ionic liquid over five runs and the results are provided in Table 2. The yield of the ester product is consistently high. In each reaction, *N*,*N*′-dicyclohexylurea (DCU) formed as a by-product. This remained in the ionic liquid after ether extraction and did not interfere with subsequent reactions. No reaction was observed between ferrocenemonocarboxylic acid and 4-methoxyphenol in [bmim][BF_4] in the absence of DCC. The results presented in Table 1 apart from those in entries 3 and 4 are based on reaction times of 24 h. The 24 h reaction period is normally used for DCC/DMAP promoted esterifications in CH_2Cl_2. To investigate the potential effect of the ionic liquid on reaction rate, the reaction of ferrocenemonocarboxylic acid and 4-methoxyphenol was carried out for 3 and 6 h. After 3 h (Table 1, entry 3), the yield of the ester was very low and it was difficult to purify. It was also difficult to extract unreacted ferrocenemonocarboxylic acid from the ionic liquid. The yield of ester after 6 h was excellent suggesting that the 24 h reaction time is unnecessary. Further studies are underway to investigate the generality of this esterification reaction in ionic liquids and to investigate the possibility of catalytic esterification reactions.

Experimental

General

Infrared spectra were recorded on a Perkin Elmer 1600 series Fourier Transform IR spectrometer as KBr discs. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance 300 MHz spectrometer as solutions in $CDCl_3$. Mass spectra were recorded on a VG70-SEQ/MSSMS2 spectrometer at the Cape

Green Context

The use of DCC/DMAP methodology is very effective for the introduction of the ester functionality under mild conditions. However, standard methodology involves a chlorinated solvent for the reaction which reduces the green chemistry credentials of the method. Here non-volatile ionic liquids are used to overcome this problem. Product yields for ferrocenyl ester synthesis are good and, very importantly, the solvents can be reused several times with no loss in activity. ***JHC***

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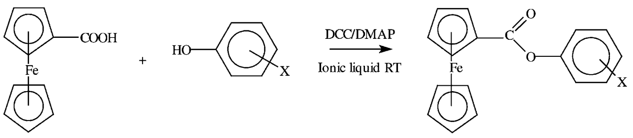
Technikon. Ferrocenemonocarboxylic acid (98%) was purchased from Strem (USA) and was used without further purification. The phenols were commercial samples and were purified either by column chromatography or recrystallization prior to use.

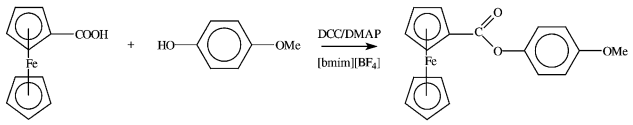
Table 1 Yields of esters from the reaction of ferrocenemonocarboxylic acid and substituted phenols†



Entry	Ionic liquid[a]	X	Yield of ester[bc] (%)
1	[bmim][BF$_4$]	4-OMe	86
2	[bmim][PF$_6$]	4-OMe	85
3	[bmim][BF$_4$]	4-OMe	14[d]
4	[bmim][BF$_4$]	4-OMe	84[e]
5	[bmim][BF$_4$]	3-OMe	95
6	[bmim][BF$_4$]	4-Me	89
7	[bmim][PF$_6$]	4-Me	83
8	[bmim][BF$_4$]	4-Bu^t	82
9	[bmim][BF$_4$]	H	85
10	[bmim][PF$_6$]	H	91
11	[bmim][BF$_4$]	4-Cl	100
12	[bmim][PF$_6$]	4-Cl	83
13	[bmim][BF$_4$]	2-Cl	92
14	[bmim][PF$_6$]	2-Cl	81
15	[bmim][BF$_4$]	4-CHO	96
16	[bmim][BF$_4$]	4-NO$_2$	83
17	[bmim][PF$_6$]	4-NO$_2$	83
18	[bmim][BF$_4$]	4-Br	88

[a] Procedure for the preparation of [bmim][BF$_4$] and [bmim][PF$_6$]. The ionic liquids were both prepared from [bmim][Cl].[10] To a solution of [bmim][Cl] (1 equiv.) in anhydrous acetone at room temperature was added either sodium tetrafluoroborate (1 equiv.) or sodium hexafluorophosphate (1 equiv.). The reaction was stirred for 24 h at room temperature (20 °C) and was then filtered through a plug of Celite. The volatiles were finally removed *in vacuo*. [b] Yield represents the isolated yield of the esters based on the starting ferrocenemonocarboxylic acid. [c] Esters were isolated and characterised by IR, NMR (^{1}H) and MS spectroscopy. [d] As in general reaction except reaction time 3 h. [e] As in general reaction except reaction time 6 h.

Table 2 Results for recycling reactions‡



Reaction	1	2	3	4	5
Yield of ester[a] (%)	86	85	85	86	84

[a] Yields represent overall isolated yields from ferrocenemonocarboxylic acid.

Acknowledgements

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Notes and references

† *General reaction*: [bmim][BF$_4$] and [bmim][PF$_6$] were deaerated by purging with nitrogen overnight and were subjected to three cycles of the freeze–thaw degassing procedure. Ferrocenemonocarboxylic acid (0.44 mmol), the substituted phenol (0.44 mmol), 1,3-dicyclohexylcarbodiimide (0.53 mmol) (DCC) and *N*,*N*-dimethylaminopyridine (0.21 mmol) (DMAP) were added to degassed [bmim][BF$_4$] (6 cm^3) or [bmim][PF$_6$] (6 cm^3) contained in a 25 cm^3 round bottom flask. The mixture was mechanically shaken on a flask shaker for 30 min and thereafter stirred for 24 h. During this time, an off-white precipitate formed. Stirring was stopped and the products were extracted from the ionic liquid using diethyl ether (9 × 5 cm^3). The ether extracts were combined, washed with water (3 × 20 cm^3) and dried over anhydrous sodium sulfate. After removing the diethyl ether *in vacuo*, the residue was passed through a short silica gel column. The ester products were eluted using CH$_2$Cl$_2$ and unreacted FcCOOH was stripped off the column using diethyl ether. An alternative solvent system for the successful elution and purification of the esters was hexane–diethyl ether (1 : 5) avoiding the use of undesirable chlorinated solvents.

‡ *Typical procedure* for recycling reaction: [bmim][BF$_4$] was deaerated by purging with nitrogen overnight and was then subjected to three cycles of the freeze–thaw degassing procedure. Ferrocenemonocarboxylic acid (0.44 mmol), 4-methoxyphenol (0.44 mmol), DCC (0.53 mmol) and DMAP (0.21 mmol) were added to the degassed [bmim][BF$_4$] (6 cm^3) contained in a 25 cm^3 round bottom flask. The rest of the procedure was as given in the general procedure except that after ether extraction and removal of residual ether from the ionic liquid under reduced pressure, the remaining ionic liquid was reused. Before reuse, the ionic liquid was again subjected to the freeze–thaw procedure of degassing and was reused without removing the *N*,*N*′-dicyclohexylurea. The recycling experiments were repeated as above.

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Metal mediated allylation of carbonyl compounds in ionic liquids

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In, Sn and Zn metals mediate the allylation of carbonyl compounds in [bmim][BF$_4$] or [emim][BF$_4$] to give the corresponding homoallylic alcohols in good to excellent yields. Tin was found to be the metal of choice among the metals examined.

Introduction

One of the aims of green chemistry is to replace the use of volatile organic solvents with clean solvents as reaction media for chemical synthesis.[1] Water,[2] supercritical carbon dioxide[3] and ionic liquids[4] are currently the clean solvents being investigated most extensively. These three solvents complement each other in terms of their boiling points, viscosity and, in particular, solubility characteristics towards various reactants. However, a common problem that is faced by these three clean solvents is their reactivity towards Grignard or organolithium reagents. These organometallic reagents are very useful and important in organic synthesis, and yet they are well known to react with water or carbon dioxide. It is also likely that they will react with quaternary salts, structures which are common for ionic liquids. Alternative organometallic reactions must be sought for these solvents. Recently, Barbier–Grignard type reactions using In,[5] Zn[6] and Sn[7] in aqueous media have been extensively studied and found to be useful for organic synthesis. In the case of Zn or Sn, acidic, thermal or ultrasonic activation was often necessary to induce the reaction to occur. In addition, reduction and/or pinacol coupling of the carbonyl compounds were often obtained as side reactions. Furthermore, the use of aqueous media places some inherent limitations on synthesis. Thus, water sensitive substrates such as imines[8] or hydrophobic compounds insoluble in water tend to present difficulties in these reactions. Allyation of aldehydes with indium in supercritical carbon dioxide has been briefly investigated.[9] The reaction was found to be effective in giving the homoallylic alcohols in reasonable yields. Thus far, few metal mediated reactions in ionic liquids have been examined; the only example appears to have been the generation of a Reformatsky-type reagent from zinc powder and ethyl bromodifluoroacetate.[10,11] Herein, we explore Barbier–Grignard type allylation reactions in ionic liquids using indium, tin and zinc.

Experimental

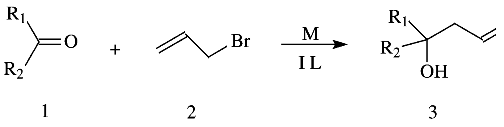
1-Butyl-3-methylimidazolium tetrafluoroborate ([bmim][BF$_4$]) was prepared from the bromide which was in turn prepared from bromobutane and *N*-methylimidazole using the recently reported microwave-assisted procedure.[12] 1-Ethyl-3-methylimidazolium tetrafluoroborate ([emim][BF$_4$]) was similarly prepared.

Typical procedure for the allylation reaction in ionic liquids

To [bmim][BF$_4$] (2 ml) was added the tin metal powder (0.24 g, 2 mmol), followed by benzaldehyde (0.106 g, 1 mmol) and cinnamyl bromide (0.236 g, 1.2 mmol). The reaction mixture was stirred vigorously overnight at room temperature. The mixture was extracted with diethyl ether (3 × 10 ml), and the ether extract was evaporated *in vacuo*. The residue was purified through flash column chromatography on silica gel (*n*-hexane–ethyl acetate) to give the homoallylic alcohol product (0.224 g), pure according to ^{1}H NMR. Specific conditions and yields are given in Tables 1, 2 and 3.

Results and discussion

Using allyl bromide and benzaldehyde as the standard conditions, several metals were examined for their ability to mediate the allylation reaction (Scheme 1). It was found (Table 1) that indium, tin and zinc were quite effective in mediating the reaction to give the product homoallylic alcohol (**3**) in essentially quantitative yield. By contrast, magnesium was



Scheme 1

Green Context

Despite the popularity of ionic liquids as non-volatile solvents for organic reactions, very few papers have described metal-mediated reactions in ionic liquids. This paper describes the use of several metals as reagents for allylation reactions in ionic liquids. High conversions can be achieved at room temperature making these good examples of clean synthesis. ***JHC***

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found to be quite ineffective, even used in excess. This is somewhat surprising, since magnesium is generally considered as a reactive metal. Previously, it has been argued that the reactivity of metal is associated with a low first ionization potential (IP) by favouring single electron transfer (SET) processes in these reactions.[5] While the first IP of magnesium (= 7.65 eV) is higher than that of either indium (5.70 eV) or tin (7.34 eV), it is nevertheless lower than that of zinc (9.39 eV). This suggests that other factors may be involved in determining the reactivity of metals.[13] One possibility in the case of magnesium is its ease of forming insoluble oxide on its surface, especially if the ionic liquid solvent is contaminated with some moisture. The alternative possibility that allylmagnesium bromide may have been formed but quenched *in situ* was considered unlikely because unreacted allyl bromide could be recovered.

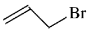
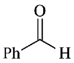
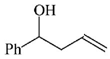
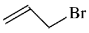
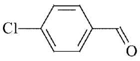
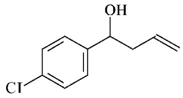
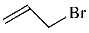
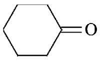
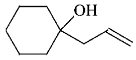
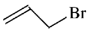
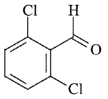
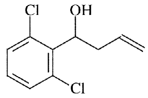
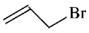
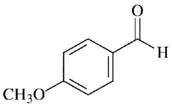
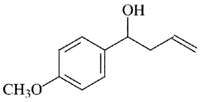
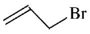
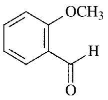
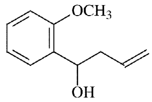
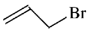
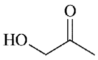
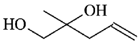
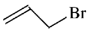
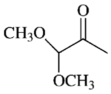
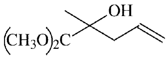
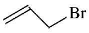
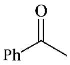
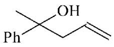
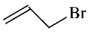
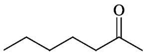
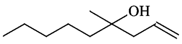
Table 1 Yields of 1-phenylbut-3-en-1-ol with various molar ratios of benzaldehyde (PhCH=O) : allyl bromide : metal

	PhCH=O : allylBr : M	Yield[a] (%) [bmim][BF$_4$]	Yield[a] (%) [emim][BF$_4$]
M = Sn	1 : 1 : 1	100	100
	1 : 1 : 0.75	67	
	1 : 1 : 0.5	38	
	1 : 1 : 0.25	14	
M = In	1 : 1.5 : 1	100	87
	1 : 1 : 1	74	
M = Zn	1 : 3 : 3	98	
	1 : 2 : 2	34	
	1 : 1 : 1	0	
M = Mg	1 : 1 : 1	0	
	1 : 3 : 3	0	
	1 : 3 : 10	2	

All the reactions were carried out at 1 mmol scale of benzaldehyde at room temperature in ionic liquids (2 ml) by stirring the reaction mixture overnight.[a] Isolated yield.

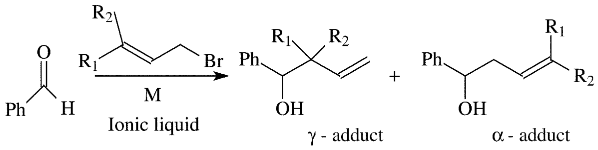
In aqueous media, indium is considered the metal of choice for the allylation of carbonyl compounds because the reaction can be carried out at room temperature, with no need for activation and few side reactions. It is interesting to note that in ionic liquids, both tin and zinc are as effective as indium in mediating the allylation reaction at room temperature, giving excellent yields of the product homoallylic alcohols. Another interesting observation is the amount of allyl bromide required. It was found that for complete conversion of benzaldehyde to the product, 3 equivalents of allyl bromide was required in the zinc mediated reaction. By contrast, 1.5 equivalents was required in the indium case, and only 1 equivalent of allyl bromide was sufficient in the tin case. These observations have implication in chemical synthesis since tin is more readily available and less expensive than indium. The need for less allyl bromide suggests that tin is the metal of choice in the allylation of carbonyl compounds in ionic liquids. Furthermore, we showed that one equivalent of tin is required for complete

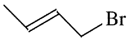
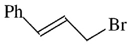
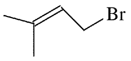
Table 2 Metal-mediated allylation of carbonyl compounds in ionic liquids

Entry	Allyl halide	Carbonyl compd.	C=O : AllylBr : M Sn/bmim	C=O : AllylBr : M In/bmim	C=O : AllylBr : M Sn/emim	Product	Yield[a] (%) Sn/bmim	Yield[a] (%) In/bmim	Yield[a] (%) Sn/emim
1			1 : 1 : 1	1 : 1.5 : 1	1 : 1 : 1		100	100	100
			1 : 1 : 1	1 : 1.5 : 1	1 : 1 : 1		71	60	55
3			1 : 1 : 1	1 : 1.5 : 1	1 : 2 : 2		79	71	100
4			1 : 1 : 1	1 : 1.5 : 1	1 : 1 : 1		96	88	100
5			1 : 1 : 1	1 : 1.5 : 1	1 : 1 : 1		94	96	96
6			1 : 1 : 1	1 : 1.5 : 1	1 : 1 : 1		90	84	100
7			1 : 3 : 3[b]	1 : 1.5 : 1	1 : 3 : 3[b]		63	67	70
8			1 : 2 : 2[b]	1 : 1.5 : 1	1 : 2 : 2[b]		100	75	100
9			1 : 2 : 2[b]	1 : 1.5 : 1	1 : 2 : 2[b]		52	91	100
10			1 : 1 : 1	1 : 1.5 : 1	1 : 1 : 1		100	100	48

All the reactions were carried out at 1 mmol scale of carbonyl compounds at room temperature in ionic liquids (2 ml) by stirring the reaction mixture overnight unless otherwise noted.[a] Isolated yield; [b] Reactions were performed at room temperature for 10 h, followed by heating to 40 °C for another 10 h.

Table 3 Regio- and diastereo-selectivity in metal-mediated allylations of benzaldehyde in ionic liquids



Entry	Allyl halide	C=O : allylBr : M	M/Solvent	Yield^a (%)	α:γ^b	*syn* : *anti*^{b}
1		1 : 1 : 1	Sn/bmim	75	0 : 100	43 : 57
2		1 : 1.5 : 1	In/bmim	87	0 : 100	58 : 42
3		1 : 1 : 1	Sn/emim	75	0 : 100	42 : 58
4		1 : 1.2 : 2^c	Sn/bmim	100	0 : 100	4 : 96
5		1 : 2 : 3^c	In/bmim	100	0 : 100	37 : 63
6		1 : 1.5 : 2^c	Sn/emim	74	0 : 100	0 : 100
7		1 : 1.2 : 2^c	Sn/bmim		0 : 100	
8		1 : 1.5 : 1	In/bmim	91	0 : 100	
9		1 : 1.2 : 2^c	Sn/emim	85	0 : 100	

All the reactions were carried out at 1 mmol scale of carbonyl compounds at room temperature in ionic liquids (2 ml) by stirring the reaction mixture overnight unless otherwise noted.^{a} Isolated yield; ^{b} Determined by ^{1}H NMR; ^{c} Reactions were performed at room temperature for 10 h, followed by heating to 40 °C for another 10 h.

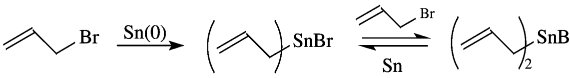
allylation of benzaldehyde. When less than stoichiometric amount of tin was used, the yield of the homoallylic alcohol began to decline.

A number of carbonyl compounds were allylated with tin and indium and their results are summarized in Table 2. It is clear that both aldehydes and ketones are allylated readily. The reaction is therefore more general than the indium mediated reaction under the solvent free conditions[13] where ketones were less readily allylated. Hydrophobic compounds such as 2,6-dichlorobenzaldehyde presented no particular difficulty, so the reaction may complement that of the aqueous conditions. Furthermore, acid sensitive functional groups such as acetal was left unchanged.[14] The reaction conditions may well be useful for other water sensitive functional groups. As expected, hydroxy groups required no protection and the allylation of hydroxyacetone occurred uneventfully.

We have also examined the reaction of benzaldehyde with a number of unsymmetrical allylic bromides (Scheme 2, Table 3). In all cases, the reaction proceeded regioselectively to give carbon–carbon bond formation at the more substituted allylic carbon. The regioselectivity is similar to those observed in aqueous media.[5,15] In the coupling of crotyl bromide with benzaldehyde, the product was a nearly 50 : 50 mixture of the *anti*/*syn* diasteromers. However, with cinnamyl bromide, the product was predominantly the *anti*-diasteromer. The diastereoselectivity is similar to that observed for these metals in aqueous media.[16]

A perceived advantage of ionic liquids as reaction media is the ability to tune the physical properties of an ionic liquid by the choice of cation and anion.[4] We compared the tin mediated reactions in two ionic liquids, [bmim][BF$_4$] and [emim][BF$_4$] (Table 2). The reactions proceeded well in either solvent, with comparable yields. However, in a few cases, the yield of the product was clearly superior in one solvent over the other. There is no discernable pattern at this time, and the choice of ionic liquid for a particular reaction will have to be determined experimentally.

We have previously demonstrated that, in aqueous media, indium and tin reacted with allyl bromide to give the allyl metal intermediates with finite lifetimes in the aqueous environment.[7,17] Magnesium and zinc, on the other hand, are believed to mediate the allylation reaction in aqueous acidic media through a metal surface reaction.[18] In the specific case of the reaction of tin and allyl bromide in D$_2$O, we were able to show by ^{1}H NMR that two allyltin species were formed. Allyltin(II) bromide was formed first and subsequently followed by the formation of diallyltin(IV) dibromide. Either species can react with carbonyl compounds to give the homoallylic alcohols (Scheme 2).[7] We have similarly followed the reaction of tin and allyl bromide in [bmim][BF$_4$] by ^{1}H NMR.



Scheme 2

The characteristic signal of the allylic protons of allyl bromide at 3.9 ppm quickly declined in intensity and two sets of new signals at 2.4 ppm (d, J = 8.6 Hz) and 2.9 ppm (d, J = 8.3 Hz) appeared in a ratio of 1 : 3 after 30 min. These new signals are attributed to the formation of allyltin(II) bromide and diallyltin(IV) dibromide respectively. Their chemical shifts are comparable to similar signals observed in D$_2$O for allyltin(II) bromide and diallyltin(IV) dibromide at 2.2 ppm and 2.5 ppm respectively.[7] Interestingly, when [emim][BF4] was used as the solvent, the relative intensities of the two signals were 3 : 1 in 30 min. This suggests that in the formation of the allyltin intermediates according to Scheme 2, the insertion of Sn(0) to allyl bromide to form allyltin(II) bromide is the faster step in [emim][BF$_4$], whereas the insertion of Sn(II) to allyl bromide to form diallytin(IV) dibromide is the faster step in [bmim][BF$_4$]. Allylindium intermediates were also detected in the reaction of allyl bromide and indium in [emim][BF$_4$]. After 30 min, the ^{1}H NMR of the mixture showed two sets of new signals at 1.7 and 2.2 ppm. These two new NMR signals are similar to those formed in the reaction of allyl bromide with indium in DMF and have been attributed to allylindium(I) and allylindium(III) dibromide respectively.[17]

In conclusion, we have demonstrated that metal mediated allylation of carbonyl compounds can be carried out effectively in ionic liquids. Tin is found to be the metal of choice giving high conversions at room temperature. True organometallic intermediates in ionic liquids were formed and observed by NMR for tin and indium.

Acknowledgments

This work was supported by the Areas of Excellence Scheme established under the University Grants Committee of the Hong Kong Special Administrative Region, China (Project No. AoE/P-10/01). We thank the Hong Kong Polytechnic University for financial support. T. H. C. acknowledges the support of McGill University for the granting of a leave.

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13 P. C. Andrews, A. C. Peatt and C. L. Raston, *Green Chem.*, 2001, **3**, 313.
14 A. McCluskey, *Green Chem.*, 1999, **1**, 167.
15 T. P. Loh, K.-T. Tan, J.-Y. Yang and C.-L. Xiang, *Tetrahedron Lett.*, 2001, **42**, 8701.
16 M. B. Issac and T. H. Chan, *Tetrahedron Lett.*, 1995, **36**, 8957.
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Temperature-dependent microscopic solvent properties of ‘dry’ and ‘wet’ 1-butyl-3-methylimidazolium hexafluorophosphate: correlation with $E_T(30)$ and Kamlet–Taft polarity scales

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As a result of heightened awareness of a wealth of potential in clean manufacturing processes, room temperature ionic liquids (RTILs) have been the target of increased investigation. As an integral part of the green chemistry movement, RTILs have found application in synthesis, catalysis, polymerization, industrial cleaning, liquid/liquid extraction, and separations. While some groundwork has been laid, the optimal utilization and tailoring of these solvents has been hobbled by an incomplete understanding of their solvent properties, particularly at the molecular level. In this work, we use solvatochromic measurements to determine ‘energy of transition’ $E_T(30)$ values and Kamlet–Taft solvent parameters (α, β, π^*) for the relatively hydrophobic RTIL 1-butyl-3-methylimidazolium hexafluorophosphate, $[\text{bmim}]^+[PF_6]^-$, as a function of temperature (10–70 °C) and water content (50 ppm or less water, ‘dry’ or 2% water (v/v), ‘wet’). The results of these experiments demonstrate that dry $[\text{bmim}]^+[PF_6]^-$ exhibits a hydrogen bond donor strength on the order of short chain alcohols with a linear temperature dependence. Dry and wet $[\text{bmim}]^+[PF_6]^-$ exhibit hydrogen bond acceptor abilities, which are weak functions of temperature, intermediate between that of water and acetonitrile. The π^* parameter for wet and dry $[\text{bmim}]^+[PF_6]^-$ is higher than short chain alcohols, but lower than water or dimethylsulfoxide at ambient conditions, and it exhibits a strong linear temperature dependence. Finally, the addition of water to $[\text{bmim}]^+[PF_6]^-$ does not affect the β and π^* values significantly.

Introduction

Room temperature ionic liquids (RTILs) are liquids composed entirely of ions that are molten at room temperature. Although there are several classes of RTILs, most share common properties such as a wide electrochemical window, high conductivity/ionic mobility, broad liquid temperature range (~300 °C), negligible vapor pressure, chemical and thermal stability, and the ability to solvate a variety of organic and inorganic species.[1–9] One key feature of RTILs is that certain bulk properties (*e.g.*, melting point, viscosity, hydrophobicity) can be tailored by varying the nature of the cation and/or anion, allowing one to customize a RTIL for specific needs.

Most recently, air- and moisture-stable RTILs have been developed.[10–14] Most of these RTILs are based on *N*,*N*′-dialkylmethylimidazolium, *N*-alkylpyridinium, tetraalkylammonium, or tetraalkylphosphonium cations with typical anions including $[BF_4]^-$, $[PF_6]^-$, $[CF_3SO_3]^-$ and $[(CF_3SO_3)_2N]^-$. The types of RTILs have been discussed regularly in the recent literature.[15–56] For example, air- and moisture-stable RTILs have been used as solvents for a wide range of chemical reactions including hydrodimerization,[15] hydrogenation[16–21] dimerization,[22] polymerization,[23,24] alkylation,[25] Friedel–Crafts reactions,[26–29] Heck coupling reactions,[30,31] Diels–Alder reactions,[32–34] enzymatic catalysis,[35–38] silica aerogel synthesis,[39] nucleophilic displacement reactions,[40] and pharmaceutical synthesis.[41] These solvent systems have also been used as stationary phases in gas chromatography (GC),[42–49] as mobile phases in liquid chromatography (LC),[50] in solar cells,[51] and in conjunction with polymers to produce gel electrolytes.[52] RTILs have also gained popularity as ‘green’ alternatives for volatile organic solvents in a number of industrial processes and separation technologies.[1,2,4,53–57]

Despite the increasing use of air- and moisture-stable RTILs as solvents for a wide range of chemical reactions and extractions, very few studies have been conducted to explore their polarity and how the cations and anions influence solvation on the molecular level. Several recent publications exploring the polarity of imidazolium-based RTILs report polarities similar to that of short chain alcohols, although the reported solvent parameters varied significantly depending on

Green Context

The study of alternative solvent systems is one of the largest areas of research in the context of green chemistry. However, a shortage of physical data on some of the newer solvent systems gives us an incomplete understanding of their properties. This in turn hampers their exploitation on a commercial scale. Here potentially valuable data on the solvent parameters for room temperature ionic liquids is reported. The effects of water and temperature on these are especially noteworthy. *JHC*

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the exact probe molecule that is used.[13,56–62] Among these studies, 1-butyl-3-methylimidazolium hexafluorophosphate, $[bmim]^+[PF_6]^-$, has become the most popular RTIL for investigation. For example, Rogers and coworkers found that the partition coefficients for simple substituted benzenes in the $[bmim]^+[PF_6]^-$/water system are approximately an order-of-magnitude less than the corresponding octane-1-ol/water partition coefficients.[53] These authors also discovered the tendency for charged solutes to remain in the aqueous phase with obvious implications for the separation and recovery of products from reactions and the potential for recycling without generating secondary waste. Related studies of imidazolium-based RTILs as GC stationary phases have offered insight into their polarity and interaction with model solutes.[48,49] Armstrong *et al.* have investigated $[bmim]^+$-based RTILs with $[Cl]^-$, $[PF_6]^-$ and $[BF_4]^-$ anions.[48] These authors reported that these particular RTILs behave as low-polarity stationary phases toward non-polar compounds while firmly retaining those with proton donor or acceptor groups. Blanchard and Brennecke determined the solubility of several classes of organic solutes (*e.g.*, alcohols, amides, ketones, benzenes, hexanes) in $[bmim]^+[PF_6]^-$, reporting the highest solubilities for organics with the potential for strong intermolecular interactions such as those possessing large dipole moments.[58] Finally, studies on $[bmim]^+[PF_6]^-$ are complicated because this particular RTIL can absorb small amounts of adventitious water (up to 2.3% (w/w), 3.1% (v/v)) and the absorbed water affects the bulk solvent properties (*i.e.*, viscosity or density) and may therefore alter the local solvent microenvironment surrounding a solute.[63]

Although the information void on solvation within RTILs is closing, more studies are clearly needed to more fully understand these unique solvent system. In this paper we investigate several organic solvatochromic probe molecules (solutes) dissolved in $[bmim]^+[PF_6]^-$ and we determine the Kamlet–Taft solvent parameters (α, β, π^*) and $E_T(30)$ values as a function of temperature and water content. Experiments on ‘dry’ $[bmim]^+[PF_6]^-$ were conducted when the water content within the RTIL was < 50 ppm. Experiments on ‘wet’ $[bmim]^+[PF_6]^-$ were performed on samples that contained 2.0% (v/v) water. Cloud-point titrations indicate complete miscibility of the added water at this level in $[bmim]^+[PF_6]^-$ over the entire temperature range studied.

Results and discussion

Although solvent effects on organic reactivity and spectroscopic transitions have been studied for more than a century, the concept of *solvent polarity*, while easily grasped in a qualitative sense, eludes rigorous and precise definition. The IUPAC recommendation for the definition of solvent polarity specifies *that the polarity is the sum of all possible, non-specific and specific, intermolecular interactions between the solute ions or molecules and solvent molecules, excluding such interactions leading to definite chemical alterations of the ions or molecules of the solute*.[64] Because these manifold intermolecular forces include Coulomb interactions, directional interactions between dipoles (and quadrupoles or higher multipole moments), inductive, dispersive, hydrogen-bonding, and charge-transfer forces, as well as solvophobic interactions, not surprisingly single macroscopic physical parameters (*e.g.*, dielectric constants, dipole moments, refractive indices) or functions thereof cannot adequately describe solvent polarity. This inadequacy, coupled with the lack of comprehensive theoretical expressions, has led to the introduction of empirical solvent polarity scales based on solvent interactions with a reference solute.[65,66] Several polarity scales, based on solvatochromic probes, have been devised over the years, including the *Y*-scale introduced by Winstein, Dong and Winnik's *Py*-scale, Kosower's *Z*-scale, Dubois' Φ-scale, the Reichardt $E_T(30)$ scale, Gutmann's donor (DN) and acceptor numbers (AN), and the linear solvation energy relationship (LSER) developed by Kamlet and Taft.[65,66]

Temperature-dependent $E_T(30)$ values in dry and wet $[bmim]^+[PF_6]^-$

The $E_T(30)$ scale, based on the large negative solvatochromic shift of the long-wavelength intramolecular π–π^* charge-transfer (CT) absorption band of Reichardt's pyridinium *N*-phenoxide betaine dye (historically, the dye numbered 30 in the first publication by Dimroth, Reichardt *et al.*), is one of the most popular empirical solvent polarity scales. Calculated from the absorbance maximum, λ_{max}, of the CT-band of Reichardt's dye 30:[65]

$$E_T(30)\ (\text{kcal mol}^{-1}) = 28591/\lambda_{max}\ (\text{nm}) \qquad (1)$$

The molar transition energy for CT absorption [*i.e.*, $E_T(30)$] is influenced approximately equally by the solvent hydrogen-bond donating (HBD) ability and the solvent dipolarity/polarizability (*vide infra*).

The $E_T(30)$ values based on Reichardt's dye 30 for dry $[bmim]^+[PF_6]^-$ (sub-50 ppm water; for reference, a water level under 100 ppm is considered rigorously dry[63]) between 10 and 70 °C is presented in Fig. 1 (●). By way of comparison, our room-temperature $E_T(30)$ value for dry $[bmim]^+[PF_6]^-$ (52.4 kcal mol^{-1} at 30 °C) is identical, given the measurement imprecision, to values reported by Fletcher *et al.* (52.5 kcal mol^{-1})[59] and Gordon and coworker (52.3 kcal mol^{-1})[62] as well as the value determined indirectly by using 4-(*N*,*N*-dimethylamino)phthalimide by Aki et al. (52.4 kcal mol^{-1}).[61] The recovered $E_T(30)$ values are similar to those for short chain alcohols (*e.g.*, the value for ethanol is 51.9 kcal mol^{-1} at 25 °C and 1 bar). Studying a series of 1,3-dialkylimidazolium cation-based ionic liquids, Gordon and coworkers showed that $E_T(30)$ is a good indicator of the HBD ability of the imidazole ring hydrogens to the phenoxide group on Reichardt's dye 30.[62] Interestingly, the thermochromism evident in Fig. 1 clearly suggests monotonic changes in the HBD ability of dry $[bmim]^+[PF_6]^-$ with temperature. In fact, there is a linear correlation of the $E_T(30)$ solvent parameter with temperature

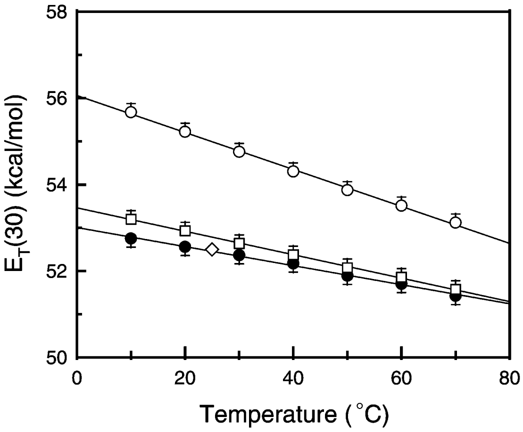

Fig. 1 Effects of temperature on the $E_T(30)$ values in dry and wet $[bmim]^+[PF_6]^-$. Symbols: (●) $E_T(30)$ in dry $[bmim]^+[PF_6]^-$ measured using the $E_T(30)$ probe. (□) $E_T(30)$ in dry $[bmim]^+[PF_6]^-$ estimated using the $E_T(33)$ probe. (○) $E_T(30)$ in wet $[bmim]^+[PF_6]^-$ estimated using the $E_T(33)$ probe. (◇) Results from Fletcher *et al.*,[59] Aki *et al.*,[61] and Gordon and cowokers[62] on $[bmim]^+[PF_6]^-$ at room temperature. See text for details.

(T) for dry $[bmim]^+[PF_6]^-$ that follows: $E_T(30) = 53.0 - 0.022T$; $r^2 = 0.995$, $s = 0.035$ where r^2 is the correlation coefficient and s is the standard error of the fit. This negative thermochromism arises from the increased differential stabilization of the highly dipolar zwitterionic betaine ground state ($\mu_g \approx 15$ D) relative to the less dipolar excited state ($\mu_e \approx 6$ D) with decreased solution temperature.[62]

We next questioned how the presence of residual water added intentionally to $[bmim]^+[PF_6]^-$ affects the observed $E_T(30)$ and its temperature dependence. Toward this end, we prepared a $[bmim]^+[PF_6]^-$ sample and intentionally added water (2.0% v/v) but kept the water concentration below its known solubility limit. Unfortunately, these solutions faded from violet to colorless when the water was added. This result is consistent with protonation at the phenolic oxygen in Reichardt's dye 30 (pK_a = 8.65).[67] Due to the potential for HF formation *via* disproportionation of $[PF_6]^-$,[63] and because a betaine dye must remain deprotonated to function as a solvatochromic indicator, we opted to use a less basic version of Reichardt's dye 30, the dichloro-substituted betaine dye (2,6-dichloro-4-(2,4,6-triphenyl-1-pyridinio)phenolate (Reichardt's dye 33, pK_a of 4.78)) whose CT absorption band position has an established correlation with Reichardt's dye 30.[65,67] To confirm the viability of this secondary standard for the $[bmim]^+[PF_6]^-$ system, we used Reichardt's dye 33 to initially estimate the $E_T(30)$ for the dry $[bmim]^+[PF_6]^-$. The results of this exercise are presented in Fig. 1 (□). The observed $E_T(30)$ values that we recover by using Reichardt's dye 33 and their temperature dependence are within the measurement precision of the direct $E_T(30)$ measurements. This result argues that Reichardt's dye 33 is suitable for estimating the $E_T(30)$ values in systems where one cannot use the $E_T(30)$ probe directly. We use Reichardt's dye 33 to determine $E_T(30)$ for the wet $[bmim]^+[PF_6]^-$.

Results for the wet $[bmim]^+[PF_6]^-$ sample (Fig. 1 ○) clearly show that just 2% water (v/v) alters the solvent's HBD capacity significantly ($E_T(30) = 56.1–0.043T$; $r^2 = 0.998$, $s = 0.045$) and the temperature dependence is nearly doubled.

An interesting possibility in any mixed solvent system is the solute's preferential solvation by one of the components (*i.e.*, a local augmentation of a particular component in a solute's local environment relative to the bulk solution's composition) in the mixture.[68] To determine if such a scenario is operating for the $[bmim]^+[PF_6]^-$/water system, we calculated the theoretical spectral response (*i.e.*, $E_T(30)$ values) based on the assumption that the overall response is simply a weighted sum of the responses in the pure solvents:

$$E_T(30) = x_w E_T(30)_w + (1 - x_w) E_T(30)_b \tag{2}$$

In eqn. (2), x_w is the mole fraction of water ($x_w \approx 0.19$) and $E_T(30)_w$ and $E_T(30)_b$ are the $E_T(30)$ values in pure water[69] and dry $[bmim]^+[PF_6]^-$, respectively. As shown in Fig. 2, the temperature-dependent $E_T(30)$ values for the binary $[bmim]^+[PF_6]^-$/water mixture that we calculate from eqn. (2) (solid line) agree remarkably well with our experimental results. In fact, the average deviation from the calculated values is only 0.16 kcal mol^{-1} suggesting a complete lack of preferential solvation (*i.e.*, a lack of synergism) at this water level and across the entire temperature range for this particular probe. (Note: There appears to be slightly more deviation below ~30 °C).

Temperature-dependent Kamlet–Taft solvent parameters in dry and wet $[bmim]^+[PF_6]^-$

For solvatochromic shifts, the LSER of Kamlet and Taft has been widely applied in the following simplified form:[65,66]

$$XYZ = (XYZ)_0 + s(\pi^* + d\delta) + a\alpha + b\beta \tag{3}$$

In this expression XYZ is a solvent-dependent solute property (*e.g.*, the logarithm of a rate or equilibrium constant or a spectral position) and $(XYZ)_0$ is the regression value for a reference solvent system (*e.g.*, a nonpolar medium or the gas phase), π^* is the solvent dipolarity/polarizability, α is the solvent hydrogen-bond donating (HBD) acidity, and β is the solvent hydrogen-bond accepting (HBA) basicity, and is δ polarizability correction term that is 0.0 for non-halogenated aliphatic solvents, 0.5 for polyhalogenated aliphatic solvents, and 1.0 for aromatics. s, d, a and b are solvent-independent correlation coefficients.

The π^* parameters were estimated by using *N*,*N*-diethyl-4-nitroaniline, a non-hydrogen bond donor solute:

$$\nu_{max} = \nu_0 + s\pi^* \tag{4}$$

where ν_{max} is the position of the absorbance maximum; ν_0 = 27.52 kK and $s = -3.182$.[66]

The β values for solvent hydrogen-bond acceptor basicities were determined by using the enhanced solvatochromic shift ($-\Delta\Delta\nu(1–2)$) of 4-nitroaniline relative to the homomorphic *N*,*N*-diethyl-4-nitroaniline.

$$\beta = [1.035\nu(2)_{max} - \nu(1)_{max} + 2.64 \text{ kK}]/2.80 \tag{5}$$

Here, $\nu(1)_{max}$ and $\nu(2)_{max}$ are the observed absorbance maxima for 4-nitroaniline and *N*,*N*-diethyl-4-nitroaniline, respectively.[65,66]

The α values for solvent hydrogen-bond donor acidities were determined by using the $E_T(30)$ and π^* values.[65,66]

$$\alpha = [E_T(30) - 14.6(\pi^* - 0.23\delta) - 30.31]/16.5; \ \delta = 1.0 \tag{6}$$

The temperature-dependent π^* values for dry (●) and wet (○) $[bmim]^+[PF_6]^-$ are shown in Fig. 3A (values are also compiled in Table 1). Whether wet or dry, the dipolarity/polarizability of $[bmim]^+[PF_6]^-$ decreases continuously with increasing temperature in a parallel manner. While the π^* values for wet $[bmim]^+[PF_6]^-$ are, on average, higher at every temperature relative to that of dry $[bmim]^+[PF_6]^-$ they do not appear to be significantly different given our measurement imprecision. The data in Fig. 3A can be described by $\pi^* = 0.937 - 6.48 \times 10^{-4}T$ ($r^2 = 0.984$, $s = 0.002$) and $\pi^* = 0.956 - 6.47 \times 10^{-4}T$ ($r^2 = 0.982$, $s = 0.002$) for dry and wet $[bmim]^+[PF_6]^-$, respectively. At ambient temperatures, the $[bmim]^+[PF_6]^-$ π^* value is slightly lower than that of dimethyl sulfoxide and water. Surprisingly, the dipolarity/polarizability of $[bmim]^+[PF_6]^-$ is much higher than that of short chain alcohols (0.5–0.6 spans the range from methanol to 1-butanol), being ethylene glycol- or benzyl alcohol-like.

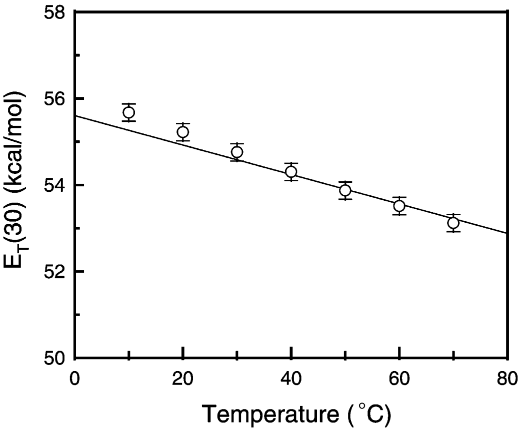

Fig. 2 Predicted (—) *versus* experimental (○) $E_T(30)$ for 2.0% (v/v) water dissolved in $[bmim]^+[PF_6]^-$.

The temperature-dependent α values for dry (●) and wet (○) $[\mathrm{bmim}]^+[\mathrm{PF}_6]^-$ are shown in Fig. 3B. In general, β is not different for dry and wet $[\mathrm{bmim}]^+[\mathrm{PF}_6]^-$ at any temperature investigated and it is not a strong function of temperature. Between 10 and 70 °C, the $[\mathrm{bmim}]^+[\mathrm{PF}_6]^-$ hydrogen-bond acceptor basicity is also far lower than that of shorter chain alcohols and it is intermediate between that of water and acetonitrile. Very few polar organic solvents possess a HBA ability as low as that of $[\mathrm{bmim}]^+[\mathrm{PF}_6]^-$. Among the ethers, esters, orthoesters, aldehydes, ketones, amides, carbamates, ureas, amines, sulfoxides, nitriles, pyridines and alcohols only anisole and water possess similar β values.

The temperature-dependent α values for dry (●) and wet (○) $[\mathrm{bmim}]^+[\mathrm{PF}_6]^-$ are shown in Fig. 3C. The data in Fig. 3C can be described by $\alpha = 0.778 - 1.07 \times 10^{-3}T$ ($r^2 = 0.996$, $s = 0.002$) and $\alpha = 0.919 - 2.04 \times 10^{-3}T$ ($r^2 = 0.998$, $s = 0.002$) for dry and wet $[\mathrm{bmim}]^+[\mathrm{PF}_6]^-$, respectively. These results suggest a hydrogen-bond donor acidity for dry $[\mathrm{bmim}]^+[\mathrm{PF}_6]^-$ that is similar to short chain alcohols, a fact in good agreement with our $E_\mathrm{T}(30)$ studies and recent literature suggesting such.[13,57–62] As expected from the correlation in eqn. (6), upon the addition of water, α increases in a manner which parallels the changes in $E_\mathrm{T}(30)$.

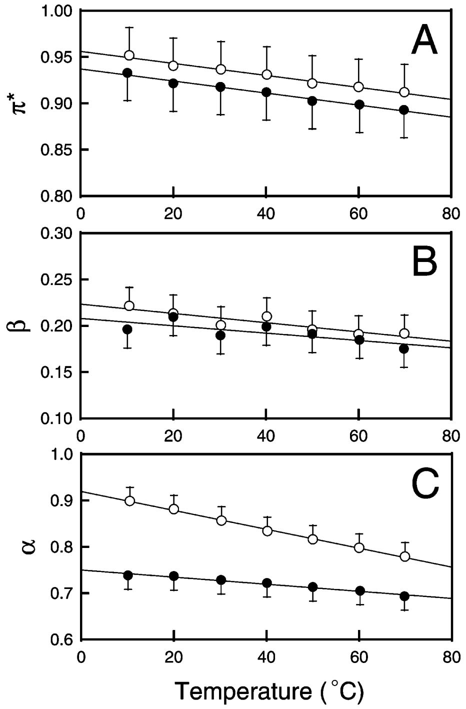

Fig. 3 Recovered temperature-dependent Kamlet–Taft parameters for dry (●) and wet (○) $[\mathrm{bmim}]^+[\mathrm{PF}_6]^-$. (Panel A) π^* values. (Panel B) β values. (Panel C) α values. See text for details.

Table 1 Recovered solvent parameters for wet and dry $[\mathrm{bmim}]^+[\mathrm{PF}_6]^-$

	Solvent parameters for $[\mathrm{bmim}]^+[\mathrm{PF}_6]^-$ (dry/wet)[a]			
Temp/°C	π^* (± 0.03)	β (± 0.02)	α (± 0.03)	$E_\mathrm{T}(30)$[b]/kcal mol^{-1} (± 0.2)
10.0	0.93/0.95	0.20/0.22	0.77/0.90	53.2/55.7
20.0	0.92/0.94	0.21/0.21	0.76/0.88	52.9/55.2
30.0	0.92/0.94	0.19/0.20	0.74/0.86	52.6/54.8
40.0	0.91/0.93	0.20/0.21	0.73/0.83	52.4/54.3
50.0	0.90/0.92	0.19/0.20	0.72/0.82	52.1/53.9
60.0	0.90/0.92	0.18/0.19	0.71/0.80	51.9/53.5
70.0	0.89/0.91	0.17/0.19	0.70/0.78	51.6/53.1

[a] 'dry' refers to less than 50 ppm water; 'wet' refers to 2% (v/v) water. [b] These $E_\mathrm{T}(30)$ values are secondary values determined by means of the more acidic dichloro-substituted $E_\mathrm{T}(33)$ betaine dye; *cf.* refs. 65 and 66.

Conclusions

We have determined the $E_\mathrm{T}(30)$ and Kamlet–Taft solvent parameters (α, β, π^*) for dry and wet $[\mathrm{bmim}]^+[\mathrm{PF}_6]^-$ between 10 and 70 °C. $[\mathrm{bmim}]^+[\mathrm{PF}_6]^-$ is shown to be a remarkable amphiprotic solvent with no peer among the traditional organic solvents. While $E_\mathrm{T}(30)$ and Kamlet–Taft studies are suggestive of temperature- and moisture-dependent hydrogen bond donor strengths akin to the short chain alcohols, hydrogen bond acceptor abilities were weak functions of temperature and added water, lying between those of water and acetonitrile. Most solvents possessing such low nucleophilicities are generally regarded as non-polar. However, the dipolarity/polarizability of $[\mathrm{bmim}]^+[\mathrm{PF}_6]^-$ under ambient conditions is 55–95% higher than the lower chain alcohols and only 10–15% below that of water or dimethyl sulfoxide decreasing linearly with increasing temperature. Our work with $E_\mathrm{T}(30)$ and $E_\mathrm{T}(33)$ shows that added water has no significant effect on the β and π^* values and preferential solvation is absent or at best modest below ~ 30 °C for these probes. Additional work is clearly needed using other probes with differing structures and susceptibilities. Overall, our results suggest the possibility of changing the solvent power (solvency) of $[\mathrm{bmim}]^+[\mathrm{PF}_6]^-$ for organic solutes by variation of temperature and the addition of modifiers or co-solvents. Further, the choice of cation and anion are likely to have a distinct influence on the microscopic solvent properties of room-temperature ionic liquids, a prospect currently under investigation.

Experimental

Chemicals and reagents

4-Nitroaniline and (2,6-diphenyl-4-(2,4,6-triphenyl-1-pyridinio)phenolate (Reichardt's dye 30) were used as received from Sigma. HPLC grade (⩾99.0%) (2,6-dichloro-4-(2,4,6-triphenyl-1-pyridinio)phenolate (Reichardt's dye 33) was from Fluka. *N*,*N*-diethyl-4-nitroaniline was purchased from Frinton laboratories and used without further purification. 1-Butyl-3-methylimidazolium hexafluorophosphate ($[\mathrm{bmim}]^+[\mathrm{PF}_6]^-$) was purchased from Covalent Associates, Inc., and stored within a dry box.

Methods

Individual stock solutions of 4-nitroaniline, *N*,*N*-diethyl-4-nitroaniline, and Reichardt's dye 30 and 33 were prepared in ethanol. To prepare a given dye/$[\mathrm{bmim}]^+[\mathrm{PF}_6]^-$ solution, the appropriate amount of the dye stock solution was micropipetted into a clean dry quartz cuvette. Residual ethanol was then evaporated under a gentle stream of argon gas. A clean dry Teflon stirring flea was added to the cuvette to aid in later stirring. Within a dry box, $[\mathrm{bmim}]^+[\mathrm{PF}_6]^-$ was added to the cuvette, the cuvette was capped and sealed, and the sample was mixed for an appropriate time prior to experimental measurements. For all results reported here, the dye concentration in the $[\mathrm{bmim}]^+[\mathrm{PF}_6]^-$ was such that it had an absorbance between 0.15 and 0.22 (there was no evidence for dye aggregation at these solute concentrations). The purity and water level within the $[\mathrm{bmim}]^+[\mathrm{PF}_6]^-$ were determined as reported in the literature.[56] Here, 'dry' $[\mathrm{bmim}]^+[\mathrm{PF}_6]^-$ refers to a water content of no more than 50 ppm.

All absorbance measurements were performed by using a Milton-Roy Spectronic, Model 1201. Temperature-dependent absorbance studies were performed by using a VWR, Model 1140 temperature bath (± 0.1 °C). Absorption peaks were fit to Gaussian profiles to determine absorbance maxima.

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Selective oxidation of styrene to acetophenone in the presence of ionic liquids†

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Palladium-catalyzed oxidation of styrene (Wacker reaction) in the presence of 1,3-dialkylimidazolium cation based ionic liquids is described under relatively benign conditions using hydrogen peroxide. The effects of various reaction parameters and a comparison of this approach with the corresponding reactions under pressurized conditions have been made.

Introduction

The conventional use of volatile solvents in a chemical reaction is of ecological and economic concern. The reduction/replacement of volatile organic solvents from the reaction medium is of utmost importance in the realm of green chemistry. Thus, the quest for a recyclable and nonvolatile reaction media is at the forefront in this field of research wherein fused organic salts, consisting of ions, are now emerging as possible alternatives. A proper choice of cation and anion is required to design ionic salts that are liquids at room temperature and are appropriately termed room temperature ionic liquids (RTILs).

Several preparations of common RTILs consisting of *N*,*N′*-dialkylimidazolium, alkylammonium, alkylphosphonium or *N*-alkylimidazolium as cations are now available[1] including some that are obtainable *via* solvent-free routes.[1*b*,*c*] Most of these ionic salts are good solvents for a wide range of organic and inorganic materials and are stable enough to air, moisture and heat. They are polar but consist of poorly coordinating ions, are immiscible with a number of organic solvents, and provide a polar alternative for biphasic systems. The salient features of these ionic liquids are that they have negligible vapor pressure, provide accelerated reaction rates, possess enhanced potential for recycling, in addition to their compatibility with a variety of organic compounds and organometallic catalysts.[2]

The Wacker reaction is an important method for the functionalization of alkenes and can be typically represented by the palladium (Pd) catalyzed oxidation of ethylene to acetaldehyde.[3] The oxidation of higher terminal alkenes to methyl ketones is a significant application of this reaction which is normally achieved over a Pd(II) catalyst using molecular oxygen (O_2) or excess hydrogen peroxide (H_2O_2) as oxidizing agents.[4] Several research groups have investigated the selective oxidation of styrene to acetophenone and related carbonyls.[5–10] Acetophenone is an important feedstock for a variety of pharmaceuticals and is industrially prepared by the acetylation of benzene using acetyl chloride/acetic anhydride.[11]

Wacker oxidation of styrene with excess of oxidant in acetic acid provides acetophenone (~55% yield).[5] The oxidation of styrene using a palladium chloride ($PdCl_2$) catalyst in a phase transfer reaction delivers ~56% yield of acetophenone in addition to benzaldehyde and benzoic acid.[6] An improved yield of acetophenone is reportedly obtained *via* the H_2O_2 oxidation of styrene catalyzed by $PdCl_2$ in a microemulsion, but the process involves the use of expensive surfactants, organic solvent, and excess H_2O_2 (4 times that of the substrate).[7] Other rapidly deactivating catalyst systems such as TS-1 have also been used for styrene oxidation, which leads to the formation of phenyl acetaldehyde as the major product.[8] The major drawback with most of the above processes is the low efficiency of H_2O_2 utilization.

The utility of water-soluble palladium clathrate complexes has also been explored in reverse phase-transfer styrene oxidation,[9] a process that involves the preparation of an expensive complex palladium catalyst and suffers from drawbacks of poor catalyst recovery. Jiang *et al.* have studied the oxidation of olefins using molecular oxygen in supercritical carbon dioxide ($scCO_2$) alone or $scCO_2$ admixed with alcohols using $PdCl_2/CuCl_2$ catalyst.[10] However, even after prolonged reaction time (24 h), the overall conversion and the selectivity for acetophenone formation are very low. Consequently, the development of a simpler, efficient and environmentally friendly method for the selective oxidation of styrene to acetophenone is a desirable research endeavor.

The present study evaluates the effect of imidazolium-based ionic liquids as potential co-catalysts on the selective oxidation of styrene to acetophenone using hydrogen peroxide as oxidant and palladium chloride as catalyst. The effect of temperature, use of co-oxidants, and pressurized reaction conditions have also been investigated for this oxidation reaction (Scheme 1).

Green Context

The classical production of acetophenone is a wasteful process. Alternatives to the Friedel–Crafts route are needed, and Pd catalysed Wacker chemistry is a potentially clean route. Using hydrogen peroxide and a highly active catalyst could provide a very acceptable method, starting from styrene. Such work has been investigated, with modest yields and often inadequate recovery of the catalyst. This work shows that yields are much improved in ionic liquids, with improved recovery being possible. *DJM*

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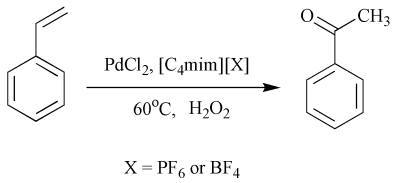

Scheme 1

Results and discussion

The oxidation of styrene with H_2O_2 in the presence of palladium chloride and various ionic liquids is conducted and the results are summarized in Table 1. No acetophenone formation is observed in the absence of palladium chloride (entry 12, Table 1). The study shows that a catalytic amount of ionic liquids (~2.5 wt% of substrate) bearing imidazolium cation helps to enhance the reaction rate. The effects of 1-butyl-3-methylimidazolium tetrafluoroborate ([C_4mim][BF_4]) and 1-butyl-3-methylimidazolium hexafluorophosphate ([C_4mim][PF_6]) are evaluated and both are found to be suitable for the enhancement of reaction rate.

The optimum mole ratio of H_2O_2 to styrene is found to be 1.15, which is far less than the amounts used in earlier protocols. Relatively, only trace amounts of contaminants such as benzaldehyde, benzoic acid and 1-phenyl-1,2-ethanediol are detected. A large excess of H_2O_2 (3 times that of substrate) affords good conversion but the unreacted H_2O_2 undergoes rapid decomposition in some experiments (entry 10, Table 1). The gradual addition of hydrogen peroxide, on the other hand, enhances the formation of above-mentioned side products (entry 11, Table 1). Oxidations conducted at room temperature show no acetophenone formation (entries 1, 4, and 8, Table 1), whereas at elevated temperature (80 °C), rapid decomposition of H_2O_2 occurs (entries 3 and 6, Table 1). The optimum temperature for high conversion and product selectivity is found to be 60 °C. A control experiment without palladium chloride under the same conditions results only in less than 2% styrene consumption.

A plausible mechanistic pathway delineating the synergistic participation of ionic liquids in the enhancement of oxidation may include the formation of an oxaziridinium ion type intermediate involving the imidazolium cation similar to what has been described recently.[12,13] The imidazolium cation may be enhancing the activation of H_2O_2 which, in turn, reoxidizes palladium(0) to palladium(II), the latter being the catalyst for the oxidation of styrene. The salient feature of this method is that it provides high isolated yield of acetophenone (79%) without employing any volatile organic solvent, surfactant or complex palladium catalysts.

In view of the recent studies on oxidation of styrene with molecular oxygen in carbon dioxide media[10] and to compare our results, we also examined the reaction in a batch reactor under pressurized conditions. The effects of concentration of H_2O_2 (Table 2), pressure (Table 3), and temperature (Table 4) were evaluated using carbon dioxide (CO_2) or nitrogen as an inert gas to pressurize the reaction vessel. The oxidation of styrene to acetophenone is influenced by the concentration of H_2O_2 (Table 2). However, the effect tapers off when H_2O_2 concentration is 2.5 mmol/mmol of styrene and beyond (entries 3 and 4, Table 2). The oxidation in water with O_2 as co-oxidant, on the other hand, leads to the formation of more benzoic acid (entry 8 and 9, Table 2). It is apparent that the ionic liquid does

Table 1 Palladium catalyzed oxidation of styrene with hydrogen peroxide in the presence of ionic liquid[a]

					Selectivity	
Entry	Ionic liquid	IL amount (g)	Temp./°C	Conversion (%)	Acetophenone (%)	Benzaldehyde (%)
1	—	—	30	0	—	—
2	—	—	60	60	70	21
3	—	—	80	65	65	2[b]
4	[C_4mim][PF_6]	0.25	30	0	—	—
5	[C_4mim][PF_6]	0.25	60	100	91	4
6	[C_4mim][PF_6]	0.25	80	70	70	10[b]
7	[C_4mim][PF_6]	0.5	60	100	88	8
8	[C_4mim][BF_4]	0.25	30	0	—	—
9	[C_4mim][BF_4]	0.25	60	100	92	5
10	[C_4mim][BF_4]	0.25	60	90	81	4[c]
11	[C_4mim][BF_4]	0.25	60	80	78	10[d]
12	[C_4mim][BF_4]	0.25	60	2	0	1[e]

[a] *Reaction conditions*: reactions are carried out in a 150 mL round-bottomed flask fitted with a condenser for 3 h; styrene (100 mmol, 10.4 g), 30% H_2O_2 (115 mmol), $PdCl_2$ (0.5 mmol). [b] Exothermic decomposition of H_2O_2. [c] H_2O_2: 2.5 mmol/mmol of styrene. [d] Gradual addition of H_2O_2 (0.1 mL min^{-1}). [e] Without palladium chloride

Table 2 Effect of oxygen and H_2O_2 concentration on oxidation of styrene[a]

				Selectivity		
Entry	Temp./°C	H_2O_2/styrene (mmol/mmol)	Conversion (%)	Acetophenone (%)	Benzaldehyde (%)	Benzoic acid (%)
1	65	1.30	75	60	32	6
2	65	2.20	90	67	26	5
3	65	2.70	100	68	23	7
4	65	3.50	100	71	24	3
5	80	2.20	96	54	28	16
6	80	2.70	100	61	29	9
7	80	2.70	88	29	60	9[b]
8	80	0.44	50	12	40	46[c]
9	65	0	100	5	20	75[c,d]

[a] *Reaction conditions*: styrene (100 mmol), $PdCl_2$ (0.5 mmol), CO_2 (20.68 bar), time = 5 h, [C_4mim][BF_4] (0.25 g). [b] Cuprous chloride (1 mmol). [c] Oxygen (10.3 bar) and CO_2 (10.3 bar). [d] Water (10 mL), time (10 h).

Table 3 Effect of pressure on oxidation of styrene[a]

Entry	Pressure/bar	Conversion (%)	Selectivity Acetophenone (%)	Benzaldehyde (%)	Benzoic acid (%)
1	2.72	68	46	45	7[b]
2	10.34	88	58	35	6[c]
3	20.68	100	68	23	7[c]
4	34.03	100	72	21	5[c]
5	20.68	92	66	26	8[d]
6	34.03	94	69	26	6[d]

[a] *Reaction conditions*: styrene (100 mmol), $PdCl_2$ (0.5 mmol), temperature = 65 °C, time = 5 h, H_2O_2 (267 mmol), $[C_4mim][BF_4]$ (0.25 g). [b] In the absence of added pressure. [c] CO_2 pressure. [d] Nitrogen pressure.

Table 4 Effect of temperature on the oxidation of styrene with H_2O_2 under pressure[a]

Entry	Temp./°C	$[C_4mim][BF_4]$/g	Conversion (%)	Selectivity Acetophenone (%)	Benzaldehyde (%)	Benzoic acid (%)
1	30	0.25	0	—	—	—
2	50	0.25	24	8	54	37
3	65	0.25	90	67	27	5
4	80	0.25	96	56	29	15
5	80	0.00	83	49	31	19

[a] *Reaction conditions*: styrene (100 mmol), 30% H_2O_2 (220 mmol), $PdCl_2$ (0.5 mmol), CO_2 (20.68 bar), time = 5 h.

enhance the oxidation of styrene under pressure as the conversion increases from 83 to 96% and the selectivity for acetophenone formation increases from 49 to 56% (entries 4 and 5, Table 4). No discernable reaction is observed at room temperature with only 24% conversion attainable at 50 °C (entries 1 and 2, Table 4) under pressure (20.68 bar, CO_2). The optimum temperature for maximum conversion to acetophenone is also found to be 60–65 °C.

In contrast to the reaction at atmospheric pressure, the conversion and product selectivity in a closed reactor is influenced by two competing oxidants, namely hydrogen peroxide and molecular oxygen, the latter being responsible for the generation of benzaldehyde and benzoic acid. The pressure due to carbon dioxide or nitrogen reduces the partial pressure of oxygen thus promoting the hydrogen peroxide oxidation pathway leading to more acetophenone formation. The increased decomposition of the hydrogen peroxide at elevated temperature (80 °C) results in lower peroxide concentration, thus reducing the acetophenone selectivity (entries 4 and 5, Table 4).

Conclusions

In summary, ionic liquid enhances the activity and selectivity of palladium catalyzed oxidation of styrene to acetophenone with a low styrene to H_2O_2 ratio (1 : 1.15). The present method provides a ‘greener’ and economical alternative for the preparation of acetophenone compared with the traditional protocols *via* the acetylation of benzene that generate hydrogen chloride or acetic acid as byproduct or require complex catalyst systems in the presence of harmful organic solvents or phase transfer reagents.

Experimental

General procedures for the oxidation of styrene

Reaction at atmospheric pressure: in a typical reaction, 1-butyl-3-methyl imidazolium tetrafluoroborate (0.25 g), styrene (100 mmol), palladium chloride (0.5 mmol), and 30% H_2O_2 (115 mmol) as oxidant were stirred at 60 °C in a round-bottomed flask fitted with a condenser. TLC and GC-MS were used to follow the progress of the reaction. Upon completion of the reaction, the mixture was cooled to room temperature and the product extracted into diethyl ether (3 × 5 mL), washed with water (2 × 5 mL) and dried over anhydrous magnesium sulfate. The removal of solvent under reduced pressure afforded crude acetophenone, which upon column chromatography afforded an analytically pure product (79%).

Reaction in a batch reactor: the reaction mixture is charged into a 500 mL capacity stainless steel autoclave fitted with a mechanical stirrer and a temperature controller (Model FC Series, Pressure Products Inc, Erie, PA, USA). The contents of the reactor were stirred continuously (300 rpm) while raising the reactor temperature to the desired setting. After attaining the requisite temperature, the reactor was pressurized with nitrogen or carbon dioxide (20.68 bar) and the reaction was allowed to proceed. After the completion of reaction, the reactor was cooled to room temperature and the products were isolated as described earlier.

The analysis of the ensuing products was carried out using a Hewlett-Packard 6890 Gas Chromatograph using a HP-5 5% phenyl methyl siloxane capillary column (30 m × 320 μm × 0.25 μm) and a quadruple mass filter equipped HP 5973 Mass Selective Detector under a temperature programmed heating from 313–473 K at 10° min^{-1}. Samples were analyzed in duplicate with an injection volume of 1.0 μL. Quantification of the products was obtained using a multi-point calibration curve for each product.

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HRP-mediated polymerizations of acrylamide and sodium acrylate

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Previously, we reported the horseradish peroxidase (HRP) mediated free radical polymerization of methyl methacrylate.[1] The reaction medium was restricted to water/water-miscible co-solvent mixtures that solubilize both the monomer and enzyme. This paper describes HRP-mediated acrylamide polymerizations in aqueous medium with and without the addition of surfactants. Also, studies were conducted on polymerizations in concentrated emulsions using sorbitane monooleate as the surfactant. In aqueous medium, within 3 h, 98% yields of poly(acrylamide) were attained. By adding either anionic bis(2-ethylhexyl)sodium sulfosuccinate (AOT) or cationic cetyltrimethylammonium bromide (CTAB), the polymerization proceeded more rapidly so that within 60 and 75 min, respectively, 94% polymer yields were reached. When conducted in a concentrated emulsion formed with sodium monooleate, nearly quantitative yields resulted in 1.25 h. The weight average molecular weight (M_w) of the products ranged from 128 to 210 K and 106 to 154 K in aqueous medium and concentrated emulsions, respectively. In both of the above reaction systems, there was no apparent effect of the enzyme on the regulation of chain stereochemistry. The HRP-mediated polymerization of sodium acrylate conducted in aqueous medium gave poly(sodium acrylate) in yields up to 88% within 24 h with M_w *ca*. 119 K.

Introduction

Enzymes have proven to be powerful catalysts for the polymerization of a wide variety of monomers and macromonomers.[2,3] They represent a family of 'environmentally friendly' natural catalysts that can function under mild reaction conditions. Horseradish peroxidase (HRP) is an oxido-reductase that acts on hydrogen peroxide and/or alkyl peroxide as an oxidant[4] and on several reducing substrates such as phenol, hydroquinone, pyrogallol, catechol, aniline and *p*-aminobenzoate.[5] The oxidative coupling of a variety of substrates such as phenols and aromatic amines catalyzed by HRP in the presence of hydrogen peroxide have been reported in aqueous,[6] non-aqueous media,[7–9] and at interfaces.[10]

The potential of using HRP and other oxidases to catalyze the free radical polymerization of vinyl monomers was first reported by Derango *et al.*[11] The polymers were formed in the presence of a large excess of oxidant (monomer : oxidant, 1.66 : 1.0 vol/vol, for *e.g.* 1.41 : 1.0 mol/mol for 2-hydroxyethyl methacrylate). Unfortunately, these workers gave only qualitative descriptors to describe whether a polymer was formed without further information on the polymer structure. Kobayashi and coworkers[12] reported the HRP-catalyzed polymerization of phenylethyl methacrylate. Similar to Derango *et al*,[11] Kobayashi and coworkers[12] also published the formation of polymer using large quantities of oxidant (equimolar with respect to the monomer). More recently, the HRP-mediated free radical polymerization of acrylamide in water was reported.[13,14] These polymerizations took place when β-diketones were used as initiators and the molar ratio of hydrogen peroxide to monomer was 1–66.[13,14] That β-diketones will react under such conditions is related to their weakly bonded α-hydrogens. In fact, it had previously been shown that cyclic β-ketones, such as 5,5-dimethyl-1,3-cyclohexanedione, are substrates for chloroperoxidases which belong to the same subclass of enzymes as HRP (E.C. 1.11.a and 1.11.1.7, respectively).[15] By analogy to phenol, it was assumed that the enolic tautomeric form of 2,4-pentanedione is a key intermediate in the catalytic pathway.

This paper reports on the influence of reaction conditions and experimental variables to further extend our understanding of HRP-mediated free radical vinyl monomer polymerizations. Polymerizations of acrylamide and sodium acrylate were carried out at room temperature using HRP as an oxidoreductase, hydrogen peroxide as the oxidant and 2,4-pentanedione as the reductant. The influence of anionic (AOT) and cationic (CTAB) surfactants on HRP-mediated acrylamide polymerizations is reported. Behari *et al.*[16-18] and others[19] have also studied the effect of surfactant addition to free-radical polymerizations of acrylamide, but where chemical catalysts were used. Thus, comparisons were made between acrylamide polymerization kinetics when surfactants were added to these different polymerization systems. HRP-mediated polymerizations of acrylamide at room temperature were also studied in concentrated emulsions. A concentrated emulsion is a gel-like system whose internal phase ratio is greater than 0.74 (the volume fraction of the most compact arrangement of spheres of equal size).[20] Concentrated emulsions are of particular interest since, compared to inverse emulsion polymerizations, a much

Green Context

Utilising nature's catalysts is a very attractive option in a green chemistry context. Here we can read of the use of a horseradish peroxidase for the free radical polymerisation of acrylamide and sodium acylate. Reactions can be carried out in water at ambient temperatures. They are shown to be a viable alternative to conventional free radical methods.
JHC

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smaller amount of organic solvent is needed to produce polymer latexes.

Results and discussion

In our studies of horseradish peroxidase mediated free radical polymerization of acrylamide/sodium acrylate polymerizations, all three reagents, the enzyme, the initiator and the oxidant need to be present for the polymerization to take place. In the absence of horseradish peroxidase, hydrogen peroxide or 2,4-pentanedione, no polymer formation was observed. Three different commercial peroxidases, horseradish peroxidase (HRP) type I, HRP type II, and soybean peroxidase (SBP) were evaluated to compare their catalytic activities for acrylamide polymerization. The reducing substrate 2,4-pentanedione and hydrogen peroxide were used in the ratio 1.5 : 1.0 mol/mol. The ratio of acrylamide to 2,4-pentanedione was fixed at 44 : 1 based on previous work by our laboratory on HRP II mediated methyl methacrylate polymerizations.[1] Comparative studies were conducted at room temperature (25 °C), in an aqueous medium, for 3 h (Table 1). The oxidases evaluated were normalized based on weight, *i.e.* the same quantities by weight of the oxidases were taken to determine their activity for acrylamide polymerization. HRP II and SBP appeared most promising. For example, the yields of poly(acrylamide) when using HRP II, HRP I and soybean peroxidase (SBP) were 98, 98 and 51%, respectively (entries 7, 8 and 9, Table 1). Furthermore, HRP II and SBP catalyzed polymerizations for 3 h gave poly(acrylamide) with M_w values of 209 and 282 K, and polydispersity index (PDI, M_w/M_n) values of 2.7 and 2.9, respectively (Table 1, entries 7 and 9). HRP I gave poly(acrylamide) having M_w and PDI values of 176K and 2.4, respectively (Table 1, entry 8). Based on the above results, their relative availability and cost, HRP II was selected for more detailed studies of its ability to mediate poly(acrylamide) polymerizations. A polymerization reaction carried out in the presence of denatured horseradish peroxidase (enzyme heated at 70 °C for 24 h) did not result in significant polymer formation.

The HRP II-mediated polymerization of acrylamide in water was monitored as a function of reaction time (Table 1, entries 1–7). There was an initial induction period of 60 min, where little polymerization occurred. The yields of poly(acrylamide) successively increased from 24 to 98% from 1.5 to 3 h. Measurements by GPC showed that the weight average molecular weight (M_w) of poly(acrylamide) products increased with reaction time (Table 1, entries 4–7) and ranged between approximately 128 and 209 K. Such an increase in molecular weight is not unusual for similar polymerizations with chemical catalysts systems.[19] The tacticity for polyacrylamide (Table 1, entry 7) as determined by ^{13}C NMR showed that the polymer is atactic.[21] The methine carbon along the main chain of poly(acrylamide) gives rise to three distinct signals (triad sensitivity) which are further subdivided giving information at the pentad level. The low field and high field triplet peaks are assigned to rr (syndiotactic) and mm (isotactic) sequences, respectively. The central peak corresponds to heterotactic sequences (mr + rm). Thus, the repeat unit sequence distribution (Table 1, entry 7) by observation of triads using C_α (CH) resonances, gave syndio- (rr = 35%), hetero- (mr or rm = 51%) and isotactic (mm = 14%). Previously, we showed that the horseradish peroxidase mediated polymerization of methyl methacrylate (MMA) in different reaction conditions results in stereo-regular polymers with high syn-diad fractions.[1] However, in the present study, the poly(acrylamide) obtained was atactic.

Table 1 HRP II mediated free radical polymerization of acrylamide in aqueous medium, in presence of AOT surfactant, in the presence of CTAB surfactant and in sorbitane monooleate concentrated emulsion

Entry	System	Time/min	Isolated yield (%)	$10^{-3}M_w$/ g mol^{-1}	PDI
1	Aqueous	30	—	—	—
2	Aqueous	45	—	—	—
3	Aqueous	60	2	N.D	N.D
4	Aqueous	90	24	128	2.7
5	Aqueous	120	72	132	2.9
6	Aqueous	150	83	178	2.9
7	Aqueous	180	98	209	2.7
8	Aqueous	180(HRP I)	98	176	2.4
9	Aqueous	180(SBP)	51	282	2.9
10	Aqueous + AOT	35	2	212	2.3
11	Aqueous + AOT	40	25	139	3.1
12	Aqueous + AOT	50	91	131	2.9
13	Aqueous + AOT	60	94	141	3.2
14	Aqueous + CTAB	40	2	282	2.9
15	Aqueous + CTAB	45	55	229	2.2
16	Aqueous + CTAB	50	81	192	2.3
17	Aqueous + CTAB	60	91	133	2.6
18	Aqueous + CTAB	75	94	134	3.2
19	Conc. emulsion	30	10	N.D	N.D
20	Conc. emulsion	45	85	154	5.2
21	Conc. emulsion	60	87	110	4.8
22	Conc. emulsion	75	99	107	4.2

Previously, HRP was used to polymerize *p*-alkylphenols at oil/water (reverse micelles)[22–24] and air/water (Langmuir–Blodgett trough) interfaces.[25] Poly(*p*-alkyphenols) prepared in reverse micelles exhibited more uniform molecular weight distribution than those prepared in bulk organic solvents.[23,24] Also, Behari *et al.*[16–18] used surfactants to increase the kinetics of acrylamide free-radical polymerization with traditional catalyst systems. These findings encouraged us to study HRP-catalyzed acrylamide polymerizations in the presence of surfactants and in concentrated emulsions.

For aqueous HRP-mediated acrylamide polymerization, the induction period of 60 min without surfactant was reduced to 35 and 40 min when anionic bis(2-ethylhexyl)sodium sulfosuccinate (AOT) and cationic cetyltrimethylammonium bromide (CTAB) were used. Thus, both anionic and cationic additives enhanced the rate of the polymerization giving 94% isolated polymer yields in 60 and 75 min, respectively (see Fig. 1 and Table 1, entries 13 and 18). The M_w (PDI) values for poly(acrylamide)s formed by using anionic and cationic surfactants for 60 and 75 min reaction times were 141 000 (3.2) and 131 000 (3.2), respectively (see Table 1, entries 13 and 18). Behari *et al.*[18] studied the effect of adding anionic (sodium oleate, sodium lauryl sulfate) and cationic (CTAB) surfactants above their CMC values to aqueous acrylamide polymerizations catalyzed by peroxydiphosphate/activator redox systems. Similar to the finding above, the addition of anionic surfactants enhanced the rate of acrylamide polymerization. However, in

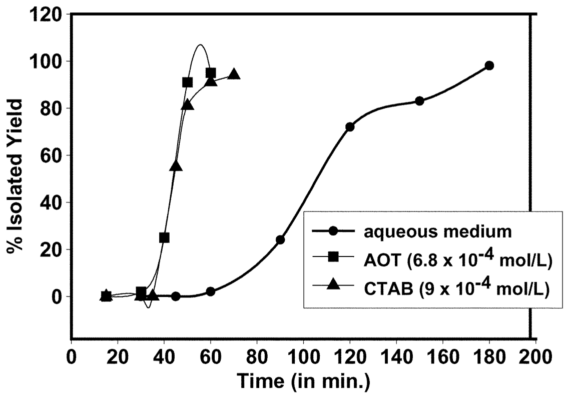

Fig. 1 Horseradish peroxidase mediated polymerization of acrylamide in aqueous medium with and without the addition of surfactants.

contrast to the present study, CTAB addition resulted in a decrease in the kinetics of acrylamide polymerization.[19] Further work will be needed to explain this difference in response of the chemical and enzyme-based catalyst systems to CTAB.

The HRP-mediated polymerization of acrylamide, in a concentrated emulsion using toluene in the dispersed phase, and sorbitane monooleate as an oil-soluble liquid surfactant (hydrophile : lipophile balance of 4.3), was performed. When the acrylamide polymerization was conducted in an aqueous medium without surfactant addition, a 1 h induction period and a total reaction time of 3 h was required to reach nearly quantitative polymer formation. However, by using the emulsion technique (oil in water), the one-hour induction period was greatly reduced so that nearly quantitative polymer formation occurred within 1.25 h (Fig. 2, Table 1, entry 22). This is consistent with traditional free-radical polymerization systems when one moves from solution to emulsion polymerizations. For example, potassium peroxidisulfate catalyzed acrylamide polymerizations were found to occur more rapidly in a concentrated emulsion (dispersed in decane, internal phase ratio of 0.94) than in aqueous solution.[20] The product formed by this emulsion polymerization, after 1.25 h, had an M_w and PDI of 107 000 and 4.2, respectively (Table 1, entry 22). The repeat unit sequence distribution of this product was analyzed by ^{13}C NMR. From observation of triads using C_α (CH) resonances, the sequence distribution was as follows: syndio- (rr = 34%), hetero- (mr and rm = 51%) and isotactic (mm = 15%). From these results, the randomness factor R was calculated ($R = 4[mm][rr]/[mr]^2$) and found to be 0.8. Since the value of R is near to 1.0, propagation closely follows Bernoulli statistics.[25] Comparison of the repeat unit sequence for polyacrylamides prepared in this study to those from peroxide initiated chemical polymerizations shows that they are similar. This suggests that HRP is not specifically associated with the propagating chain and the incoming monomer in such a way that might regulate chain stereoregularity.

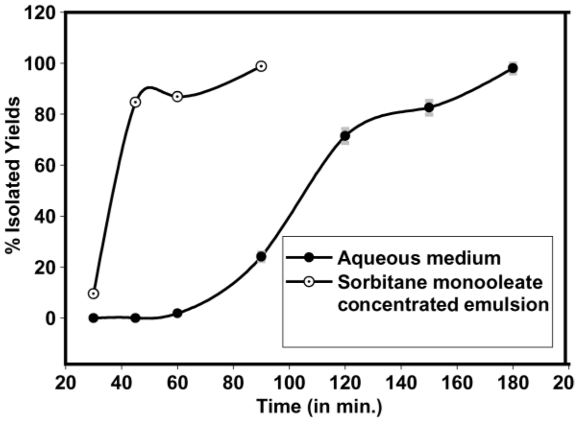

Fig. 2 Horseradish peroxidase mediated free radical polymerization of acrylamide in aqueous medium and in sorbitane monooleate concentrated emulsion (the error bars were generated by mean deviation of two replicates of reaction).

The molecular weight of the polyacrylamide obtained by using a concentrated emulsion was smaller than that synthesized in the aqueous medium (Table 1, entries 7 and 22). It may be that the transfer of hydrogen radical from the surfactant hydrophilic head-group to the propagating chain end results in higher rates of chain termination and, consequently, lower molecular weights than the reactions conducted in the aqueous medium.

HRP-mediated polymerization of sodium acrylate

The HRP-mediated polymerization of sodium acrylate at room temperature was studied in aqueous medium. The reducing substrate 2,4-pentanedione and hydrogen peroxide were used in the ratio 1.5 : 1.0 mol/mol. The polymer yields increased from 38 to 88% from 2 to 24 h, respectively. Measurements by GPC showed that the weight average molecular weight (M_w) of poly(sodium acrylate)s formed ranged from 191 to 242 K (Table 2).

Table 2 HRP II mediated free radical polymerization of sodium acrylate in aqueous medium

Time/h	Isolated yield (%)	$10^{-3}M_w$/g mol^{-1}	PDI
2	38	242	5.0
4	44	212	5.1
6	49	200	5.3
8	79	203	4.9
16	85	208	5.0
24	88	191	5.2

Conclusions

Horseradish peroxidase type II (HRP II) was studied for the catalysis of acrylamide and sodium acrylate polymerizations at room temperature. HRP II functioned as an oxidant with hydrogen peroxide to transfer electrons under mild conditions to 2,4-pentanedione. We believe that 2,4-pentanedione then acts as the free radical initiator species for chain growth. When acrylamide was polymerized in aqueous solution, the addition of either AOT or CTAB was found to significantly reduce the lag-time for chain initiation and propagation reactions. With the addition of AOT or CTAB to acrylamide polymerizations in aqueous media, 94% isolated polymer yields were obtained in 60 and 75 min, respectively. Comparison of acrylamide polymerizations in aqueous media without surfactant versus in concentrated emulsions showed that the latter gave more rapid polymerizations but products with broader polydispersity. In addition, the above strategy for HRP-mediated free-radical polymerizations was found useful with sodium acrylate. Hence, after a 24 h polymerization in aqueous medium without surfactant, poly(acrylate) was prepared in 88% yield, M_w *ca.* 191 K, and PDI = 5.2. The chain stereochemistry of the polymers formed was found to be similar to that for free-radical polymerizations carried out without enzyme. This suggests that the propagating chain and the incoming monomer do not associate in such a way that would regulate chain stereoregularity. Currently, acrylamide polymerizations are performed with potassium peroxidisulfate at 40 °C or with azo compounds at 60 °C. Photoinitiators or redox polymerization systems that are used at around 40 °C must be stored at low temperatures under inert conditions due to their inherent instability. The chemical systems often involve heavy metals and/or toxic substances. Their storage requirements are costly and energy intensive. Since peroxidases are natural, safe, and stable in the absence of peroxides, they do not require stringent storage precautions. In addition, future work on enzyme-catalyzed free-radical polymerizations may lead to insights on how they can be more broadly used to control the stereochemistry during propagation reactions. Thus, considering current advantages and future opportunities, enzymatic free-radical polymerization have important environmental benefits.

Experimental

Materials

Horseradish peroxidase (Type II, activity 235 purpullogallin units/mg), Horserdish peroxidase (Type I, activity 100 purpullogallin units/mg), Soybean peroxidase (90 purpullogallin units/mg), hydrogen peroxide (30% (w/v)) were obtained from Sigma chemical company. 2,4-Pentanedione from Aldrich was distilled prior to use. Acrylamide, sodium acrylate, dioctyl sulfosuccinate sodium salt, cetyltrimethylammonium bromide, sorbitane monooleate, methanol obtained from Aldrich were used as received.

Instrumentation

Nuclear magnetic resonance. All polymer solutions were PFG filtered prior to analysis to remove interference that might have arisen due to the presence of small molecule impurities. The NMR data were recorded on Bruker AMX500 and DMX400 spectrometers. The ^{13}C NMR spectra were obtained using gated-decoupling and using an 8-s recycle delay between scans for 10K scans for quantitation of resonances. ^1H NMR spectra were recorded using a 4-second recycle delay between scans. The distribution of repeat unit sequences that differ in stereochemistry was analyzed for poly(acrylamide) by observing the NMR signals due to the methine carbon region in the ^{13}C NMR.[21]

Molecular weight measurements. The weight average molecular weights (M_w) of the polymer samples were determined by gel permeation chromatography (GPC). Studies by GPC were carried out using a Waters, Inc. Model 510 pump, two Shodex KB 80m and one Shodex KB 802.5 column, and a Waters 410 differential refractometer. The software used for molecular weight calculations was millennium chromatography manager version 2.15. Sodium dihydrogen phosphate, 20 mM, pH 7.0, was used as the eluent. Analyses were carried out at 35 °C, flow rate 1 mL min^{-1} and with injection volumes of 10 μL. Polyethylene glycol standards with narrow polydispersity were used to generate a calibration curve.

Polymerization reactions

Polymerization of acrylamide in aqueous medium. Acrylamide (2.92 mmol in 4 mL water) in a dual inlet ampule was purged with nitrogen for 10 min. Into the above solution, HRP (8 mg in 0.2 mL water), hydrogen peroxide (0.046 mmol) and 2,4-pentanedione (0.068 mmol) were successively injected while stirring. The reactions were carried out at room temperature for a predetermined time period while maintaining both stirring and a nitrogen atmosphere. After the predetermined time, the reaction mixture was poured into an excess of methanol. The resulting precipitate was filtered off, washed with methanol and dried *in vacuo* (50 °C, 30 mmHg, 24 h). The enzyme was soluble in methanol and thus removed from the polymer.

Polymerization of acrylamide in aqueous medium in presence of surfactant. Acrylamide (2.92 mmol) was added to a solution of distilled water (3.75 mL) and CTAB (9.0×10^{-4} mol/L, 50 μL) or AOT (6.8×10^{-4} mol/L, 50 μL) in a dual inlet ampule under nitrogen atmosphere. An example of a typical reaction is the successive addition under a nitrogen atmosphere of 0.2 mL of HRP (40 mg mL^{-1}, 8 mg of enzyme), hydrogen peroxide (0.046 mmol) and 2,4-pentanedione (0.068 mmol). The reaction mixture was maintained under nitrogen with stirring at room temperature for a predetermined time period. Then, the reaction mixture was poured into a large excess of methanol. The precipitate obtained was separated by filtration, washed with methanol and then with hot chloroform (to remove surfactant), and dried (*in vacuo*, 50 °C, 30 mmHg, 24 h).

Polymerization of acrylamide in concentrated emulsion. Toluene (42 μL) and sorbitane monooleate (17.2 μL) were degassed in a dual inlet ampule for 10 min. Acrylamide (2.92 mmol) dissolved in water (0.45 mL) was added to the surfactant solution with stirring. To the above was added HRP (8 mg in 0.3 mL water), hydrogen peroxide (0.046 mmol) and 2,4-pentanedione (0.068 mmol) while vigorously stirring. The polymerization was carried out under a nitrogen stream for different time periods. The polyacrylamide was isolated by precipitation in methanol and then dried in a vacuum oven (50 °C, 30 mmHg, 24 h).

Polymerization of sodium acrylate in aqueous medium. Sodium acrylate (4 mmol) was added to a solution of distilled water (1.5 mL) in a dual inlet ampule under nitrogen atmosphere. An example of a typical reaction is the successive addition under a nitrogen atmosphere of HRP (11.4 mg in 0.5 mL water), hydrogen peroxide (0.064 mmol) and 2,4-pentanedione (0.097 mmol). The reaction mixture was maintained under nitrogen with stirring at room temperature for a predetermined time period. Then, the reaction mixture was poured into a large excess of methanol. The precipitate obtained was separated by filtration, washed with methanol and dried (*in vacuo*, 50 °C, 30 mmHg, 24 h).

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Alumina-supported formate for the hydrogenation of alkenes

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Under microwave and thermal conditions hydrogenation of alkenes may be achieved in excellent yields using a cheap recyclable transfer hydrogenation source supported on alumina in presence of Wilkinson's catalyst.

Introduction

In recent years the use of reagents and catalysts immobilised on solid supports has received considerable attention. Such reagents not only simplify purification processes but also help prevent release of reaction residues into the environment. They may also be easily used in automated combinatorial and parallel synthesis protocols. Reagents supported on organic polymers and within and/or on the surface of inorganic matrices have all been reported.[1,2]

Use of microwave irradiation to promote chemical reactions has also been extensively exploited.[3] It has been demonstrated that application of microwave irradiation to organic reactions not only results in reduced reaction times but also improves yield compared to those obtained under conventional reaction conditions. Under microwave conditions reactions are performed using minimal amounts of solvent and in some cases in the absence of solvent, consequently such processes result in formation of reduced quantities of waste. Combined with the rapid reaction times and improved yields normally observed, these processes may therefore be considered as environmentally acceptable.

Microwave assisted catalytic transfer hydrogenation, using metal catalysts in conjunction with a suitable hydrogen donor (usually ammonium formate) has also been achieved.[4] These reactions have been shown to proceed with high levels of efficiency and have been adapted not only for the hydrogenation of alkenes but also for the reduction of nitro compounds and the selective removal of *O*- and *N*-benzyl protecting groups.[5]

During our studies on microwave assisted hydrogenation reactions we reported how use of the diformate salt of tetramethylethylenediamine provided an ideal alternative to ammonium formate for isotopic labelling of alkenes using Wilkinson's catalyst.[6] In a more recent paper, we described a polymer supported transfer hydrogenation source and its use with Wilkinson's catalyst for the reduction of electron deficient alkenes in good yield.[7] We also demonstrated that the yield of the microwave promoted reaction was improved compared to that obtained *via* the thermal route.[7] We also demonstrated that use of the polymer supported transfer hydrogenation source resulted in a considerably simplified purification and removed the possibility of sublimation and release of ammonia. These problems are frequently encountered when using large quantities of ammonium formate as the transfer hydrogenation source.

In this paper we describe how formic acid supported on basic alumina may also be used as a transfer hydrogenation source. We also demonstrate that the alumina aids purification at the end of the reaction by acting as a scavenger for Wilkinson's catalyst, reducing the need for purification.

Results and discussion

Initially the reaction between 3-phenylpropenoic acid and alumina-supported formic acid using Wilkinson's catalyst was studied. Alumina-supported formic acid was synthesised as follows.

A chromatography column packed with basic alumina (Brockmann grade 1) was eluted five times with a 20% solution of formic acid in dichloromethane. The alumina was removed and dried under reduced pressure for 24 h until a free flowing powder was produced. The solid thus obtained was ready for further application in hydrogenation reactions. The loading of formic acid on the alumina was determined as 2 mmol g^{-1} by potentiometric titration.

A mixture of *E*-3-phenylpropenoic acid, alumina-supported hydrogen donor and Wilkinson's catalyst was suspended in a minimum quantity of DMSO (*ca.* 0.5 ml) and irradiated at 100 W for 30 s. The mixture produced was cooled to room temperature, diluted with dichlormethane (0.5 ml) and filtered and the solvent was removed under reduced pressure to yield a white crystalline solid identified as 3-phenylpropanoic acid (90%). Fortuitously the Wilkinson's catalyst used in the reaction was sequested by alumina at the filtration stage. The alumina can therefore, also be considered as a scavenger for the catalyst, in addition to being a support for formate. At the end of the reaction the Wilkinson's catalyst can be recovered from the alumina by washing with ethanol.

For the purpose of comparison the corresponding hydrogenation under conventional thermal conditions (70 °C, 4 h) was carried out to demonstrate the benefit of the application of microwave irradiation for this reaction. In this case the reaction yield was 80%.

In order to demonstrate the scope of this reaction a range of alkenes were treated with the alumina-supported transfer hydrogenation source and Wilkinson's catalyst under micro-

Green Context

Transfer hydrogenations are often mild and selective and are widely utilised. These methods employ a sacrificial hydrogen source such as an alcohol to deliver the reductant. Here an alumina-supported formate is used as the source of hydrogen and Wilkinson's catalyst is used. Microwaves assist the reaction by increasing rates and reducing solvent volume. A nice touch is that the alumina support adsorbs the catalyst from solution, aiding further the recovery of the product—the catalyst can be easily re-liberated after separation. ***DJM***

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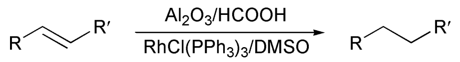
wave and thermal conditions. The results obtained from these studies are presented in Table 1.

Compared to the classical thermal approach, in all cases the reaction yields showed an improvement of 10–25% by application of microwave conditions, this is particularly noteworthy for pentenoic acid (Table 1, entry 6) and *N*,*N*′-dimethyl cinnamide (Table 1, entry 8). Particularly significant however, is that for the microwave assisted reactions a significantly reduced solvent volume (0.5 ml) is required.

Table 1 Hydrogenation of alkenes using alumina-supported formate and Wilkinson's catalyst under microwave and thermal conditions[8]



1 - 8 **9 - 16**

Entry	Alkene	R	R′	Product[a]	Yield (%)[b] (microwave)	Yield (%)[c] (thermal)
1	**1**	Ph	CO_2H	**9**	95	80
2	**2**	Ph	CO_2Me	**10**	88	75
3	**3**	Ph	CO_2Et	**11**	70	62
4	**4**	Ph	CHO	**12**	60	50
5	**5**	Ph	$COCH_3$	**13**	95	88
6	**6**	Et	CO_2H	**14**	73	50
7	**7**	Ph	CN	**15**	95	95
8	**8**	Ph	$CON(CH_3)_2$	**16**	95	70

[a] All products gave satisfactory spectroscopic data. [b] All microwave irradiations were conducted at 100 W for 30 s. [c] All thermal reactions were performed at 70 °C for 4 h in DMSO.

Conclusions

In conclusion we have shown that formic acid may be supported on alumina and used as a transfer hydrogenation source for the reduction of alkenes using Wilkinson's catalyst.

The most advantageous features are a substantial reduction of reaction time and the reduced volume of solvent employed compared to the reaction performed by the more conventional thermal route. Also the use of a hydrogen donor supported on an inorganic solid support such as alumina has also simplified the purification procedure by acting as a scavenger for Wilkinson's catalyst.

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8 In a typical experiment, *E*-3-phenylpropenoic acid (0.025 g), alumina-supported hydrogen donor (0.500 g) and Wilkinson's catalyst (0.005 g) were suspended in DMSO (0.5 ml) in a glass vial equipped with a screw cap. The reaction mixture was irradiated with microwaves at 100 W for 30 s. On cooling, the mixture was diluted with dichloromethane (0.5 ml) and filtered under gravity. The filtrate on evaporation under reduced pressured, gave white crystals identified as 3-phenylpropanoic acid by comparison of their spectroscopic data (^1H NMR, ^{13}C NMR, IR and MS) and mp with those of an authentic sample (0.024 g, 95%).